COPD/Emphysema PubMed search results covering the period 19/01/2019-26/04/2019

Cohort and case-control studies

Search strategy: ("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR "emphysema"[MeSH Major Topic]) AND ("Cohort Studies"[MeSH Terms] OR "Case-Control Studies"[MeSH Terms]) AND English[lang] AND ("2018/07/26"[CDAT] : "3000"[CDAT])

Antus, B., O. Drozdovszky, et al. (2016). **"Assessment of exhaled carbon monoxide in exacerbations of chronic obstructive pulmonary disease."** Physiol Int **103**(2): 211-219.

Introduction Exhaled carbon monoxide (eCO) has been widely implicated as a pulmonary biomarker in respiratory diseases. The aim of this study was to investigate whether the treatment of patients with severe acute exacerbation of chronic obstructive pulmonary disease (AECOPD) could be aided by monitoring the changes in eCO. Methods The levels of eCO along with routine clinical parameters were analyzed in 29 current smoker and 33 ex-smoker COPD patients, first at the time of hospital admission, and again at discharge following the standard treatment. Patients with AECOPD were also stratified according to sputum bacteria. Results At exacerbation, the levels of eCO were increased in current smokers compared to ex-smokers (6.0 [2.0-9.5] versus 1.0 [1.0-2.0] ppm, p < 0.001). Similarly, eCO levels were higher in smokers after treatment (7.0 [2.0-12.5] versus 1.0 [1.0-2.0] ppm, p < 0.001). Treatment of AECOPD did not affect eCO concentrations. The levels of eCO were not statistically different between bacterial and non-bacterial AECOPD either. Investigating a subgroup of current smoker patients (n = 15), there was a significant correlation between the levels of eCO and blood carboxyhemoglobin concentrations both at exacerbation and discharge. No associations were found between eCO and lung function or blood gas parameters. Conclusion Our results suggest that monitoring eCO during the treatment of AECOPD is of limited clinical value.

https://akademiai.com/doi/abs/10.1556/036.103.2016.2.8

Ban, W. H., H. H. Kang, et al. (2018). **"Clinical significance of nuclear factor erythroid 2-related factor 2 in patients with chronic obstructive pulmonary disease."** Korean J Intern Med **33**(4): 745-752.

Background/Aims: Several studies have identified a role for nuclear factor erythroid 2-related factor 2 (Nrf2) in the development of chronic obstructive pulmonary disease (COPD). However, the relationship between the plasma Nrf2 level and the extent of systemic inflammation associated with COPD status remains unclear. METHODS: Patients diagnosed with COPD were recruited from St. Paul's Hospital, The Catholic University of Korea, between July 2009 and May 2012. Patients were classified into two groups according to the severity of their symptoms on initial presentation, a COPD-stable group (n = 25) and a COPD-exacerbation group (n = 30). Seventeen patients were enrolled as a control group (n = 17). The plasma levels of Nrf2 and other systemic inf lammatory biomarkers, including interleukin 6 (IL-6), surfactant protein D (SP-D), and C-reactive protein (CRP), were measured. We collected clinical data including pulmonary function test results, and analyzed the relationships between the biomarker levels and the clinical parameters. RESULTS: Plasma Nrf2 and CRP levels significantly increased in a stepwise manner with an increase in inflammatory status (control vs. COPD-stable vs. COPD-exacerbation) (p = 0.002, p < 0.001). Other biomarkers of systemic inflammation (IL-6, SP-D) exhibited similar tendencies, but significant differences were not apparent. Furthermore, we observed negative correlations between the plasma level of Nrf2 and both the forced expiratory volume in 1 second (FEV1) (r = -0.339, p = 0.015) and the forced expiratory ratio (FEV1/forced vital capacity [FVC]) (r = -0.342, p = 0.014). However, CRP level was not correlated with any measured parameter. Conclusions: Plasma Nrf2 levels gradually increased in line with disease severity and the extent of systemic inflammation in patients with COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6030408/pdf/kjim-2017-030.pdf

Belchamber, K. B., C. M. Thomas, et al. (2018). **"Comparison of fluticasone propionate and budesonide on COPD macrophage and neutrophil function."** Int J Chron Obstruct Pulmon Dis **13**: 2883-2897.

Background: Inhaled corticosteroid use is associated with increased rates of pneumonia in COPD patients. The underlying mechanism is unknown, although recent data suggest that pneumonia is more frequent in patients treated with fluticasone propionate (FP) than budesonide. Macrophages and neutrophils from COPD patients are deficient in clearing bacteria, and this might explain increased bacterial colonization in COPD. Inhaled corticosteroid may further suppress this response; therefore, we examined the effect of FP and budesonide on phagocytosis of common respiratory pathogens by monocyte-derived macrophages (MDMs) and neutrophils. Methods: MDMs from COPD patients (n=20-24) were preincubated with FP or budesonide for 1 or 18 hours, after which phagocytosis of fluorescently labeled inert beads or heat-killed Haemophilus influenzae/Streptococcus pneumoniae were measured fluorimetrically after 1 or 4 hours. Additionally, CXCL8, IL6, and TNFalpha concentrations in supernatants by ELISA, MDM-scavenger-receptor expression by flow cytometry, and MDM ability to kill bacteria were measured. Neutrophils from COPD patients (n=8) were preincubated with corticosteroids for 1 hour and bacteria phagocytosis measured by flow cytometry. Results: After 1 hour's preincubation, neither corticosteroid altered MDM phagocytosis of beads or H. influenzae; however, budesonide (10(-7) M) increased S. pneumoniae phagocytosis by 23% (P<0.05). After 18 hours' preincubation, neither corticosteroid altered MDM phagocytosis of any prey, although H. influenzae phagocytosis by budesonide was significantly greater compared to FP at 10(-6) and 10(-5) M (P<0.05). The 1-hour preincubation with either corticosteroid inhibited bacteria-induced CXCL8 release (at 10(-7) and 10(-5) M, P<0.05); however, this effect was lost at 18-hour preincubation. There was no change in receptor expression, bacterial killing, or neutrophil phagocytosis by either corticosteroid. Conclusion: These data suggest that dissolved FP and budesonide do not have an overall effect on MDM or neutrophil phagocytosis of bacteria.

https://www.dovepress.com/getfile.php?fileID=44491

Braunlich, J. and H. Wirtz (2018). **"Nasal high-flow in acute hypercapnic exacerbation of COPD."** Int J Chron Obstruct Pulmon Dis **13**: 3895-3897.

https://www.dovepress.com/getfile.php?fileID=46647

Budde, J., P. Agarwal, et al. (2018). **"Can an Emergency Department Observation Unit Reduce Hospital Admissions for COPD Exacerbation?"** Lung **196**(3): 267-270.

Studies on observation unit (OU) use to avoid a hospital admission from the emergency department (ED) have found variable effects on health care resource utilization, and these effects have not been studied in acute exacerbation of chronic obstruction pulmonary disease (AECOPD). We retrospectively collected data for all AECOPD-related ED visits (age > 40) to an urban, academic medical center between February 2013 and April 2017. We examined the total proportion of visits admitted to the hospital before and after availability of an OU and the proportion of visits discharged directly from the ED using segmented regression analysis. There was a 12.8% reduction in hospital admissions after OU availability (79.6 vs. 66.8%, p = 0.0049) without a change in the proportion discharged directly from the ED (p = 0.65). The availability of an OU can decrease hospital AECOPD admissions without affecting the number of patients discharged directly from the ED.

https://link.springer.com/article/10.1007%2Fs00408-018-0102-1

Callea, F., I. Giovannoni, et al. (2018). **"Mineralization of alpha-1-antitrypsin inclusion bodies in Mmalton alpha-1-antitrypsin deficiency."** Orphanet J Rare Dis **13**(1): 79.

BACKGROUND: Alpha-1-antitrypsin (AAT) deficiency (AATD) of Z, Mmalton, Siiyama type is associated with liver storage of the mutant proteins and liver disease. The Z variant can be diagnosed on isoelectric focusing (IEF) while Mmalton and Siiyama may be missed or misdiagnosed with this technique. Therefore, molecular analysis is mandatory for their characterization. In particular, that holds true for the Mmalton variant as on IEF profile it resembles the wild M2 subtype. METHODS: This is a retrospective analysis involving review of medical records and of liver biopsy specimens from a series of Mmalton, Z and Siiyama Alpha-1-antitrypsin deficiency patients. The review has been implemented by additional histological stains, electron microscopic observations and 3-D modeling studies of the sites of the mutations. RESULTS: Z, Mmalton and Siiyama liver specimen contained characteristic intrahepatocytic PAS-D globules. The globules differed in the three variants as only Mmalton cases showed dark basophilic precipitates within the AAT inclusions. The precipitates were visualized in haematoxylin-eosin (H.E.) stained preparations and corresponded to calcium precipitates as demonstrated by von Kossa staining. On immunohistochemistry, ZAAT inclusions were stained by polyclonal as well as monoclonal noncommercial anti-AAT antibody (AZT11), whilst Mmalton and Siiyama inclusion bodies remained negative with the monoclonal anti-Z antibody. 3-D protein analysis allowed to predict more severe misfolding of the Mmalton molecule as compared to Z and Siiyama that could trigger anomalous interaction with endoplasmic reticulum chaperon proteins, namely calcium binding proteins. CONCLUSIONS: Mmalton AAT inclusion bodies contain calcium precipitates inside them that allow the differential diagnosis with Siiyama and ZAAT inclusions in routine histological sections. The study has confirmed the specificity of the monoclonal AZT11 for the Z mutant. Thus, the combination of these two features is crucial for the distinction between the three variants and for predicting the genotype, whose confirmation would definitely require molecular analysis. Our study provides new data on the pathomorphogenesis of Mmalton inclusion bodies whose mineralization could play a central role in disease pathogenesis of Mmalton that is distinct from the Z and Siiyama variants. Calcium is known to be a major effector of cell death either via the increased intracellular concentration or the alteration of homeostasis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5956786/pdf/13023_2018_Article_821.pdf

Chen, R., L. Xing, et al. (2018). **"Prediction of prognosis in chronic obstructive pulmonary disease patients with respiratory failure: A comparison of three nutritional assessment methods."** Eur J Intern Med **57**: 70-75.

OBJECTIVES: Due to their increased energy expenditure, chronic obstructive pulmonary disease (COPD) patients with respiratory failure are susceptible to malnutrition. This study aimed to compare the predictive values of the following three widely used nutritional assessment methods for the clinical prognosis of COPD patients with respiratory failure: body mass index (BMI), Nutritional Risk Screening 2002 (NRS 2002), and serum albumin (ALB) level. METHODS: COPD patients with respiratory failure treated in our center from June 2013 to June 2016 were retrospectively included. Patient BMI, NRS 2002 and ALB values were measured to assess their nutritional status. A multivariable analysis was conducted, and receiver operating characteristic (ROC) curves were generated to explore the predictive factors for clinical prognoses. RESULTS: A total of 438 qualified patients were enrolled in our study. Multivariable analysis revealed that the BMI and ALB values independently predicted in-hospital mortality, the BMI and NRS 2002 predicted 1-year mortality, and all three methods (BMI, NRS 2002, and ALB) predicted 30-day readmission after discharge ($P<0.05$). Regarding the results of the AUROC analysis, the optimal cutoff values that maximized the ability to predict the prognosis were an ALB level of 30.5g/L for in-hospital mortality, an NRS 2002 score of 3 points for 1-year mortality, and an ALB level of 30.1g/L for readmission within 30days following discharge. CONCLUSIONS: For COPD patients with respiratory failure, ALB level was superior for predicting in-hospital mortality and 30-day readmission after discharge, and NRS 2002 was superior for long-term prognosis of 1-year mortality.

https://www.ejinme.com/article/S0953-6205(18)30238-3/fulltext

Chen, X., J. Liu, et al. (2018). **"Progranulin is a novel biomarker for predicting an acute exacerbation of chronic obstructive pulmonary disease."** Clin Respir J **12**(10): 2525-2533.

BACKGROUND: Progranulin is a pleiotropic glycosylated protein precursor that plays an important role in inflammation. Limited data exist regarding the role of progranulin in the acute exacerbation of chronic obstructive pulmonary disease (AECOPD). OBJECTIVES: The study is to assess the efficiency of progranulin as a circulating biomarker of AECOPD. METHODS: The plasma progranulin levels were measured and compared in patients with AECOPD (n = 52), patients with stable COPD (n = 56), and healthy controls (n = 36). In patients with AECOPD, plasma progranulin levels were measured repeatedly on the last day of hospitalization. Demographical data, pulmonary function, and laboratory parameters were recorded. RESULTS: Patients with AECOPD had higher plasma progranulin levels than both stable COPD patients and healthy controls (158.77 +/- 48.17, 109.00 +/- 25.05, 93.67 +/- 14.71 ng/mL, respectively; P < .001). In patients with AECOPD, the plasma progranulin levels significantly decreased on the last day of hospitalization compared with those on the first day of hospitalization (138.51 +/- 44.68 vs. 158.77 +/- 48.17 ng/mL, P = .042). The progranulin levels were negatively correlated to FEV1%pred but positively correlated to neutrophil-to-lymphocyte ratio and C-reactive protein in all patients with COPD. Multivariate logistic regression and ROC analysis revealed progranulin (odds ratio 1.05, 95% confidence interval 1.03-1.08, P < .001) as an independent predictor of AECOPD, with an area under the curve of 0.82. CONCLUSIONS: Progranulin may be a valuable blood biomarker of AECOPD and progranulin may be involved in the pathogenesis of AECOPD by disturbing inflammatory responses.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12952

Choi, H. S., J. O. Na, et al. (2018). **"Which GOLD B patients progress to GOLD D with the new classification?"** Int J Chron Obstruct Pulmon Dis **13**: 3233-3241.

Background: The 2017 GOLD guidelines revised assessment of COPD by eliminating the FEV1 criterion. Aim: First, we explored the redistribution of 2011 GOLD groups by reference to the 2017 GOLD criteria. Second, we investigated the characteristics of GOLD B patients and the natural course of GOLD B patients according to the 2017 GOLD guidelines. Methods: In total, 2,010 COPD patients in the Korean COPD Subgroup Study cohort were analyzed at baseline and 1 year after enrollment. Results: The 2011 GOLD C patients were redistributed to the 2017 A (64.5%) and C (35.4%) groups. The 2011 GOLD D patients were redistributed to the 2017 B (61.6%) and D (38.6%) groups. The GOLD B patients constituted 62.7% of all patients according to the 2017 classification. Such patients exhibited higher % predicted FEV1 values, longer six-minute walk distances, fewer symptoms, and lower inflammatory marker levels than GOLD D patients. Most GOLD B patients remained in that group (69.1%), but 13.8% progressed to group D at 1-year follow-up. The factors associated with progression from GOLD B to GOLD D were older age, higher modified Medical Research Council (mMRC) and St George's Respiratory Questionnaire (SGRQ) symptom scores, and a lower % predicted FEV1 value. Conclusion: Severe symptoms, poorer health status, and greater airflow limitation increased patients' risk of exacerbation and progression from group B to group D when the 2017 GOLD criteria were applied.

https://www.dovepress.com/getfile.php?fileID=45250

Chuaychoo, B., R. Tungtrongchitr, et al. (2018). **"Correlation of vitamin D binding protein gene polymorphism and protein levels in chronic obstructive pulmonary disease compared with non-chronic obstructive pulmonary disease subjects."** Per Med **15**(5): 371-379.

AIM: The risk of vitamin D binding protein (DBP) variations in chronic obstructive pulmonary disease (COPD) compared with non-COPD Thai males were investigated. MATERIALS & METHODS: The rs7041 and rs4588 polymorphisms of the DBP gene and protein level were measured in 136 COPD and 68 non-COPD Thai males. RESULTS: In the COPD group, GC1-1 gave increased forced expiratory volume at 1 s % predicted compared with GC1-2 but with no significant difference. Significantly lower average DBP serum levels were observed in COPD than non-COPD subjects. Positive correlation between serum DBP and forced expiratory volume at 1 s % predicted was observed in non-COPD subjects. DISCUSSION &

CONCLUSION: DBP variations might be associated with risk factors in COPD caused by both inflammatory and vitamin D circulation processes.

https://www.futuremedicine.com/doi/10.2217/pme-2018-0005

Crimi, C., E. Heffler, et al. (2018). **"Utility of ultrasound assessment of diaphragmatic function before and after pulmonary rehabilitation in COPD patients."** Int J Chron Obstruct Pulmon Dis **13**: 3131-3139.

Background: Pulmonary rehabilitation (PR) may improve respiratory symptoms and skeletal muscle strength in patients with COPD. We aimed to evaluate changes in ultrasound (US) measurements of diaphragmatic mobility and thickness after PR in COPD patients and to test its correlation with PR outcomes. Methods: Twenty-five COPD patients were enrolled and underwent a diaphragm US assessment before and after a 12-week PR program. Results: We found a correlation between the intraindividual percentage of change in the diaphragmatic length of zone of apposition at functional residual capacity (DeltaLzapp%) and the change in 6-minute walking distance (6MWD) after PR (rho=0.49, P=0.02). DeltaLzapp% was significantly higher in patients with improved 6MWD and COPD Assessment Test (CAT) score (mean rank=12.03+/-2.57 vs 6.88+/-4.37; P=0.02). A DeltaLzapp% of >/=10% was able to discriminate among patients with improved 6MWD, with a sensitivity of 83% and a specificity of 74%. The area under the receiver operating characteristic curve for DeltaLzapp% was 0.83. A cutoff value of >/=9% of DeltaLzapp% had a positive predictive value in discriminating a reduction in >/=2 points of CAT score after PR, with a sensitivity and a specificity of 80% and 62%, respectively. Conclusion: Diaphragm US assessment represents a useful prognostic marker of PR outcomes in COPD patients.

https://www.dovepress.com/getfile.php?fileID=45074

Dai, L., J. He, et al. (2018). **"The association of elevated circulating endocan levels with lung function decline in COPD patients."** Int J Chron Obstruct Pulmon Dis **13**: 3699-3706.

Background: Endocan is thought to be a novel inflammatory marker that is associated with a variety of inflammatory diseases. However, its role in the pathogenesis of COPD remains unclear. This study aims to explore the potential role of endocan in COPD. Methods: In total, 27 healthy volunteers, 55 COPD patients and 36 acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients were included in the study. Basic demographic characteristics, clinical features and blood samples were collected. Magnetic luminex screening assays were used to detect the concentration of endocan, Fas and Fas ligand (Fas-L) in plasma. Differences between groups were compared using an Independent sample t-test, Welch's t-test, chi-squared test and Wilcoxon rank sum test. The correlations of plasma endocan with lung function parameters, Fas and Fas-L were analyzed by Pearson's partial correlation test (adjusted for age, gender, body mass index and smoking history) and multiple linear regression. Results: Plasma endocan levels in COPD patients were significantly higher than those in healthy volunteers (509.7+/-18.25 pg/mL vs 434.8+/-18.98 pg/mL (P=0.0124)), and AECOPD patients had the highest levels of endocan (524.7+/-27.18 pg/mL). Correlation analysis showed that circulating endocan had a negative correlation to FEV1/FVC, FEV1/predictive and FVC (adjusted r=-0.213, P=0.03; adjusted r=-0.209, P=0.034; and adjusted r=-0.300, P=0.002, respectively), and had a positive correlation to Fas (adjusted r=0.280, P=0.004). Conclusion: Our study shows that elevated circulating endocan levels are associated with reduced lung ventilation function in COPD and AECOPD patients. In addition, endocan may influence apoptosis in COPD, suggesting that endocan may play a role in COPD pathogenesis.

https://www.dovepress.com/getfile.php?fileID=46097

de Miguel-Diez, J., A. Lopez-de-Andres, et al. (2018). **"Influence of COPD on outcomes of patients hospitalized with heart failure: Analysis of the Spanish National Hospital Discharge Database (2001-2015)."** Int J Cardiol **269**: 213-219.

OBJECTIVE: To examine trends in incidence and outcomes of heart failure (HF) hospitalizations among patients with or without chronic obstructive pulmonary disease (COPD) in Spain (2001-2015). METHODS: We used national hospital discharge data to select hospital admissions for HF as primary diagnosis. Incidence, comorbidities, diagnostic and therapeutic procedures, length of hospital stay (LOHS), readmissions rate, costs and in hospital mortality (IHM) was analyzed according to the presence or absence of COPD. Charlson comorbidity index (CCI) was used to assess comorbidity. RESULTS: We identified 1,501,811 admissions for HF (19.55% with COPD). Incidence was significantly higher in COPD patients for all years analyzed. We found a significant increase in crude incidence over time in both groups of patients. Overall the incidence was 2.42-times higher among COPD patients (IRR 2.42; 95%CI 2.39-2.46). The joinpoint analysis showed that among men with COPD admissions for HF increased by 2.90% per year. Time trend analyses showed a significant decrease in IHM for both groups. Factors independently associated with higher IHM in both groups included: female gender, higher age, comorbidities according to CCI, longer LOHS and readmissions. The presence of COPD was not associated with a higher IHM in patients hospitalized with HF (OR0.98, 95%CI 0.96-1.01). CONCLUSIONS: Among men suffering COPD the incidence of HF hospitalizations increased from 2001 to 2015. Incidence of hospitalizations was more than twice higher in the COPD population. IHM decreased over time in both groups. Female gender and readmission predict higher IHM. There were no differences in mortality between patients with and without COPD.

https://www.internationaljournalofcardiology.com/article/S0167-5273(18)33503-4/fulltext

Dogra, S., J. Good, et al. (2018). **"Physical activity and sedentary time are related to clinically relevant health outcomes among adults with obstructive lung disease."** BMC Pulm Med **18**(1): 98.

BACKGROUND: The purpose of the current study was to determine the association between sedentary time and physical activity with clinically relevant health outcomes among adults with impaired spirometry and those with or without self-reported obstructive lung disease (asthma or COPD). METHODS: Data from participants of the Canadian Longitudinal Study on Aging were used for analysis (n = 4156). Lung function was assessed using spirometry. Adults were said to have impaired spirometry if their Forced Expiratory Volume in 1 s was <5th percentile lower limit of normal (LLN). A modified version of the Physical Activity Scale for the Elderly was used to assess sitting time and physical activity levels. Healthcare use and quality of life outcomes were assessed using self report. RESULTS: Among those with asthma, participating in strengthening activities was associated with lower odds of reporting poor perceived health (OR = 0.65, CI: 0.53, 0.79), poor perceived mental-health (OR = 0.73, CI: 0.60, 0.88), unhealthy aging (OR = 0.68, CI: 0.56, 0.83), and reporting an emergency department visit in the past 12 months (OR = 0.76, CI: 0.60, 0.95). Among those with COPD, those who reported highest weekly sedentary time had higher odds of reporting poor perceived health (OR = 2.70, CI: 1.72, 4.24), poor perceived mental-health (OR = 1.99, CI: 1.29, 3.06), and unhealthy aging (OR = 3.04, CI: 1.96, 4.72). Among those below the LLN, sitting time (OR = 2.57, CI: 1.40, 4.72) and moderate intensity physical activity (OR = 0.23, CI: 0.09, 0.63) were associated with overnight hospital stays. CONCLUSIONS: Higher physical activity levels and lower sedentary time may be associated with lower healthcare use and better quality of life. This research may have implications related to the use of physical activity for improving health outcomes and quality of life among adults with obstructive lung disease or impaired spirometry.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5992845/pdf/12890_2018_Article_659.pdf

Fabbri, L. M., B. Beghe, et al. (2018). **"Blood eosinophils for the management of COPD patients?"** Lancet Respir Med **6**(11): 807-808.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30417-X/fulltext

Gallo, M. C., C. Kirkham, et al. (2018). **"Changes in IgA Protease Expression Are Conferred by Changes in Genomes during Persistent Infection by Nontypeable Haemophilus influenzae in Chronic Obstructive Pulmonary Disease."** Infect Immun **86**(8)Nontypeable Haemophilus influenzae (NTHi) is an exclusively human pathobiont that plays a critical role in the course and pathogenesis of chronic obstructive pulmonary disease (COPD). NTHi causes acute exacerbations of COPD and also causes persistent infection of the lower airways. NTHi expresses four IgA protease variants (A1, A2, B1, and B2) that play different roles in virulence. Expression of IgA proteases varies among NTHi strains, but little is known about the frequency and mechanisms by which NTHi modulates IgA protease expression during infection in COPD. To assess expression of IgA protease during natural infection in COPD, we studied IgA protease expression by 101 persistent strains (median duration of persistence, 161 days; range, 2 to 1,422 days) collected longitudinally from patients enrolled in a 20-year study of COPD upon initial acquisition and immediately before clearance from the host. Upon acquisition, 89 (88%) expressed IgA protease. A total of 16 of 101 (16%) strains of NTHi altered expression of IgA protease during persistence. Indels and slipped-strand mispairing of mononucleotide repeats conferred changes in expression of igaA1, igaA2, and igaB1 Strains with igaB2 underwent frequent changes in expression of IgA protease B2 during persistence, mediated by slipped-strand mispairing of a 7-nucleotide repeat, TCAAAAT, within the open reading frame of igaB2 We conclude that changes in iga gene sequences result in changes in expression of IgA proteases by NTHi during persistent infection in the respiratory tract of patients with COPD.

https://iai.asm.org/content/iai/86/8/e00313-18.full.pdf

Galvis, J. N., M. V. Vargas, et al. (2019). **"Impact of Chronic Obstructive Pulmonary Disease on Laparoscopic Hysterectomy Outcome."** Jsls **23**(1)Background and Objectives: Limited research exists on the association between chronic obstructive pulmonary disease (COPD) and morbidity and mortality after laparoscopic hysterectomy. The objective of this study is to examine the following: 1) which demographics and comorbidities are most likely to present concurrently in patients with COPD? 2) Are patients with COPD undergoing laparoscopic hysterectomy at increased risk for development of postoperative complications within 30 days? Methods: Retrospective cohort study using data collected from 2007 to 2016 from the American College of Surgeons National Surgical Quality Improvement Program database. All patients who underwent laparoscopic hysterectomy were identified by Current Procedural Terminology codes and stratified based on COPD status. Univariate and multivariate analyses were completed to define odds ratios for postoperative complications within 30 days of laparoscopic hysterectomy. Results: This study included 100,518 laparoscopic hysterectomy patients (COPD = 1,130 [1.12%]); (no COPD = 99,388 [98.8%]). Patients with COPD developed more postoperative complications, including pneumonia, reintubation, renal insufficiency, and sepsis. COPD was identified as an independent risk factor for pneumonia (OR, 4.098; 95% CI, 2.222-7.519) and reintubation (OR, 4.348; 95% CI, 2.387-7.937). Patients with COPD had extended length of hospital stay. Conclusion: Patients with COPD who undergo laparoscopic hysterectomy have increased risk of experiencing postoperative pneumonia, reintubation, renal insufficiency, and sepsis. Overall, postoperative complication rates remain low, but gynecologists should consider the pulmonary disease status of patients when assessing preoperative risk.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6342248/pdf/e2018.00089.pdf

Ge, J., S. Geng, et al. (2019). **"Long noncoding RNAs antisense noncoding RNA in the INK4 locus (ANRIL) correlates with lower acute exacerbation risk, decreased inflammatory cytokines, and mild GOLD stage in patients with chronic obstructive pulmonary disease."** J Clin Lab Anal **33**(2): e22678.

BACKGROUND: We aimed to assess the predictive value of long noncoding RNAs antisense noncoding RNA in the INK4 locus (lncRNAs ANRIL) for acute exacerbation of chronic obstructive pulmonary disease (COPD) and evaluate its correlation with inflammatory cytokines as well as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage in COPD patients. METHODS: A total of 136 acute exacerbations of COPD (AECOPD) patients, 138 stable COPD patients, and 140 healthy controls (HCs) were consecutively recruited, and plasma samples were collected. Real-time polymerase chain reaction was used to detect lncRNA ANRIL expression. Enzyme-linked immunosorbent assay was performed to detect inflammatory cytokines expressions. RESULTS: LncRNA ANRIL expression was lower in AECOPD patients compared with stable COPD patients and HCs (Both P < 0.001). Receiver operating characteristic curves revealed lncRNA ANRIL could distinguish AECOPD patients from HCs (area under curve (AUC):0.700, 95% CI: 0.638-0.762) and stable COPD patients (AUC: 0.659, 95% CI: 0.594-0.724). For inflammatory cytokines, lncRNA ANRIL expression was negatively correlated with TNF-alpha (P < 0.001), IL-1beta (P = 0.015), IL-8 (P = 0.008), IL-17A (P = 0.002), and LTB-4 (P = 0.004) in AECOPD patients, while it was negatively correlated with TNF-alpha (P = 0.049), IL-1beta (P = 0.005), IL-17A (P = 0.030), and LTB-4 (P = 0.011) in stable COPD patients. Furthermore, lncRNA ANRIL expression negatively correlated with GOLD stage in AECOPD patients (P = 0.001), but not in stable COPD patients (P = 0.131). CONCLUSION: LncRNA ANRIL associates with lower acute exacerbation risk, decreased inflammatory cytokines, and mild GOLD stage in COPD patients.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/jcla.22678

Gerdes, M., F. Gallefoss, et al. (2019). **"The EU project "United4Health": Results and experiences from automatic health status assessment in a Norwegian telemedicine trial system."** J Telemed Telecare **25**(1): 46-53.

INTRODUCTION: Patients with chronic obstructive pulmonary disease require help in daily life situations to increase their individual perception of security, especially under worsened medical conditions. Unnecessary hospital (re-)admissions and home visits by doctors or nurses shall be avoided. This study evaluates the results from a two-year telemedicine field trial for automatic health status assessment based on remote monitoring and analysis of a long time series of vital signs data from patients at home over periods of weeks or months. METHODS: After discharge from hospital treatment for acute exacerbations, 94 patients were recruited for follow-up by the trial system. The system supported daily measurements of pulse and transdermal peripheral capillary oxygen saturation at patients' homes, a symptom-specific questionnaire, and provided nurses trained to use telemedicine ("telenurses") with an automatically generated health status overview of all monitored patients. A colour code (green/yellow/red) indicated whether the patient was stable or had a notable deterioration, while red alerts highlighted those in most urgent need of follow-up. The telenurses could manually overwrite the status level based on the patients' conditions observed through video consultation. RESULTS: Health status evaluation in 4970 telemonitor datasets were assessed retrospectively. The automatic health status determination (subgroup of 33 patients) showed green status at 46% of the days during a one-month monitoring period, 28% yellow status, and 19% red status (no data reported at 7% of the days). The telenurses manually downrated approximately 10% of the red or yellow alerts. DISCUSSION: The evaluation of the defined real-time health status assessment algorithms, which involve static rules with personally adapted elements, shows limitations to adapt long-term home monitoring with adequate interpretation of day-to-day changes in the patient's condition. Thus, due to the given sensitivity and specificity of such algorithms, it seems challenging to avoid false high alerts.

Gorska, K., P. Nejman-Gryz, et al. (2018). **"Comparative Study of IL-33 and IL-6 Levels in Different Respiratory Samples in Mild-to-Moderate Asthma and COPD."** Copd **15**(1): 36-45.

IL-6 and IL-33 are involved in the inflammatory process in obstructive lung diseases. In contrast to IL-6, few data on the expression of IL-33 in different biological samples from asthma and COPD patients are available.

The aim was to evaluate the expressions of IL-33 and IL-6 in bronchial mucosa and to compare these expressions with the concentrations of both cytokines in various respiratory samples from patients with mild-to-moderate asthma and COPD. Serum, induced sputum and exhaled breath condensate IL-6 and IL-33 levels, as well as their expression in bronchial mucosa were evaluated in 22 asthma and 33 COPD patients. There were significant differences between bronchial mucosa IL-6, but not IL-33 expression in asthma and COPD. Serum and IS IL-6 concentrations were higher in COPD than in asthma (3.4 vs. 2.02 pg/mL, p = 0.002 and 16.5 vs. 12.7 pg/mL, p = 0.007, respectively); IL-33 levels reached similar values in asthma and COPD in all investigated samples. In both diseases, the lowest levels of IL-6 and IL-33 were found in EBC. EBC levels of both cytokines did not correlate with their expression in other materials. The IL-33 and IL-6 are detectable in serum, IS and EBC not only in asthma but also in COPD patients. In the COPD group, serum and IS IL-6 concentrations were statistically higher than in the asthma group. The tissue expression of IL-33 and IL-33 concentrations in the investigated biological samples were on a comparable level in both diseases. Our findings may suggest that IL-33 activation is a common pathway in asthma and COPD.

https://www.tandfonline.com/doi/full/10.1080/15412555.2017.1416074

Guo, X., H. Nie, et al. (2018). **"The role of plasma N-terminal brain natriuretic pro-peptide in diagnosing elderly patients with acute exacerbation of COPD concurrent with left heart failure."** Int J Chron Obstruct Pulmon Dis **13**: 2931-2940.

Introduction: Acute exacerbation of COPD (AECOPD) and left heart failure (LHF) commonly exist together in clinical practice. However, the identification of AECOPD concurrent with LHF is currently challenging. Our study aimed to investigate the role of plasma N-terminal brain natriuretic pro-peptide (NT-proBNP) in diagnosing elderly patients with AECOPD associated with LHF. Methods and results: LHF was diagnosed in patients with AECOPD according to echocardiographic criteria, and the levels of NT-proBNP in plasma were measured by quantitative electrochemiluminescence assay. Among the 655 patients with AECOPD, 158 (24.1%) had comorbid LHF, whether systolic (n=108, 68.4%) or diastolic (n=50, 31.6%). The plasma concentrations of NT-proBNP in elderly patients with AECOPD associated with LHF were markedly elevated, compared with those with only AECOPD (4,542.5 and 763.0 ng/L, respectively, P<0.01). The receiver operating characteristic curve indicated a diagnostic cutoff value of 1,677.5 ng/L of NT-proBNP in plasma for ascertaining the presence of LHF in AECOPD, with a sensitivity of 87.9%, a specificity of 88.5%, and an accuracy of 88.4%. Conclusion: The plasma level of NT-proBNP may be a useful indicator in diagnosing AECOPD associated with LHF.

https://www.dovepress.com/getfile.php?fileID=44638

Hawcutt, D. B., B. Francis, et al. (2018). **"Susceptibility to corticosteroid-induced adrenal suppression: a genome-wide association study."** Lancet Respir Med **6**(6): 442-450.

BACKGROUND: A serious adverse effect of corticosteroid therapy is adrenal suppression. Our aim was to identify genetic variants affecting susceptibility to corticosteroid-induced adrenal suppression. METHODS: We enrolled children with asthma who used inhaled corticosteroids as part of their treatment from 25 sites across the UK (discovery cohort), as part of the Pharmacogenetics of Adrenal Suppression with Inhaled Steroids (PASS) study. We included two validation cohorts, one comprising children with asthma (PASS study) and the other consisting of adults with chronic obstructive pulmonary disorder (COPD) who were recruited from two UK centres for the Pharmacogenomics of Adrenal Suppression in COPD (PASIC) study. Participants underwent a low-dose short synacthen test. Adrenal suppression was defined as peak cortisol less than 350 nmol/L (in children) and less than 500 nmol/L (in adults). A case-control genome-wide association study was done with the control subset augmented by Wellcome Trust Case Control Consortium 2 (WTCCC2) participants. Single nucleotide polymorphisms (SNPs) that fulfilled criteria to be advanced to replication were tested by a random-effects inverse variance meta-analysis. This report presents the primary analysis. The PASS study is registered in the European Genome-phenome Archive (EGA). The PASS study is complete whereas the PASIC study is ongoing. FINDINGS: Between November,

2008, and September, 2011, 499 children were enrolled to the discovery cohort. Between October, 2011, and December, 2012, 81 children were enrolled to the paediatric validation cohort, and from February, 2010, to June, 2015, 78 adults were enrolled to the adult validation cohort. Adrenal suppression was present in 35 (7%) children in the discovery cohort and six (7%) children and 17 (22%) adults in the validation cohorts. In the discovery cohort, 40 SNPs were found to be associated with adrenal suppression (genome-wide significance p<1 x 10(-6)), including an intronic SNP within the PDGFD gene locus (rs591118; odds ratio [OR] 7.32, 95% CI 3.15-16.99; p=5.8 x 10(-8)). This finding for rs591118 was validated successfully in both the paediatric asthma (OR 3.86, 95% CI 1.19-12.50; p=0.02) and adult COPD (2.41, 1.10-5.28; p=0.03) cohorts. The proportions of patients with adrenal suppression by rs591118 genotype were six (3%) of 214 patients with the GG genotype, 15 (6%) of 244 with the AG genotype, and 22 (25%) of 87 with the AA genotype. Meta-analysis of the paediatric cohorts (discovery and validation) and all three cohorts showed genome-wide significance of rs591118 (respectively, OR 5.89, 95% CI 2.97-11.68; p=4.3 x 10(-9); and 4.05, 2.00-8.21; p=3.5 x 10(-10)). INTERPRETATION: Our findings suggest that genetic variation in the PDGFD gene locus increases the risk of adrenal suppression in children and adults who use corticosteroids to treat asthma and COPD, respectively. FUNDING: Department of Health Chair in Pharmacogenetics.

https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(18)30058-4.pdf

Hida, T., Y. Yamada, et al. (2019). **"Decreased and slower diaphragmatic motion during forced breathing in severe COPD patients: Time-resolved quantitative analysis using dynamic chest radiography with a flat panel detector system."** Eur J Radiol **112**: 28-36.

OBJECTIVE: To assess the diaphragmatic motion in chronic obstructive pulmonary disease (COPD) patients during forced breathing by time-resolved quantitative analysis using dynamic chest radiography and to demonstrate the characteristics and the difference from that in normal subjects. MATERIALS AND METHODS: Thirty-one COPD patients and a matched control of 31 normal subjects on age, sex, height, and weight, who underwent chest radiographs during forced breathing using dynamic chest radiography, were included in this study. COPD patients were classified based on the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD 1, n = 3; GOLD 2, n = 12; GOLD 3, n = 13; GOLD 4, n = 3). We measured excursions and peak motion speeds of the diaphragms for each participant. We compared the results among GOLD 1/2, GOLD 3/4 groups and normal subjects and investigated associations between the data, and participants' demographics, or pulmonary function. RESULTS: The excursions of bilateral diaphragms were significantly decreased in the GOLD 3/4 group relative to normal subjects (right, 39.8 +/- 15.3 mm vs. 52.7 +/- 15.1 mm, P = 0.030; left, 43.7 +/- 14.0 mm vs. 56.9 +/- 15.5 mm, P = 0.017; mean +/- standard deviation) and the GOLD 1/2 group (right, 39.8 +/- 15.3 mm vs. 54.4 +/- 16.7 mm, P = 0.036; left, 43.7 +/- 14.0 mm vs. 60.5 +/- 13.9 mm, P = 0.008). The peak motion speeds of the left diaphragm in the inspiratory phase were slower in the GOLD 1/2 group than in normal subjects (24.5 +/- 8.0 mm/s vs. 33.6 +/- 14.0 mm/s, P = 0.038), and in the GOLD 3/4 group than in normal subjects (25.6 +/- 6.8 mm/s vs. 33.6 +/- 14.0 mm/s, P = 0.067). The excursions of the diaphragms showed correlation with VC, %VC, and FEV1, while the peak motion speeds showed no significant correlation with pulmonary function tests. CONCLUSIONS: Time-resolved quantitative analysis of diaphragms with dynamic chest radiography indicated differences in diaphragmatic motion between COPD groups and normal subjects during forced breathing. The excursions of the diaphragms during forced breathing were significantly lower in the GOLD 3/4 group than those in the GOLD 1/2 group and normal subjects.

https://www.ejradiology.com/article/S0720-048X(18)30471-6/pdf

Hirano, R., M. Fujita, et al. (2018). **"Inhaled corticosteroids might not increase the risk of pneumonia in patients with chronic obstructive pulmonary disease in Japan."** Int J Chron Obstruct Pulmon Dis **13**: 3503-3509.

Background: The use of inhaled corticosteroid (ICS) in patients with chronic obstructive pulmonary disease (COPD) decreases the frequency of COPD exacerbations. Recently, pneumonia was reported as a complication of ICS in patients with COPD. However, there have been few reports concerning the relationship between ICS and pneumonia in Japan. Moreover, there is little information on the types of ICS. Patients and methods: To clarify these issues, we investigated the occurrence of pneumonia in Japanese patients with COPD. We retrospectively investigated the occurrence of pneumonia in patients with COPD in our hospital from January 2009 to August 2013. Morbidity and mortality, ICS use, age, sex, and COPD classification were investigated. A group of patients with COPD who received ICS and a group of patients with COPD who did not receive ICS were compared each other. Results: Fifty-one patients developed pneumonia among 639 (7.98%) patients with COPD. Among 252 ICS-treated patients with COPD, 13 (5.16%) developed pneumonia, and among 387 ICS-untreated patients with COPD, 38 (9.82%) developed pneumonia. The mortality rate in ICS-treated patients with COPD was 7.7%, while that in ICS-untreated patients was 10.5% (P=0.767). Fluticasone/salmeterol use tended to show a higher risk of pneumonia than budesonide/formoterol use. The use of ICS did not increase the risk of pneumonia or mortality due to pneumonia in Japanese patients with COPD. Conclusion: ICS might not increase the risk of pneumonia in Japanese patients with COPD. In regard to pneumonia, ICS can be safely used in Japanese patients with COPD. Because there are apparent differences in lung diseases among races, appropriate treatment should be investigated in each country.

https://www.dovepress.com/getfile.php?fileID=45512

Hsieh, M. J., S. Y. Huang, et al. (2018). **"The impact of 2011 and 2017 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines on allocation and pharmacological management of patients with COPD in Taiwan: Taiwan Obstructive Lung Disease (TOLD) study."** Int J Chron Obstruct Pulmon Dis **13**: 2949-2959.

Background: This nationwide study was performed to evaluate the evolution of distributions of patients with COPD according to the 2011 and 2017 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines and to assess the concordance between the prescribed medications and the pharmacological management recommended by the two distinct classification systems in Taiwan. Subjects and methods: Data were retrospectively retrieved from stable COPD patients in 11 participating hospitals across Taiwan. Patients were grouped according to GOLD 2011 and 2017 guidelines respectively. Definitions of undertreatment and overtreatment were based on the pharmacological recommendations in the individual guidelines. Results: A total of 1,053 COPD patients were included. The percentages of patients in GOLD 2011 groups A, B, C and D were 18.4%, 40.6%, 6.7% and 34.2%, respectively. When reclassified according to the GOLD 2017, the percentages of group A and B increased to 23.3% and 63.2%, and groups C and D decreased to 1.9% and 11.6%, respectively. Up to 67% of patients in GOLD 2011 groups C and D were reclassified to GOLD 2017 groups A and B. The pharmacological concordance rate was 60.9% for GOLD 2011 and decreased to 44.9% for GOLD 2017. Overtreatment was found in 29.5% of patients according to GOLD 2011 and the rate increased to 46.1% when classified by the GOLD 2017. The major cause of overtreatment was unnecessary inhaled corticosteroids and the main cause of undertreatment was a lack of maintenance long-acting bronchodilators. Conclusion: The distribution of COPD patients in Taiwan was more uneven with the GOLD 2017 than with the GOLD 2011. A pharmacological discordance to the guidelines was identified. Updated guidelines with reclassification of COPD patients resulted in more discordance between prescribed medications and the guidelines. Physicians should make proper adjustments of the prescriptions according to the updated guidelines to ensure the mostly appropriate treatment for COPD patients.

https://www.dovepress.com/getfile.php?fileID=44736

Iyer, A. S., J. M. Wells, et al. (2018). **"Life-Space mobility and clinical outcomes in COPD."** Int J Chron Obstruct Pulmon Dis **13**: 2731-2738.

Background: Social isolation is a common experience in patients with COPD but is not captured by existing patient-reported outcomes, and its association with clinical outcomes is unknown. Methods: We prospectively enrolled adults with stable COPD who completed the University of Alabama at Birmingham Life Space Assessment (LSA) (range: 0-120, restricted Life-Space mobility: </=60 and a marker of social isolation in older adults); six-minute walk test (6MWT), and the University of California at San Diego Shortness of Breath Questionnaire, COPD Assessment Test, and Hospital Anxiety and Depression Scale. The occurrence of severe exacerbations (emergency room visit or hospitalization) was recorded by review of the electronic record up to 1 year after enrollment. We determined associations between Life-Space mobility and clinical outcomes using regression analyses. Results: Fifty subjects had a mean +/- SD %-predicted FEV1 of 42.9+/-15.5, and 23 (46%) had restricted Life-Space mobility. After adjusting for age, gender, %-predicted FEV1, comorbidity count, inhaled corticosteroid/long-acting beta2-agonist use, and prior cardiopulmonary rehabilitation, subjects with restricted Life-Space had an increased risk for severe exacerbations (adjusted incidence rate ratio 4.65, 95% CI 1.19-18.23, P=0.03). LSA scores were associated with 6MWD (R=0.50, P<0.001), dyspnea (R=-0.58, P<0.001), quality of life (R=-0.34, P=0.02), and depressive symptoms (R=-0.39, P=0.005). Conclusion: Restricted Life-Space mobility predicts severe exacerbations and is associated with reduced exercise tolerance, more severe dyspnea, reduced quality of life, and greater depressive symptoms.

https://www.dovepress.com/getfile.php?fileID=44111

Jakobsson, J. K. F., H. L. Aaltonen, et al. (2018). **"Altered deposition of inhaled nanoparticles in subjects with chronic obstructive pulmonary disease."** BMC Pulm Med **18**(1): 129.

BACKGROUND: Respiratory tract deposition of airborne particles is a key link to understand their health impact. Experimental data are limited for vulnerable groups such as individuals with respiratory diseases. The aim of this study is to investigate the differences in lung deposition of nanoparticles in the distal lung for healthy subjects and subjects with respiratory disease. METHODS: Lung deposition of nanoparticles (50 and 100 nm) was measured after a 10 s breath-hold for three groups: healthy never-smoking subjects (n = 17), asymptomatic (active and former) smokers (n = 15) and subjects with chronic obstructive pulmonary disease (n = 16). Measurements were made at 1300 mL and 1800 mL volumetric lung depth. Each subject also underwent conventional lung function tests, including post bronchodilator FEV1, VC, and diffusing capacity for carbon monoxide, DL,CO. Patients with previously diagnosed respiratory disease underwent a CT-scan of the lungs. Particle lung deposition fraction, was compared between the groups and with conventional lung function tests. RESULTS: We found that the deposition fraction was significantly lower for subjects with emphysema compared to the other subjects ($p = 0.001$-0.01), but no significant differences were found between healthy never-smokers and smokers. Furthermore, the particle deposition correlated with pulmonary function tests, FEV1%Pred ($p < 0.05$), FEV1/VC%Pred ($p < 0.01$) and DL,CO ($p < 0.0005$) when all subjects were included. Furthermore, for subjects with emphysema, deposition fraction correlated strongly with DL,CO (Pearson's $r = 0.80$-0.85, $p < 0.002$) while this correlation was not found within the other groups. CONCLUSIONS: Lower deposition fraction was observed for emphysematous subjects and this can be explained by enlarged distal airspaces in the lungs. As expected, deposition increases for smaller particles and deeper inhalation. The observed results have implications for exposure assessment of air pollution and dosimetry of aerosol-based drug delivery of nanoparticles.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6080394/pdf/12890_2018_Article_697.pdf

Janson, C., G. Johansson, et al. (2018). **"Identifying the associated risks of pneumonia in COPD patients: ARCTIC an observational study."** Respir Res **19**(1): 172.

BACKGROUND: Inhaled corticosteroids (ICS) are associated with an increased risk of pneumonia in patients with chronic obstructive pulmonary disease (COPD). Other factors such as severity of airflow limitation and concurrent asthma may further raise the possibility of developing pneumonia. This study assessed the risk of pneumonia associated with ICS in patients with COPD. METHODS: Electronic Medical Record data

linked to National Health Registries were collected from COPD patients and matched reference controls in 52 Swedish primary care centers (2000-2014). Levels of ICS treatment (high, low, no ICS) and associated comorbidities were assessed. Patients were categorized by airflow limitation severity. RESULTS: A total of 6623 patients with COPD and 48,566 controls were analyzed. Patients with COPD had a more than 4-fold increase in pneumonia versus reference controls (hazard ratio [HR] 4.76, 95% confidence interval [CI]: 4.48-5.06). ICS use increased the risk of pneumonia by 20-30% in patients with COPD with forced expiratory volume in 1 s >/= 50% versus patients not using ICS. Asthma was an independent risk factor for pneumonia in the COPD population. Multivariate analysis identified independent predictors of pneumonia in the overall population. The highest risk of pneumonia was associated with high dose ICS (HR 1.41, 95% CI: 1.23-1.62). CONCLUSIONS: Patients with COPD have a greater risk of pneumonia versus reference controls; ICS use and concurrent asthma increased the risk of pneumonia further.

http://spiral.imperial.ac.uk/bitstream/10044/1/63751/2/s12931-018-0868-y.pdf

Januszek, R., A. Dziewierz, et al. (2018). **"Chronic obstructive pulmonary disease and periprocedural complications in patients undergoing percutaneous coronary interventions."** PLoS One **13**(10): e0204257.

BACKGROUND: The relationship between chronic obstructive pulmonary disease (COPD) and periprocedural complications of percutaneous coronary interventions (PCIs) is influenced by several factors. We aimed to investigate the association between COPD, its complication type and rate in patients undergoing PCI. METHODS: Data were prospectively collected using the Polish Cardiovascular Intervention Society national registry (ORPKI) on all PCIs performed in Poland between January 2015 and December 2016. COPD was present in 5,594 of the 221,187 patients undergoing PCI. We assessed the frequency and predictors of periprocedural complications in PCI. RESULTS: Patients with COPD were elder individuals (70.3 +/- 9.9 vs. 67 +/- 10.8 years; $p < 0.05$). We noted 145 (2.6%) periprocedural complications in the COPD group and 4,121 (1.9%) in the non-COPD group ($p < 0.001$). The higher incidence of periprocedural complications in the COPD patients was mainly attributed to cardiac arrest ($p = 0.001$), myocardial infarctions ($p = 0.002$) and no-reflows ($p < 0.001$). COPD was not an independent predictor of all periprocedural complications. On the other hand, COPD was found to be an independent predictor of increased no-reflow risk (odds ratio [OR] 1.447, 95% CI 1.085-1.929; $p = 0.01$), and at the same time, of decreased risk of periprocedural allergic reactions (OR 0.117, 95% CI 0.016-0.837; $p = 0.03$). CONCLUSIONS: In conclusion, periprocedural complications of PCIs are more frequent in patients with COPD. COPD is an independent positive predictor of no-reflow and a negative predictor of periprocedural allergic reactions.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6166928/pdf/pone.0204257.pdf

Jeong, I., J. H. Lim, et al. (2018). **"Gene expression profile of human lung in a relatively early stage of COPD with emphysema."** Int J Chron Obstruct Pulmon Dis **13**: 2643-2655.

Purpose: As only some smokers develop COPD with emphysema, we explored the molecular pathogenesis of early-stage COPD with emphysema using gene expression profiling of human lung tissues. Patients and methods: First, 110 subjects who had smoked more than ten pack-years were classified into three groups: COPD with emphysema, COPD without emphysema, and healthy smokers. COPD and emphysema were confirmed by post-bronchodilator forced expiratory volume in 1 second/forced vital capacity <0.7 and by chest computed tomography. Lung tissues obtained surgically from the 110 subjects were processed and used for RNA-Seq analysis. Results: Among the 110 subjects, 29 had COPD with emphysema, 21 had COPD without emphysema, and 60 were healthy smokers; their mean post-bronchodilator forced expiratory volume in 1 second values were 78%, 80%, and 94%, respectively. Using RNA-Seq, we evaluated 16,676 genes expressed in lung tissues. Among them, 1,226 genes in the COPD with emphysema group and 434 genes in the COPD without emphysema group were differentially expressed genes compared to the expression in healthy smokers. In the COPD with emphysema group,

ACER2 and LMAN2L were markedly increased and decreased, respectively. In the COPD without emphysema group, the CHRM3 gene, previously reported to be associated with COPD, and HDAC10 were markedly increased and decreased, respectively. Conclusion: Our study identified differences in gene expression in subjects with COPD according to emphysema status using RNA-Seq transcriptome analysis. These findings may have mechanistic implications in COPD.

https://www.dovepress.com/getfile.php?fileID=43954

Jiang, J., Y. Xia, et al. (2018). **"miR-190a-5p participates in the regulation of hypoxia-induced pulmonary hypertension by targeting KLF15 and can serve as a biomarker of diagnosis and prognosis in chronic obstructive pulmonary disease complicated with pulmonary hypertension."** Int J Chron Obstruct Pulmon Dis **13**: 3777-3790.

Purpose: miR-190a-5p expression alters dynamically in response to hypoxia. However, the role of miR-190a-5p expression in hypoxia-induced pulmonary hypertension (PH) remains unclear. We sought to correlate the miR-190a-5p expression levels with the severity, diagnosis, and prognosis of PH in relation to chronic obstructive pulmonary disease (COPD-PH). Additionally, we evaluated the effect of miR-190a-5p through in vitro experiments on human pulmonary endothelial cells (HPECs) that were exposed to hypoxia and in vivo experiments using an animal model of hypoxia-induced PH. Methods: Circulating miR-190a-5p levels were measured from 73 patients with PH and 32 healthy controls through quantitative real-time PCR. The levels of miR-190a-5p and the expression of Kruppel-like factor 15 (KLF15) were analyzed in HPECs that were exposed to hypoxia, and the effects of antagomir-190a-5p in mice with chronic hypoxia-induced PH were tested. Target gene analysis was performed by Western blot and luciferase assay. Results: The miR-190a-5p level was significantly higher in patients with COPD-PH than in the healthy controls. Higher miR-190a-5p levels were associated with a greater severity of COPD-PH. In vitro experiments on HPECs showed that exposure to hypoxia increased the miR-190a-5p levels significantly. KLF15 was validated as a target of miR-190a-5p. Transfection with miR-190a-5p mimicked inhibition of KLF15 expression in HPECs. In the mouse model of PH, antagomir-190a-5p reduced right ventricular systolic pressure and enhanced the KLF15 expression levels in lung tissue. Conclusion: miR-190a-5p regulates hypoxia-induced PH by targeting KLF15. The circulating levels of miR-190a-5p correlate with the severity of COPD-PH, thereby confirming the diagnostic and prognostic value of this parameter in COPD-PH.

https://www.dovepress.com/getfile.php?fileID=46329

Jones, P. W., H. Mullerova, et al. (2018). **"Cardiovascular Disease Does Not Predict Exacerbation Rate or Mortality in Chronic Obstructive Pulmonary Disease."** Am J Respir Crit Care Med **197**(3): 400-403.

http://spiral.imperial.ac.uk/bitstream/10044/1/50018/2/Jones%20et%20al.pdf

Kaplan, S. A. (2018). **"Re: Association between Chronic Obstructive Pulmonary Disease and Increased Risk of Benign Prostatic Hyperplasia: A Retrospective Nationwide Cohort Study."** J Urol **200**(6): 1138-1141.

Kawachi, S. and K. Fujimoto (2019). **"Usefulness of a Newly Developed Spirometer to Measure Dynamic Lung Hyperinflation following Incremental Hyperventilation in Patients with Chronic Obstructive Pulmonary Disease."** Intern Med **58**(1): 39-46.

Objective This study was performed to determine the usefulness of a newly developed spirometer for the quantitative assessment of dynamic lung hyperinflation (DLH) following incremental hyperventilation in chronic obstructive pulmonary disease (COPD). Methods The subjects were 54 patients with COPD and 25 healthy volunteers. Each subject was asked to hyperventilate for 30 seconds with stepwise increments starting at the resting respiration rate and increasing to respiratory rates of 20, 30, and finally 40 breaths/min while using a newly developed spirometer. The relationship between the observed inspiratory capacity (IC) reduction following incremental hyperventilation as an index of DLH and spirometry or the 6-minute walking distance was examined. Results The IC did not decrease significantly from the resting IC, even when the respiratory rate was increased, in the healthy volunteer group. However, in the COPD patient group, the IC decreased with increases in the respiratory rate. Significant correlations were found between all IC parameters and the severity of COPD. A significant negative correlation was also found between the decreased IC and the 6-minute walking distance. Conclusion These findings suggest that the quantitative assessment of DLH following incremental hyperventilation using the newly developed spirometer may be useful for the assessment of pathophysiological impairment in patients with COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6367078/pdf/1349-7235-58-0039.pdf

Kim, Y. S., K. C. Cha, et al. (2019). **"Risk Factors of Extensive Subcutaneous Emphysema after Closed-Tube Thoracostomy for Spontaneous Pneumothorax."** Am Surg **85**(2): e71-e73.

Korytina, G. F., L. Z. Akhmadishina, et al. (2019). **"Associations of the NRF2/KEAP1 pathway and antioxidant defense gene polymorphisms with chronic obstructive pulmonary disease."** Gene **692**: 102-112.

BACKGROUND AND OBJECTIVE: Chronic obstructive pulmonary disease (COPD) is a complex chronic inflammatory disease of the respiratory system affecting primarily distal respiratory pathways and lung parenchyma. This work was designed as a case-control study aimed at investigating the association of the NRF2/KEAP1 signaling system, and antioxidant defense gene polymorphisms with COPD in population from Russia. METHODS: Ten SNPs: NFE2L2 (rs35652124), KEAP1 (rs1048290), MPO (rs2333227), PRNP (rs1799990), PTGR1 (rs2273788), HSPA1A (rs1008438), TXNRD2 (rs1139793), GSR (rs1002149), SIRT2 (rs10410544), and PTGS1 (rs1330344) were genotyped by the real-time polymerase chain reaction (TaqMan assays) in a case-control study (425 COPD patients and 457 controls, from the same region of Russia, representatives of Tatar population). Logistic regression was used to detect the association of SNPs in different models. Linear regression analyses were performed to estimate the relationship between SNPs and lung function parameters and smoking pack-years. THE RESULTS: In our population, a significant associations of KEAP1 (rs1048290) (P=0.0015, OR=0.72 in additive model), HSPA1A (rs1008438) (P=0.006, OR=2.26 in recessive model), GSR (rs1002149) (P=0.037, OR=1.31 in additive model) with COPD were revealed. NFE2L2 (rs35652124), PRNP (rs1799990), and HSPA1A (rs1008438) were significantly associated with COPD only in smokers. In nonsmokers, significant association was established for GSR (rs1002149). KEAP1 (rs1048290) was associated with COPD in both groups. The relationship between KEAP1 (rs1048290), NFE2L2 (rs35652124), and HSPA1A (rs1008438) and smoking pack-years was found (P=0.005, P=0.0028, P=0.015). A significant genotype-dependent variation of forced vital capacity and forced expiratory volume in 1s was observed for SIRT2 (rs10410544) (P=0.04), NFE2L2 (rs35652124) (P=0.028), and PRNP (rs1799990) (P=0.044).

Kubysheva, N., S. Soodaeva, et al. (2018). **"Soluble HLA-I and HLA-II Molecules Are Potential Prognostic Markers of Progression of Systemic and Local Inflammation in Patients with COPD."** Dis Markers **2018**: 3614341.

Soluble molecules of the major histocompatibility complex play an important role in the development of various immune-mediated diseases. However, there is not much information on the participation of these proteins in the pathogenesis of chronic obstructive pulmonary disease (COPD). The aim of our work was to determine the content of soluble molecules of the major histocompatibility complex of classes I and II (sHLA-I and sHLA-II) in the exhaled breath condensate (EBC) and in the blood serum in patients with moderate to severe COPD during the exacerbation and stable phase. We investigated 105 patients (male) with COPD aged 46-67 and 21 healthy nonsmoking volunteers (male) comparable in age. The content of sHLA-I and sHLA-II molecules was studied using ELISA. We found an increase in the level of sHLA-I and sHLA-II molecules in EBC, as well as an enhancement in the serum content of sHLA-II in all the examined COPD patients compared to healthy nonsmoking volunteers. The revealed negative correlation between the serum concentration of sHLA-II and values of FEV1 and FEV1/FVC in all examined patients with COPD gives a possibility to consider the content of these proteins as an additional systemic marker of disease severity. The maximum endobronchial and serum concentrations of sHLA-I and sHLA-II were detected in patients with severe COPD during the exacerbation. The negative associations between the content of these molecules in EBC and serum and the parameters of lung function in patients with severe COPD were established. These findings suggest a pathogenetic role of sHLA-I and sHLA-II molecules in the mechanisms of the development and progression of local and systemic inflammation in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6288564/pdf/DM2018-3614341.pdf

Lai, C. C., C. H. Wu, et al. (2018). **"The association between COPD and outcomes of patients with advanced chronic kidney disease."** Int J Chron Obstruct Pulmon Dis **13**: 2899-2905.

Objective: The aim of this study was to investigate the impact of COPD on the outcomes of patients with advanced chronic kidney disease (CKD). Patients and methods: All patients with advanced CKD from 2000 to 2010 were identified from the Taiwanese National Health Insurance Research Database. Associations between COPD and the risk of long-term dialysis and all-cause mortality were assessed. Results: A total of 33,399 advanced CKD patients were enrolled, of whom 31,536 did not have COPD (non-COPD group) and 1,863 had COPD (COPD group). The incidence of end-stage renal disease (ESRD) was higher for those with COPD than those without COPD (744.2 per 1,000 person-years vs 724.6 per 1,000 person-years, adjusted HR [aHR] 1.04; 95% CI 0.96-1.12). The cumulative incidence rates of ESRD were similar between the COPD and non-COPD groups (log-rank test, P=0.356). Overall, the patients with COPD had a higher risk of death than those without COPD (151.7 per 1,000 person-years vs 125.5 per 1,000 person-years, aHR 1.22; 95% CI 1.11-1.33). The cumulative mortality rate was higher in the COPD group than in the non-COPD group (log-rank test, P<0.001). Conclusion: COPD increased the risk of mortality among the advanced CKD patients in this study, especially the elderly and male patients. In contrast, COPD did not increase the risk of ESRD among the advanced CKD patients.

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Lastrucci, V., S. D'Arienzo, et al. (2018). **"Diagnosis-related differences in the quality of end-of-life care: A comparison between cancer and non-cancer patients."** PLoS One **13**(9): e0204458.

BACKGROUND: Cancer, chronic heart failure (CHF), and chronic obstructive pulmonary disease (COPD) in the advanced stages have similar symptom burdens and survival rates. Despite these similarities, the majority of the attention directed to improving the quality of end-of-life (EOL) care has focused on cancer. AIM: To assess the extent to which the quality of EOL care received by cancer, CHF, and COPD patients in the last month of life is diagnosis-sensitive. METHODS: This is a retrospective observational

study based on administrative data. The study population includes all Tuscany region residents aged 18 years or older who died with a clinical history of cancer, CHF, or COPD. Decedents were categorized into two mutually exclusive diagnosis categories: cancer (CA) and cardiopulmonary failure (CPF). Several EOL care quality outcome measures were adopted. Multivariable generalized linear model for each outcome were performed. RESULTS: The sample included 30,217 decedents. CPF patients were about 1.5 times more likely than cancer patients to die in an acute care hospital (RR 1.59, 95% C.I.: 1.54-1.63). CPF patients were more likely to be hospitalized or admitted to the emergency department (RR 1.09, 95% C.I.: 1.07-1.10; RR 1.15, 95% C.I.: 1.13-1.18, respectively) and less likely to use hospice services (RR 0.08, 95% C.I.: 0.07-0.09) than cancer patients in the last month of life. CPF patients had a four- and two-fold higher risk of intensive care unit admission or of undergoing life-sustaining treatments, respectively, than cancer patients (RR 3.71, 95% C.I.: 3.40-4.04; RR 2.43, 95% C.I.: 2.27-2.60, respectively). CONCLUSION: The study has highlighted the presence of significant differences in the quality of EOL care received in the last month of life by COPD and CHF compared with cancer patients. Further studies are needed to better elucidate the extent and the avoidability of these diagnosis-related differences in the quality of EOL care.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6155541/pdf/pone.0204458.pdf

Levin, K., B. Borg, et al. (2018). **"Characteristics of patients who progress from bridging to long-term oxygen therapy."** Intern Med J **48**(11): 1376-1381.

BACKGROUND: Patients with persistent hypoxia following an acute hospital admission may be discharged with 'bridging' domiciliary oxygen as per criteria defined by the Thoracic Society of Australia and New Zealand. The need for continuous long-term oxygen therapy (LTOT) is then reassessed at a clinic review 1-2 months later. AIM: To describe the characteristics of patients discharged from an acute hospital admission with continuous short-term oxygen therapy (STOT), and subsequently to investigate for differences between subjects who proceeded to qualify for continuous LTOT versus those who were able to cease STOT at review. METHODS: This is a retrospective cohort study involving all subjects discharged from Alfred Health between 2011 and 2015 inclusive with bridging domiciliary oxygen. Multiple biochemical, physiological and demographic characteristics were collated and analysed. RESULTS: Of all patients prescribed continuous STOT at time of discharge, 47.3% qualified for LTOT at outpatient review. This cohort had a significantly lower PaO2 measurement at time of discharge, compared with those who no longer qualified. CONCLUSION: PaO2 at time of discharge provides a signal with the potential to identify who will require continuous LTOT following an acute hospital admission. Additionally, this study highlights the need to re-evaluate patients' oxygen requirements during a period of clinical stability.

https://onlinelibrary.wiley.com/doi/abs/10.1111/imj.13737

Li, X., V. E. Ortega, et al. (2018). **"Genome-wide association study of lung function and clinical implication in heavy smokers."** BMC Med Genet **19**(1): 134.

BACKGROUND: The aim of this study is to identify genetic loci associated with post-bronchodilator FEV1/FVC and FEV1, and develop a multi-gene predictive model for lung function in COPD. METHODS: Genome-wide association study (GWAS) of post-bronchodilator FEV1/FVC and FEV1 was performed in 1645 non-Hispanic White European descent smokers. RESULTS: A functional rare variant in SERPINA1 (rs28929474: Glu342Lys) was significantly associated with post-bronchodilator FEV1/FVC ($p = 1.2 \times 10(-8)$) and FEV1 ($p = 2.1 \times 10(-9)$). In addition, this variant was associated with COPD (OR = 2.3; $p = 7.8 \times 10(-4)$) and severity (OR = 4.1; p = 0.0036). Heterozygous subjects (CT genotype) had significantly lower lung function and higher percentage of COPD and more severe COPD than subjects with the CC genotype. 8.6% of the variance of post-bronchodilator FEV1/FVC can be explained by SNPs in 10 genes with age, sex, and pack-years of cigarette smoking ($P < 2.2 \times 10(-16)$). CONCLUSIONS: This study is the first to show genome-wide significant association of rs28929474 in SERPINA1 with lung function. Of clinical importance, heterozygotes of rs28929474 (4.7% of subjects) have significantly reduced pulmonary function, demonstrating a major impact in smokers. The multi-gene model is significantly associated

with CT-based emphysema and clinical outcome measures of severity. Combining genetic information with demographic and environmental factors will further increase the predictive power for assessing reduced lung function and COPD severity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6090900/pdf/12881_2018_Article_656.pdf

Lin, C. S., C. Y. Chen, et al. (2019). **"Defining risk of general surgery in patients with chronic obstructive pulmonary diseases."** Qjm **112**(2): 107-113.

Background: The relationship between chronic obstructive pulmonary disease (COPD) and perioperative outcomes remains incompletely understood. Our purpose is to evaluate the features of postoperative adverse outcomes for geriatric surgical patients with COPD receiving non-thoracic surgeries. Aim: To evaluate the potential impact of COPD history on the outcome after general surgery. Design: A retrospective cohort study with matching procedure by propensity score. Methods: We conducted a nationwide study of 15 359 COPD patients aged 65 years and older who received major non-thoracic surgeries in 2008-2013 from the Taiwan National Health Insurance Research Database. Comprehensive matching procedure with propensity score were used to select 15 359 surgical patients without COPD for comparison. Major postoperative complications and 30-day in-hospital mortality were evaluated among patients with and without COPD by calculating adjusted odds ratios (ORs) and 95% CIs. Results: Patients with COPD had significantly increased risk for postoperative complications, including pneumonia (OR = 90.3; 95% CI: 60.3-135), septicemia (OR = 3.11; 95% CI: 2.82-3.43), acute renal failure (OR = 2.53; 95% CI: 2.11-3.02), pulmonary embolism (OR = 2.74; 95% CI: 1.52-4.96), and 30-day postoperative mortality (adjusted OR = 2.09; 95% CI: 1.76-2.50), compared with surgical patients without COPD. Longer length of hospital stay and higher medical expenditures were also noted in COPD patients than those without COPD. Conclusions: Geriatric patients with COPD showed significantly higher postoperative adverse outcome rates with risk of 30-day mortality nearly twofold when compared with patients without COPD. Our findings remind surgical care team pay more attention to this specific population.

https://academic.oup.com/qjmed/article-abstract/112/2/107/5136375?redirectedFrom=fulltext

Linde, P., G. Hanke, et al. (2018). **"Unpredictable episodic breathlessness in patients with advanced chronic obstructive pulmonary disease and lung cancer: a qualitative study."** Support Care Cancer **26**(4): 1097-1104.

PURPOSE: The internationally consented definition and categorization describe two categories of episodic breathlessness: predictable (with known triggers) and unpredictable. The link of known triggers only to predictable episodes can be read that unpredictable episodes have none known trigger. Our aim was to illuminate patients' experiences with episodes of unpredictable breathlessness, to collect descriptions of the episodes' impact on the patients' lives, and, in turn, the patients' individual coping strategies in this connection. DESIGN: Qualitative study using semi-structured in-depth interviews with patients suffering from unpredictable episodes of breathlessness and chronic obstructive pulmonary disease (COPD; Global Initiative for Obstructive Lung Disease III and IV) or lung cancer (all stages). Interviews were audio-recorded, transcribed verbatim, and analyzed using Framework Analysis. RESULTS: One hundred one patients were screened in a large university hospital; ten participants fulfilled the inclusion criteria and provided consent. The experienced episodes were evaluated as unpleasant and with higher intensity compared to predictable episodes. Non-pharmacological interventions were identified as useful coping strategies. Interestingly, although patients experienced the episodes in an unpredictable manner, a trigger could be detected retrospectively for the majority of cases (mostly emotions (especially panic) and, occasionally, physical exertion). Unpredictable episodes are less frequent than previously assumed. CONCLUSION: The unpredictability of unpredictable breathless episodes refers to the patients' experience that these episodes occur "out-of-the-blue." However, a known trigger can be identified for the majority of unpredictable breathless episodes. These are therefore triggered as well. Further research

needs to describe more possible triggers, to inquire the prevalence of unpredictable episodic breathlessness, and to develop effective management strategies.

https://link.springer.com/article/10.1007%2Fs00520-017-3928-9

Lipworth, B., C. R. Kuo, et al. (2018). **"Current appraisal of single inhaler triple therapy in COPD."** Int J Chron Obstruct Pulmon Dis **13**: 3003-3009.

A single inhaler containing inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA)/long-acting muscarinic antagonist (LAMA) is a more convenient way of delivering triple therapy in patients with COPD. Single triple therapy has been shown to be superior at reducing exacerbations and improving quality of life compared to LABA/LAMA, especially in patients with a prior history of frequent exacerbations and blood eosinophilia, who have ICS responsive disease. The corollary is that patients with infrequent exacerbations who are noneosinophilic may be safely de-escalated from triple therapy to LABA/LAMA without loss of control. Pointedly, there is a substantially increased risk of pneumonia associated with the triple therapy containing fluticasone furoate but not beclometasone dipropionate or budesonide. Since triple therapy is also better than ICS/LABA at reducing exacerbations and improving lung function, symptoms, and quality of life, this brings into question the rationale for using ICS/LABA. Hence, we propose a simplified pragmatic decision process based on symptoms, prior to exacerbation history, and blood eosinophils to select which patients should be given a single triple inhaler or LABA/LAMA. Differences in patient preference of inhaler device, formulations and drugs will also determine which triple inhaler prescribers elect to use.

https://www.dovepress.com/getfile.php?fileID=44832

Liu, X., K. Deng, et al. (2019). **"8-Hydroxy-2'-deoxyguanosine as a biomarker of oxidative stress in acute exacerbation of chronic obstructive pulmonary disease."** Turk J Med Sci **49**(1): 93-100.

Background/aim: 8-Hydroxy-2'-deoxyguanosine (8-OHdG) is a biomarker of oxidative stress and has been implicated in many diseases. The aim of this study was to investigate the clinical value of plasma 8-OHdG level in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Materials and methods: A total of 154 subjects were enrolled in this study, including 20 healthy volunteers, 24 COPD patients in the stable phase, and 110 AECOPD patients. Peripheral blood samples, demographic information, and clinical characteristics were collected from all subjects at the time of being recruited into the study. Plasma 8-OHdG level was detected by enzyme-linked immunosorbent a ss ay. Results: 8-OHdG was increased in patients with AECOPD compared to healthy subjects and patients with stable COPD, especially in smokers. It also increased with the GOLD stage, mMRC grade, CAT score, and group level of combined COPD assessment. Additionally, further analysis revealed that 8-OHdG was negatively correlated with FEV1, FEV1% predicted, and FEV1/FVC and positively correlated with C-reactive protein, procalcitonin, and neutrophil CD64. Conclusion: 8-OHdG is associated with spirometric severity, symptomatic severity, exacerbation risk, and inflammatory biomarkers in AECOPD patients, suggesting it as a promising biomarker for reflecting disease severity and guiding the choice of optimal therapeutic decision.

Lopez-Giraldo, A., T. Cruz, et al. (2018). **"Characterization, localization and comparison of c-Kit+ lung cells in never smokers and smokers with and without COPD."** BMC Pulm Med **18**(1): 123.

BACKGROUND: c-Kit + lung stem cells have been described in the human healthy lung. Their potential relation with smoking and/or chronic obstructive pulmonary disease (COPD) is unknown. METHODS: We characterized and compared c-Kit+ cells in lung tissue of 12 never smokers (NS), 15 smokers with

normal spirometry (S) and 44 COPD patients who required lung resectional surgery. Flow cytometry (FACS) was used to characterize c-Kit+ cells in fresh lung tissue disaggregates, and immunofluorescence (IF) for further characterization and to determine their location in OCT- embedded lung tissue. RESULTS: We identified 4 c-Kit+ cell populations, with similar proportions in NS, S and COPD: (1) By FACS, c-Kit(high)/CD45+ cells (4.03 +/- 2.97% (NS), 3.96 +/- 5.30% (S), and 5.20 +/- 3.44% (COPD)). By IF, these cells were tryptase+ (hence, mast cells) and located around the airways; (2) By IF, c-Kit(low)/CD45+/triptase- (0.07 +/- 0.06 (NS), 0.03 +/- 0.02 (S), and 0.06 +/- 0.07 (COPD) cells/field), which likely correspond to innate lymphoid cells; (3) By FACS, c-Kit(low)/CD45-/CD34+ (0.95 +/- 0.84% (NS), 1.14 +/- 0.94% (S) and 0.95 +/- 1.38% (COPD)). By IF these cells were c-Kit(low)/CD45-/CD31+, suggesting an endothelial lineage, and were predominantly located in the alveolar wall; and, (4) by FACS, an infrequent c-Kit(low)/CD45-/CD34- population (0.09 +/- 0.14% (NS), 0.08 +/- 0.09% (S) and 0.08 +/- 0.11% (COPD)) compatible with a putative lung stem cell population. Yet, IF failed to detect them and we could not isolate or grow them, thus questioning the existence of c-Kit+ lung stem-cells. CONCLUSIONS: The adult human lung contains a mixture of c-Kit+ cells, unlikely to be lung stem cells, which are independent of smoking status and/or presence of COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6066937/pdf/12890_2018_Article_688.pdf

Ma, X., X. Jiao, et al. (2018). **"The Function of Ophiocordyceps sinensis in Airway Epithelial Cell Senescence in a Rat COPD Model."** Can Respir J **2018**: 6080348.

Ophiocordyceps sinensis (O. sinensis) seems to be able to alleviate airway epithelial cell senescence in chronic obstructive pulmonary disease (COPD). The objective of the study is to evaluate the effect of O. sinensis on airway epithelial senescence in the COPD model both in vitro and in vivo. We observed the expression of P16 and P21 in the airway epithelia of 30 patients with COPD. The optimal concentration of O. sinensis and exposure time of the cigarette smoke extract (CSE) were determined in vitro, and senescence-associated beta-galactosidase (SA-beta-gal) and 5-bromodeoxyuridine (BrdU) were used to evaluate the senescence and proliferation of human bronchial epithelial (16HBE) cells pretreated with O. sinensis by staining kits. COPD model rats were treated with O. sinensis at various concentrations to determine the changes in P16 and P21 expression in airway epithelial tissues. It was found that the expression levels of P16 and P21 were higher in the airway epithelia of COPD patients than those in the control group based on immunohistochemical staining, real-time quantitative PCR, and western blotting. The CSE could induce 16HBE cell senescence, and O. sinensis could alleviate CSE-induced senescence and promote the proliferation of 16HBE cells. The expression levels of P16 and P21 were also higher in the airway epithelia of COPD model rats; however, the levels of P16 and P21 in the groups treated with all concentrations of O. sinensis were obviously lower than those in the COPD model group based on real-time quantitative PCR and western blotting. In conclusion, the CSE can induce airway epithelium senescence, and O. sinensis can inhibit CSE-induced cellular senescence, both in vitro and in vivo.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5902013/pdf/CRJ2018-6080348.pdf

Mateu-Jimenez, M., V. Curull, et al. (2018). **"Profile of epigenetic mechanisms in lung tumors of patients with underlying chronic respiratory conditions."** Clin Epigenetics **10**: 7.

Background: Chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and epigenetic events underlie lung cancer (LC) development. The study objective was that lung tumor expression levels of specific microRNAs and their downstream biomarkers may be differentially regulated in patients with and without COPD. Methods: In lung specimens (tumor and non-tumor), microRNAs known to be involved in lung tumorigenesis (miR-21, miR-200b, miR-126, miR-451, miR-210, miR-let7c, miR-30a-30p, miR-155 and miR-let7a, qRT-PCR), DNA methylation, and downstream biomarkers were determined (qRT-PCR and immunoblotting) in 40 patients with LC (prospective study, subdivided into LC-COPD and LC, N = 20/group). Results: Expression of miR-21, miR-200b, miR-210, and miR-let7c and DNA methylation were greater in lung tumor specimens of LC-COPD than of LC patients. Expression of downstream markers PTEN, MARCKs, TPM-1, PDCD4, SPRY-2, ETS-1, ZEB-2, FGFRL-1, EFNA-3, and k-RAS

together with P53 were selectively downregulated in tumor samples of LC-COPD patients. In these patients, tumor expression of miR-126 and miR-451 and that of the biomarkers PTEN, MARCKs, FGFRL-1, SNAIL-1, P63, and k-RAS were reduced. Conclusions: Biomarkers of mechanisms involved in tumor growth, angiogenesis, migration, and apoptosis were differentially expressed in tumors of patients with underlying respiratory disease. These findings shed light into the underlying biology of the reported greater risk to develop LC seen in patients with chronic respiratory conditions. The presence of an underlying respiratory disease should be identified in all patients with LC as the differential biological profile may help determine tumor progression and the therapeutic response. Additionally, epigenetic events offer a niche for pharmacological therapeutic targets.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771157/pdf/13148_2017_Article_437.pdf

Meira, L., R. Boaventura, et al. (2018). **"Alpha-1 Antitrypsin Deficiency Detection in a Portuguese Population."** Copd **15**(1): 4-9.

Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant disease characterised by low serum levels of this molecule. Its epidemiology remains unknown in many countries, mainly due to its underdiagnosed state and lack of patients' registries. We aim to evaluate and characterise a sample of Portuguese individuals tested for AATD, between 2006 and 2015, based on a retrospective analysis from the database of a laboratory offering AATD genetic diagnosis service. 1684 individuals were considered, covering almost every region in Portugal. Genetic diagnosis resulted from requests of clinicians from different areas of expertise, mainly pulmonology (35.5%). Most subjects could be distributed into more common genotypes: MZ (25.4%, n = 427), MS (15.5%, n = 261), SZ (11.2%, n = 188), ZZ (9.4%, n = 158) and SS (5.6%, n = 95). 9.5% of the subjects were found to carry at least one rare deleterious allele, including the recently described PGaia, Q0Oliveira do Douro, Q0Vila Real and a novel SGaia variant. This study comprises 417 subjects (24.7%) with severe to very severe AATD and 761 carriers (45.2%), 22.7% of those identified by familial screening. The present study represents the most complete survey of AATD in Portugal so far and discloses a high rate of severe and very severe deficiency cases, attributed not only to ZZ and SZ genotypes but also to a large number of rare combinations with other null and deficiency alleles. It also uncovers a low awareness to AATD among the medical community, highlighting the need to create a Portuguese national registry and AATD guidelines and increase the awareness about this condition.

https://www.tandfonline.com/doi/full/10.1080/15412555.2017.1414779

Mendez, A., P. Labra, et al. (2018). **"Low rates of participation and completion of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease in primary health care."** Rev Med Chil **146**(11): 1304-1308.

BACKGROUND: Only 6% of patients with chronic obstructive pulmonary disease (COPD) participate in pulmonary rehabilitation programs (PR) and only 50% of those who participate, complete these programs. AIM: To determine rates of PR program participation and completion among patients with COPD in Chile. MATERIAL AND METHODS: Analysis of a database available at the Ministry of Health, which included data of 277491 patients with COPD (55% females) and their participation in PR programs, between 2014 and 2016. RESULTS: Forty percent of patients were over 75 years of age. Participation rates in PR programs ranged from 2.4 to 2.9%. Rates of completion ranged from 26 to 36%. CONCLUSIONS: There is a low rate of participation in PR programs among patients with COPD. Approximately one third of participants complete these programs.

https://scielo.conicyt.cl/pdf/rmc/v146n11/0717-6163-rmc-146-11-1304.pdf

Mohammed, J., E. Derom, et al. (2018). **"Cardiac Autonomic Function and Reactivity Tests in Physically Active Subjects with Moderately Severe COPD."** Copd **15**(1): 51-59.

Patients with chronic obstructive pulmonary disease (COPD) show impairments in the autonomic nervous systems (ANS) function, which is responsible for cardiac autonomic regulation. This study assessed the autonomic function and cardio-vagal reactivity in conveniently sampled subjects with COPD participating in a pulmonary rehabilitation (PR) program. Twenty-six subjects with COPD and 22 age and gender matched control subjects were evaluated. R-R intervals were collected at rest in supine position. Thereafter, resting autonomic function parameters comprising linear and nonlinear analyses of heart rate variability (HRV) and baroreceptor sensitivity (BRS) were calculated. Autonomic reactivity tests comprising deep breathing (DB), Valsalva maneuver (VM), and head up tilt (HUT) were also performed. The results of this study indicated that resting autonomic function variables were generally reduced in COPD compared to controls. However, this difference was only statistically significant for a few HRV parameters: mean RR intervals, low frequency (LF), standard deviation of dispersion of points perpendicular to the line-of-identity (SD1), and approximate entropy (ApEn) ($p < 0.05$). The results also indicated that all cardio-vagal indices following the autonomic reactivity tests were comparable between COPD and controls ($p > 0.05$). It was concluded that subtle autonomic impairments exists in physically active COPD patients, and these autonomic function deficits were mainly recognized by resting HRV indices and not autonomic reactivity tests.

https://www.tandfonline.com/doi/full/10.1080/15412555.2017.1412414

Mohan, D., J. R. Forman, et al. (2018). **"Fibrinogen does not relate to cardiovascular or muscle manifestations in COPD: cross-sectional data from the ERICA study."** Thorax **73**(12): 1182-1185.

Cardiovascular and skeletal muscle manifestations constitute important comorbidities in COPD, with systemic inflammation proposed as a common mechanistic link. Fibrinogen has prognostic role in COPD. We aimed to determine whether aortic stiffness and quadriceps weakness are linked in COPD, and whether they are associated with the systemic inflammatory mediator-fibrinogen. Aortic pulse wave velocity (aPWV), quadriceps maximal volitional contraction (QMVC) force and fibrinogen were measured in 729 patients with stable, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II-IV COPD. The cardiovascular and muscular manifestations exist independently (P=0.22, chi(2)). Fibrinogen was not associated with aPWV or QMVC (P=0.628 and P=0.621, respectively), making inflammation, as measured by plasma fibrinogen, an unlikely common aetiological factor.

https://thorax.bmj.com/content/73/12/1182.long

Moleres, J., A. Fernandez-Calvet, et al. (2018). **"Antagonistic Pleiotropy in the Bifunctional Surface Protein FadL (OmpP1) during Adaptation of Haemophilus influenzae to Chronic Lung Infection Associated with Chronic Obstructive Pulmonary Disease."** MBio **9**(5)Tracking bacterial evolution during chronic infection provides insights into how host selection pressures shape bacterial genomes. The human-restricted opportunistic pathogen nontypeable Haemophilus influenzae (NTHi) infects the lower airways of patients suffering chronic obstructive pulmonary disease (COPD) and contributes to disease progression. To identify bacterial genetic variation associated with bacterial adaptation to the COPD lung, we sequenced the genomes of 92 isolates collected from the sputum of 13 COPD patients over 1 to 9 years. Individuals were colonized by distinct clonal types (CTs) over time, but the same CT was often reisolated at a later time or found in different patients. Although genomes from the same CT were nearly identical, intra-CT variation due to mutation and recombination occurred. Recurrent mutations in several genes were likely involved in COPD lung adaptation. Notably, nearly a third of CTs were polymorphic for null alleles of ompP1 (also called fadL), which encodes a bifunctional membrane protein that both binds the human carcinoembryonic antigen-related cell adhesion molecule 1 (hCEACAM1) receptor and imports long-chain fatty acids (LCFAs). Our computational studies provide plausible three-dimensional models for FadL's interaction with hCEACAM1 and LCFA binding. We show that recurrent fadL mutations are likely a case of antagonistic pleiotropy, since loss of FadL reduces

NTHi's ability to infect epithelia but also increases its resistance to bactericidal LCFAs enriched within the COPD lung. Supporting this interpretation, truncated fadL alleles are common in publicly available NTHi genomes isolated from the lower airway tract but rare in others. These results shed light on molecular mechanisms of bacterial pathoadaptation and guide future research toward developing novel COPD therapeutics.IMPORTANCE Nontypeable Haemophilus influenzae is an important pathogen in patients with chronic obstructive pulmonary disease (COPD). To elucidate the bacterial pathways undergoing in vivo evolutionary adaptation, we compared bacterial genomes collected over time from 13 COPD patients and identified recurrent genetic changes arising in independent bacterial lineages colonizing different patients. Besides finding changes in phase-variable genes, we found recurrent loss-of-function mutations in the ompP1 (fadL) gene. We show that loss of OmpP1/FadL function reduces this bacterium's ability to infect cells via the hCEACAM1 epithelial receptor but also increases its resistance to bactericidal fatty acids enriched within the COPD lung, suggesting a case of antagonistic pleiotropy that restricts DeltafadL strains' niche. These results show how H. influenzae adapts to host-generated inflammatory mediators in the COPD airways.

https://mbio.asm.org/content/mbio/9/5/e01176-18.full.pdf

Mostafavi, B., S. Diaz, et al. (2018). **"Lung function and CT lung densitometry in 37- to 39-year-old individuals with alpha-1-antitrypsin deficiency."** Int J Chron Obstruct Pulmon Dis **13**: 3689-3698.

Background: Alpha-1-antitrypsin (AAT) deficiency is a hereditary disorder that predisposes to emphysema. A cohort of severe (PiZZ) and moderate (PiSZ) AAT-deficient newborn infants was identified by the Swedish national neonatal AAT screening program in 1972-1974 and has been followed-up since birth. Our aim was to study whether the cohort has signs of emphysema in pulmonary function tests (PFTs) and computed tomography (CT) densitometry at 38 years of age in comparison with an age-matched control group, randomly selected from the population registry. Methods: Forty-one PiZZ, 18 PiSZ, and 61 control subjects (PiMM) underwent complete PFTs, measurement of resistance and reactance in the respiratory system by impulse oscillometry (IOS)/forced oscillation technique (FOT), and CT densitometry. The results were related to self-reported smoking habits. Results: The total lung capacity (TLC) % of the predicted value was significantly higher in the PiZZ ever-smokers than in the PiZZ never-smokers ($P<0.05$), PiSZ never-smokers ($P=0.01$) and the PiMM never-smokers ($P=0.01$). The residual volume (RV) % of the predicted value was significantly higher in the PiZZ ever-smokers compared to the PiMM never-smokers ($P<0.01$). The PiZZ ever-smokers had a significantly lower carbon monoxide transfer coefficient (Kco) than the PiSZ never-smokers ($P<0.01$) and PiMM never-smokers ($P<0.01$). Respiratory system resistance at 5 Hz ($P<0.01$), at 20 Hz ($P<0.01$), and the area of low reactance (Alx; $P<0.05$) were significantly lower and respiratory system reactance at 5 Hz ($P<0.05$) was significantly higher in PiZZ subjects compared to the PiMM subjects. No statistically significant differences in the CT densitometry parameters were found between the Pi subgroups. Conclusion: The physiological parameters in the PiZZ ever-smokers showed evidence of hyperinflation and emphysema before the age of 40 years.

https://www.dovepress.com/getfile.php?fileID=45999

Mueller, J., S. Karrasch, et al. (2019). **"Automated MR-based lung volume segmentation in population-based whole-body MR imaging: correlation with clinical characteristics, pulmonary function testing and obstructive lung disease."** Eur Radiol **29**(3): 1595-1606.

OBJECTIVES: Whole-body MR imaging is increasingly utilised; although for lung dedicated sequences are often not included, the chest is typically imaged. Our objective was to determine the clinical utility of lung volumes derived from non-dedicated MRI sequences in the population-based KORA-FF4 cohort study. METHODS: 400 subjects (56.4 +/- 9.2 years, 57.6% males) underwent whole-body MRI including a coronal T1-DIXON-VIBE sequence in inspiration breath-hold, originally acquired for fat quantification. Based on MRI, lung volumes were derived using an automated framework and related to common predictors, pulmonary function tests (PFT; spirometry and pulmonary gas exchange, n = 214) and

obstructive lung disease. RESULTS: MRI-based lung volume was 4.0 +/- 1.1 L, which was 64.8 +/- 14.9% of predicted total lung capacity (TLC) and 124.4 +/- 27.9% of functional residual capacity. In multivariate analysis, it was positively associated with age, male, current smoking and height. Among PFT indices, MRI-based lung volume correlated best with TLC, alveolar volume and residual volume (RV; r = 0.57 each), while it was negatively correlated to FEV1/FVC (r = 0.36) and transfer factor for carbon monoxide (r = 0.16). Combining the strongest PFT parameters, RV and FEV1/FVC remained independently and incrementally associated with MRI-based lung volume (beta = 0.50, p = 0.04 and beta = - 0.02, p = 0.02, respectively) explaining 32% of the variability. For the identification of subjects with obstructive lung disease, height-indexed MRI-based lung volume yielded an AUC of 0.673-0.654. CONCLUSION: Lung volume derived from non-dedicated whole-body MRI is independently associated with RV and FEV1/FVC. Furthermore, its moderate accuracy for obstructive lung disease indicates that it may be a promising tool to assess pulmonary health in whole-body imaging when PFT is not available. KEY POINTS: * Although whole-body MRI often does not include dedicated lung sequences, lung volume can be automatically derived using dedicated segmentation algorithms * Lung volume derived from whole-body MRI correlates with typical predictors and risk factors of respiratory function including smoking and represents about 65% of total lung capacity and 125% of the functional residual capacity * Lung volume derived from whole-body MRI is independently associated with residual volume and the ratio of forced expiratory volume in 1 s to forced vital capacity and may allow detection of obstructive lung disease.

https://link.springer.com/article/10.1007%2Fs00330-018-5659-9

Munhoz da Rocha Lemos Costa, T., F. M. Costa, et al. (2018). **"Bone mineral density and vertebral fractures and their relationship with pulmonary dysfunction in patients with chronic obstructive pulmonary disease."** Osteoporos Int **29**(11): 2537-2543.

To evaluate bone mineral density (BMD) and morphometric vertebral fractures (MVF) in chronic obstructive pulmonary disease (COPD) patients in comparison with two control groups. BMD was lower in the disease group (DG) and was associated with the worst disease severity and prognosis. The prevalence of MVF was high and greater in the DG than in the control groups. INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is associated with osteoporosis and vertebral fractures. It is still unclear whether the presence of fractures and changes in bone mineral density (BMD) are associated with disease severity and prognosis. The aim of this study was to evaluate BMD and morphometric vertebral fractures (MVF) in COPD patients in comparison with two control groups and to correlate these parameters with indices of COPD severity (VEF1 and GOLD) and prognosis (BODE). METHODS: This was a cross-sectional study in COPD patients (disease group, DG) who underwent BMD and vertebral fracture assessment (VFA). Two control groups were used: smokers without COPD (smoker group, SG) and healthy never-smoker individuals (never-smoker group, NSG). RESULTS: The DG comprised 121 patients (65 women, mean age 67.9 +/- 8.6 years). Altered BMD was observed in 88.4% of the patients in the DG, which was more prevalent when compared with the control groups ($p < 0.001$). The BMD values were lower in the DG than in the control groups ($p < 0.05$). BMD was associated with the worst disease severity and prognosis ($p < 0.05$). The prevalence of MVF was high (57.8%) and greater than that in the SG (23.8%) and the NSG (14.8%; $p < 0.001$). The prevalence of fractures was not associated with disease severity and prognosis. CONCLUSIONS: COPD patients have a higher prevalence of MVF and low BMD, and the latter was associated with the severity and poor prognosis of the disease.

https://link.springer.com/article/10.1007%2Fs00198-018-4643-1

Nguyen, H. Q., M. L. Moy, et al. (2018). **"Applying the pragmatic-explanatory continuum indicator summary to the implementation of a physical activity coaching trial in chronic obstructive pulmonary disease."** Nurs Outlook **66**(5): 455-463.

BACKGROUND: Observational studies show that physical inactivity is associated with worse outcomes in chronic obstructive pulmonary disease (COPD). Despite practice guidelines recommending regular physical

activity (PA), there are no large-scale experimental studies to confirm that patients at high risk for COPD exacerbations can increase their PA and consequently, have improved outcomes. PURPOSE: The purpose of this case study is to describe the use of a widely accepted pragmatic trials framework for the design and implementation of a pragmatic clinical trial (PCT) of PA coaching for COPD in a real-world setting. METHOD: The aim of the trial was to determine the effectiveness of a 12-month PA coaching intervention (Walk On!) compared to standard care for 2,707 patients at high risk for COPD exacerbations from a large integrated health care system. The descriptions of our implementation experiences are anchored within the pragmatic-explanatory continuum indicator summary (PRECIS-2) framework. DISCUSSION: Facilitators of PCT implementation include early and ongoing engagement and support of multiple stakeholders including patients, health system leaders, administrators, physician champions, and frontline clinicians, an organizational/setting that prioritizes positive lifestyle behaviors, and a flexible intervention that allows for individualization. Pragmatic challenges include reliance on electronic data that are not complete or available in real-time for patient identification, timing of outreach may not synchronize with patients' readiness for change, and high turnover of clinical staff drawn from the existing workforce. DISCUSSION: PRECIS-2 is a useful guide for organizing decisions about study designs and implementation approaches to help diverse stakeholders recognize the compromises between internal and external validity with those decisions.

https://www.nursingoutlook.org/article/S0029-6554(17)30683-8/fulltext

Ohi, M., Y. Toiyama, et al. (2019). **"Risk factors and measures of pulmonary complications after thoracoscopic esophagectomy for esophageal cancer."** Surg Today **49**(2): 176-186.

PURPOSE: Postoperative pulmonary complications (PCs) after thoracoscopic esophagectomy for esophageal cancer (EC) still occur too frequently. We conducted this study to identify the risk factors for PCs developing in EC patients who undergo thoracoscopic esophagectomy. METHODS: The subjects of this retrospective study were 89 patients with EC who underwent thoracoscopic esophagectomy in our department between January 2010 and December 2015. Univariate and multivariate logistic regression analyses were used to evaluate the association between the incidence of PC and clinical factors. In January 2016, we introduced a new prophylactic intervention for reducing the incidence of delirium and assessed its significance for PCs. RESULTS: PCs developed in 19 patients (21.3%). Univariate analysis revealed the following risk factors: age (> 69 years), ratio of the forced expiratory volume in 1 s to forced vital capacity (< 70%), chronic obstructive pulmonary disease (COPD), and postoperative delirium. Multivariate analysis found that COPD and postoperative delirium were independent risk factors for PCs. Our new intervention for delirium significantly reduced its occurrence ($p = 0.00004$) and also the frequency of PCs ($p = 0.04148$). CONCLUSIONS: Postoperative delirium and COPD were risk factors for PCs in patients who underwent thoracoscopic esophagectomy. Our intervention study showed clearly that reducing the occurrence of postoperative delirium could decrease the incidence of PCs.

https://link.springer.com/article/10.1007%2Fs00595-018-1721-0

Ojuawo, O. B., A. O. Aladesanmi, et al. (2019). **"Profile of patients with chronic obstructive pulmonary disease in Ilorin who were never-smokers."** Niger J Clin Pract **22**(2): 221-226.

Background: The most recognized risk factor for chronic obstructive pulmonary disease (COPD) worldwide is cigarette smoking. However, recent surveys have revealed an increasing trend from nonsmoking causes especially from biomass exposure. This study, therefore, aimed to determine the proportion of patients and the clinical pattern of COPD among never-smokers in Ilorin. Subjects and Methods: This is a retrospective study in which case records of patients with clinical diagnosis of COPD from January 2013 to December 2017 were reviewed. Data were collected with respect to their sociodemographic characteristics, clinical details, comorbid illnesses, and severity of the disease. Results: A total of 135 case records of patients with COPD were reviewed, of which 66 had spirometric confirmation of the disease. In all, 38 (57.6%) of them were never-smokers with a male-to-female ratio of 1:1.1. The mean age of the subjects was 64.5 +/- 11.7 years. Cough and exertional dyspnea were the most common symptoms

(89.5% each), and systemic hypertension was the most common comorbid illness. Firewood exposure constituted the most common nonsmoking risk factor (47.4%), and the majority of the patients had mild COPD. When compared with ever-smokers, the mean post bronchodilator lung function parameters were found to be significantly better in never-smokers. Conclusion: Over half of COPD cases in Ilorin were never-smokers with firewood exposure as the main risk factor. This study has further highlighted the need for increased awareness of the hazards of biomass fuel exposure in our setting.

http://www.njcponline.com/article.asp?issn=1119-3077;year=2019;volume=22;issue=2;spage=221;epage=226;aulast=Ojuawo

Palmberg, L., B. M. Sundblad, et al. (2018). **"Cholinergic mechanisms in an organic dust model simulating an acute exacerbation in patients with COPD."** Int J Chron Obstruct Pulmon Dis **13**: 3611-3624.

Background: Exposure in a pig barn induces airway inflammation that has similarities with the response observed in acute exacerbations in COPD. Methods: A total of 15 smokers with COPD and 15 healthy non-smokers were exposed for 2 hours in a pig barn (in vivo exposure). Symptoms were assessed, lung function measured, and blood and sputum samples taken before and after exposure. Blood neutrophils were isolated and stimulated ex vivo with dust from a pig barn and acetylcholine, and inflammatory markers were analyzed. Results: In vivo exposure caused more symptoms and greater lung function fall in COPD patients than in controls. Baseline concentrations of MMP9, TIMP1, IL6, CXCL8, in sputum and neutrophil blood count were higher in COPD patients than in controls. In vivo exposure increased MMP9, TIMP1, IL6, CXCL8, TNFalpha, and LTB4 in sputum and MMP9 and IL6 in blood, with no difference between the groups, and serum CRP increased more in COPD subjects. Expression of choline acetyltransferase and acetylcholinesterase on sputum and blood cells was similar in the groups and uninfluenced by in vivo exposure. Dust exposure ex vivo increased choline acetyltransferase expression in neutrophils, but the dust and acetylcholine response did not differ between the groups before and after in vivo exposure. Conclusion: COPD patients exposed in a pig barn experience symptoms similar to those in acute exacerbations and lung function deterioration that is unrelated to bronchial responsiveness. Cholinergic mechanisms are involved in the inflammatory response to dust, with no difference between COPD and non-smokers.

https://www.dovepress.com/getfile.php?fileID=45863

Paul, R., J. Lee, et al. (2018). **"miR-422a suppresses SMAD4 protein expression and promotes resistance to muscle loss."** J Cachexia Sarcopenia Muscle **9**(1): 119-128.

BACKGROUND: Loss of muscle mass and strength are important sequelae of chronic disease, but the response of individuals is remarkably variable, suggesting important genetic and epigenetic modulators of muscle homeostasis. Such factors are likely to modify the activity of pathways that regulate wasting, but to date, few such factors have been identified. METHODS: The effect of miR-422a on SMAD4 expression and transforming growth factor (TGF)-beta signalling were determined by western blotting and luciferase assay. miRNA expression was determined by qPCR in plasma and muscle biopsy samples from a cross-sectional study of patients with chronic obstructive pulmonary disease (COPD) and a longitudinal study of patients undergoing aortic surgery, who were subsequently admitted to the intensive care unit (ICU). RESULTS: miR-422a was identified, by a screen, as a microRNA that was present in the plasma of patients with COPD and negatively associated with muscle strength as well as being readily detectable in the muscle of patients. In vitro, miR-422a suppressed SMAD4 expression and inhibited TGF-beta and bone morphogenetic protein-dependent luciferase activity in muscle cells. In male patients with COPD and those undergoing aortic surgery and on the ICU, a model of ICU-associated muscle weakness, quadriceps expression of miR-422a was positively associated with muscle strength (maximal voluntary contraction $r = 0.59$, $P < 0.001$ and $r = 0.51$, $P = 0.004$, for COPD and aortic surgery, respectively). Furthermore, pre-surgery levels of miR-422a were inversely associated with the amount of muscle that would be lost in the first post-operative week ($r = -0.57$, $P < 0.001$). CONCLUSIONS: These data suggest that differences in miR-422a expression contribute to the susceptibility to muscle wasting associated

with chronic and acute disease and that at least part of this activity may be mediated by reduced TGF-beta signalling in skeletal muscle.

http://spiral.imperial.ac.uk/bitstream/10044/1/50363/2/miR-422%20revised.pdf

Pevni, D., Z. Aizer, et al. (2018). **"Are two internal thoracic grafts better than one in patients with chronic obstructive lung disease? Analysis of 387 cases between 1996-2011."** PLoS One **13**(8): e0201227.

OBJECTIVES: Bilateral internal thoracic artery (ITA) grafting is associated with improved survival. However, potential survival benefit of using two ITA`s in patients with chronic lung disease (CLD) is questionable due to their increased risk of sternal wound infection (SWI) compared to operations incorporating single ITA (SITA). The purpose of this study is to compare early and long-term outcome of bilateral internal thoracic artery (BITA) grafting to that of grafting with single internal thoracic grafts and vein grafts or radial artery (SITA) in CLD patients with multi-vessels coronary disease. METHODS: One hundred and forty eight CLD patients who underwent BITA between 1996 and 2011 were compared with 239 who underwent SITA at the same period. RESULTS: SITA patients were more often female, more likely to have insulin treated diabetes (DM), DM with end organ damage, neurologic dysfunction and unstable angina. Despite of the difference in preoperative characteristics, early mortality (5.4% vs. 5.4%, in the SITA and BITA respectively, p = 0 < .999) and occurrences of SWI (6.3% vs 9.5%, p = 0.320) and strokes (3.8% vs 5.4%,p = 0.611) were not significantly different between groups. BITA patients did not have better Kaplan-Meier 10 year survival (52.8% vs. 42.6%, p = 0.088) and after matching, BITA and SITA had similar adjusted survival (HR 0.983[95%CI 0.755-1.280] p = 0.901) (cox model). CONCLUSION: Our study results suggest that in patients with CLD, the choice of BITA grafting technique did not provide survival benefit compared to SITA with other conduits.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6089414/pdf/pone.0201227.pdf

Pirina, P., E. Zinellu, et al. (2018). **"Circulating serotonin levels in COPD patients: a pilot study."** BMC Pulm Med **18**(1): 167.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major and increasing global health problem. Serotonin is a neurotransmitter that participates in several pulmonary functions and it has been involved in oxidative stress, which plays essential roles in the pathogenesis of COPD. The current study aimed at establishing the levels of circulating serotonin in COPD, and investigating eventual relations between serotonin and oxidative stress markers. METHODS: Whole blood serotonin was assessed in 43 consecutive patients with stable COPD and in 43 age and sex-matched healthy controls. RESULTS: Serotonin blood levels were significantly higher in COPD patients than in controls (median 0.81 mumol/L, IQR: 0.61-4.02 vs 0.65 mumol/L, IQR: 0.53-1.39, p = 0.02). The univariate logistic regression analysis evidenced that serotonin levels are independently associated with presence of COPD (crude OR = 7.29, 95% CI: 1.296-41.05, p = 0.003) and such an association was confirmed also after adjusting for several confounders (OR 21.92, 95% CI 2.02-237.83; p = 0.011). CONCLUSIONS: Our study showed higher levels of circulating serotonin in COPD and an inverse correlation with the worsening of airway obstruction. Future studies are necessary to investigate the clinical utility of this finding.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225723/pdf/12890_2018_Article_730.pdf

Ponomarev, D., O. Kamenskaya, et al. (2018). **"Chronic Lung Disease and Mortality after Cardiac Surgery: A Prospective Cohort Study."** J Cardiothorac Vasc Anesth **32**(5): 2241-2245.

OBJECTIVE: To investigate the 1-year survival in cardiac surgical patients with lung disease, including previously undiagnosed cases. DESIGN: Prospective cohort study. SETTING: Tertiary hospital. PARTICIPANTS: Patients scheduled for elective coronary artery bypass graft (CABG) surgery. INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Pulmonary function tests (PFTs) were performed in 454 patients before surgery. Abnormal respiratory patterns were defined as follows: obstructive (forced expiratory volume in 1 second/forced vital capacity <0.70), restrictive (forced expiratory volume in 1 second/forced vital capacity >/=0.70 and forced vital capacity <80% of predicted), and mixed. Overall 1-year mortality was 3.3%. Among 31 patients with documented chronic obstructive pulmonary disease (COPD), mortality was 9.6%, hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.02-12.80, p = 0.04. Of 423 patients without history of COPD, 57 obstructive, 46 restrictive, and 4 mixed abnormal patterns were identified. Of a total of 72 with obstructive lung disease confirmed by PFT (ie, 15 of COPD patients and 57 newly identified cases), 6.9% died, HR 2.75, 95% CI 0.98-8.07, p = 0.06. When combined with cases of COPD where a respiratory abnormality was confirmed (26 patients), newly diagnosed obstructive lung disease (57 patients) was significantly associated with 1-year mortality, HR 4.13, 95% CI 1.50-11.42, p = 0.006. The adjustment for EuroSCORE II did not change the results. CONCLUSIONS: Combination of confirmed preexisting lung disease and newly diagnosed cases provides a clear link to mid-term mortality.

https://www.jcvaonline.com/article/S1053-0770(17)31001-7/fulltext

Rokkjaer, N. and S. Solund (2018). **"Nine deaths among 29 patients with severe mental illness identified with high mortality using SSEPP."** Nord J Psychiatry **72**(8): 543-548.

PURPOSE: It is an established consensus that patients suffering from Severe Mental Illness (SMI) often have somatic comorbidities and a shortened life expectancy. In this study, we examine to what extent previously unknown comorbidities can be revealed if patients suffering from SMI are examined by a specialist in general medicine using the new clinical tool of Systematic Somatic Examinations of Psychiatric Patients (SSEPP). METHODS: SSEPP is a detailed, in-depth questioning and clinical evaluation performed by a specialist in General medicine. A total of 112 patients were recruited from asylums for patients suffering from chronic and severe psychiatric disorders in the Copenhagen area. Diagnosis within SMI led to 106 patients included. 6 patients had no SMI diagnosis and were excluded. Four years later, deaths in the cohort were registered. RESULTS: Ninety percent of examined patients were found to have previously unknown indications for medical treatment. Nine deaths occurred among the examined patients during follow-up. All deaths happened among the 29 patients identified with high expected risk of ischemic manifestation (31%, p < .0001). CONCLUSIONS: In this study, SSEPP is shown to be capable of: Identifying previously unknown and/or undertreated somatic comorbidity in patients with SMI. Identifying the patients with the highest risk of ischemic manifestation with a score of 9 deaths/29 patients. This is statistically significant (p < .0001). This study suggests that patients with SMI in every psychiatric ward be systematically examined for somatic comorbidity by GPs especially trained with tools like SSEPP.

https://www.tandfonline.com/doi/full/10.1080/08039488.2018.1489893

Sakornsakolpat, P., D. Prokopenko, et al. (2019). **"Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations."** Nat Genet **51**(3): 494-505.

Chronic obstructive pulmonary disease (COPD) is the leading cause of respiratory mortality worldwide. Genetic risk loci provide new insights into disease pathogenesis. We performed a genome-wide association study in 35,735 cases and 222,076 controls from the UK Biobank and additional studies from the International COPD Genetics Consortium. We identified 82 loci associated with P < 5 x 10(-8); 47 of these were previously described in association with either COPD or population-based measures of lung function. Of the remaining 35 new loci, 13 were associated with lung function in 79,055 individuals from the SpiroMeta consortium. Using gene expression and regulation data, we identified functional enrichment of COPD risk loci in lung tissue, smooth muscle, and several lung cell types. We found 14 COPD loci shared with either asthma or pulmonary fibrosis. COPD genetic risk loci clustered into groups based on associations with quantitative imaging features and comorbidities. Our analyses provide further support for the genetic susceptibility and heterogeneity of COPD.

https://www.nature.com/articles/s41588-018-0342-2

Sanders, C. L., A. Ponte, et al. (2018). **"The Effects of Inflammation on Alpha 1 Antitrypsin Levels in a National Screening Cohort."** Copd **15**(1): 10-16.

Alpha 1 Antitrypsin (AAT) is a highly polymorphic serum protein. Several genetic variants are associated with varying degrees of decreased serum levels; however, these levels can rise in response to infection, inflammation, injury and estrogen levels. Although the effect of inflammation is well established, it has never been studied quantitatively with respect to specific genotypes in a large representative sample. Using data from a national AAT deficiency-targeted screening cohort, we evaluated AAT levels of patients with normal and deficiency genotypes in response to inflammation, indicated by elevated serum C-reactive protein (CRP). Additionally, we utilized a regression analysis to adjust for the effect of inflammation for each genotype. Across all stratified genotype groups, increased AAT levels were observed in patients with CRP >/=5 mg/L. Different AAT phenotypes reacted differently in the acute phase; M showed a strong response and Z a reduced reaction. Nevertheless, we discovered that inflammation significantly masked clinically relevant base AAT levels in some PI(*)MZ individuals; approximately a quarter of PI(*)MZ samples showed signs of inflammation. Median AAT levels (mg/dL) in the presence of inflammation are given for several genotypes; numbers in parentheses are levels from the cohort without inflammation/adjusted levels from the cohort with inflammation using the newly devised algorithm: PI(*)MM: 162 (142/140); PI(*)MS: 136 (117/115); PI(*)MZ: 104 (85/89); PI(*)MF: 161 (132/141); PI(*)SS: 115 (96/91); PI(*)SZ: 66 (54/50). We conclude that simultaneous determinations of CRP and AAT levels, and genotyping are clinically valuable in defining AAT variants and that the effect of inflammation can be adjusted for.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2017.1401600?needAccess=true

Schmid-Mohler, G., A. L. Caress, et al. (2019). **""Thrust out of normality"-How adults living with cystic fibrosis experience pulmonary exacerbations: A qualitative study."** J Clin Nurs **28**(1-2): 190-200.

AIM AND OBJECTIVES: To explore the experience of pulmonary exacerbation from the perspective of adults with cystic fibrosis. BACKGROUND: While management of pulmonary exacerbations is a pillar of cystic fibrosis care, little is known of patients' perspectives. Understanding the patient's experience is essential for developing and evaluating interventions in support of patient self-management. DESIGN: Qualitative study with longitudinal study in a subsample. METHODS: The study took place from 2015-2016 in a university hospital. Eighteen patients with cystic fibrosis were included who were >/=18 years of age and had no solid organ transplant. Patients' experiences were explored through semistructured interviews and analysed using framework analysis. They each participated in one interview, with a subsample (N = 7) being interviewed twice during and once after antibiotic therapy. RESULTS: Patients (11 men and 7 women; median age 29.5 years, range 19-55 years; median FEV1 45%, range FEV1 23%-105%) experienced pulmonary exacerbations as disruptions of their normality, which led to a substantial increase in their emotional distress. Exacerbations represented a period of threat and domination by CF; that is, symptoms and treatment consumed energy, restricted physical activity and daily life roles. "Noting change," "waiting until antibiotics help," "returning to normality" and "establishing a new normality" characterised their descriptions of the pulmonary exacerbation trajectory. Emotional distress was the major driver for patients' self-management, and personal goals and illness beliefs influenced also patients' self-management decisions. CONCLUSION: The experienced degree and source of emotional distress are drivers for self-management decisions in patients with cystic fibrosis who experience a pulmonary exacerbation. RELEVANCE TO CLINICAL PRACTICE: Our data provide new understanding that will be essential to informing clinical practice, future patient-reported outcomes measures and intervention development.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/jocn.14646

Sheikh, M. A. (2018). **"Child maltreatment, psychopathological symptoms, and onset of diabetes mellitus, hypothyroidism and COPD in adulthood."** J Affect Disord **241**: 80-85.

BACKGROUND: The aim of this study was to assess the associations between child maltreatment (CM), psychopathological symptoms, and onset of diabetes mellitus, hypothyroidism (i.e., low metabolism), and chronic bronchitis/emphysema/COPD in adulthood. METHODS: The present analysis used cross-sectional data collected in 2007-2008 within the Tromso Study, Norway (N=12,981). CM was measured with a single item, and self-reported information on psychopathological symptoms and physical health outcomes was used. The associations between CM, psychopathological symptoms, and physical health outcomes were assessed with linear and Poisson regression models. Mediation was assessed with difference-in-coefficients method. RESULTS: In the fully-adjusted models, CM was associated with higher levels of anxiety and depression, psychological distress, difficulty in sleeping, insomnia, and use of sleeping pills and antidepressants in adulthood ($p<0.05$). Moreover, CM was associated with a more than two-folds increased risk of consultation with psychiatrist ($p<0.001$), a 26% increased risk of forgetfulness ($p<0.001$), a 15% increased risk of decline in memory ($p<0.001$), and a 96% increased risk of psychiatric problems ($p<0.001$) over the course of life. In the fully-adjusted models, CM was associated with a 27-82% increased risk of physical health outcomes in adulthood ($p<0.05$). Indicators of psychopathological symptoms significantly ($p<0.05$) mediate the associations between CM and physical health outcomes. LIMITATIONS: The design of this study is cross-sectional, and all measures are self-reported. CONCLUSION: The associations between retrospectively-reported CM and physical health outcomes in adulthood are partially driven by psychopathological symptoms in adulthood.

Shi, L., B. Zhu, et al. (2018). **"Selection of AECOPD-specific immunomodulatory biomarkers by integrating genomics and proteomics with clinical informatics."** Cell Biol Toxicol **34**(2): 109-123.

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) as a serious event has high mortality and medical costs. Systemic inflammation and immune response are the major factors influencing the outcome and quality of patient with AECOPD. On basis of identification and validation of AECOPD-specific inflammatory biomarkers, the present study aimed to identify AECOPD-specific immunomodulatory mediators by evaluating dynamic genomic and proteomic profiles of peripheral blood mononuclear cells (PBMCs) and plasma in patients with AECOPD on day 1, 3, and 10 after the hospital admission, to compare with healthy controls or patients with stable COPD. We found that genes and proteins of C1QC and C1RL were co-differentially up-expressed in patients with COPD or AECOPD, while haptoglobin (HP), ORM1, SERPING1, and C3 were identified as a panel of AECOPD-specific immunomodulatory mediators. We also found that inflammatory stimuli could up-regulate osteopontin (OPN)-associated HP expression through the PI3K signal pathway in A549 cells. Block of autocrine production of OPN by gene inhibition could reduce HP production from inflammation-induced lung epithelial cells. The complex network of AECOPD- or COPD-specific immunomodulatory mediators will benefit the development of precision or personalized medicine strategies for prevention and treatment of AECOPD.

https://link.springer.com/article/10.1007%2Fs10565-017-9405-x

Shrine, N., A. L. Guyatt, et al. (2019). **"New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries."** Nat Genet **51**(3): 481-493.

Reduced lung function predicts mortality and is key to the diagnosis of chronic obstructive pulmonary disease (COPD). In a genome-wide association study in 400,102 individuals of European ancestry, we define 279 lung function signals, 139 of which are new. In combination, these variants strongly predict COPD in independent populations. Furthermore, the combined effect of these variants showed generalizability across smokers and never smokers, and across ancestral groups. We highlight biological pathways,

known and potential drug targets for COPD and, in phenome-wide association studies, autoimmune-related and other pleiotropic effects of lung function-associated variants. This new genetic evidence has potential to improve future preventive and therapeutic strategies for COPD.

https://www.nature.com/articles/s41588-018-0321-7

Somborac-Bacura, A., S. Popovic-Grle, et al. (2018). **"Cigarette Smoke Induces Activation of Polymorphonuclear Leukocytes."** Lung **196**(1): 27-31.

INTRODUCTION: Cigarette smoking is a major risk factor for chronic obstructive pulmonary disease (COPD). Exposure to cigarette smoke may stimulate inflammatory response and activate polymorphonuclear leukocytes (PMN) thus resulting in secretion of cellular proteases. The aim of our study was to explore the effect of cigarette smoke extract (CSE) on the release of matrix metalloproteinase-9 (MMP-9) from PMN. METHODS: The study included 23 patients with stable COPD and 9 healthy controls. PMN were isolated from blood of all participants and exposed to 4% CSE or basal culture medium (0% CSE) for 20 h. MMP-9 concentration in PMN culture media was measured using the ELISA method. RESULTS: Exposure of PMN to 4% CSE did not cause cytotoxic effects, as determined by no changes in lactate dehydrogenase (LDH) activity in PMN culture media when compared to untreated PMN (P = 0.689). In basal conditions, PMN of COPD patients released significantly more MMP-9 compared with PMN of healthy controls (P = 0.016). However, concentration ratio of MMP-9 released from PMN exposed to 4% CSE or 0% CSE of each participant was significantly higher for healthy subjects than for COPD patients (P = 0.025). CONCLUSION: Cigarette smoke induces activation of PMN in healthy controls. However, chronically activated PMN in COPD patients could not be further stimulated by in vitro exposure to CSE. Constantly raised amount of MMP-9 released into the tissues may be involved in the degradation of extracellular matrix in the lungs as seen in COPD patients.

https://link.springer.com/article/10.1007%2Fs00408-017-0077-3

Su, V. Y., H. F. Liao, et al. (2018). **"Proton pump inhibitors use is associated with a lower risk of acute exacerbation and mortality in patients with coexistent COPD and GERD."** Int J Chron Obstruct Pulmon Dis **13**: 2907-2915.

Objective: The effect of antacid therapy for patients with COPD and gastroesophageal reflux disease (GERD) remains unclear. Patients and methods: This nationwide population-based study was conducted using data from Taiwan's National Health Insurance Research Database, and enrolled COPD patients with or without GERD. Patients with COPD who were not prescribed COPD medications were excluded. Patients with GERD who underwent upper gastrointestinal endoscopy or 24-hour pH monitoring and received at least 1 antacid were enrolled as symptomatic GERD group. The primary endpoint was acute exacerbation and mortality. Results: This study included 3,485 patients with COPD and symptomatic GERD, and 13,938 patients with COPD alone and covered 12,806.57 and 56,809.78 person-years, respectively, from 2000 to 2011. After multivariate adjustment, symptomatic GERD was associated with acute exacerbation (adjusted hazard ratio [HR]: 1.35, 95% CI: 1.23-1.48, p<0.0001) and mortality (HR: 1.42, 95% CI: 1.25-1.61, p<0.0001). In the COPD with symptomatic GERD group, use of proton pump inhibitors was associated with a lower risk of acute exacerbation and mortality (acute exacerbation, HR 0.31, 95% CI: 0.20-0.50, p<0.0001; mortality, HR 0.36, 95% CI: 0.20-0.65, p=0.0007), whereas no significant benefit was observed for histamine2-receptor antagonists. Conclusion: Use of proton pump inhibitors was associated with a lower risk of acute exacerbation and mortality in the patients with COPD and symptomatic GERD.

https://www.dovepress.com/getfile.php?fileID=44553

Tan, L. C., W. J. Yang, et al. (2018). **"(1)H-NMR-based metabolic profiling of healthy individuals and high-resolution CT-classified phenotypes of COPD with treatment of tiotropium bromide."** Int J Chron Obstruct Pulmon Dis **13**: 2985-2997.

Background: Heterogeneity of COPD results in different therapeutic effects for different patients receiving the same treatment. COPD patients need to be individually treated according to their own characteristics. The purpose of this study was to explore the differences in different CT phenotypic COPD by molecular metabolites through the use of metabolomics. Methods: According to the characteristics of CT imaging, 42 COPD patients were grouped into phenotype E (n=20) or phenotype M (n=24). Each COPD patient received tiotropium bromide powder for inhalation for a therapeutic period of 3 months. All subjects were assigned into phenotype E in pre-therapy (EB, n=20), phenotype E in post-therapy (EA, n=20), phenotype M in pre-therapy (MB, n=22), phenotype M in post-therapy (MA, n=22), or normal control (N, n=24). The method of metabolomics based on (1)H nuclear magnetic resonance ((1)H-NMR) was used to compare the changes in serum metabolites between COPD patients and normal controls and between different phenotypes of COPD patients in pre- and post-therapy. Results: Patients with COPD phenotype E responded better to tiotropium bromide than patients with COPD phenotype M in terms of pulmonary function and COPD assessment test scores. There were differences in metabolites in COPD patients vs normal control people. Differences were also observed between different COPD phenotypic patients receiving the treatment in comparison with those who did not receive treatment. The changes of metabolites involved lactate, phenylalanine, fructose, glycine, asparagine, citric acid, pyruvic acid, proline, acetone, ornithine, lipid, pyridoxine, maltose, betaine, lipoprotein, and so on. These identified metabolites covered the metabolic pathways of amino acids, carbohydrates, lipids, genetic materials, and vitamin. Conclusion: The efficacy of tiotropium bromide on COPD phenotype E is better than that of phenotype M. Metabolites detected by (1)H-NMR metabolomics have potentialities of differentiation of COPD and healthy people, discrimination of different COPD phenotypes, and giving insight into the individualized treatment of COPD.

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Tao, H., H. Onoda, et al. (2018). **"The impact of coexisting lung diseases on outcomes in patients with pathological Stage I non-small-cell lung cancer."** Interact Cardiovasc Thorac Surg **26**(6): 1009-1015.

OBJECTIVES: Cigarette smoking is a well-known cause of interstitial lung disease (ILD), pulmonary emphysema and lung cancer. Coexisting pulmonary disease can affect prognosis in patients with lung cancer. The aim of this study was to determine the influence of pulmonary disease on outcomes in patients with a smoking history who had undergone surgery for pathological Stage I non-small-cell lung cancer. METHODS: Medical records of 257 patients with a smoking history who underwent surgery for pathological Stage I non-small-cell lung cancer between June 2009 and December 2014 were reviewed. Coexisting ILDs were evaluated using high-resolution computed tomography. The degree of pulmonary emphysema was determined using image analysis software according to the Goddard classification. The impact of clinicopathological factors on outcome was evaluated. RESULTS: Among the 257 patients, ILDs were detected via high-resolution computed tomography in 60 (23.3%) patients; of these, usual interstitial pneumonia (UIP) patterns and non-UIP patterns were seen in 25 (9.7%) and 35 (13.6%) patients, respectively. The degree of pulmonary emphysema was classified as none, mild and moderate and included 50 (19.5%), 162 (63.0%) and 45 (17.5%) patients, respectively. The 5-year overall survival, cancer-specific survival and relapse-free survival were 80.7%, 88.0% and 74.9%, respectively, during a median follow-up period of 50.5 months. In multivariate analysis, the presence of a UIP pattern was shown to be an independent risk factor for poor outcome. CONCLUSIONS: The presence of a UIP-pattern ILD on high-resolution computed tomography images was shown to be a risk factor for poor outcome in patients with a smoking history who had undergone surgery for pathological Stage I non-small-cell lung cancer.

https://watermark.silverchair.com/ivx441.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAlUwggJRBgkqhkiG9w0BBwagggJCMIICPgIBADCCAjcGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQM2rZMDu5a2bwNii0PAgEQgIICCAP-YrPdOqN5h2Eyak_PJ0YVYjw-XxorltXaLUO5Rd2cTBXaUKC5aAXaskD-ZME2nC8iNDnVmNQnel5UajY8GJ0xF3dpEy2jGZMV1XAZJO5h30trGJoUVER8YXDIDTUyDAqiuO_em7l5Nv

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6V7Ra5LbhMgXvmcOgUXDCHNt_L8Mc3F6VIlB6sFaUVouw7TeRqIrmb80LUqceBmSg1kKVuJBD0Dhy0aB5V74UPDgMoPfPMnhecrfyT0MoQNFxMu-H4_FmBuZfCFl_k2R0adnr_l6-pZhEC0CmhUOiDmSDEzPTRe7KwmgtADkqOGYt1mg5G2_KRnWQFQU0qCmSNf8CwUBTft8hfghCYgBYkW7o0xTs2Q9Y3RiaflmAua-tsmwZG3e6vk_UIl0EqDfMqqAhxP1gEgfLhDlo6WjvDRHHjM9S_CegCRJwAUPH3eAZDf5nvZk670zDXZVR63DdFQmL0XKPqjeb03my_jxCPjnzhCblydTYyZqE4Y1fN6_wgg_-loMxv2xAr5ADA6cTEhUM24ErDGijWh4X2sgDxoVv3JVhn5rI6gcCL0uCqpjvidft83x2xF0vSLY_ESRcVVRTqa69qCXoJjdU3Msx-blA9OSSdgTkWBgVrl_lv6_2cb9n-K3rz6ScjXjXltw6Mm3V_w0z6h-tYieJc-twwL-RgHD1TZNdXk

Thierry, F., M. F. Ferreira, et al. (2019). **"Canine and feline emphysematous gastritis may be differentiated from gastric emphysema based on clinical and imaging characteristics: Five cases."** Vet Radiol Ultrasound **60**(2): 136-144.

Gastric pneumatosis is an imaging finding defined as the presence of gas foci in the gastric wall. In humans, this imaging feature can result from one of two separate clinical entities: life-threatening emphysematous gastritis or clinically benign gastric emphysema. This retrospective case series study describes the clinical and imaging features in five animals diagnosed with spontaneous gastric pneumatosis without gastric dilatation-volvulus. Three canine and two feline cases of spontaneous gastric pneumatosis were identified on radiographic and ultrasonographic examinations. In addition to gastric pneumatosis, one dog and two cats presented concomitant systemic signs such as lethargy, hematemesis, anemia, or leukocytosis. Two dogs remained asymptomatic or presented mild gastrointestinal signs. Portal gas was described in two dogs and one cat, and pneumoperitoneum in one dog. These features were not considered clinically significant. The dog and two cats with systemic signs were euthanized due to clinical deterioration and diagnosed with emphysematous gastritis. The gastric pneumatosis of both dogs without systemic signs resolved while on medical management without antibiotic therapy. These latter cases were interpreted as consistent with gastric emphysema. Findings from the current study indicated that gastric pneumatosis can occur without gastric dilatation-volvulus in cats and dogs and that a combination of clinical and imaging characteristics may help to differentiate between potentially life-threatening emphysematous gastritis and relatively benign gastric emphysema. More studies are needed to determine the etiology and risk factors associated with these conditions.

https://onlinelibrary.wiley.com/doi/abs/10.1111/vru.12691

Titova, O. N., M. A. Petrova, et al. (2018). **"Efficacy of Arbidol in the prevention of virus-induced exacerbations of bronchial asthma and chronic obstructive pulmonary disease."** Ter Arkh **90**(8): 48-52.

AIM: To assess the efficacy and safety of Arbidol in the influenza and ARVI preventing in patients with asthma and chronic obstructive pulmonary disease (COPD). MATERIALS AND METHODS: This study was an open label and prospective during epidemic period of 2016-2017 years. 100 outpatients aged 18 to 80 years with verified asthma and/or COPD, were enrolled to therapy group, and received oral umifenovir 200 mg once daily for 14 days and then 200 mg twice a week for 3 weeks.The medical records data for the same epidemic period of 2016-2017 seasons of the same patients during witch they received no prophylaxis was taken as a control. The data analysis was made by applying parametric and nonparametric statistical methods. RESULTS: Seasonal and post-exposure prophylaxis using umifenovir was associated with 2.6-times reduction in influenza and ARVI morbidity compared to control. In diseased patients (ARVI) of the therapy group the number of patients with mild illness prevailed (62.2%) and was significantly differed from control (37.1%). Severity of catarrhal symptoms and intoxication, was reduced with umifenovir prophylaxis course and were mild in 67.6% and 67.6% respectively of therapy group compared with 43.3% and 46.4% of control. Influenza and ARVI complications were only detected in control group (4 cases). The percentage of patients with incidents of underlying disease exacerbation was 42% in therapy group and 93% in control group. Also, exacerbation in the therapy group were mild in 59.5% and 34.4%

in control group, while moderate exacerbation prevailed in control group and was in 59.1% of cases with was significantly higher then in therapy group (39.3%). Results in more frequent use of adjuvant in the control group compared with the therapy group (81.7% and 59.5% respectively). Patients of control group had a higher risk of hospitalizations due to underlying disease aggravation (11.8%), compared with therapy group (9.5%) but these differences were not significant. CONCLUSION: Seasonal and post-exposure prophylaxis with Arbidol reduce influenza and ARVI morbidity in patients with asthma and COPD during epidemic period, frequency and severity of chronic obstructive pulmonary disease aggravations resulting in decrease in the number of hospitalizations. Also, prophylaxis with Arbidol reduced the severity of catarrhal symptoms and intoxication.

Tokes-Fuzesi, M., I. Ruzsics, et al. (2018). **"Role of microparticles derived from monocytes, endothelial cells and platelets in the exacerbation of COPD."** Int J Chron Obstruct Pulmon Dis **13**: 3749-3757.

Background: Microparticles (MPs) are shedding membrane vesicles released from activated blood and endothelial cells under inflammatory conditions. The role of endothelial MPs (EMPs) in pathophysiology of COPD is relatively well known. However, the release and function of MPs of other cellular origins, eg, platelets, red blood cells and leukocytes, are not clearly evaluated in COPD. Purpose: The aim of this study was to measure EMPs and other cell-derived circulating MPs in stable and exacerbated COPD patients. Patients and methods: A total of 50 patients with COPD and 19 healthy volunteers were enrolled in the study. EMPs (CD31+, CD62E+) and platelet-derived (CD61+, CD41+, CD42a+, PAC1+), red blood cell-derived (GlyA+) and leukocyte-derived (CD45+, CD13+, CD14+, CD56+) MPs were measured. Flow cytometry (FC) was performed on Beckman Coulter FC500 analyzer. MP reference gate was set using 0.3-0.5-0.9 microm microbeads with MP size gates of 0.5-1.0 microm. Results: All the measured MPs were significantly ($P<0.001$) higher in COPD patients than in the controls. Furthermore, CD62E+, CD41+, CD42a+ and CD14+ MP values were significantly ($P<0.001$) increased in exacerbated COPD compared to stable COPD. These MPs showed significant ($P<0.001$) inverse correlation with FEV1/FVC, as well. Conclusion: In this study, we describe a reliable flow cytometric assay for MP analysis that was successfully applied in COPD. Besides EMPs, COPD is accompanied by an increased concentration of various MPs in the systemic circulation; particularly, platelet- and monocyte-derived MPs seem to be important in exacerbation.

https://www.dovepress.com/getfile.php?fileID=46242

Wallace, A. E., S. Kaila, et al. (2019). **"Health Care Resource Utilization and Exacerbation Rates in Patients with COPD Stratified by Disease Severity in a Commercially Insured Population."** J Manag Care Spec Pharm **25**(2): 205-217.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality and is associated with substantial economic burden. There is a lack of data regarding COPD outcomes and costs in a real-world setting, particularly by Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity. OBJECTIVES: To (a) characterize a commercially insured U.S. population with COPD and (b) assess prevalence of exacerbations, health care resource utilization (HCRU), costs, and treatment patterns in a cohort of patients with confirmed COPD, overall and stratified by GOLD stage. METHODS: This retrospective observational cohort study used administrative claims data from the HealthCore Integrated Research Database to identify patients with >/= 1 inpatient, emergency room (ER), or office visit claim for COPD between January 1, 2012, and November 30, 2013, and continuous enrollment for 1 year before and 2 years after the first COPD diagnosis date. Patients with a spirometry claim within 12 months were eligible for medical record abstraction to confirm COPD diagnosis (forced expiratory volume in 1 second [FEV1]/forced vital capacity ratio < 0.7) and GOLD 1-4 classification (based on postbronchodilator FEV1 percent predicted). HCRU, costs, treatment patterns, and rate of moderate/severe exacerbation were identified from diagnosis up to 24 months. Outcomes were analyzed by univariate analysis stratified by GOLD classification. Multivariable analysis was conducted to

assess associations between GOLD classification and outcomes of interest. RESULTS: 53,484 patients newly diagnosed with COPD were identified who met initial inclusion criteria: 14,293 (27%) had a qualifying spirometry claim, and 1,505 had confirmed COPD (GOLD 1, 333 [22%]; GOLD 2, 823 [55%]; GOLD 3, 317 [21%]; GOLD 4, 32 [2%]). Patients with greater disease severity had higher rates of moderate/severe COPD exacerbations (GOLD 1 and 2, 40.4 and 48.9 per 100 person-years, respectively; GOLD 3 and 4, 83.6 and 89.1 per 100 person-years, respectively). All-cause and COPD-related inpatient admissions, COPD-related office visits, and COPD-related ER visits were more prevalent with more severe GOLD classification. Mean annual COPD-related medical costs increased with GOLD classification ($5,945 for GOLD 1 patients, $18,070 for GOLD 4). COPD maintenance medication was filled by 42%, 56%, 73%, and 75% of patients in GOLD 1-4 (57% overall), respectively; combination corticosteroid/long-acting beta2-agonist inhalers were the most commonly used medication, regardless of GOLD classification. Patients with more severe disease had greater adherence (range 44%-68% of days covered for GOLD 1-4) and persistence (range 107-209 days for GOLD 1-4). CONCLUSIONS: Trends toward increases in exacerbations, HCRU, and costs were observed as airflow limitation worsened. Adherence and persistence with COPD maintenance therapy was suboptimal even with severe disease. DISCLOSURES: This study was supported by Boehringer Ingelheim Pharmaceuticals (Ridgefield, CT), which was given the opportunity to review the manuscript for medical and scientific accuracy, as well as intellectual property considerations. Willey and Singer are employees of HealthCore (parent company Anthem), which received funding from Boehringer Ingelheim to complete this study. Wallace and Shinde were employed by HealthCore at the time of this study. Wallace and Singer report stock ownership in Anthem. Napier is an employee of Anthem. Kaila, Bayer, and Shaikh are employees of Boehringer Ingelheim Pharmaceuticsls. Portions of this research were presented at the following conferences: (a) A. Wallace, S. Kaila, V. Zubek, A. Shaikh, M. Shinde, V. Willey, M. Napier, and J. Singer, Healthcare resource utilization, costs, and exacerbation rates in patients with COPD stratified by GOLD airflow limitation classification in a US commercially insured population, presented at AMCP Nexus 2017; October 16-19, 2017; Dallas, TX; and (b) A.E. Wallace, V. Zubek, S. Kaila, A. Shaikh, M. Shinde, V. Willey, M.B. Napier, and J.R. Singer, Real-world treatment patterns among newly diagnosed COPD patients according to GOLD airflow limitation severity classification in a U.S. commercially insured/Medicare Advantage population, presented at CHEST 2017 Annual Meeting; October 28-November 1, 2017; Toronto, Ontario, Canada.

Wei, X., N. Yu, et al. (2018). **"The features of AECOPD with carbon dioxide retention."** BMC Pulm Med **18**(1): 124.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) with carbon dioxide retention is associated with a worsening clinical condition and the beginning of pulmonary ventilation decompensation. This study aimed to identify the factors associated with carbon dioxide retention. METHODS: This was a retrospective study of consecutive patients with COPD (meeting the Global Initiative for Chronic Obstructive Lung Disease diagnostic criteria) hospitalized at The Ninth Hospital of Xi'an Affiliated Hospital of Xi'an Jiaotong University between October 2014 and September 2017. The baseline demographic, clinical, laboratory, pulmonary function, and imaging data were compared between the 86 cases with carbon dioxide retention and the 144 cases without carbon dioxide retention. RESULTS: Compared with the non-carbon dioxide retention group, the group with carbon dioxide retention had a higher number of hospitalizations in the previous 12 months ($p = 0.013$), higher modified Medical Research Council (mMRC) dyspnea scores ($p = 0.034$), lower arterial oxygen pressure ($p = 0.018$), worse pulmonary function (forced expiratory volume in one second/forced vital capacity [FEV1/FVC; $p < 0.001$], FEV1%pred [$p < 0.001$], Z5%pred [$p = 0.004$], R5%pred [$p = 0.008$], R5-R20 [$p = 0.009$], X5 [$p = 0.022$], and Ax [$p = 0.011$]), more severe lung damage (such as increased lung volume [$p = 0.011$], more emphysema range [$p = 0.007$], and lower mean lung density [$p = 0.043$]). FEV1 < 1 L (odds ratio [OR] = 4.011, 95% confidence interval [CI]: 2.216-7.262) and emphysema index (EI) > 20% (OR = 1.926, 95% CI: 1.080-3.432) were independently associated with carbon dioxide retention in COPD. CONCLUSION: Compared with the non-carbon dioxide retention group, the group with carbon dioxide retention had different clinical, pulmonary function, and imaging features. FEV1 < 1 L and EI > 20% were independently associated with carbon dioxide retention in AECOPD. TRIAL REGISTRATION: ChiCTR-OCH-14004904 . Registered 25 June 2014.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6066936/pdf/12890_2018_Article_691.pdf

Wen, C. P. and W. Gao (2018). **"PM2.5: an important cause for chronic obstructive pulmonary disease?"** Lancet Planet Health **2**(3): e105-e106.

https://www.sciencedirect.com/science/article/pii/S2542519618300251?via%3Dihub

Yakubek, G. A., G. L. Curtis, et al. (2018). **"Chronic Obstructive Pulmonary Disease Is Associated With Short-Term Complications Following Total Hip Arthroplasty."** J Arthroplasty **33**(6): 1926-1929.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. Furthermore, COPD patients are at increased risk of complications following surgery. The purpose of this study was to evaluate the postoperative total hip arthroplasty (THA) outcomes of COPD patients. Specifically, we asked the following questions: (1) Is COPD associated with adverse perioperative outcomes and (2) Does COPD increase the risk of short-term complications following THA? METHODS: The American College of Surgeons National Surgical Quality Improvement Program database was used to identify 64,796 patients who underwent THA between 2008 and 2014. A total of 2426 patients with COPD were identified. COPD and non-COPD cohorts were compared based on the following outcomes: hospital length-of-stay, operative times, discharge disposition, and 30-day postoperative complications. RESULTS: COPD patients were found to have a longer length-of-stay and be discharged to an extended care facility ($P < .001$). COPD patients were also at significantly ($P < .05$) increased risk for any complication, such as mortality, myocardial infarction, pneumonia, septic shock, unplanned reintubation, use of a mechanical ventilator >48 hours, deep infection, require a blood transfusion, return to operating room, and a readmission within 30 days postoperatively. CONCLUSIONS: COPD patients are more likely to suffer from postoperative complications following THA when compared to non-COPD patients. Many of these complications are medical, pulmonary evaluation and medical optimization are a critical step in preoperative management for these patients.

https://www.arthroplastyjournal.org/article/S0883-5403(18)30005-6/fulltext

Yamada, H., N. Hida, et al. (2018). **"Effects of a single long-acting muscarinic antagonist agent and a long-acting muscarinic antagonist/long-acting beta2-adrenoceptor agonist combination on lung function and symptoms in untreated COPD patients in Japan."** Int J Chron Obstruct Pulmon Dis **13**: 3141-3147.

Background: A large body of evidence suggests that long-acting beta2-adrenoceptor agonist (LABA)/long-acting muscarinic antagonist (LAMA) combinations induce a strong synergistic bronchodilatory effect in human isolated airways. Moreover, a recent post hoc analysis demonstrated clinical synergism between LABAs and LAMAs, which induces a synergistic improvement not only in lung function but also in dyspnea in COPD patients. Aim: The aim of this study is to examine the baseline factors related to improvement in lung function or clinical symptoms that results from the administration of LAMA or LAMA/LABA and to compare the differences in improvement in lung function or clinical symptoms between LAMA and LAMA/LABA. Methods: Among 829 patients with COPD who were treated with LAMA or LAMA/LABA in our hospital, 112 patients (aged 40-89 years) matched the criteria. Of these 112 patients, 71 received LAMA (LAMA group) and 41 received LAMA/LABA (LAMA/LABA group) as the initial treatment. Various examination results such as lung function test values, symptom change, and frequency of exacerbations were compared between the two groups. Results: Compared with the monotherapy, the combination therapy significantly improved the FEV1, inspiratory capacity (IC), and total COPD assessment test (CAT) scores. Comparing the improvement in each domain of the CAT produced by the combination therapy with that of the monotherapy, larger improvements were found for the domains of going out and

sleeping. The frequency of exacerbations during the 24 weeks was significantly lower in the combination therapy group than in the LAMA monotherapy group (P=0.034). Although no relationship was found between improvement in FEV1 and any pretreatment factors in the LAMA/LABA group, the improvement in the CAT score was strongly related to the baseline CAT score, smoking index, and air trapping index (P-value <1x10(-4)). Conclusion: In this study of clinical practice, we found that LAMA/LABA combination therapy improved the clinical symptoms of COPD and IC and that the effects of the combination therapy were consistent with those observed in previous clinical trials.

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Yamakawa, H., T. Takemura, et al. (2018). **"Emphysematous change with scleroderma-associated interstitial lung disease: the potential contribution of vasculopathy?"** BMC Pulm Med **18**(1): 25.

BACKGROUND: Pulmonary emphysema combined with systemic sclerosis (SSc)-associated interstitial lung disease (ILD) occurs more often in smokers but also in never-smokers. This study aimed to describe a new finding characterized by peculiar emphysematous change with SSc-associated ILD (SSc-ILD). METHODS: We conducted a retrospective review of 21 consecutive patients with SSc-ILD diagnosed by surgical lung biopsy and focused on the radio-pathological correlation of the emphysematous change. RESULTS: Pathological pulmonary emphysema (p-PE) with SSc-ILD was the predominant complication in 16 patients (76.2%) with/without a smoking history, of whom 62.5% were never-smokers. A low attenuation area (LAA) within interstitial abnormality on high-resolution computed tomography (HRCT) was present in 31.3%. Diffusing capacity of the lung for carbon monoxide (DLCO) was lower, disease extent on HRCT higher, and intimal/medial thickening in muscular pulmonary arteries more common in the patients with p-PE with SSc-ILD. However, forced vital capacity (FVC) was well preserved regardless of whether p-PE was observed. Most SSc-ILD patients had pulmonary microvasculature changes in arterioles (90.5%), venules (85.7%), and interlobular veins (81.0%). CONCLUSIONS: Pulmonary emphysematous changes (LAA within interstitial abnormalities on HRCT and destruction of fibrously thickened alveolar walls) are specific and novel radio-pathological features of SSc-ILD. Peripheral vasculopathy may help to destroy the fibrously thickened alveolar walls, resulting in emphysematous change in SSc-ILD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5791248/pdf/12890_2018_Article_591.pdf

Yu, N., H. Yuan, et al. (2019). **"Determination of vascular alteration in smokers by quantitative computed tomography measurements."** Medicine (Baltimore) **98**(7): e14438.

A new method of quantitative computed tomography (CT) measurements of pulmonary vessels are applicable to morphological studies and may be helpful in defining the progression of emphysema in smokers. However, limited data are available on the relationship between the smoking status and pulmonary vessels alteration established in longitudinal observations. Therefore, we investigated the change of pulmonary vessels on CTs in a longitudinal cohort of smokers.Chest CTs were available for 287 current smokers, 439 non-smokers, and 80 former smokers who quit smoking at least 2 years after the baseline CT. CT images obtained at the baseline and 1 year later were assessed by a new quantitative CT measurement method, computing the total number of pulmonary vessels (TNV), mean lung density (MLD), and the percentage of low-attenuation areas at a threshold of -950 (density attenuation area [LAA]%950). Analysis of variance (ANOVA) and the independent sample t test were used to estimate the influence of the baseline parameters. The t paired test was employed to evaluate the change between the baseline and follow-up results.The current smokers related to have higher whole-lung MLD, as well as less and lower TNV values than the non-smokers (P <.05). But no significant differences in LAA%950 were found between smokers and non-smokers. After one year, the increase in LAA%950 was more rapid in the current (additional 0.3% per year, P <. 05-.01) than in the former smokers (additional 0.2% per year, P = .3). Additionally, the decline in TNV was faster in the current (additional -1.3 per year, P <.05-.01) than that in the former smokers (additional -0.2 per year, P = .6). Current smoke, pack-years, weight, and lung volume independently predicted TNV at baseline (P <.001) in multivariate analysis.The

findings of this study reveal that the decline in the pulmonary vessels in smokers can be measured and related to their smoking status.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6408080/pdf/medi-98-e14438.pdf

Zeidler, M. R., J. L. Martin, et al. (2018). **"Sleep disruption as a predictor of quality of life among patients in the subpopulations and intermediate outcome measures in COPD study (SPIROMICS)."** Sleep **41**(5)Study Objectives: Sleep quality is poor among patients with chronic obstructive pulmonary disease (COPD), and studies show that sleep disturbance is associated with low overall quality of life in this population. We evaluated the impact of patient-reported sleep quality and sleep apnea risk on disease-specific and overall quality of life within patients with COPD enrolled in the SPIROMICS study, after accounting for demographics and COPD disease severity. Methods: Baseline data from 1341 participants [892 mild/moderate COPD (FEV1 >/= 50% predicted); 449 severe COPD (FEV1 < 50%)] were used to perform three nested (blocks) regression models to predict quality of life (Short Form-12 mental and physical components and St. George's Respiratory Questionnaire). Dependent measures used for the nested regressions included the following: Block1: demographics and smoking history; Block 2: disease severity (forced expiratory volume 1 s; 6 min walk test); Block 3: risk for obstructive sleep apnea (OSA; Berlin questionnaire); and Block 4: sleep quality (Pittsburgh Sleep Quality Index [PSQI]). Results: Over half of participants with COPD reported poor sleep quality (Mean PSQI 6.4 +/- 3.9; 50% with high risk score on the Berlin questionnaire). In all three nested regression models, sleep quality (Block 4) was a significant predictor of poor quality of life, over and above variables included in blocks 1-3. Conclusions: Poor sleep quality represents a potentially modifiable risk factor for poor quality of life in patients with COPD, over and above demographics and smoking history, disease severity, and risk for OSA. Improving sleep quality may be an important target for clinical interventions. Clinical Trial: SPIROMICS. Clinical Trial URL: http://www2.cscc.unc.edu/spiromics/. Clinical Trial Registration: ClinicalTrials.gov NCT01969344.

https://watermark.silverchair.com/zsy044.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAlcwggJTBgkqhkiG9w0BBwagggJEMIICQAIBADCCAjkGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMRKvlXywNyIspVT8OAgEQgIICChLsoS0nIBdoaiBcqRudzUwKT0sDr06fxCLcQYEqXAvzHpVgU_Wn7koEu4Pkw8U-8iL3QrSyv-Hi2M5DCLJkI6vzTibNBHL40Io4jW_MmN35Pq3qibyFyAwN_rbQzLCnhhAvxjf9iEvIxkTKsH6_Ma_s4oOdTeE197Nf9L5DhJqsYg4QchnJjET9_6K1hSXHmo8WerTKNf6lpjFenj4Wh0x6RF1kS4fp1asPN27J_G0lfZO4ct-26P55BCiJZkYYkK0gxP33h7zefVM4Dt6OuTIaVgIjMIoWzf6_jJgGG0RniNknZ03dLUteKKCx36yNpxRmJrXylrfI62MkudY-CpW-t9OYH4xZNeKRbGpXms4HzLK076j0WoXPmHg7xaUvmjkXyFKdrbcIDw4nJbuvID0KcUGU93gWDwaLpZa8I9qvhPO9oN2-usa1ztJcrNrZ8OnklzHdYGNdGGbjZJ6xhWKY4UZIy1FqWRv3sjEa4z1wk9LyT3aG8IIFvseHV9bLu68YQvWSZKj70psOvm7438gqhuPqq-3a6P10JPCW4f6rgvXbImY2K2wKyXEzH-FE9peHbVAWID8OsCw6PDIUxhQ9Lsb_ItdZHz-HAgkAF3esc0Oitv-xgUW84yfi70ZSKY-S1eHkgYW6CQWL9h1KJLdHhe3bP3Bvu4_vaz01WrrrBQF6RloIPwZ0hQ

Cohort and case-control studies – in process

Search strategy: (COPD[Title] OR Emphysema[Title] OR Chronic Obstructive Pulmonary Disease[Title] OR Chronic Bronchitis[Title]) AND (inprocess[sb] OR Publisher[sb]) AND ("cohort"[All Fields] OR "follow-up"[All Fields] OR "longitudinal"[All Fields] OR "prospective"[All Fields] OR "retrospective"[All Fields] OR "Case-control"[All Fields]) AND English[lang]

Akhter, S., U. A. Warraich, et al. (2019). **"Assessment and comparison of APACHE II (Acute Physiology and Chronic Health Evaluation), SOFA (Sequential Organ Failure Assessment) score and CURB 65 (Confusion; Urea; Respiratory Rate; Blood Pressure), for prediction of inpatient mortality in Acute Exacerbation of Chronic Obstructive Pulmonary Disease."** J Pak Med Assoc **69**(2): 211-215.

OBJECTIVE: To assess and compare the role of Acute Physiology and Chronic Health Evaluation, Sequential Organ Failure Assessment, and Confusion Urea Respiratory Rate Blood Pressure scores in predicting inpatient

mortality for patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease.. Design: The retrospective study was conducted at the Jinnah Post-graduate Medical Centre, Karachi, and comprised data of all consecutive Acute Exacerbation of Chronic Obstructive Pulmonary Disease patients from December 1, 2013, to December 31, 2014. Logistic regression model and non-parametric tests were employed using SPSS 22.. RESULTS: There were 95 patients whose medical records were studied. The overall mean age was 60.79+/-12.39 years. Mortality rate was of 26(27.6%). Median hospital stay was 11.5 days (interquartile range: 9-17 days) in survivors and 4 days (2-8 days) in non-survivors. Out of the three scales used, Confusion Urea Respiratory Rate Blood Pressure-65 score showed the greatest difference between survivors and non-survivors (p <0.05). Significant higher scores were observed in non survivors with Type 2 than Type 1 respiratory failure (p<0.05). There was significant association of mortality with baseline partial pressure of oxygen and oxygen saturation (p<0.05 each). CONCLUSIONS: Confusion Urea Respiratory Rate Blood Pressure-65score determined at the time of admission had significant ability to predict inpatient mortality..

Akiki, Z., D. Fakih, et al. (2016). **"Surfactant protein D, a clinical biomarker for chronic obstructive pulmonary disease with excellent discriminant values."** Exp Ther Med **11**(3): 723-730.

Biological markers can help to better identify a disease or refine its diagnosis. In the present study, the association between surfactant protein D (SP-D) and chronic obstructive pulmonary disease (COPD) was studied among subjects consulting for respiratory diseases or symptoms and was compared with C-reactive protein (CRP) and fibrinogen. A further aim of this study was to identify the optimal cut-off point of SP-D able to discriminate COPD patients. A case-control study including 90 COPD patients, 124 asthma patients and 180 controls was conducted. Standardized questionnaires were administered and lung function tests were performed. Biological markers were measured in blood samples according to standardized procedures. The association between SP-D and COPD was investigated using logistic regression models. Receiver-operating characteristic curves were used for threshold identification. SP-D levels above the median value were positively associated with COPD [adjusted odds ratio (OR)=3.86, 95% confidence interval (CI): 1.51-9.85, P=0.005). No associations with COPD or asthma were found for CRP or fibrinogen levels. Scores for COPD diagnosis in all COPD patients or ever-smoker COPD patients were identified (sensitivity, 76.4 and 77.8%; specificity, 89.3 and 88.5%, respectively). The results indicate that SP-D can differentiate COPD from other respiratory symptoms or diseases. Used with socio-demographic characteristics and respiratory symptoms, SP-D is able to discriminate COPD patients from controls, particularly among smokers.

https://www.hal.inserm.fr/inserm-01764320/document

Aksoy, E., S. Gungor, et al. (2018). **"A Revised Treatment Approach for Hospitalized Patients with Eosinophilic and Neutrophilic Exacerbations of Chronic Obstructive Pulmonary Disease."** Turk Thorac JOBJECTIVES: The choice of treatment according to the inflammation type in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has been of recent interest. This study investigated the role of novel biomarkers, hospital outcomes, and readmission rates in the first month in patients with eosinophilic or neutrophilic AECOPD. MATERIALS AND METHODS: We conducted a retrospective observational cohort study in a Chest Teaching Hospital with hospitalized AECOPD patients. Subjects' characteristics, hemogram results, C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet/mean platelet volume (PLT/MPV), length of hospital stay, mortality, and steroid use were recorded. Eosinophilic AECOPD defined as peripheral blood eosinophilia (PBE) was >2% and neutrophilic AECOPD as PBE </=2%. Readmission within 28 days of discharge was recorded. RESULTS: Of 2727(31.5% females) patients, eosinophilic AECOPD was found in 510 (18.7%) patients. Leucocytes, CRP, NLR, and PLR were significantly higher in neutrophilic AECOPD than in eosinophilic AECOPD (p<0.001). Steroid use and mortality rate were 45% and 0.6% in eosinophilic AECOPD and 71%, and 1.4% in neutrophilic AECOPD, respectively (p=0.001, p=0.19). Age >75 years,

albumin <2.5 g/dL, CRP >50 mg/dL, and PLT/MPV <20x103 were found to be risks factors for hospital mortality (p<0.05 each). Readmission rates within 28 days of discharge were 5% (n=136), and this rate was higher in eosinophilic AECOPD patients not taking steroids (p<0.001). CONCLUSION: NLR, PLR, and CRP levels were higher in neutrophilic AECOPD compared with eosinophilic AECOPD. These markers decreased with treatment in neutrophilic AECOPD. A PLT/MPV ratio of <20x103 resulted in an increased mortality rate. Thus, appropriate steroid therapy may reduce readmission rates in the first 28 days after discharge in eosinophilic AECOPD.

Akyea, R. K., T. M. McKeever, et al. (2019). **"Predicting fracture risk in patients with chronic obstructive pulmonary disease: a UK-based population-based cohort study."** BMJ Open **9**(4): e024951.

OBJECTIVE: To assess the incidence of hip fracture and all major osteoporotic fractures (MOF) in patients with chronic obstructive pulmonary disease (COPD) compared with non-COPD patients and to evaluate the use and performance of fracture risk prediction tools in patients with COPD. To assess the prevalence and incidence of osteoporosis. DESIGN: Population-based cohort study. SETTING: UK General Practice health records from The Health Improvement Network database. PARTICIPANTS: Patients with an incident COPD diagnosis from 2004 to 2015 and non-COPD patients matched by age, sex and general practice were studied. OUTCOMES: Incidence of fracture (hip alone and all MOF); accuracy of fracture risk prediction tools in COPD; and prevalence and incidence of coded osteoporosis. METHODS: Cox proportional hazards models were used to assess the incidence rates of osteoporosis, hip fracture and MOF (hip, proximal humerus, forearm and clinical vertebral fractures). The discriminatory accuracies (area under the receiver operating characteristic [ROC] curve) of fracture risk prediction tools (FRAX and QFracture) in COPD were assessed. RESULTS: Patients with COPD (n=80 874) were at an increased risk of fracture (both hip alone and all MOF) compared with non-COPD patients (n=308 999), but this was largely mediated through oral corticosteroid use, body mass index and smoking. Retrospectively calculated ROC values for MOF in COPD were as follows: FRAX: 71.4% (95% CI 70.6% to 72.2%), QFracture: 61.4% (95% CI 60.5% to 62.3%) and for hip fracture alone, both 76.1% (95% CI 74.9% to 77.2%). Prevalence of coded osteoporosis was greater for patients (5.7%) compared with non-COPD patients (3.9%), p<0.001. The incidence of osteoporosis was increased in patients with COPD (n=73 084) compared with non-COPD patients (n=264 544) (adjusted hazard ratio, 1.13, 95% CI 1.05 to 1.22). CONCLUSION: Patients with COPD are at an increased risk of fractures and osteoporosis. Despite this, there is no systematic assessment of fracture risk in clinical practice. Fracture risk tools identify those at high risk of fracture in patients with COPD.

https://bmjopen.bmj.com/content/bmjopen/9/4/e024951.full.pdf

Almagro, P., P. Martinez-Camblor, et al. (2019). **"External Validation and Recalculation of the CODEX Index in COPD Patients. A 3CIAplus Cohort Study."** Copd: 1-10.

The CODEX index was developed and validated in patients hospitalized for COPD exacerbation to predict the risk of death and readmission within one year after discharge. Our study aimed to validate the CODEX index in a large external population of COPD patients with variable durations of follow-up. Additionally, we aimed to recalculate the thresholds of the CODEX index using the cutoffs of variables previously suggested in the 3CIA study (mCODEX). Individual data on 2,755 patients included in the COPD Cohorts Collaborative International Assessment Plus (3CIA+) were explored. A further two cohorts (ESMI AND EGARPOC-2) were added. To validate the CODEX index, the relationship between mortality and the CODEX index was assessed using cumulative/dynamic ROC curves at different follow-up periods, ranging from 3 months up to 10 years. Calibration was performed using univariate and multivariate Cox proportional hazard models and Hosmer-Lemeshow test. A total of 3,321 (87.8% males) patients were included with a mean +/- SD age of 66.9 +/- 10.5 years, and a median follow-up of 1,064 days (IQR 25-75% 426-1643), totaling 11,190 person-years. The CODEX index was statistically associated with mortality in the short- (</=3 months), medium- (</=1 year) and long-term (10 years), with an area

under the curve of 0.72, 0.70 and 0.76, respectively. The mCODEX index performed better in the medium-term (<1 year) than the original CODEX, and similarly in the long-term. In conclusion, CODEX and mCODEX index are good predictors of mortality in patients with COPD, regardless of disease severity or duration of follow-up.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1484440

Alsumrain, M., F. De Giacomi, et al. (2019). **"Combined pulmonary fibrosis and emphysema as a clinicoradiologic entity: Characterization of presenting lung fibrosis and implications for survival."** Respir Med **146**: 106-112.

BACKGROUND: The prevalence of classifiable and unclassifiable causes of lung fibrosis and its implications for survival are mostly unknown in combined pulmonary fibrosis and emphysema (CPFE). MATERIALS AND METHODS: Patients with >10% involvement of both emphysema and lung fibrosis seen over 11yearsat our institution were reviewed independently by expert radiologists for fibrotic and emphysematous findings and overall fibrotic CT pattern. Underlying interstitial lung disease (ILD) diagnoses and baseline demographic and clinical characteristics were collated and assessed for predictors of comparative survival. RESULTS: In this retrospective cohort, 179 CPFE patients were identified and categorized as 58 usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF) (32%), 42 secondary ILD (23%), and 79 unclassifiable ILD (44%). The most prevalent (47%) radiologic pattern was 'unclassifiable', followed by 'consistent' and 'possible' UIP pattern in 38%. Adjusted predictors of mortality for the cohort as a whole included age (HR 1.03[1.01-1.06], P=0.002), percent predicted diffusing capacity for carbon monoxide (unit HR 0.97 [0.96-0.99], P=0.001), honeycombing (HR 1.58 [1.02-2.43], P=0.04), and right ventricular dysfunction (HR 2.28 [1.39-3.97], P=0.002). Survival was similar between CPFE with secondary ILD and CPFE with UIP/IPF, while CPFE with unclassifiable ILD had better comparative survival (Log rank=0.026). CONCLUSIONS: Our findings suggest only about a third of CPFE patients represent suspected UIP/IPF; the majority were clinically and radiologically unclassifiable ILD whose survival was comparatively better. Identifiable or secondary causes of lung fibrosis in CPFE occurred in about a fifth of presenting patients.

https://www.resmedjournal.com/article/S0954-6111(18)30387-1/pdf

Alter, P., H. Watz, et al. (2019). **"Effects of airway obstruction and hyperinflation on electrocardiographic axes in COPD."** Respir Res **20**(1): 61.

BACKGROUND: COPD influences cardiac function and morphology. Changes of the electrical heart axes have been largely attributed to a supposed increased right heart load in the past, whereas a potential involvement of the left heart has not been sufficiently addressed. It is not known to which extent these alterations are due to changes in lung function parameters. We therefore quantified the relationship between airway obstruction, lung hyperinflation, several echo- and electrocardiographic parameters on the orientation of the electrocardiographic (ECG) P, QRS and T wave axis in COPD. METHODS: Data from the COPD cohort COSYCONET were analyzed, using forced expiratory volume in 1 s (FEV1), functional residual capacity (FRC), left ventricular (LV) mass, and ECG data. RESULTS: One thousand, one hundred and ninety-five patients fulfilled the inclusion criteria (mean +/- SD age: 63.9 +/- 8.4 years; GOLD 0-4: 175/107/468/363/82). Left ventricular (LV) mass decreased from GOLD grades 1-4 (p = 0.002), whereas no differences in right ventricular wall thickness were observed. All three ECG axes were significantly associated with FEV1 and FRC. The QRS axes according to GOLD grades 0-4 were (mean +/- SD): 26.2 degrees +/- 37.5 degrees , 27.0 degrees +/- 37.7 degrees , 31.7 degrees +/- 42.5 degrees , 46.6 degrees +/- 42.2 degrees , 47.4 degrees +/- 49.4 degrees . Effects of lung function resulted in a clockwise rotation of the axes by 25 degrees -30 degrees in COPD with severe airway disease. There were additional associations with BMI, diastolic blood pressure, RR interval, QT duration and LV mass. CONCLUSION: Significant clockwise rotations of the electrical axes as a function of airway obstruction and lung hyperinflation were shown. The changes are likely to result from both a change of the anatomical orientation of the heart within the thoracic cavity and a reduced LV mass in COPD. The influences on the electrical axes reach an extent that could bias the ECG interpretation. The magnitude

of lung function impairment should be taken into account to uncover other cardiac disease and to prevent misdiagnosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6437876/pdf/12931_2019_Article_1025.pdf

Amariei, D. E. and R. M. Reed (2019). **"The role of statins in chronic obstructive pulmonary disease: is cardiovascular disease the common denominator?"** Curr Opin Pulm Med **25**(2): 173-178.

PURPOSE OF REVIEW: The pleiotropic anti-inflammatory effects of statins that have proven to improve outcomes in cardiovascular disease have also been of interest in the treatment of COPD, a disease with considerable morbidity and little available treatment that improves mortality. In-vitro and animal studies have supported biologic plausibility of statin therapy for lung health and function. Retrospective observational studies in humans have echoed this potential as well but confirmatory data from randomized studies are limited and somewhat disappointing. RECENT FINDINGS: Despite discouraging clinical trial results, the possibility remains that statins can help patients with COPD characterized by systemic inflammation. At the same time, increasing recognition of the considerable cardiovascular disease burden and its suboptimal treatment in patients with COPD has also contributed to continued enthusiasm for statin use in COPD. SUMMARY: When it comes to defining the role for statins as a disease-modifying therapy, the jury is still out; however, the importance of more careful cardiovascular risk stratification that includes assessing levels of inflammatory markers in patients with COPD and the benefit of statins in those with increased risk is gaining increasing recognition.

Andersson, C., P. W. Hansen, et al. (2019). **"Mortality associated with cardiovascular drugs in patients with chronic obstructive pulmonary disease and right-sided heart failure - A danish nationwide registry-based study."** Eur J Intern MedBACKGROUND: The optimal medical treatment in patients with chronic obstructive pulmonary disease (COPD) and right-sided heart failure (RHF) is unknown. We aimed to estimate the risks of all-cause mortality associated with the current clinical use of various cardiovascular drugs in this patient-group. METHODS: We followed all patients with registered COPD and RHF (defined as a diagnosis of pulmonary hypertension plus use of loop-diuretics) for the risk of all-cause mortality (Jan 1, 1995 to Dec 31, 2015) using the Danish nationwide administrative registries. The association between mortality and claimed prescriptions for cardiovascular drugs was assessed by multivariable Cox regression models. RESULTS: 5991 patients (mean age 74+/-standard deviation 10years, 51% women) were included. Of these, 1440 (24%) used beta-blockers, 2149 (36%) renin-angiotensin system inhibitors [RASi], 1340 (22%) oral anticoagulants, 1376 (23%) calcium channel blockers, 1194 (20%) statins, 1824 (30%) spironolactone, and 2099 (35%) low-dose aspirin. During an average follow-up of 2.2years (+/-standard deviation 2.8, min-max 0-19.6years), 5071 (85%) died, corresponding to a mortality rate of 38 per 100 person-years (95% confidence interval 37-39). Compared to no use, beta-blockers were associated with adjusted hazards ratio 0.90 (95% confidence interval 0.84-0.98), RASi 0.92 (0.86-0.98), calcium channel blockers 0.86 (0.80-0.92), spironolactone 1.17 (1.10-1.24), statins 0.85 (0.78-0.92), oral anticoagulants 0.87 (0.79-0.95), and aspirin 0.99 (0.93-1.05). Propensity-score matched analyses and inverse-probability-weighted models yielded similar results. CONCLUSION: Several cardiovascular drugs may be associated with lowered mortality in COPD and RHF. Given the grave prognosis, randomized clinical trials are warranted to test this hypothesis.

https://www.ejinme.com/article/S0953-6205(19)30058-5/fulltext

Aramburu, A., I. Arostegui, et al. (2019). **"COPD classification models and mortality prediction capacity."** Int J Chron Obstruct Pulmon Dis **14**: 605-613.

Objective: Our aim was to assess the impact of comorbidities on existing COPD prognosis scores. Patients and methods: A total of 543 patients with COPD (FEV1 <80% and FEV1/FVC <70%) were included between January 2003 and January 2004. Patients were stable for at least 6 weeks before inclusion and were followed for 5 years without any intervention by the research team. Comorbidities and causes of death were established from medical reports or information from primary care medical records. The GOLD system and the body mass index, obstruction, dyspnea and exercise (BODE) index were used for COPD classification. Patients were also classified into four clusters depending on the respiratory disease and comorbidities. Cluster analysis was performed by combining multiple correspondence analyses and automatic classification. Receiver operating characteristic curves and the area under the curve (AUC) were calculated for each model, and the DeLong test was used to evaluate differences between AUCs. Improvement in prediction ability was analyzed by the DeLong test, category-free net reclassification improvement and the integrated discrimination index. Results: Among the 543 patients enrolled, 521 (96%) were male, with a mean age of 68 years, mean body mass index 28.3 and mean FEV1% 55%. A total of 167 patients died during the study follow-up. Comorbidities were prevalent in our cohort, with a mean Charlson index of 2.4. The most prevalent comorbidities were hypertension, diabetes mellitus and cardiovascular diseases. On comparing the BODE index, GOLDABCD, GOLD2017 and cluster analysis for predicting mortality, cluster system was found to be superior compared with GOLD2017 (0.654 vs 0.722, P=0.006), without significant differences between other classification models. When cardiovascular comorbidities and chronic renal failure were added to the existing scores, their prognostic capacity was statistically superior (P<0.001). Conclusion: Comorbidities should be taken into account in COPD management scores due to their prevalence and impact on mortality.

https://www.dovepress.com/getfile.php?fileID=48451

Avdeev, S. N., N. V. Truschenko, et al. (2018). **"Treatment of exacerbations of chronic obstructive pulmonary disease."** Ter Arkh **90**(12): 68-75.

AIM: To assess the quality of medical care provided in large Russian hospitals to patients with COPD exacerbation. MATERIALS AND METHODS: The study included patients with acute exacerbations of COPD hospitalized into three large clinical hospitals in Moscow. The diagnosis of "COPD exacerbation" was established in accordance with current clinical recommendations. We collected the data about patients' demography, clinical signs and symptoms, blood gas analysis, chest radiography, drug therapy, oxygen therapy and respiratory support. The follow-up period was 90 days. The obtained data were compared with the data of patients from the multicenter study "European COPD Audit". RESULTS: The leading clinical symptoms in COPD exacerbation were dyspnea (95.4%) and sputum production (60.7%). The majority of patients with COPD received short-acting beta2-agonists (77.4%), systemic steroids (85.1%), antibiotics (79.0%) and theophyllines (48.1%). Noninvasive ventilation was performed in 8.6% of patients, oxygen therapy - in 23,8% of patients, pulmonary rehabilitation - in only 6,2% of patients. Chest radiography was performed in 97.9% of patients, pulmonary function tests - in 79.8%, blood gases analysis - in 19.3% of patients. The mean duration of hospitalization was 18.2+/-3.9 days, repeated hospitalization within 90 days occurs in 36.2% of patients. In-hospital mortality was 3.3%. CONCLUSION: Based on the results of the study practical recommendations for improving the quality of medical care in acute exacerbations of COPD are proposed.

Bade, B. C., E. C. DeRycke, et al. (2019). **"Sex Differences in Veterans Admitted to the Hospital for COPD Exacerbation."** Ann Am Thorac SocRATIONALE: As chronic obstructive pulmonary disease (COPD) prevalence in women has outpaced that in men, COPD-related hospitalization and mortality are now higher in women. Presentation, evaluation, and treatment of COPD differ between women and men. Despite higher smoking rates in Veterans, little work has characterized differences in Veterans with COPD by sex. OBJECTIVES: We determined risk factors for 30-day readmission amongst Veterans hospitalized for COPD exacerbations and how they differed by sex. METHODS: We performed a

retrospective observational analysis of Veterans receiving primary care in Veterans Health Affairs (VHA) facilities. We included VA-based hospitalizations for Veterans with a COPD exacerbation (identified by International Classification of Disease, 9th revision (ICD-9) codes) who survived to discharge between fiscal years 2012-2015. Primary outcome was 30-day readmission. Predictors ascertained prior to hospitalization included smoking status (current, former, never), pulmonary function testing (PFT), pulmonary medication prescriptions, and medical and psychiatric comorbidities (identified by ICD-9 codes). We created combined and sex-stratified multi-variate logistic regression models to identify associations with 30-day readmission. RESULTS: Our sample included 48,888 Veterans (4% women). Compared to men, women Veterans were younger, more likely to be non-white, and differed in smoking status. Women were more likely to have asthma, drug use, and several psychiatric comorbidities. Before hospitalization, women were less likely to have PFTs (76% vs. 78%, p=0.01) or be treated with anti-muscarinic (43% vs. 48%) or combined long-acting bronchodilator/inhaled corticosteroid (61% vs. 64%) inhalers. Women were more likely to receive nicotine replacement therapy (all p<0.01). Women had shorter length of stay (median days: 2 vs. 3; p=0.04) and lower 30-day readmission rate (20 vs. 22%; p=0.01). In adjusted models including both sexes, age, anti-muscarinic use, comorbidities, and diagnosis of drug or alcohol use were associated with readmission; there was no association with sex and readmission risk. In models stratified by sex, associations were similar between women and men. CONCLUSION: This study suggests differences between women and men hospitalized for COPD regarding presentation, evaluation, and management. Readmission is strongly influenced by comorbidities, suggesting individualized and comprehensive case management may reduce readmission risk for women and men with COPD.

Bak, S. H., H. Y. Park, et al. (2019). **"Predicting clinical outcome with phenotypic clusters using quantitative CT fibrosis and emphysema features in patients with idiopathic pulmonary fibrosis."** PLoS One **14**(4): e0215303.

BACKGROUND: The clinical course of IPF varies. This study sought to identify phenotyping with quantitative computed tomography (CT) fibrosis and emphysema features using a cluster analysis and to assess prognostic impact among identified clusters in patient with idiopathic pulmonary fibrosis (IPF). Furthermore, we evaluated the impact of fibrosis and emphysema on lung function with development of a descriptive formula. METHODS: This retrospective study included 205 patients with IPF. A texture-based automated system was used to quantify areas of normal, emphysema, ground-glass opacity, reticulation, consolidation, and honeycombing. Emphysema index was obtained by calculating the percentage of low attenuation area lower than -950HU. We used quantitative CT features and clinical features for clusters and assessed the association with prognosis. A formula was derived using fibrotic score and emphysema index on quantitative CT. RESULTS: Three clusters were identified in IPF patients using a quantitative CT score and clinical values. Prognosis was better in cluster1, with a low extent of fibrosis and emphysema with high forced vital capacity (FVC) than cluster2 and cluster3 with higher fibrotic score and emphysema (p = 0.046, and p = 0.026). In the developed formula [1.5670-fibrotic score(%)*0.04737-emphysema index*0.00304], a score greater >/= 0 indicates coexisting of pulmonary fibrosis and emphysema at a significant extent despite of normal spirometric result. CONCLUSIONS: Cluster analysis identified distinct phenotypes, which predicted prognosis of clinical outcome. Formula using quantitative CT values is useful to assess extent of pulmonary fibrosis and emphysema with normal lung function in patients with IPF.

https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0215303&type=printable

Beghe, B., L. M. Fabbri, et al. (2019). **"Three-Year Hospitalization and Mortality in Elderly Smokers with Chronic Obstructive Pulmonary Disease or Chronic Heart Failure."** Respiration **97**(3): 223-233.

BACKGROUND: In elderly smokers, chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) usually present with dyspnoea. COPD and CHF are associated -almost invariably with concomitant

chronic diseases, which contribute to severity and prognosis. OBJECTIVES: We investigated similarities and differences in the clinical presentation, concomitant chronic diseases and risk factors for -mortality and hospitalization at 3-year follow-up in elderly smokers/ex-smokers with a primary diagnosis of COPD or CHF recruited and followed in specialized centers. METHODS: We examined 144 patients with COPD and 96 with CHF, >/=65 years, >/=20 pack/years, and measured COPD Assessment Test (CAT) score, modified Medical Research Council, NYHA, and Charlson Index, routine blood test, estimated glomerular filtration rate, HRCT scan, 6-min walk test. In addition, in each patient we actively searched for CHF, COPD, peripheral vascular disease, and metabolic syndrome. RESULTS: COPD and CHF patients had mild to moderate disease, but the majority was symptomatic. Comorbidities were highly prevalent and often unrecognized in both groups. COPD and CHF patients had a similar risk of hospitalization and death at 3 years. Lower glomerular filtration rate, shorter 6MWT, and ascending aorta calcification score >/=2 were independent predictors of mortality in COPD, whereas previous 12 months hospitalizations, renal disease, and heart diameter were in CHF patients. Lower glomerular filtration rate value, higher CAT score, and lower FEV1/FVC ratio were associated with hospitalization in COPD, while age, lower FEV1% predicted, and peripheral vascular disease were in CHF. CONCLUSIONS: There are relevant similarities and differences between patients with COPD and CHF even when admitted to specialized outpatient centers, suggesting that these patients should be manage in multidisciplinary units.

https://www.karger.com/Article/Abstract/492286

Ben Anes, A., H. Ben Nasr, et al. (2019). **"The Cu/Zn superoxide dismutase +35A/C (rs2234694) variant correlates with altered levels of protein carbonyls and glutathione and associates with severity of COPD in a Tunisian population."** Free Radic Res: 1-11.

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality that has been associated with inflammation and oxidative stress. The purpose of the present case-control study was to determine the relationships between oxidative stress-related genetic variants and the risk and severity of COPD, as well as, the influence of these variants on inflammatory and oxidative stress parameters. Genotyping of superoxide dismutase 1 (SOD1) + 35 A/C (rs2234694), catalase [A-21T (rs7943316), C-262T (rs1001179)] and glutathione peroxidase 1 (reduced glutathione (GSH)-Px1) 198Pro/Leu (rs1050450) was carried out in 143 patients with COPD and 216 healthy controls using PCR-RFLP. Serum levels of IL-6 and TNF-alpha were determined by enzyme-linked immunosorbent assays (ELISA), while the levels of reduced GSH, total antioxidant status (TAS), H2O2, lipid peroxides (TBARS) and protein carbonyls (PCs) were determined using spectrophotometric methods. We also evaluated the activities of GSH-Px, catalase, and superoxide dismutase (SOD) in both plasma and erythrocytes. We did not observe significant differences in the genotype and allele frequencies of chosen variants between COPD patients and healthy controls. A significant correlation was retrieved between the SOD1 + 35A/C variant and disease severity (odds ratios (OR) = 0.15, p = 0.04). In addition, patients having the +35AC genotype presented increased plasma levels of GSH and a reduced level of PCs (p = 0.03, p = 0.04, respectively). The present data highlighted the important role of antioxidant enzymes and their genetic variants in the oxidative stress-mediated pathogenesis and progression of COPD.

https://www.tandfonline.com/doi/full/10.1080/10715762.2019.1572888

Bermingham, M. L., R. M. Walker, et al. (2019). **"Identification of novel differentially methylated sites with potential as clinical predictors of impaired respiratory function and COPD."** EBioMedicineBACKGROUND: The causes of poor respiratory function and COPD are incompletely understood, but it is clear that genes and the environment play a role. As DNA methylation is under both genetic and environmental control, we hypothesised that investigation of differential methylation associated with these phenotypes would permit mechanistic insights, and improve prediction of COPD. We investigated genome-wide differential DNA methylation patterns using the recently released 850K Illumina EPIC array. This is the largest single population, whole-genome epigenetic study to date. METHODS: Epigenome-wide association studies (EWASs) of respiratory function and COPD were

performed in peripheral blood samples from the Generation Scotland: Scottish Family Health Study (GS:SFHS) cohort (n=3781; 274 COPD cases and 2919 controls). In independent COPD incidence data (n=149), significantly differentially methylated sites (DMSs; p<3.6x10(-8)) were evaluated for their added predictive power when added to a model including clinical variables, age, sex, height and smoking history using receiver operating characteristic analysis. The Lothian Birth Cohort 1936 (LBC1936) was used to replicate association (n=895) and prediction (n=178) results. FINDINGS: We identified 28 respiratory function and/or COPD associated DMSs, which mapped to genes involved in alternative splicing, JAK-STAT signalling, and axon guidance. In prediction analyses, we observed significant improvement in discrimination between COPD cases and controls (p<.05) in independent GS:SFHS (p=.016) and LBC1936 (p=.010) datasets by adding DMSs to a clinical model. INTERPRETATION: Identification of novel DMSs has provided insight into the molecular mechanisms regulating respiratory function and aided prediction of COPD risk. Further studies are needed to assess the causality and clinical utility of identified associations. FUND: Wellcome Trust Strategic Award 10436/Z/14/Z.

https://www.ebiomedicine.com/article/S2352-3964(19)30217-8/pdf

Bernocchi, P., S. Scalvini, et al. (2016). **"A multidisciplinary telehealth program in patients with combined chronic obstructive pulmonary disease and chronic heart failure: study protocol for a randomized controlled trial."** Trials **17**(1): 462.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) frequently coexist, significantly reducing patients' quality of life and increasing morbidity and mortality. For either single disease, a multidisciplinary disease-management approach supported by telecommunication technologies offers the best outcome in terms of prolonged survival and reduced hospital readmissions. However, no data exist in patients with combined COPD/CHF. We planned a randomized controlled trial to investigate the feasibility and efficacy of an integrated, home-based, medical/nursing intervention plus a rehabilitation program versus conventional care in patients with coexisting COPD/CHF. The purpose of the paper is to describe the rationale and design of the trial. METHODS/DESIGNS: Patients, after inpatient rehabilitation, were randomly assigned to the intervention or control group, followed for 4 months at home, then assessed at 4 and 6 months. The intervention group followed a telesurveillance (telephone contacts by nurse and remote monitoring of cardiorespiratory parameters) and home-based rehabilitation program (at least three sessions/week of mini-ergometer exercises, callisthenic exercises and twice weekly pedometer-driven walking, plus telephone contacts by a physiotherapist). Telephone follow-up served to verify compliance to therapy, maintain exercise motivation, educate for early recognition of signs/symptoms, and verify the skills acquired. At baseline and 4 and 6 months, the 6-min Walk Test, dyspnea and fatigue at rest, oxygenation (PaO2/FiO2), physical activity profile (PASE questionnaire), and QoL (Minnesota and CAT questionnaires) were assessed. During the study, serious clinical events (hospitalizations or deaths) were recorded. DISCUSSION: Currently, no studies have assessed the impact of a telehealth program in patients with combined COPD and CHF. Our study will show whether this approach is effective in the management of such complex, frail patients who are at very high risk of exacerbations. TRIAL REGISTRATION: Network per la prevenzione e la sanita pubblica, CCM, Ministero della Salute "Modelli innovativi di gestione integrata telegestita ospedale-territorio del malato cronico a fenotipo complesso: studio di implementazione, validazione e impatto," registered on 14 January 2014. ClinicalTrials.gov Identifier: NCT02269618 , registered on 17 October 2014.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5034626/pdf/13063_2016_Article_1584.pdf

Bhatt, S. P., G. R. Washko, et al. (2019). **"Imaging Advances in Chronic Obstructive Pulmonary Disease. Insights from the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) Study."** Am J Respir Crit Care Med **199**(3): 286-301.

The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study, which began in 2007, is an ongoing multicenter observational cohort study of more than 10,000 current and former smokers. The study is aimed at understanding the etiology, progression, and heterogeneity of chronic obstructive

pulmonary disease (COPD). In addition to genetic analysis, the participants have been extensively characterized by clinical questionnaires, spirometry, volumetric inspiratory and expiratory computed tomography, and longitudinal follow-up, including follow-up computed tomography at 5 years after enrollment. The purpose of this state-of-the-art review is to summarize the major advances in our understanding of COPD resulting from the imaging findings in the COPDGene study. Imaging features that are associated with adverse clinical outcomes include early interstitial lung abnormalities, visual presence and pattern of emphysema, the ratio of pulmonary artery to ascending aortic diameter, quantitative evaluation of emphysema, airway wall thickness, and expiratory gas trapping. COPD is characterized by the early involvement of the small conducting airways, and the addition of expiratory scans has enabled measurement of small airway disease. Computational advances have enabled indirect measurement of nonemphysematous gas trapping. These metrics have provided insights into the pathogenesis and prognosis of COPD and have aided early identification of disease. Important quantifiable extrapulmonary findings include coronary artery calcification, cardiac morphology, intrathoracic and extrathoracic fat, and osteoporosis. Current active research includes identification of novel quantitative measures for emphysema and airway disease, evaluation of dose reduction techniques, and use of deep learning for phenotyping COPD.

Bodduluri, S., A. S. K. Puliyakote, et al. (2018). **"Airway fractal dimension predicts respiratory morbidity and mortality in COPD."** J Clin Invest **128**(12): 5374-5382.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is characterized by airway remodeling. Characterization of airway changes on computed tomography has been challenging due to the complexity of the recurring branching patterns, and this can be better measured using fractal dimensions. METHODS: We analyzed segmented airway trees of 8,135 participants enrolled in the COPDGene cohort. The fractal complexity of the segmented airway tree was measured by the Airway Fractal Dimension (AFD) using the Minkowski-Bougliand box-counting dimension. We examined associations between AFD and lung function and respiratory morbidity using multivariable regression analyses. We further estimated the extent of peribronchial emphysema (%) within 5 mm of the airway tree, as this is likely to affect AFD. We classified participants into 4 groups based on median AFD, percentage of peribronchial emphysema, and estimated survival. RESULTS: AFD was significantly associated with forced expiratory volume in one second (FEV1; $P < 0.001$) and FEV1/forced vital capacity (FEV1/FVC; $P < 0.001$) after adjusting for age, race, sex, smoking status, pack-years of smoking, BMI, CT emphysema, air trapping, airway thickness, and CT scanner type. On multivariable analysis, AFD was also associated with respiratory quality of life and 6-minute walk distance, as well as exacerbations, lung function decline, and mortality on longitudinal follow-up. We identified a subset of participants with AFD below the median and peribronchial emphysema above the median who had worse survival compared with participants with high AFD and low peribronchial emphysema (adjusted hazards ratio [HR]: 2.72; 95% CI: 2.20-3.35; $P < 0.001$), a substantial number of whom were not identified by traditional spirometry severity grades. CONCLUSION: Airway fractal dimension as a measure of airway branching complexity and remodeling in smokers is associated with respiratory morbidity and lung function change, offers prognostic information additional to traditional CT measures of airway wall thickness, and can be used to estimate mortality risk. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT00608764.
FUNDING: This study was supported by NIH K23 HL133438 (SPB) and the COPDGene study (NIH Grant Numbers R01 HL089897 and R01 HL089856). The COPDGene project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovion and GlaxoSmithKline.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6264725/pdf/jci-128-120693.pdf

Bogart, M., R. H. Stanford, et al. (2019). **"Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population."** Int J Chron Obstruct Pulmon Dis **14**: 343-352.

Introduction: This longitudinal, retrospective cohort study of patients with COPD describes baseline characteristics, adherence, and persistence following initiation of inhaled corticosteroids (ICS)/long-acting beta2-agonists (LABA)/long-acting muscarinic antagonists (LAMA) from multiple inhaler triple therapy (MITT). Methods: Patients aged >/=40 years receiving MITT between January 2012 and September 2015 were identified from the IQVIA Real-world Data Adjudicated Claims-USA database. MITT was defined as subjects with >/=1 overlapping days' supply of three COPD medications (ICS, LABA, and LAMA). Adherence (proportion of days covered, PDC) and discontinuation (defined as a gap of 1, 30, 60, or 90 days of supply in any of the three components of the triple therapy) were calculated for each patient over 12 months of follow-up. In addition, analyses were stratified by number of inhalers. Results: In total, 14,635 MITT users were identified (mean age, 62 years). Mean PDC for MITT at 12 months was 0.37%. Mean PDC for the ICS/LABA and LAMA component at 12 months was 49% (0.49+/-0.31; median, 0.47) and 54% (0.54+/-0.33; 0.56), respectively. The proportion of adherent patients (PDC >/=0.8) at 12 months was 14% for MITT. Allowing for a 30-day gap from last day of therapy, 86% of MITT users discontinued therapy during follow-up. Conclusion: Patients with COPD had low adherence to and persistence with MITT in a real-world setting. Mean PDC for each single inhaler component was higher than the mean PDC observed with MITT. Reducing the number of inhalers may improve overall adherence to intended triple therapy.

https://www.dovepress.com/getfile.php?fileID=48135

Bonnesen, B., G. Baunbaek Egelund, et al. (2019). **"Is chronic obstructive pulmonary disease a risk factor for death in patients with community acquired pneumonia?"** Infect Dis (Lond) **51**(5): 340-347.

BACKGROUND: It is still a matter of debate whether the outcome of community acquired pneumonia is more severe in patients with chronic obstructive pulmonary disease. We aimed to determine whether chronic obstructive pulmonary disease was associated with increased mortality and to identify risk-factors for mortality in patients with community acquired pneumonia and chronic obstructive pulmonary disease. METHODS: Retrospective cohort study comparing patients with community acquired pneumonia and chronic obstructive pulmonary disease to patients without chronic obstructive pulmonary disease. We included 1309 patients with community acquired pneumonia admitted from 2011 until 2012 (243 patients with chronic obstructive pulmonary disease and 1066 without chronic obstructive pulmonary disease). RESULTS: At admission patients with community acquired pneumonia and chronic obstructive pulmonary disease presented with more severe pneumonia as measured by CURB-65 score compared to patients without chronic obstructive pulmonary disease. Mortality on day 30 was generally high, and higher among patients with community acquired pneumonia and chronic obstructive pulmonary disease compared to those without chronic obstructive pulmonary disease (16.0% versus 11.3%, p = .04). In an adjusted analysis, however, chronic obstructive pulmonary disease was not independently associated with 30-d mortality (odds ratio 0.94, confidence interval 95% 0.59-1.50). Factors related to mortality in patients with community acquired pneumonia and chronic obstructive pulmonary disease were age, premorbid condition, severity of pneumonia as determined by CURB-65 score, and pleural effusion and multi-lobular infiltrate on chest X-ray. CONCLUSIONS: Chronic obstructive pulmonary disease was not independently associated with 30-d mortality in patients with community acquired pneumonia.

https://www.tandfonline.com/doi/abs/10.1080/23744235.2019.1565416

Bonnevie, T., M. Allingham, et al. (2019). **"The six-minute stepper test is related to muscle strength but cannot substitute for the one repetition maximum to prescribe strength training in patients with COPD."** Int J Chron Obstruct Pulmon Dis **14**: 767-774.

Purpose: There are many barriers to pulmonary rehabilitation, including a limited access to evaluation centers. To cope with these difficulties, field tests are often used to prescribe endurance training. As field tests are

related to muscle strength, they could also be used to prescribe strength training and increase the access to pulmonary rehabilitation in rural area. However, their validity for this purpose has never been studied. Patients and methods: The relationship between the 6-minute stepper test (6MST), 6-minute walk test, maximal workload achieved during cardiopulmonary exercise testing (Wpeak), and one repetition maximum (1RM) was assessed in 35 patients with COPD through a retrospective chart review to derive predictive equation of the 1RM from these tests. The effectiveness of these equations to prescribe strength training at 70% of the 1RM was assessed in an independent cross-validation group of 34 patients with COPD. Results: There was a moderate relationship between the 6MST, Wpeak and the 1RM (r=0.44 and r=0.41, respectively, both P</=0.01). Whatever the test, the prescription of strength training using the estimated 1RM compared with the measured 1RM resulted in a mean absolute difference and a mean bias of about 30 kg. Conclusion: The use of the 6MST and Wpeak for the prescription of strength training would result in a clinically not acceptable error. Therefore, they should not be used as a substitute for the 1RM to prescribe strength training.

https://www.dovepress.com/getfile.php?fileID=48833

Borne, Y., W. Ashraf, et al. (2019). **"Socioeconomic circumstances and incidence of chronic obstructive pulmonary disease (COPD) in an urban population in Sweden."** Copd: 1-7.

The association between socioeconomic circumstances and incidence of chronic obstructive pulmonary disease (COPD) was investigated in an urban population in Sweden. The study included all 40-89 year-old inhabitants in Malmo, Sweden (N = 117,479) without previous hospitalization due to COPD, who were followed over 14 years for COPD related hospital admissions. The Malmo Preventive Project (MPP) cohort (n = 27,358) with information on biological and lifestyle factors was also used to study the association between socioeconomic circumstances and COPD. The Swedish hospital discharge register was used to record incidence of COPD hospitalizations. A total of 2,877 individuals (47.5% men) were discharged from hospital with COPD as the primary diagnosis during follow-up in Malmo. Low annual income (hazard ratio (HR): 2.23; 95%CI: 1.97-2.53, P < 0.001) and rented (vs. self-owned) housing (HR: 1.41; 1.30-1.52, P < 0.001) were associated with a higher risk for COPD. In addition, compared to married subjects, divorced (HR: 1.61; 1.46-1.78, P < 0.001) and widowed (HR: 1.30; 1.16-1.46, P < 0.001) individuals had an increased risk for hospitalization due to COPD. Low income, low occupation and being divorced or widowed were similarly associated with COPD in the MPP cohort, after adjustments for smoking, FEV1, BMI, age and sex. However, socioeconomic circumstances were not associated with COPD in analyses restricted to never smokers. Low socioeconomic circumstances were associated with an increased risk of COPD after adjustments for biological and lifestyle risk factors including smoking status. However, this relationship was not significant in those who never smoked.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2019.1582618?needAccess=true

Borras-Santos, A., J. Garcia-Aymerich, et al. (2018). **"Determinants of the Appearance and Progression of Early-Onset Chronic Obstructive Pulmonary Disease in Young Adults. A Case-Control Study with Follow-up."** Arch BronconeumolINTRODUCTION AND OBJECTIVES: Determinants of chronic obstructive pulmonary disease (COPD) in the early stages of its natural history are not well known. Improving our knowledge of these factors will help to design interventions that can modify prognosis. Study objectives are: a) to characterize a COPD population of young adults aged 35-50 years from a multidimensional point of view; b) to compare these patients with smokers with normal lung function; and c) to create a cohort of young adults aged 35-50 years (smokers or former smokers), with and without COPD, who will be followed in the future to improve understanding of the natural history of the disease. PARTICIPANTS AND METHOD: This is a case-control multicenter study aimed at establishing a well-characterized cohort of young adults, smokers or former-smokers, with and without COPD, for subsequent follow-up. A total of 311 participants (101 cases and 210 controls) were selected from approximately 30 primary care settings and 12 hospitals in 8 Spanish regions. Subjects were smokers or former smokers (>10 pack-years) aged 35-50 years. Diagnosis of COPD was based on a post-bronchodilator result of

FEV1/FVC<70%. The main study variables were: questionnaires on health, symptoms, exacerbations and daily physical activity, lung function tests, blood and sputum samples, and low-dose computed tomography. In the statistical analysis, COPD patient characteristics will be described and compared with control subjects using a logistic regression analysis.

Boulet, L. P., M. E. Boulay, et al. (2019). **"Longitudinal comparison of outcomes in patients with smoking-related asthma-COPD overlap and in non-smoking asthmatics with incomplete reversibility of airway obstruction."** Int J Chron Obstruct Pulmon Dis **14**: 493-498.

Background: There is a need to characterize the impact of the smoking status on the clinical course of asthmatics with incomplete reversibility of airway obstruction (IRAO). Objective: To compare longitudinal health care use, symptom control, and medication needs between smoking and non-smoking asthmatics with IRAO. Materials and methods: This was a 12-month follow-up of a cross-sectional study comparing asthmatics with IRAO according to their tobacco exposure. One group had a tobacco exposure >/=20 pack-years and was considered to have asthma-COPD overlap (ACO) and the second with a past tobacco exposure <5 pack-years was considered as non-smokers with IRAO (NS-IRAO). Study participants were contacted by telephone every 3 months to document exacerbation events and symptom control. Results: A total of 111 patients completed all follow-up telephone calls: 71 ACO and 40 NS-IRAO. The number of exacerbations per patient over the 12-month follow-up was similar in both groups. However, ACO reported worse symptom control throughout the follow-up as compared to NS-IRAO, although no significant variations within a group were observed over the study period. Conclusion: Although asthma control scores were poorer in ACO patients over 1 year compared to NS-IRAO, exacerbation rate was similar and low in both groups of asthmatics. These observations suggest that poorer asthma control in ACO was not driven by the number of exacerbations but may reflect the influence of chronic airway changes related to the COPD component.

https://www.dovepress.com/getfile.php?fileID=48305

Bozek, A., J. Jarzab, et al. (2018). **"Fall episodes in elderly patients with asthma and COPD - A pilot study."** J Asthma: 1-5.

OBJECTIVE: Evidence of an increased risk of falls in patients with chronic obstructive pulmonary disease (COPD) exists; however, this has not been studied in elderly asthmatic patients. The aim of the study was to determine the incidence of falls in elderly patients who were diagnosed with bronchial asthma compared to subjects with COPD. METHODS: A 12-month prospective observational study in elderly outpatients with diagnosis of either asthma or COPD was conducted. All of the participants were monitored on the following parameters: falls, comorbidities, drug therapy, and The Berg Balance Scale. The rate of falls was shown as an incidence ratio. Cluster analysis for subgroups with similar features was performed on all patients included in the study. Two clusters of frequent fallers were determined. RESULTS: The fall incidence rate in falls per person per year was 1.41 (95% CI: 0.86-1.96) in asthmatic patients and 1.49 (95% CI: 1.05-2.11) in the COPD group. Frequent fallers were more prevalent in the COPD group, with 32% in this group compared to 28% in the groups of patients with asthma. In cluster analysis, frequent fallers were grouped into two models characterized by polytherapy, depression symptoms, hospitalizations, coronary disease, dementia, and diagnosis of COPD or asthma. CONCLUSION: Elderly asthmatic patients presented a high rate of falls, which is comparable to that of patients with COPD.

https://www.tandfonline.com/doi/full/10.1080/02770903.2018.1474365

Bremmer, D. N., M. A. Moffa, et al. (2019). **"Acute Exacerbations of Chronic Obstructive Pulmonary Disease With a Low Procalcitonin Concentration: Impact of Antibiotic Therapy."** Clin Infect Dis **68**(5): 725-730.

BACKGROUND: Patients admitted with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) often are prescribed antibiotics. Studies have shown that the use of procalcitonin (PCT) to guide the decision to initiate antibiotic therapy in AECOPD has resulted in less antibiotic use and similar outcomes compared with standard of care. We evaluated patients with AECOPD and low PCT concentrations to determine whether antibiotic therapy was associated with improved outcomes. METHODS: We retrospectively evaluated adult patients admitted with AECOPD who had a peak PCT concentration <0.25 microg/mL. Patients were evaluated based on their antibiotic exposure: </=24 hours vs >24 hours. We also evaluated outcomes based upon the duration of azithromycin therapy: </=24 hours vs >24 hours. The primary outcome was all-cause 30-day readmissions. Secondary outcomes included length of stay (LOS) and COPD-related 30-day readmissions. RESULTS: One hundred sixty-one and 195 patients received </=24 hours vs >24 hours of antibiotic therapy, respectively. The cohort with </=24 hours of antibiotics had a shorter LOS (2.8 vs 3.7 days; P = .01). There were no differences in all-cause 30-day readmissions (15.5% vs 17.4%; P = .63) or COPD-related 30-day readmissions (11.2% vs 12.3%; P = .74). Additionally, patients receiving </=24 hours of azithromycin had a shorter LOS (3.0 vs 3.8 days; P = .002) and there were no differences in all-cause 30-day readmissions (16.2% vs 17.1%; P = .82) or COPD-related 30-day readmissions (11.9% vs 11.6%; P = .94). CONCLUSIONS: For adult patients hospitalized with nonsevere AECOPD and low PCT concentrations, antibiotic therapy beyond 24 hours did not improve outcomes.

https://academic.oup.com/cid/article-abstract/68/5/725/5047438?redirectedFrom=fulltext

Breyer-Kohansal, R., S. Hartl, et al. (2019). **"The European COPD audit : Adherence to guidelines, readmission risk and hospital care for acute exacerbations in Austria."** Wien Klin Wochenschr **131**(5-6): 97-103.

OBJECTIVE: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are the major reason for COPD hospitalization and increased risk for readmissions. The organizational structure of Austrian hospitals provides the opportunity to investigate the impact of specialized respiratory care compared to general care on adherence to guidelines and readmission in AECOPD. METHODS: The data from the European COPD audit, a prospective observational non-interventional cohort trial were analyzed. In total, 823 patients admitted due to AECOPD in 26 hospitals (specialized respiratory care vs. general care) within Austria were included. Patients characteristics and outcomes (length of stay, readmission rate, and mortality) were analyzed in relation to hospital resources (personnel and equipment) and adherence to international guidelines. RESULTS: Patients admitted to general care had more comorbidities (Charlson comorbidity index: 2.6+/- 1.7 vs. 2.0+/- 1.4; p< 0.05) and a shorter length of stay (10.7+/- 7.8 days vs. 12.0+/- 10.2 days; p< 0.05). Patients admitted to specialized respiratory care more often underwent blood gas analysis and non-invasive ventilation (98.4% vs. 81.5% and 68.6% vs. 26.7%, p< 0.01; respectively). In multivariate analysis, the risk for AECOPD readmission was lower (odds ratio, OR 0.72 [0.51;0.91]; p< 0.05) in patients admitted to specialized respiratory care. CONCLUSION: A greater adherence to COPD guidelines with respect to blood gas analysis and non-invasive ventilation and decreased AECOPD readmission risk was observed for patients admitted to specialized respiratory care. Adherence to guidelines may have the potential to decrease COPD readmission rates.

https://link.springer.com/article/10.1007%2Fs00508-019-1441-5

Budde, J., P. Agarwal, et al. (2019). **"Follow-up Soon After Discharge May Not Reduce COPD Readmissions."** Chronic Obstr Pulm Dis **6**(2)We evaluated whether visiting a primary care provider (PCP) or medical subspecialist within 10 days of discharge reduces 30-day readmissions following hospitalization for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Data were retrospectively collected from electronic health records for AECOPD-related hospitalizations at an urban, academic medical center for patients 40 years of age or older between June 2011 and June 2016. Primary outcome

was probability of all-cause 30-day readmission. Follow-up was defined as visiting a PCP or any medical subspecialist within 10 days of discharge. Generalized linear mixed models were used to examine the association between hospital readmissions and a visit to a PCP or medical subspecialist. Of the 2653 hospital discharges, 17.6% (n=468) had a 30-day readmission. Follow-up did not affect 30-day readmission risk (adjusted odds ratio 1.14; 95% confidence interval 0.89, 1.47). Prompt follow-up is not associated with a reduced risk of 30-day readmission following AECOPD, highlighting the need for a comprehensive approach to chronic obstructive pulmonary disease (COPD).

https://journal.copdfoundation.org/Portals/0/JCOPDF/Files/Volume6-Issue2/JCOPDF-2018-0149-Budde.pdf

Bui, K. L., S. Mathur, et al. (2019). **"Fixed Handheld Dynamometry Provides Reliable and Valid Values for Quadriceps Isometric Strength in People With Chronic Obstructive Pulmonary Disease: A Multicenter Study."** Phys TherBACKGROUND: Quadriceps weakness is associated with poor clinical outcomes in chronic obstructive pulmonary disease (COPD). However, quadriceps isometric strength assessment has not been routinely adopted in clinical practice because of the lack of homogeneity in the devices and protocols and the lack of reliability studies. OBJECTIVE: The objectives of this study were to determine the test-retest reliability and the criterion validity of a commercially available handheld dynamometer for evaluating the quadriceps isometric maximal voluntary contraction (iMVCquad) using a standardized protocol and to investigate the relationship between iMVCquad and functional capacity in people with COPD. DESIGN: This was a prospective, observational, multicenter trial. METHODS: Participants with mild to severe COPD from 4 Canadian sites were tested on 2 separate days. Five iMVCquad measurements were obtained following a standardized procedure with a fixed handheld dynamometer (iMVCquad-HHD), and then 5 iMVCquad measurements were obtained with a computerized dynamometer (iMVCquad-CD; the gold standard). Functional capacity was assessed with the Short Physical Performance Battery (SPPB). ICCs, standard errors of measurement, Bland-Altman plots, and Spearman correlation coefficients were used for analyses. RESULTS: Sixty-five participants (mean age = 69 years [SD = 8]; forced expiratory volume in 1 second = 48% of predicted value [SD = 21]) completed the study. The mean iMVCquad-HHD values on visits 1 and 2 were 102.7 (SD = 51.6) and 105.6 (SD = 58.8) N.m, respectively; the standard error of measurement was 11.4 N.m. The between-visits ICC for iMVCquad-HHD was 0.95 (95% CI = 0.92-0.97), with a mean bias of 2.0 (Bland-Altman plot). There was a strong correlation between iMVCquad-HHD and iMVCquad-CD (Spearman correlation coefficient = 0.86). There was no correlation between iMVCquad-HHD and SPPB total score. LIMITATIONS: Participants included had stable COPD with few comorbidities and were more physically active than the general population of people with COPD; results might not be applied to patients with acute exacerbations of the disease or more comorbidities. Assessments' order between handheld and computerized dynamometers has not been randomized but analyses did not highlight any systematic bias nor learning effect. CONCLUSIONS: Quadriceps strength assessment can be implemented in a reliable and valid way in people with COPD using a fixed handheld dynamometer and standardized procedure. This protocol should be established in clinical practice to facilitate the assessment of muscle strength in people with COPD.

https://academic.oup.com/ptj/advance-article-abstract/doi/10.1093/ptj/pzz059/5426226?redirectedFrom=fulltext

Burkes, R. M. and M. B. Drummond (2019). **"Initiating drug therapy in early stage chronic obstructive pulmonary disease: does it impact the course and outcome?"** Curr Opin Pulm Med **25**(2): 132-137.
PURPOSE OF REVIEW: Early chronic obstructive pulmonary disease (COPD) is emerging in importance for the clinical and research settings. This review will highlight a proposed definition of early COPD, examine early and midlife factors that lead to development of early COPD and review the literature pertaining to the treatment of mild COPD to gain insight into potential therapeutic approaches for early disease. RECENT FINDINGS: Early COPD can be defined as disease occurring in patients younger than 50 years in age with a 10-pack-year or more smoking history and abnormal spirometry, imaging or lung function decline. Childhood exposures (maternal smoking and recurrent respiratory infections), childhood and

adult asthma, and smoking affect middle-age lung function. Multiple studies of long-acting muscarinic antagonists (LAMAs) in mild COPD have shown improvements in lung function and symptoms scores. Smoking cessation also has a beneficial effect on longitudinal lung function. SUMMARY: Early COPD is an important manifestation of COPD, with a newly proposed definition and associated risk factors identified. Inferring from studies on mild COPD cohorts, LAMAs and smoking cessation may have a positive effect on longitudinal lung function and symptomatic improvement.

Burkes, R. M., A. J. Gassett, et al. (2018). **"Rural Residence and COPD Exacerbations: Analysis of the SPIROMICS Cohort."** Ann Am Thorac SocRATIONALE: Rural residence is associated with poor outcomes in several chronic diseases. The association between rural residence and chronic obstructive pulmonary disease (COPD) exacerbations remains unclear. OBJECTIVE: To determine the independent association between rural residence and COPD-related outcomes including COPD exacerbations, airflow obstruction and symptom burden. METHODS: A total of 1684 Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) participants with FEV1/FVC<0.70 had geocoding-defined rural-urban residence status determined (N=204 rural and N=1480 urban). Univariate and multivariate logistic and negative binomial regressions were performed to assess the independent association between rurality and COPD outcomes including exacerbations, lung function, and symptom burden. The primary exposure of interest was rural residence, determined by geocoding of home address to the block level at time of study enrollment. Additional covariates of interest included demographic and clinical characteristics, occupation, and occupational exposures.The primary outcome measures were exacerbations determined over the one-year course after enrollment by quarterly telephone calls and at an annual research clinic visit. Odds ratio and incidence rate of exacerbations that required treatment with medications including steroids or antibiotics (total exacerbations), and exacerbations leading to hospitalization (severe exacerbations) were determined after adjusting for relevant covariates. RESULTS: Rural residence was independently associated with 70% increase in odds of total exacerbations [OR 1.70 (95% CI 1.13-2.56); p=0.012] and 46% higher incidence rate of total exacerbations [IRR 1.46 (95% CI 1.02-2.10); p=0.039]. There was no association between rural residence and severe exacerbations. Agricultural occupation was independently associated with increased odds and incidence of total and severe exacerbations. Inclusion of agricultural occupation to analysis attenuated the association between rural residence and odds and incidence rate of total exacerbations [OR 1.52 (95% CI 1.00-2.32; p=0.05) and IRR 1.39 (95% CI 0.97 - 1.99); p=0.07]. There was no difference in symptoms or airflow obstruction between rural and urban participants. CONCLUSIONS: Rural residence is independently associated with increased odds and incidence of total, but not severe COPD exacerbations. These associations are not fully explained by agriculture-related exposures, highlighting the need for future research into potential mechanisms of increased risk of COPD exacerbations in the rural population.

Calle Rubio, M., J. J. Soler-Cataluna, et al. (2019). **"Assessing the clinical practice in specialized outpatient clinics for chronic obstructive pulmonary disease: Analysis of the EPOCONSUL clinical audit."** PLoS One **14**(2): e0211732.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is one of the main reasons for healthcare appointments and use of healthcare resources. In recent years, clinics specializing in COPD have been developed to offer improved care and optimization of recourses for patients with high complexity and frequent decompensations. However, little is known about the clinical practice in this clinical model specializing in COPD. The objectives of this study were to assess the prevalence, characteristics of specialized COPD outpatient respiratory clinics and to evaluate clinical practice in this healthcare model. METHODS: EPOCONSUL is a Spanish nationwide, observational, cross-sectional, clinical audit with prospective case recruitment including the clinical records for 4508 COPD cases from outpatient respiratory clinics over a 12-month period (May 2014-May 2015). The study evaluated clinical practice in

2378 cases from 28 hospitals with both general and specialized COPD outpatient respiratory clinics. RESULTS: Only 28 (47.5%) centers had an outpatient clinic specializing in COPD, which was characterized by longer patient visits and a higher prevalence of written protocols compared to a general clinic. Patients treated in a specialized clinic had greater obstruction severity, a higher degree of dyspnea and also suffered from more comorbidities. The majority of patients at both types of clinic were classified as high risk (81.1% versus 83%, p = 0.384) according to GesEPOC criteria. Clinical control of COPD was more frequent at specialized clinics, with significant differences in non-severe patients (70.5% versus 56.1%, p < 0.001). Testing was done more frequently in specialized clinics, with better adherence to good clinical practice recommendations. CONCLUSION: A specialized COPD outpatient clinic is a healthcare model found in few pulmonology departments that treats more severe patients and those with increased comorbidities. The COPD patients treated in a specialized clinic had a better clinical control, as defined by impact and clinical stability. It is a healthcare model to offer improved care with a higher degree of adherence to guidelines.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6364994/pdf/pone.0211732.pdf

Campos-Obando, N., L. Lahousse, et al. (2018). **"Serum phosphate levels are related to all-cause, cardiovascular and COPD mortality in men."** Eur J Epidemiol **33**(9): 859-871.

Hyperphosphatemia has been associated with increased mortality in chronic kidney disease but the nature of such a relation in the general population is unclear. To investigate the association between phosphate (P) levels and all-cause and cause-specific mortality, we assessed two cohorts from the Rotterdam Study, with follow-up of 14.5 (RS-I) and 10.9 (RS-II) years until January 2012 with availability of fasting phosphate levels. Deaths were classified according to International Classification of Diseases into 7 groups: cardiovascular, cancer, infections, external, dementia, chronic lung diseases and other causes. Sex-stratified Weibull and competing-risks models were adjusted for age, BMI and smoking. Hazard ratios are expressed per 1 mg/dL increase in phosphate levels. The total number of participants included 3731 (RS-I, 2154 women) and 2494 (RS-II, 1361 women) subjects. The main outcome measures were all-cause and cause-specific mortality. A significant positive association was found between phosphate and all-cause mortality in men (pooled HR (95% CI): 1.46 (1.26-1.69)) but not in women (0.90 (0.77-1.05)). In men, higher phosphate increased the risk for cardiovascular mortality (1.66 (1.29-2.14)), other causes (1.67 (1.16-2.40)) and chronic lung disease mortality (1.94 (1.02-3.72)), the latter driven by mortality due to chronic obstructive pulmonary disease (COPD) (4.44 (2.08-9.49)). No relations were found for mortality due to infections, cancer, dementia or external causes. In conclusion, serum P is associated with increased all-cause, cardiovascular and COPD mortality in men but not women. The association with COPD mortality is novel and needs further research on underlying mechanisms.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6133003/pdf/10654_2018_Article_407.pdf

Cen, J., H. Ma, et al. (2019). **"Monitoring peak expiratory flow could predict COPD exacerbations: A prospective observational study."** Respir Med **148**: 43-48.

BACKGROUND: Exacerbation of chronic obstructive pulmonary disease (ECOPD) is an important event during the course of the disease. It causes a more rapid decline in lung function, which is associated with hospitalization and the risk of death. Therefore, it is essential to discover approaches to early detection and prevention of ECOPD. Peak expiratory flow (PEF) can be safely used instead of spirometry which can assess the severity of COPD as a standard tool. We hypothesized that monitoring PEF could possibly be used to predict the ECOPD. METHOD: To verify this hypothesis, daily morning PEF was monitored for 6 months in 53 patients with moderate to severe COPD (mean FEV1 31.53%predicted) who were enrolled in Ningbo, China. RESULT: A total of 69 exacerbations of COPD (63 of gradual onset, six of sudden onset) were recorded in this study. Thirty cases (43.5%) of gradual onset exacerbations needed to be hospitalized, and the mean PEF significantly decreased (vs baseline) during the 5 days that preceded those exacerbations (from 161.9+/-39.4L/min to 137.9+/-36.1L/min, P<0.05, statistical power=0.92). However, this was not the case with non-hospitalized exacerbations (from 175.4+/-42.5L/min to

161.5+/-39.3L/min, P=0.172, statistical power=0.63). The ROC analysis demonstrated that 24h before hospitalized exacerbation, the optimal cutoff value of DeltaPEF for its prediction was 28L/min (17% from baseline), with a sensitivity and specificity of 76.7% and 72.7%, respectively (area under the curve [AUC]=0.84, P<0.05, statistical power=0.78). While 48h before hospitalized exacerbation, the optimal cutoff value of DeltaPEF for its prediction was 14L/min (9% from baseline), with a sensitivity and specificity of 86.7% and 66.7%, respectively (AUC=0.863, P<0.05, statistical power=0.87). CONCLUSIONS: As a rapid, inexpensive method, PEF could be used for the prediction and early detection of hospitalized exacerbation of COPD. This may provide opportunity for early intervention of ECOPD.

https://www.resmedjournal.com/article/S0954-6111(19)30019-8/fulltext

Champtiaux, N., V. Cottin, et al. (2018). **"Combined pulmonary fibrosis and emphysema in systemic sclerosis: A syndrome associated with heavy morbidity and mortality."** Semin Arthritis RheumBACKGROUND: The syndrome of combined pulmonary fibrosis and emphysema (CPFE) primarily due to tobacco smoking has been reported in connective tissue disease, but little is known about its characteristics in systemic sclerosis (SSc). METHODS: In this retrospective multi-center case-control study, we identified 36 SSc patients with CPFE, and compared them with 72 SSc controls with interstitial lung disease (ILD) without emphysema. RESULTS: Rate of CPFE in SSc patients with CT scan was 3.6%, and 7.6% among SSc patients with ILD. CPFE-SSc patients were more likely to be male (75 % vs 18%, p < 0.0001), smokers (83 % vs 33%, p < 0.0001), and to have limited cutaneous SSc (53 % vs 24% p < 0.01) than ILD-SSc controls. No specific autoantibody was significantly associated with CPFE. At diagnosis, CPFE-SSc patients had a greater decrease in carbon monoxide diffusing capacity (DLCO 39 +/- 13 % vs 51 +/- 12% of predicted value, p < 0.0001) when compared to SSc-ILD controls, whereas lung volumes (total lung capacity and forced vital capacity) were similar. During follow-up, CPFE-SSc patients more frequently developed precapillary pulmonary hypertension (PH) (44 % vs 11%, p < 10(-4)), experienced more frequent unscheduled hospitalizations (50 % vs 25%, p < 0.01), and had decreased survival (p < 0.02 by Kaplan-Meier survival analysis) as compared to ILD-SSc controls. CONCLUSIONS: The CPFE syndrome is a distinct pulmonary manifestation in SSc, with higher morbidity and mortality. Early diagnosis of CPFE by chest CT in SSc patients (especially smokers) may result in earlier smoking cessation, screening for PH, and appropriate management.

Charbonnier, J. P., E. Pompe, et al. (2019). **"Airway wall thickening on CT: Relation to smoking status and severity of COPD."** Respir Med **146**: 36-41.

Airway wall thickening in cigarette smokers is thought to be a result of inflammatory changes and airway remodeling. This study investigates if CT-derived airway wall thickening associates to disease severity in smokers with and without COPD and if airway wall thickening is reversible by smoking cessation. We examined 2000 smokers and 46 never-smokers who returned for a 5-year follow-up visit in the COPDGene-study. Multivariable regression analyses were performed at visit 1 to associate airway wall thickness (expressed as Pi10) with percent predicted forced expiratory volume in 1s (FEV1%-predicted), 6-min walking distance (6MWD), and St. George Respiratory Questionnaire (SGRQ). Longitudinal analyses were performed to assess the effect of smoking cessation on Pi10 using linear mixed models. A higher Pi10 was significantly associated with worse FEV1%-predicted, 6MWD, and SGRQ in all GOLD-stages. Longitudinal analyses showed that subjects that quit smoking significantly decreased in Pi10 (DeltaPi10=-0.18mm, p<0.001). Subjects that started smoking had a significant increase in Pi10 (DeltaPi10=0.14mm, p<0.001). Pi10 is a clinically relevant biomarker of smoking-related airway injury in smokers with and without COPD. The change in Pi10 with change in smoking status suggests that it can quantify a reversible component of smoking-related airway inflammation.

https://www.resmedjournal.com/article/S0954-6111(18)30372-X/pdf

Chen, J., Y. Chen, et al. (2014). **"Effectiveness of individual counseling for smoking cessation in smokers with chronic obstructive pulmonary disease and asymptomatic smokers."** Exp Ther Med **7**(3): 716-720.

Few studies have examined the effect of individual counseling for smoking cessation in China. The present study evaluated the efficacy of individual counseling in patients with chronic obstructive pulmonary disease (COPD) and asymptomatic smokers. This prospective randomized study evaluated 85 smokers with COPD and 105 asymptomatic smokers with normal lung function. The individuals were randomly allocated to intervention and control groups. Subjects in the intervention group were provided with individual cognitive counseling based on face-to-face individual consultation, self-help materials and nine telephone follow-ups. Subjects in the control group were provided with simple smoking cessation advice. The smoking status for all subjects and the St. George's Respiratory Questionnaire (SGRQ) for COPD patients were assessed at baseline, week 4 and month 6. The COPD patient exacerbations during the 6 months were recorded. In the total study population, individual counseling resulted in higher abstinence rates compared with those in the control: Intervention vs. control, 23.4 vs. 10.4% (P=0.007), respectively. Similar results were observed in the smokers with COPD: Intervention vs. control, 40.5 vs. 18.6% (P=0.027), respectively. However, for asymptomatic smokers, the effect of individual counseling was identified to be statistically insignificant: Intervention vs. control, 9.6 vs. 3.8% (P=0.230), respectively. SGRQ scores and COPD exacerbations were significantly improved in patients who abstained from smoking compared with those in the patients who failed to stop smoking. Airway obstruction, quitting motivation and individual counseling were predictors associated with smoking cessation. Airway obstruction was the most significant predictor of smoking cessation (odds ratio, 4.215; 95% confidence interval, 2.215-7.865). The results of the present study show that individual counseling is an effective method for smoking cessation, particularly in COPD patients. However, its efficacy in asymptomatic smokers requires confirmation in further studies.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3919914/pdf/etm-07-03-0716.pdf

Cheng, T., H. Wan, et al. (2016). **"Computed tomography manifestation of acute exacerbation of chronic obstructive pulmonary disease: A pilot study."** Exp Ther Med **11**(2): 519-529.

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an acute event characterized by the worsening of a patient's respiratory symptoms. To the best of our knowledge, few studies have investigated the computed tomography (CT) manifestation of AECOPD. Thus, the aim of the present study was to examine the CT manifestations during AECOPD. In total, 40 patients with AECOPD admitted to the emergency department were enrolled. CT images obtained at the time of exacerbation and at the 3-month follow-up were paired. Clinical characteristics and routine blood test results were also recorded. Airway dimensions and attenuation per patient were quantified from the 3rd to the 6th generation of four bronchi by Airway Inspector Slicer 2.8. The emphysema extent was also quantified and lung infiltration was detected, classified and measured. The CT images showed an increased wall area percentage (WA%) and increased mean and peak wall attenuation during the AECOPD; however, the extent of emphysema did not change significantly. In total, 60% of AECOPD patients presented with lung infiltration, compared with those at the follow-up CT scanning. The presence and extent of segmental distribution consolidation was correlated with the neutrophil percentage (N%), with a statistically significant difference observed. The total volume of lung parenchymal infiltration was correlated with the white blood cell (WBC) count and N%; however, no significant correlations were detected between the presence or extent of acinar shadow, air space consolidation with lobular distribution, ground-glass attenuation with lobular distribution, thickening of the interlobular septa and signs of infection (including the number of main symptoms, body temperature, WBC count and N%). The WA%, mean wall attenuation and peak wall attenuation increased during AECOPD, but the emphysema extent was unchanged. Lung infiltration existed frequently; however, only consolidation with segmental distribution appeared to be associated with bacterial infection.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734063/pdf/etm-11-02-0519.pdf

Cho, J., C. H. Lee, et al. (2019). **"Risk of acute exacerbations in chronic obstructive pulmonary disease associated with biomass smoke compared with tobacco smoke."** BMC Pulm Med **19**(1): 68.

BACKGROUND: Risk of exacerbations in chronic obstructive pulmonary disease (COPD) associated with biomass smoke has not been well addressed, although biomass smoke is similar in composition to tobacco smoke. METHODS: To investigate whether the risk of exacerbations in COPD associated with biomass smoke differs from that in COPD associated with tobacco smoke, we recruited patients with COPD from two Korean multicenter prospective cohorts. In a multiple linear regression model, the standardized regression coefficient (beta) of biomass smoke exposure >/=25 years was most similar to that (beta(')) of tobacco smoke exposure >/=10 pack-years (beta = - 0.13 and beta(') = - 0.14). We grouped patients with COPD into four categories based on the above cut-offs: Less Tobacco-Less Biomass, Less Tobacco-More Biomass, More Tobacco-Less Biomass, and More Tobacco-More Biomass. The main outcome was the incidence of moderate or severe exacerbations. RESULTS: Among 1033 patients with COPD, 107 were included in Less Tobacco-Less Biomass (mean age: 67 years, men: 67%), 40 in Less Tobacco-More Biomass (mean age: 70 years, men: 35%), 631 in More Tobacco-Less Biomass (mean age: 68 years, men: 98%), and 255 in More Tobacco-More Biomass (mean age: 69 years, men: 97%). The incidence rates of exacerbations were not significantly different between Less Tobacco-More Biomass and More Tobacco-Less Biomass (adjusted incidence rate ratio, 1.03; 95% confidence interval, 0.56-1.89; P = 0.921). No interaction between sex and tobacco and biomass smoke was observed. When propensity score matching with available covariates including age and sex was applied, a similar result was observed. CONCLUSIONS: Patients with COPD associated with biomass smoke and those with COPD associated with tobacco smoke had a similar risk of exacerbations. This suggests that patients with COPD associated with biomass smoke should be treated actively.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429752/pdf/12890_2019_Article_833.pdf

Conde Diez, S., A. Viejo Casas, et al. (2019). **"Impact of a homeopathic medication on upper respiratory tract infections in COPD patients: Results of an observational, prospective study (EPOXILO)."** Respir Med **146**: 96-105.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder in which airflow is obstructed. Viral or bacterial upper respiratory tract infections (URTIs) may lead to exacerbations. Homeopathic medication administration to COPD patients during the influenza-exposure period may help to reduce the frequency of common URTIs. METHODS: This prospective, observational, multicenter study was carried out in Cantabria, Spain. Patients with COPD were divided into two groups: group 1 received conventional treatment + homeopathic medication (diluted and dynamized extract of duck liver and heart; Boiron) (OG); group 2 received conventional treatment only (CG). The primary endpoint was the number of URTIs between the 4-5 months follow up (mean 4.72 +/- 0.96) from basal to last visit. Secondary endpoints included the duration of URTIs, number and duration of COPD exacerbations, use of COPD drugs, changes in quality of life (QoL), compliance, and adverse events (AEs). RESULTS: 219 patients were analyzed (OG=109, CG=110). There was a significant reduction in mean number of URTIs during the follow-up period in OG compared to CG (0.514+/-0.722 vs. 1.037+/-1.519, respectively; p=0.014). Logistic regression analysis showed a 3.3-times higher probability of suffering >/=2 URTI episodes in CG (p=0.003, n=72). OG patients having >/=1 URTI also had a significant reduction in mean URTI duration per episode (3.57+/-2.44 days OG vs. 5.22+/-4.17 days CG; p=0.012). There was no significant difference in mean number of exacerbations, mean duration of exacerbations, or QoL between OG and CG. There was a greater decrease in proportion of patients using corticosteroids for exacerbations between baseline and visit 2 in OG compared to CG (22.1% vs. 7.5% fewer respectively, p=0.005). Exacerbator phenotype patients had a significant decrease in number of URTIs (0.54+/-0.72 vs. 1.31+/-1.81; p=0.011), and fewer COPD exacerbations (0.9+/-1.3 vs. 1.5+/-1.7; p=0.037) in OG vs. CG, respectively. CONCLUSIONS: Homeopathic medication use during the influenza-exposure period may have a beneficial impact at reducing URTIs' number and duration in COPD patients and at reducing the number of COPD exacerbations in patients with the exacerbator phenotype. Further studies are needed to confirm the effects observed in this study.

https://www.resmedjournal.com/article/S0954-6111(18)30370-6/pdf

Cornwell, W. D., C. Kim, et al. (2018). **"Inflammatory signature in lung tissues in patients with combined pulmonary fibrosis and emphysema."** Biomarkers: 1-8.

BACKGROUND: The aetiology and inflammatory profile of combined pulmonary fibrosis and emphysema (CPFE) remain uncertain currently. OBJECTIVE: We aimed to examine the levels of inflammatory proteins in lung tissue in a cohort of patients with emphysema, interstitial pulmonary fibrosis (IPF), and CPFE. MATERIALS AND METHODS: Explanted lungs were obtained from subjects with emphysema, IPF, CPFE, (or normal subjects), and tissue extracts were prepared. Thirty-four inflammatory proteins were measured in each tissue section. RESULTS: The levels of all 34 proteins were virtually indistinguishable in IPF compared with CPFE tissues, and collectively, the inflammatory profile in the emphysematous tissues were distinct from IPF and CPFE. Moreover, inflammatory protein levels were independent of the severity of the level of diseased tissue. CONCLUSIONS: We find that emphysematous lung tissues have a distinct inflammatory profile compared with either IPF or CPFE. However, the inflammatory profile in CPFE lungs is essentially identical to lungs from patients with IPF. These data suggest that distinct inflammatory processes collectively contribute to the disease processes in patients with emphysema, when compared to IPF and CPFE.

https://www.tandfonline.com/doi/full/10.1080/1354750X.2018.1542458

Cosentino, E. R., M. Landolfo, et al. (2019). **"Morbidity and mortality in a population of patients affected by heart failure and chronic obstructive pulmonary disease: an observational study."** BMC Cardiovasc Disord **19**(1): 20.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) and heart failure (HF) often coexist. Moreover, elderly patients suffering from HF have a higher incidence of COPD, which further complicates their clinical condition. Indacaterol/glycopirronium has shown benefits in the treatment of COPD, with few cardiologic adverse effects. We evaluated the safety and efficacy of this therapy in patients with history of HF. METHODS: We enrolled 56 patients with a history of HF (New York Heart Association [NYHA] classes II and III) and stable COPD. We evaluated blood samples, clinical assessment, echocardiograms and basal spirometry at baseline and after 6 months of therapy with indacaterol/glycopirronium. In addition, the number of re-hospitalizations during the treatment period was evaluated. RESULTS: The treatment was well tolerated. Brain natriuretic peptide (BNP) levels were significantly reduced compared with baseline ($p < 0.001$) after 6 months of treatment, and a higher percentage of patients improved their clinical status compared with baseline ($p < 0.001$). Minor changes were noted in the hemodynamic and metabolic parameters. Significant improvements in the echocardiographic parameters were noted in HF with reduced ejection fraction (HFrEF) patients. All respiratory parameters (forced expiratory volume in 1 s [FEV1], FEV1/forced vital capacity [FVC] ratio and COPD Assessment Test [CAT] scores) improved significantly ($p < 0.001$). No hospitalizations owing to HF or COPD exacerbation occurred. One patient died of respiratory failure. CONCLUSION: Indacaterol/glycopirronium was well-tolerated and effective in the treatment of COPD in this cohort of patients with a history of HF. Further studies are needed to clarify whether this compound can have a direct role in improving overall cardiovascular function.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6335816/pdf/12872_2018_Article_986.pdf

Cousse, S., A. Gillibert, et al. (2019). **"Efficacy of a home discharge care bundle after acute exacerbation of COPD."** Int J Chron Obstruct Pulmon Dis **14**: 289-296.

Purpose: Acute exacerbations of COPD (AECOPD) are frequent and associated with a poor prognosis. A home discharge care bundle, the PRADO-BPCO program, has been set up by the French National Health

System in order to reduce readmission rate after hospitalization for AECOPD. This program includes early consultations by the general practitioner, a nurse, and a physiotherapist after discharge. The aim of our study was to evaluate the effect of the PRADO-BPCO program on the 28-days readmission rate of COPD patients after hospitalization for AECOPD. Patients and methods: This was a retrospective cohort study including all patients admitted for AECOPD in our center between November 2015 and January 2017. The readmission or death rate at 28 days after hospitalization for AECOPD was compared between patients included in the PRADO-BPCO program and patients with standard care after discharge. Inclusion in the program was decided by the physician in charge of the patient. Results: A total of 62 patients were included in the PRADO-BPCO group and 202 in the control group. At baseline, patients in the PRADO group had a more severe COPD disease and more severe exacerbations than the control group and mean inpatient stay was shorter in the PRADO group: 8.6+/-4.3 vs 10.4+/-7.4 days (P=0.034). Readmission or death rate at 28 days was similar between groups: 10 (16.1%) in the PRADO group vs 30 (14.9%) in the control group (P=0.81). Ninety-days readmission or death rate and overall survival were similar in the two groups. Conclusion: In our center, despite more severe COPD and a shorter hospitalization time, the PRADO-BPCO program failed to prove a benefit on the 28 days readmission or death rate when compared with standard care.

https://www.dovepress.com/getfile.php?fileID=47654

Coventry, P. A., A. Blakemore, et al. (2019). **"The Push and Pull of Self-Managing Mild COPD: An Evaluation of Participant Experiences of a Nurse-Led Telephone Health Coaching Intervention."** Qual Health Res **29**(5): 658-671.

Health coaching is a novel population intervention to support self-management but it is untested in people with mild disease. People with chronic obstructive pulmonary disease with mild dyspnea are a population excluded from supported self-management and whose illness might progress without intervention. We explored participants' experiences about how health coaching motivated behavior change. Interviews were conducted with 21 intervention and 10 control participants at 6 months, and 20 intervention participants at 12 months. Participants were identified from a randomized controlled trial of telephone health coaching. Data were analyzed using the framework method. Participants positively enacted behavior change to become more physically active. Participants took advantage of environmental affordances to pull themselves toward activity targets, or relied on being pushed to be more active by the health coach or significant others. Behavior change was maintained where efforts to be more active were built into the everyday lifeworld of participants.

Crisafulli, E., M. Aiello, et al. (2019). **"A High Degree of Dyspnea Is Associated With Poor Maximum Exercise Capacity in Subjects With COPD With the Same Severity of Air-Flow Obstruction."** Respir Care **64**(4): 390-397.

BACKGROUND: In patients with COPD, limited data have been reported concerning the association between dyspnea perception and exercise tests. Moreover, the perception of dyspnea has not been analyzed in patients with the same severity of air-flow obstruction. The aim of our study was to evaluate the relationship between the degree of dyspnea and exercise capacity in subjects with COPD who had the same severity of air-flow obstruction. METHODS: We assessed dyspnea perception and maximum exercise capacity by using the modified Medical Research Council dyspnea scale (mMRC) questionnaire and by using the symptom-limited incremental cardiopulmonary exercise test, respectively. A propensity score matching was used to obtain the balance between the subjects with COPD and with an mMRC questionnaire score <2 and >/=2 (mMRC score) according to the severity of air-flow obstruction. RESULTS: A total of 249 ambulatory adult patients with stable COPD (mean age, 68 y) were considered in the full cohort. After propensity score analysis, 160 subjects (65% men; mean +/- SD FEV1, 47.5 +/- 12.8% of predicted) were included in our study cohort. The subjects with an mMRC questionnaire score >/=2 in comparison with those with an mMRC questionnaire score <2 showed lower values in oxygen

uptake at peak (VO2 max) (P = .002) and in maximum work load (P < .001). In the regression models, the mMRC questionnaire score was able to predict oxygen uptake at peak (P < .001) and at maximum work load (P < .001). CONCLUSIONS: In subjects with COPD and with the same severity of air-flow obstruction, a high score in dyspnea was related to a poor maximum exercise capacity. Our results support the view that, in COPD, the severity of air-flow obstruction was less informative than symptoms in the combined assessment of the disease.

http://rc.rcjournal.com/content/64/4/390.short

Crothers, K., C. V. Rodriguez, et al. (2019). **"Accuracy of electronic health record data for the diagnosis of chronic obstructive pulmonary disease in persons living with HIV and uninfected persons."** Pharmacoepidemiol Drug Saf **28**(2): 140-147.

PURPOSE: No prior studies have addressed the performance of electronic health record (EHR) data to diagnose chronic obstructive pulmonary disease (COPD) in people living with HIV (PLWH), in whom COPD could be more likely to be underdiagnosed or misdiagnosed, given the higher frequency of respiratory symptoms and smoking compared with HIV-uninfected (uninfected) persons. METHODS: We determined whether EHR data could improve accuracy of ICD-9 codes to define COPD when compared with spirometry in PLWH vs uninfected, and quantified level of discrimination using the area under the receiver-operating curve (AUC). The development cohort consisted of 350 participants who completed research spirometry in the Examinations of HIV Associated Lung Emphysema (EXHALE) study, a pulmonary substudy of the Veterans Aging Cohort Study. Results were externally validated in 294 PLWH who performed spirometry for clinical indications from the University of Washington (UW) site of the Centers for AIDS Research Network of Integrated Clinical Systems cohort. RESULTS: ICD-9 codes performed similarly by HIV status, but alone were poor at discriminating cases from non-cases of COPD when compared with spirometry (AUC 0.633 in EXHALE; 0.651 in the UW cohort). However, algorithms that combined ICD-9 codes with other clinical variables available in the EHR-age, smoking, and COPD inhalers-improved discrimination and performed similarly in EXHALE (AUC 0.771) and UW (AUC 0.734). CONCLUSIONS: These data support that EHR data in combination with ICD-9 codes have moderately good accuracy to identify COPD when spirometry data are not available, and perform similarly in PLWH and uninfected individuals.

https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4567

Das, N., M. Topalovic, et al. (2019). **"Area under the forced expiratory flow-volume loop in spirometry indicates severe hyperinflation in COPD patients."** Int J Chron Obstruct Pulmon Dis **14**: 409-418.

Background: Severe hyperinflation causes detrimental effects such as dyspnea and reduced exercise capacity and is an independent predictor of mortality in COPD patients. Static lung volumes are required to diagnose severe hyperinflation, which are not always accessible in primary care. Several studies have shown that the area under the forced expiratory flow-volume loop (AreaFE) is highly sensitive to bronchodilator response and is correlated with residual volume/total lung capacity (RV/TLC), a common index of air trapping. In this study, we investigate the role of AreaFE% (AreaFE expressed as a percentage of reference value) and conventional spirometry parameters in indicating severe hyperinflation. Materials and methods: We used a cohort of 215 individuals with COPD. The presence of severe hyperinflation was defined as elevated air trapping (RV/TLC >60%) or reduced inspiratory fraction (inspiratory capacity [IC]/TLC <25%) measured using body plethysmography. AreaFE% was calculated by integrating the maximal expiratory flow-volume loop with the trapezoidal rule and expressing it as a percentage of the reference value estimated using predicted values of FVC, peak expiratory flow and forced expiratory flow at 25%, 50% and 75% of FVC. Receiver operating characteristics (ROC) curve analysis was used to identify cut-offs that were used to indicate severe hyperinflation, which were then validated in a separate group of 104 COPD subjects. Results: ROC analysis identified cut-offs of 15% and 20% for AreaFE% in indicating RV/TLC >60% and IC/TLC <25%, respectively (N=215). On validation (N=104), these cut-offs consistently registered the highest accuracy (80% each), sensitivity (68% and 75%) and specificity (83%

and 80%) among conventional parameters in both criteria of severe hyperinflation. Conclusion: AreaFE% consistently provides a superior estimation of severe hyperinflation using different indices, and may provide a convenient way to refer COPD patients for body plethysmography to address static lung volumes.

https://www.dovepress.com/getfile.php?fileID=48042

de Blasio, F., L. Scalfi, et al. (2019). **"Raw Bioelectrical Impedance Analysis Variables Are Independent Predictors of Early All-Cause Mortality in Patients With COPD."** ChestBACKGROUND: Bioelectrical impedance analysis (BIA) is a valuable method for estimating fat-free mass and fat mass in patients with COPD by using specific predictive equations. In addition, raw BIA variables such as high- to low-frequency impedance ratios (IRs) and phase angle, most likely as a result of providing information on muscle quality, have been related to disease severity and mortality in patients with several diseases but never in COPD. The aim of this study was to investigate the predictive role of raw BIA variables on 2-year survival in COPD. METHODS: Impedance (Z) at 5-10-50-100-250 kHz and phase angle at 50 kHz were determined in 210 patients with COPD. Three IRs were calculated: Z at 50 kHz/Z at 5 kHz (50/5 IR), Z at 100 kHz/Z at 5 kHz (100/5 IR), and Z at 250 kHz/Z at 5 kHz (250/5 IR). Demographic, respiratory, and body composition data at baseline were recorded. All-cause mortality was assessed during 2 years of follow-up. RESULTS: After the follow-up period, all-cause mortality was 13.8%. Statistically significant differences between nonsurvivors and survivors emerged in terms of age, weight, BMI, FEV1, inspiratory capacity, and modified Medical Research Council dyspnea score. With respect to nutritional variables, nonsurvivors had lower fat-free mass (P = .031), lower fat mass (P = .015), higher IRs (P < .001 for all the ratios), and lower phase angle (P < .001) compared with survivors. After adjustment for confounding factors, each unit increase of IRs and each unit decrease of phase angle were associated with a higher risk of death. CONCLUSIONS: IRs and phase angle, as raw BIA variables, are independent and powerful predictors of all-cause mortality in COPD and should be considered, together with inspiratory capacity and 6-min walk distance, as significant prognostic factors in the short- to middle-term.

https://journal.chestnet.org/article/S0012-3692(19)30008-X/fulltext

Demeyer, H., D. Donaire-Gonzalez, et al. (2019). **"Physical Activity Is Associated with Attenuated Disease Progression in Chronic Obstructive Pulmonary Disease."** Med Sci Sports Exerc **51**(5): 833-840.
INTRODUCTION: Chronic obstructive pulmonary disease (COPD) progression is variable and affects several disease domains, including decline in lung function, exercise capacity, muscle strength, and health status as well as changes in body composition. We aimed to assess the longitudinal association of physical activity (PA) with these a priori selected components of disease progression. METHODS: We studied 114 COPD patients from the PAC-COPD cohort (94% male, mean [SD], 70 yr [8 yr] of age, 54 [16] forced expiratory volume in 1 s % predicted) at baseline and 2.6 yr (0.6 yr) later. Baseline PA was assessed by accelerometry. Multivariable general linear models were built to assess the association between PA and changes in lung function, functional exercise capacity, muscle strength, health status, and body composition. All models were adjusted for confounders and the respective baseline value of each measure. RESULTS: Per each 1000 steps higher baseline PA, forced expiratory volume in 1 s declined 7 mL less (P < 0.01), forced vital capacity 9 mL less (P = 0.03) and carbon monoxide diffusing capacity 0.10 mL.min.mm Hg less (P = 0.04), while the St George's Respiratory Questionnaire symptom domain deteriorated 0.4 points less (P = 0.03), per year follow-up. Physical activity was not associated with changes in functional exercise capacity, muscle strength, other domains of health status or body composition. CONCLUSIONS: Higher PA is associated with attenuated decline in lung function and reduced health status (symptoms domain) deterioration in moderate-to-very severe COPD patients.

Demiri, S., C. Lorut, et al. (2018). **"Postoperative outcomes of frequent exacerbator patients with Chronic Obstructive Pulmonary Disease after resection of Non-Small Cells Lung Cancer."** Copd **15**(4): 361-368.

Chronic obstructive pulmonary disease (COPD) is a risk factor of post-operative complications after lung cancer resection. The influence of the "frequent exacerbator (FE)" phenotype (at least three exacerbations per year) is unknown. Postoperative outcomes of frequent exacerbators (POFE) was a prospective observational study of patients with COPD undergoing lung resection for cancer. The inclusion criteria were: age >40 years, FEV1/FVC <70%, non-urgent surgery for lung cancer, filled out self-questionnaires. The primary outcome was assessment of postoperative pulmonary complications (purulent tracheobronchitis, atelectasis, pneumonia, acute respiratory failure, need of mechanical ventilation). Secondary outcomes encompassed the prevalence of the FE phenotype and its impact on postoperative complications. A total of 682 patients were screened from June 2014 to October 2015. 93 patients with COPD were included, 21 (23%) were FE. Postoperative tracheobronchitis, atelectasis pneumonia or respiratory failure (isolated or associated) occurred in 47%, 48%, 26%, and 38% of patients, respectively. Non-invasive and invasive mechanical ventilation were necessary in 4 (4%) and 22 (23%) patients. Purulent tracheobronchitis, pneumonia and hypercapnia (this last requiring noninvasive mechanical ventilation) were more frequent in FE (p = 0.043, 0.042, 0.015); however the number of patients wth at least one respiratory complication was not different (76% vs. 52%, p = 0.056). In all patients, multivariate logistic regression identified two independent factors of postoperative respiratory complications: male sex (OR 10.6 [95% CI 1.97-57.6], p = 0.006) and the FE phenotype (OR 6.33 [1.04-38.39], p = 0.045). Occurrence of postoperative complications in patients with COPD is high. FE phenotype is an independent risk factor.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1519784

Deng, Z. C., P. Zhao, et al. (2014). **"C-reactive protein as a prognostic marker in chronic obstructive pulmonary disease."** Exp Ther Med **7**(2): 443-446.

The present study aimed to evaluate whether circulating C-reactive protein (CRP) levels are a biomarker of systemic inflammation and a significant predictor of future chronic obstructive pulmonary disease (COPD) outcome. During the study, 116 patients with stable COPD and 35 age- and gender-matched healthy subjects with normal pulmonary function were observed. Patient follow-up was also performed to evaluate the strength of the associations between CRP levels and future outcomes. The observations from the present study showed that serum CRP levels were significantly higher in stable COPD patients than in control subjects (4.48+/-0.83 vs. 1.01+/-0.27 mg/l, respectively; P<0.05). In addition, it was identified that a serum CRP concentration of >3 mg/l is a poor prognostic variable of COPD compared with a CRP concentration of </=3 mg/l [hazard ratio (HR), 2.71; 95% confidence interval (CI), 1.05-6.99; P<0.05]. A quantitative synthesis of four studies including 1,750 COPD patients was performed and statistically similar results were obtained (HR, 1.54; 95% CI, 1.14-2.07; P<0.01). The present study showed that circulating CRP levels are higher in stable COPD patients and, therefore, may be used as a long-term predictor of future outcomes. These observations highlight the importance of high sensitivity CRP assays in patients with stable COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3881036/pdf/etm-07-02-0443.pdf

Deniz, S., H. Sahin, et al. (2019). **"In Which the Gain is more from Pulmonary Rehabilitation? Asthma or COPD?"** Turk Thorac JOBJECTIVES: Pulmonary rehabilitation (PR) is useful for patients with chronic obstructive pulmonary disease (COPD) but not clear for patients with asthma. The aim of the present study was to evaluate the effectiveness of PR in patients with asthma by comparing patients with COPD. The study was designed as a retrospective case series. We recruited patients with COPD and asthma. MATERIALS AND METHODS: Demographics, respiratory symptoms, medications, smoking history,

comorbidities, exercise capacity, respiratory function tests, and quality of life (QOL) were recorded. Exercise capacity was evaluated by the 6-minute walk test (6MWT), QOL with St. George's Respiratory Questionnaire (SGRQ), 36-item Short Form Health Survey (SF-36) Quality of Life Questionnaire, and Hospital Anxiety and Depression (HAD) Scale. RESULTS: Forty-two patients with asthma and 25 COPD who completed PR were included in the study. There was no difference in terms of age and sex between the groups (p=0.100 and p=0.365, respectively); however, body mass index was higher in the asthmatic group (p=0.007). Partial oxygen pressure (pO2) difference and arterial oxygen saturation (SpO2) difference were significantly higher in the COPD group than in the asthma group after PR (p<0.05). When the patients were compared before and after PR in both groups, a significant increase was detected in exercise capacity and QOL (6MWT, HADa, SGRQ, and SF-36 in all domains) (p<0.05). When two groups are contrasted according to the difference between pre- and post-PR of variables, there was no significant difference except pO2, SpO2, and Medical Research Council (p>0.05). CONCLUSION: Physicians refer patients with COPD to PR; however, patients with asthma are not generally referred to the same frequency. We would like to emphasize that PR may be as effective as COPD in asthma.

Desai, R., U. Patel, et al. (2019). **"The burden and impact of arrhythmia in chronic obstructive pulmonary disease: Insights from the National Inpatient Sample."** Int J Cardiol **281**: 49-55.

BACKGROUND: We aimed to analyze the burden and predictors of arrhythmias and in-hospital mortality in chronic obstructive pulmonary disease (COPD)-related hospitalizations using the nationwide cohort. METHODS: We queried the National Inpatient Sample (NIS) (2010-2014) databases to identify adult COPD hospitalizations with arrhythmia. Categorical and continuous variables were compared using Chi-square and Student's t-test/ANOVA. Predictors of any arrhythmia including AF and in-hospital mortality were evaluated by multivariable analyses. RESULTS: Out of 21,596,342 COPD hospitalizations, 6,480,799 (30%) revealed co-existent arrhythmias including 4,767,401 AF-arrhythmias (22.1%) and 1,713,398 non AF-arrhythmias (7.9%). The AF or non-AF arrhythmia cohort consisted mostly of older (mean age~ 75.8 & 69.1 vs. 67.5years) white male (53.3% & 51.9% vs. 46.9%) patients compared to those without arrhythmias (p<0.001). The all-cause mortality (5.7% & 5.2 vs. 2.9%), mean length of stay (LOS) (6.4 & 6.5 vs. 5.3days), and hospital charges ($52,699.49 & $58,102.39 vs. $41,208.02) were higher with AF and non AF-arrhythmia compared to the non-arrhythmia group (p<0.001). Comorbidities such as cardiomyopathy (OR 2.11), cardiogenic shock (OR 1.88), valvular diseases (OR 1.60), congestive heart failure (OR 1.48) and pulmonary circulation disorders (OR 1.25) predicted in-hospital arrhythmias. Invasive mechanical ventilation (OR 6.41), cardiogenic shock (OR 5.95), cerebrovascular disease (OR 3.95), septicemia (OR 2.30) and acute myocardial infarction (OR 2.24) predicted higher mortality (p<0.001) in the COPD-arrhythmia cohort. CONCLUSIONS: About 30% of COPD hospitalizations revealed co-existent arrhythmias (AF 22.1%). All-cause mortality, LOS and hospital charges were significantly higher with arrhythmias. We observed racial and sex-based disparities for arrhythmias and related mortality.

https://www.internationaljournalofcardiology.com/article/S0167-5273(18)35516-5/fulltext

Di Marco, F., P. Balbo, et al. (2019). **"Early management of COPD: where are we now and where do we go from here? A Delphi consensus project."** Int J Chron Obstruct Pulmon Dis **14**: 353-360.

Purpose: There is a lack of consensus on the most appropriate early diagnostic strategy, criteria for early access to treatment and follow-up approach for patients with COPD. Materials and methods: A Delphi consensus project investigated the early management of COPD. We formulated two questionnaires for completion by pneumologists in Italy. Results: A total of 207 specialists completed questionnaire 1 and 184 of them questionnaire 2, between November 2016 and October 2017. Early diagnosis of COPD was considered uncommon for 93.2% of the expert panel. Regardless of the definition of "early diagnosis" - a diagnosis made before the clinical manifestation of the disease for most responders (60.4%) - experts were confident of the positive effects of early disease management, which they consider is effective in

modifying the natural history of the disease. Lack of awareness of the disease was considered the first limiting factor to early COPD management for 78% of respondents. The most effective steps to reduce functional decline were considered to be smoking cessation, followed by long-acting beta2-agonist (LABA)/long-acting muscarinic antagonist (LAMA), LAMA, LABA, and finally inhaled corticosteroid/LABA ($P<0.01$ for each paired comparison). Specialists considered it "inappropriate" for general practitioners to perform both the early diagnosis and therapy of COPD without the involvement of a specialist. Conclusion: Early management of COPD is uncommon, and although data on the effects of early disease management on long-term outcomes are limited, Italian experts are confident of the clinical efficacy of this approach.

https://www.dovepress.com/getfile.php?fileID=47842

Doi, H., K. Nakamatsu, et al. (2019). **"Stereotactic body radiotherapy in patients with chronic obstructive pulmonary disease and interstitial pneumonia: a review."** Int J Clin OncolStereotactic body radiation therapy (SBRT) can yield excellent local tumor control, as well as survival benefit comparable to that of surgery for early-stage lung cancer. However, in terms of toxicity, SBRT might lead to fatal radiation pneumonitis. Lung diseases, such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), are major risk factors for lung cancer. However, these patients are typically not candidates for the gold-standard treatment option, lobectomy, because of the perioperative risks. In addition, patients with poor respiratory function can be excluded in prospective clinical trials. Thus, SBRT for patients with pulmonary diseases is still challenging, but there appears to be a clinical role for this modality as an alternative treatment. However, there are few well-documented review articles on SBRT for patients with pulmonary diseases. Therefore, we aimed to review SBRT in the context of important patient-related factors, including COPD and ILD. SBRT is an acceptable alternative treatment option for patients with lung cancer who also have COPD with an equivalent risk of radiation pneumonitis to normal lung. However, latent ILD should be detected prior to treatment. The indication for SBRT should be decided by carefully considering the risks and benefit for patients with ILD.

https://link.springer.com/article/10.1007%2Fs10147-019-01432-y

Dong, Q. N., T. Ide, et al. (2019). **"Retrobulbar Orbital Emphysema Associated with Medial Orbital Wall Fracture."** J Craniofac SurgRetrobulbar emphysema is a rare condition compared to the more common orbital emphysema. It is often associated with medial orbital wall fracture with rupture of the periosteum. In some severe patients, retrobulbar emphysema can increase the intraorbital pressure and lead to orbital compartment syndrome. Less extreme patients require only conservative treatment with careful observation. There is still no standard protocol for the management of orbital emphysema in general or specifically for retrobulbar emphysema. Visual acuity is the most widely used indicator to determine whether surgical intervention is needed. The patient presented here suffered from large retrobulbar intraconal emphysema and exophthalmos without visual loss after head trauma and nose blowing. He was observed closely without surgical intervention. After the emphysema had resolved, the patient's medial orbital wall defect was reconstructed using unsintered hydroxyapatite particles/poly L-lactide via the transcaruncular approach. The postoperative course has been uneventful with more than 1 year of follow-up to date.

Donovan, L. M., L. C. Feemster, et al. (2019). **"Poor Outcomes Among Patients With Chronic Obstructive Pulmonary Disease With Higher Risk for Undiagnosed Obstructive Sleep Apnea in the LOTT Cohort."** J Clin Sleep Med **15**(1): 71-77.

STUDY OBJECTIVES: Evaluate consequences of intermediate to high risk of undiagnosed obstructive sleep apnea (OSA) among individuals with chronic obstructive pulmonary disease (COPD). METHODS: Using data from the Long Term Oxygen Treatment Trial (LOTT), we assessed OSA risk at study entry among patients with COPD. We compared outcomes among those at intermediate to high risk (modified STOP-BANG score >/= 3) relative to low risk (score < 3) for OSA. We compared risk of mortality or first hospitalization with proportional hazard models, and incidence of COPD exacerbations using negative binomial regression. We adjusted analyses for demographics, body mass index, and comorbidities. Last, we compared St. George Respiratory Questionnaire and Quality of Well-Being Scale results between OSA risk groups. RESULTS: Of the 222 participants studied, 164 (74%) were at intermediate to high risk for OSA based on the modified STOP-BANG score. Relative to the 58 low-risk individuals, the adjusted hazard ratio of mortality or first hospitalization was 1.61 (95% confidence interval 1.01-2.58) for those at intermediate to high risk of OSA. Risk for OSA was also associated with increased frequency of COPD exacerbations (adjusted incidence rate ratio: 1.78, 95% confidence interval 1.10-2.89). Respiratory symptoms by St. George Respiratory Questionnaire were 5.5 points greater (P = .05), and Quality of Well-Being Scale scores were .05 points lower (P < .01) among those at intermediate to high risk for OSA, indicating more severe respiratory symptoms and lower quality of life. CONCLUSIONS: Among individuals with COPD, greater risk for undiagnosed OSA is associated with poor outcomes. Increased recognition and management of OSA in this group could improve outcomes.

Efird, J. T., W. T. O'Neal, et al. (2013). **"The effect of race and chronic obstructive pulmonary disease on long-term survival after coronary artery bypass grafting."** Front Public Health Serv Syst Res **1**BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a known predictor of decreased long-term survival after coronary artery bypass grafting (CABG). Differences in survival by race have not been examined. METHODS: A retrospective cohort study was conducted of CABG patients between 2002 and 2011. Long-term survival was compared in patients with and without COPD and stratified by race. Hazard ratios (HR) and 95% confidence intervals (CI) were computed using a Cox regression model. RESULTS: A total of 984 (20%) patients had COPD (black n = 182; white n = 802) at the time of CABG (N = 4,801).The median follow-up for study participants was 4.4 years. COPD was observed to be a statistically significant predictor of decreased survival independent of race following CABG (no COPD: HR = 1.0; white COPD: adjusted HR = 1.9, 95% CI = 1.7-2.3; black COPD: adjusted HR = 1.6, 95% CI = 1.1-2.2). CONCLUSION: Contrary to the expected increased risk of mortality among black COPD patients in the general population, a similar survival disadvantage was not observed in our CABG population.

https://fjfsdata01prod.blob.core.windows.net/articles/files/47110/pubmed-zip/.versions/2/.package-entries/fpubh-01-00004-r1/fpubh-01-00004.pdf?sv=2015-12-11&sr=b&sig=%2FgEXISMVJnOgDOTD%2FQTZzqD2vSqkzlqSfIsRuvsGrKk%3D&se=2019-04-26T00%3A00%3A09Z&sp=r&rscd=attachment%3B%20filename%2A%3DUTF-8%27%27fpubh-01-00004.pdf

Epstein, D., Y. Barak-Corren, et al. (2019). **"Clinical Decision Support System: A Pragmatic Tool to Improve Acute Exacerbation of COPD Discharge Recommendations."** Copd: 1-7.

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are associated with significant mortality, morbidity and increased risk for further exacerbations. Therefore, appropriate measures for prevention of further exacerbations should be initiated before discharge. Unfortunately, this opportunity for treatment review and change in disease course is often missed. We designed a decision support tool to automatically generate discharge recommendations for COPD patients based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report. A pre- and post-intervention study was conducted including data from 24 months before and 18 months after the implementation of the tool. The rate of adherence of the discharge recommendations to the report was measured. Overall, 536 patients were included in the pre-intervention cohort and 367 in the intervention cohort. Demographic and clinical

features were similar between the two groups. After introduction of the tool, the percentage of patients discharged with long-acting medications increased from 42% to 84%, recommendations for smoking cessation increased from 32% to 91%, for vaccination from 13% to 92%, and for follow-up visit in a pulmonology clinic from 72% to 98%. Of the patients given prescriptions for long-acting bronchodilators, 54% purchased these after discharge versus 20% of the patients without such prescriptions. Decision-support tools can significantly improve adherence to guidelines among patients discharged after hospitalization due to Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) and potentially improve their clinical course.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1593342

Farre-Garros, R., J. Y. Lee, et al. (2019). **"Quadriceps miR-542-3p and 5p are elevated in COPD and reduce function by inhibiting ribosomal and protein synthesis."** J Appl Physiol (1985)Reduced physical performance reduces quality of life in patients with COPD. Impaired physical performance is, in part, a consequence of reduced muscle mass and function, which is accompanied by mitochondrial dysfunction. We recently showed that miR-542-3p and miR-542-5p were elevated in a small cohort of COPD patients and more markedly in critical care patients. In mice these miRNAs promoted mitochondrial dysfunction suggesting that they would affect physical performance in patients with COPD but we did not explore the association of these miRNAs with disease severity or physical performance further. We therefore quantified miR-542-3p/5p and mitochondrial rRNA expression in RNA extracted from quadriceps muscle of patients with COPD and determined their association with physical performance. As miR-542-3p inhibits ribosomal protein synthesis its ability to inhibit protein synthesis was also determined in vitro.Both miR-542-3p and -5p expression were elevated in patients with COPD (5-fold $p<0.001$) and the degree of elevation associated with impaired lung function (TLCO% and FEV1%) and physical performance (6-minute walk distance %). In COPD patients, the ratio of 12S rRNA to 16S rRNA was suppressed suggesting mitochondrial ribosomal stress and mitochondrial dysfunction and miR-542-3p/5p expression was inversely associated with mitochondrial gene expression and positively associated with p53 activity. miR-542-3p suppressed RPS23 expression and maximal protein synthesis in vitro. Our data show that miR-542-3p and -5p expression is elevated in COPD patients and may suppress physical performance at least in part by inhibiting mitochondrial and cytoplasmic ribosome synthesis and suppressing protein synthesis.

https://www.physiology.org/doi/abs/10.1152/japplphysiol.00882.2018

Fathima, M., B. Saini, et al. (2018). **"A mixed methods analysis of community pharmacists' perspectives on delivering COPD screening service to guide future implementation."** Res Social Adm PharmBACKGROUND: Studies have shown that COPD screening by community pharmacists is effective, but it is unknown if it can be successfully implemented in Australian pharmacies. OBJECTIVE: We aimed to investigate the pharmacist-perceived barriers and facilitators to the implementation of a community pharmacy-based COPD screening service guided by implementation science methodology. METHODS: Trained pharmacists participated in a 6 month longitudinal study designed and based on implementation science frameworks. Pharmacists completed feedback questionnaires pre-and post-study and participated in semi-structured telephone interviews about their experience of implementing the service, the training provided, their views on patient recruitment, their interactions with health professionals and patients, and their future recommendations for such a service. Interviews were recorded and transcribed verbatim, analysed thematically, and questionnaire and interview data were triangulated. RESULTS: Of 20 pharmacists providing questionnaire data, 15 pharmacists (male 53%; age 39.8+/-8.6yrs, rural 47%) participated in an interview. Questionnaire data revealed that pharmacists engaged positively with the service and reported that it was very useful for patients and for the profession. In-depth qualitative analysis revealed 6 main implementation themes: 1. Patient recruitment (pharmacists lacked patient recruitment skills), 2. Adaptation and entrepreneurship (protocol adaptation increased patient engagement), 3. Training and resource needs (face-to-face training was preferred for

skill-based learning), 4. Lack of GP involvement (sub-optimal GP-pharmacist collaboration), 5. Factors related to the operation or full implementation phase (high professional satisfaction, need for remuneration) and 6. Suggestions for refining the screening service (raise public awareness about the service, provide service remuneration, use electronic methods to improve GP referral uptake). A number of effective adaptations to the service were reported by pharmacists, such as advertising, recruitment practices, patient inclusion criteria and inter-professional communication with GPs which would be beneficial to implementation. CONCLUSION: This mixed methods study identified a number of key facilitators to service implementation and challenges such as difficulty with patient recruitment, low public awareness of pharmacy-based clinical services, remuneration, and sub-optimal GP-pharmacist collaboration. Working with stakeholders to identify and resolve challenges and to optimise the fit of the service for individual settings may lead to increasingly successful implementation of pharmacy-based service models.

Ferrone, M., M. G. Masciantonio, et al. (2019). **"The impact of integrated disease management in high-risk COPD patients in primary care."** NPJ Prim Care Respir Med **29**(1): 8.

Patients with chronic obstructive pulmonary disease (COPD) have a reduced quality of life (QoL) and exacerbations that drive health service utilization (HSU). A majority of patients with COPD are managed in primary care. Our objective was to evaluate an integrated disease management, self-management, and structured follow-up intervention (IDM) for high-risk patients with COPD in primary care. This was a one-year multi-center randomized controlled trial. High-risk, exacerbation-prone COPD patients were randomized to IDM provided by a certified respiratory educator and physician, or usual physician care. IDM received case management, self-management education, and skills training. The primary outcome, COPD-related QoL, was measured using the COPD Assessment Test (CAT). Of 180 patients randomized from 8 sites, 81.1% completed the study. Patients were 53.6% women, mean age 68.2 years, post-bronchodilator FEV1 52.8% predicted, and 77.4% were Global Initiative for Obstructive Lung Disease Stage D. QoL-CAT scores improved in IDM patients, 22.6 to 14.8, and worsened in usual care, 19.3 to 22.0, adjusted difference 9.3 ($p < 0.001$). Secondary outcomes including the Clinical COPD Questionnaire, Bristol Knowledge Questionnaire, and FEV1 demonstrated differential improvements in favor of IDM of 1.29 ($p < 0.001$), 29.6% ($p < 0.001$), and 100 mL, respectively ($p = 0.016$). Compared to usual care, significantly fewer IDM patients had a severe exacerbation, -48.9% ($p < 0.001$), required an urgent primary care visit for COPD, -30.2% ($p < 0.001$), or had an emergency department visit, -23.6% ($p = 0.001$). We conclude that IDM self-management and structured follow-up substantially improved QoL, knowledge, FEV1, reduced severe exacerbations, and HSU, in a high-risk primary care COPD population. Clinicaltrials.gov NCT02343055.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6438975/pdf/41533_2019_Article_119.pdf

Figueira-Goncalves, J. M., R. Golpe, et al. (2019). **"Comparison of the prognostic capability of two comorbidity indices in patients with chronic obstructive pulmonary disease, in real-life clinical practice."** Clin Respir JBACKGROUND: Comorbidities are a major cause of death in chronic obstructive pulmonary disease (COPD). The COPD-comorbidity test (COTE) index was designed to measure comorbidity burden in this disease. The objective of this study was to compare the capability of COTE and the non-COPD specific Charlson comorbidity index (CCI) to predict all-cause mortality in real-life conditions. METHODS: Retrospective observational study, carried out in two different series of consecutive COPD patients including, respectively, 790 and 439 subjects. The COTE and non-age-adjusted CCI indices were calculated and the values of the C-statistic for predicting all-cause mortality were compared for both indices. RESULTS: Median follow-up was 54 months and there were 321 deaths within this period of time. The value of the C-statistic for the CCI was significantly higher than for the COTE index in both groups. CONCLUSION: When used in real-life clinical practice, the value of the CCI to predict all-cause mortality in COPD seems higher than that of the COTE index.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13025

Folch-Ayora, A., M. I. Orts-Cortes, et al. (2019). **"Patient education during hospital admission due to exacerbation of chronic obstructive pulmonary disease: Effects on quality of life-Controlled and randomized experimental study."** Patient Educ Couns **102**(3): 511-519.

The objective of this study was to assess the effectiveness of an education program and telephone call follow-up at improving the health related quality of life (HRQL) of patients with chronic obstructive pulmonary disease (COPD). METHOD: Experimental, controlled, randomized, single blind study, masked data analysis. Duration of 2 years and 3 months. Patients hospitalised for exacerbation. The effectiveness was evaluated by calculating the absolute and relative change (%) of the St. George questionnaire scores (total and by dimensions) before and after the intervention program. Calculation of the effect of the group variable on the absolute and relative changes of the variables, Multiple Analysis of Variance (MANOVA). RESULTS: Completed study of 116 patients. Greater effects on their HRQL reported at admission (48.3 +/- SD 20.0 years). Patients in the intervention group improved significantly in their total SGRQ scores (-6.83) in absolute and relative terms and more significantly in their activity dimension (-16.05). CONCLUSIONS: The education program was effective at improving global HRQL, especially the activity dimension, in exacerbated COPD patients. PRACTICE IMPLICATIONS: This research contributes to clarifying the benefits and contents of education programs for patients with COPD; hospital admission is the suitable moment to contact these patients.

Formiga, F., A. Lopez-Soto, et al. (2005). **"Influence of acute exacerbation of chronic obstructive pulmonary disease or congestive heart failure on functional decline after hospitalization in nonagenarian patients."** Eur J Intern Med **16**(1): 24-28.

BACKGROUND: The functional decline that follows hospitalization may be especially important in frail populations such as nonagenarians. The present study examined the functional decline among nonagenarians admitted because of exacerbations of chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF). METHODS: A prospective cohort study was performed on two groups of patients who were distinguished by diagnosis in two tertiary academic medical hospitals. Sixty nonagenarian patients, admitted because of exacerbation of COPD (n=30) or CHF (n=30), were evaluated at admission, upon discharge, and 3 months post-hospitalization. The Barthel Index (BI) was used to assess functionality. The outcome we were interested in was functional decline 3 months after hospital discharge. RESULTS: The inpatient mortality rate was 10%. Overall functional status at discharge, as compared with that before admission, declined in all 54 surviving patients ($p<0.001$). At the 3-month follow-up, 37 patients were evaluated; a decline in their BI persisted in 60% of them. We did not find significant differences, either upon discharge or at 3 months post-hospitalization, in the decrease in BI rate between COPD patients and CHF patients. CONCLUSIONS: The fact that the underlying disease does not induce differences in the functional outcome of nonagenarians reinforces the importance of using a comprehensive approach at admission and after discharge for all frail patients.

https://www.ejinme.com/article/S0953-6205(04)00274-2/fulltext

Frazao, M., P. E. Silva, et al. (2018). **"Dynamic Hyperinflation Impairs Cardiac Performance During Exercise in COPD."** J Cardiopulm Rehabil PrevPURPOSE: To investigate the correlation between a plateau in minute ventilation VE during cardiopulmonary exercise tests (CPETs) and its impact on cardiac performance. METHODS: This retrospective study analyzed 2575 CPETs of patients with chronic obstructive pulmonary disease. The study randomly selected 10 patients with a plateau in the VE curve, suggesting dynamic

hyperinflation, 10 patients with normal pattern for the VE curve, and 10 healthy persons. Classic CPET variables, the new ventilation hyperinflation index, and the dynamic cardiac constraint index were analyzed. RESULTS: The patients with dynamic hyperinflation presented with lower ventilation at 100% work rate (P < .0001), without significant differences in VE at 50% and 100% work rate. Patients with dynamic hyperinflation also presented with a lower oxygen pulse (O2 pulse) at 100% (P < .0001), without significant difference in O2 pulse at 50% and 100% work rate. The subjects with dynamic hyperinflation had a higher ventilation hyperinflation index (P < .0001) and dynamic cardiac constraints index (P < .0001). The ventilation hyperinflation index correlated with the dynamic cardiac constraints index (r = 0.81, P < .0001); oxygen pulse variation (r =-0.63, P < .001); VE/VCO2 slope (r =-0.57, P < .01); work rate (r =-0.86, P < .0001); VO2 (r =-0.80, P < .0001), and VE (r =-0.83, P < .0001). CONCLUSION: There is a correlation between a plateau in the VE during CPET, suggesting hyperinflation, and it has an impact on cardiac performance.

Gadre, S. K., A. S. Jhand, et al. (2017). **"Effect of Anemia on Mortality in Mechanically Ventilated Patients With Chronic Obstructive Pulmonary Disease."** J Intensive Care Med: 885066617739561.

RATIONALE: The effect of anemia on patients with chronic obstructive pulmonary disease (COPD) requiring invasive mechanical ventilation for acute respiratory failure is unknown. OBJECTIVES: To examine the association between anemia (hemoglobin <12 g/dL) and 90-day and overall mortality in patients with COPD having acute respiratory failure requiring invasive mechanical ventilation. METHODS: Retrospective study of patients admitted to a quaternary referral medical intensive care unit (ICU) between October 2007 and December 2012 with a diagnosis of COPD and requiring invasive mechanical ventilation for acute respiratory failure of any cause. RESULTS: We identified 1107 patients with COPD who required invasive mechanical ventilation for acute respiratory failure. Mean age was 64.2 +/- 12.7 years; 563 (50.9%) were females. The mean Acute Physiology and Chronic Health Evaluation III score at ICU admission was 80.5 +/- 29.3. The median duration of mechanical ventilation was 35.7 hours (interquartile range: 20.0-54.0). In all, 885 (79.9%) patients were anemic (Hb < 12g/dL) on ICU admission, and 312 patients (28.2%) received blood transfusion during their ICU stay. A total of 351 inhospital deaths were recorded, the majority (n = 320) occurring in the ICU. The 90-day mortality, though lower in the nonanemic patients compared to the patients with anemia, was not statistically significant (35.6% vs 44.9%; hazard ratio [HR] [95% confidence interval; CI] = 1.16 [0.91 -1.48], P = .22). The overall mortality was lower in the nonanemic patients compared to patients with anemia (HR [95% CI] = 0.68 [0.55-0.83], P < .001). There was a 5% decrease in risk of death for every unit increase in hemoglobin (P = .01). There was no difference in terms of both 90-day and overall mortality in patients who received blood transfusions compared to patients who did not receive any transfusion. CONCLUSIONS: Critically ill patients with COPD requiring invasive mechanical ventilation for acute respiratory failure without anemia on admission had a better overall survival when compared to those with anemia. No difference was noted in the 90-day mortality. Further studies are needed to determine the impact of the trajectory of hemoglobin on mortality.

Gagnat, A. A., A. Gulsvik, et al. (2019). **"Comparison of two lung cancer screening scores among patients with chronic obstructive pulmonary disease: A community study."** Clin Respir J **13**(2): 114-119.

INTRODUCTION: Based on the National Lung Cancer Screening Trial (NLST), guidelines on screening programs for lung cancer have recommended low-dose computed tomography (LDCT). De Torres et al made a score for COPD patients (COPD-LUCSS) to improve their selection criteria. OBJECTIVE: To examine and compare the discriminating value of both scores in a community-based cohort of COPD patients. METHODS: Four hundred and twenty-two ever-smokers with COPD from the GenKOLS study in Bergen were merged with the Cancer Registry of Norway. We divided the patients into groups of high and low risk according to the COPD-LUCSS and the NLST criteria. Cox regression and logistic regression were

used to analyse the associations between the scores and lung cancer. We used Harrell's C and area under the curve (AUC) to estimate discriminating values and to compare the models. RESULTS: Hazard ratio for the high risk vs the low risk in the COPD-LUCSS was 3.0 (1.4-6.5 95% CI), P < 0.01. Hazard ratio for the NLST criteria was 2.2 (95% CI 1.1-4.5), P < 0.05. Harrell's C was 0.63 for the COPD-LUCSS and 0.59 for the NLST selection criteria. AUC was 0.61 for COPD-LUCSS and 0.59 for NLST criteria. Comparing tests showed no differences (P = 0.76). CONCLUSION: Although the COPD-LUCSS and the NLST criteria were associated with increased risk of lung cancer, the AUC and Harrell's C values showed that these models have poor discriminating abilities in our cohort of COPD patients. The COPD-LUCSS was not significantly better than the NLST criteria.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12988

Gainza-Miranda, D., E. M. Sanz-Peces, et al. (2019). **"Breaking Barriers: Prospective Study of a Cohort of Advanced Chronic Obstructive Pulmonary Disease Patients To Describe Their Survival and End-of-Life Palliative Care Requirements."** J Palliat Med **22**(3): 290-296.

BACKGROUND AND AIM: Consensus has been reached on the need to integrate palliative care in the follow-up examinations of chronic obstructive pulmonary disease (COPD) patients. We analyzed the survival from the initiation of follow-up by a palliative home care team (PHCT) and described the needs and end-of-life process. SETTING AND DESIGN: This study was a prospective observational cohort study of advanced COPD patients referred to a PHCT. Sociodemographic variables, survival from the start date of follow-up using the Kaplan-Meier model, health resource consumption, perceived quality of life, main symptomatology, opioid use, and advanced care planning (ACP) were analyzed. RESULTS: Sixty patients were included. The median survival was 8.3 months. Forty-two patients died at the end of the study (85% at home or in palliative care units). The most frequent cause of death was respiratory failure in 39 patients (93%), with 29 of these patients requiring sedation (69%). Dyspnea at rest, with an average of 5 (standard deviation [SD] 2) points, was the main symptom. Fifty-five patients (91%) required opioids for symptom control. The median score in the St. George's Respiratory Questionnaire was 72 (SD 13). The mean number of visits by the home team was 7 (SD 6.5). The mean number of admissions during the monitoring period was 1.5 (SD 0.15). CONCLUSIONS: The characteristics of the cohort appear suitable for a PHCT. The follow-up care provided by our multidisciplinary unit decreased the number of hospitalizations, favored the development of ACP, and enabled death at home or in palliative care units.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6391614/pdf/jpm.2018.0363.pdf

Gale, N. S., A. M. Albarrati, et al. (2019). **"Aortic Pulse Wave Velocity as a Measure of Cardiovascular Risk in Chronic Obstructive Pulmonary Disease: Two-Year Follow-Up Data from the ARCADE Study."** Medicina (Kaunas) **55**(4)Background and objectives: Cardiovascular (CV) disease is a major cause of morbidity and mortality in chronic obstructive pulmonary disease (COPD). Patients with COPD have increased arterial stiffness, which may predict future CV risk. However, the development of arterial stiffness in COPD has not yet been studied prospectively. The Assessment of Risk in Chronic Airways Disease Evaluation (ARCADE) is a longitudinal study of CV risk and other comorbidities in COPD. The aims of this analysis were to explore factors associated with aortic pulse wave velocity (aPWV) at baseline and to describe the progression of aPWV in patients with COPD and comparators over two years. Materials and methods: At baseline, 520 patients with COPD (confirmed by spirometry) and 150 comparators free from respiratory disease were assessed for body composition, blood pressure, aPWV, noninvasive measures of cardiac output, inflammatory biomarkers, and exercise capacity. This was repeated after two years, and mortality cases and causes were also recorded. Results: At baseline, aPWV was greater in COPD patients 9.8 (95% confidence interval (CI) 9.7-10.0) versus comparators 8.7 (8.5-9.1) m/s ($p < 0.01$) after adjustments for age, mean arterial pressure (MAP), and heart rate. Mean blood pressure was 98 +/- 11 in COPD patients and 95 +/- 10 mmHg in comparators at baseline ($p = 0.004$). After two years, 301 patients and 105 comparators were fully reassessed. The mean (95% CI) aPWV increased similarly in patients 0.44 (0.25-0.63) and comparators 0.46 (0.23-0.69) m/s, without a change in

blood pressure. At the two-year follow-up, there were 29 (6%) deaths in COPD patients, with the majority due to respiratory causes, with an overall dropout of 43% of patients with COPD and 30% of comparators. Conclusions: This was the first large longitudinal study of CV risk in COPD patients, and we confirmed greater aPWV in COPD patients than comparators after adjustments for confounding factors. After two years, patients and comparators had a similar increase of almost 0.5 m/s aPWV.

https://res.mdpi.com/medicina/medicina-55-00089/article_deploy/medicina-55-00089-v2.pdf?filename=&attachment=1

Gaugg, M. T., Y. Nussbaumer-Ochsner, et al. (2019). **"Real-Time Breath Analysis Reveals Specific Metabolic Signatures of COPD Exacerbations."** ChestBACKGROUND: Exacerbations of COPD are defined by acute worsening of respiratory symptoms leading to a change in therapy. Identifying altered metabolic processes in patients at risk for future exacerbations is desirable for treatment optimization, the development of new therapeutic strategies, and perhaps diagnostic value. We aimed to identify affected pathways using the profiles of volatile organic compounds in exhaled breath from patients with COPD with and without frequent exacerbations (>/= 2 exacerbations within the past 12 months). METHODS: In this matched cohort study, exhaled breath profiles from patients with COPD and frequent exacerbations ("frequent exacerbators") and without frequent exacerbations ("nonfrequent exacerbators") were analyzed during an exacerbation-free interval using real-time secondary electrospray ionization high-resolution mass spectrometry. We analyzed exhaled breath from 26 frequent exacerbators and 26 nonfrequent exacerbators that were matched in terms of age, sex, and smoking history. To obtain new pathophysiological insights, we investigated significantly altered metabolites, which can be assigned to specific pathways. Metabolites were identified by using a Wilcoxon rank-sum test. RESULTS: Metabolite levels from the omega-oxidation pathway, namely omega-hydroxy, omega-oxo, and dicarboxylic acids, were consistently decreased in frequent exacerbators. Additionally, several new nitro-aromatic metabolites, which were significantly increased in frequent exacerbators, were identified. CONCLUSIONS: Real-time breath analysis by secondary electrospray high-resolution mass spectrometry allows molecular profiling of exhaled breath, providing insights about ongoing biochemical processes in patients with COPD at risk for exacerbations. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02186639; URL: www.clinicaltrials.gov.

https://journal.chestnet.org/article/S0012-3692(19)30062-5/fulltext

Germini, F., G. Veronese, et al. (2019). **"Validation of the BAP-65 score for prediction of in-hospital death or use of mechanical ventilation in patients presenting to the emergency department with an acute exacerbation of COPD: a retrospective multi-center study from the Italian Society of Emergency Medicine (SIMEU)."** Eur J Intern Med **61**: 62-68.

Exacerbations of chronic obstructive pulmonary disease (COPDE) frequently require hospitalizations, may necessitate of invasive mechanical ventilation (IMV), and are associated with a remarkable in-hospital mortality. The BAP-65 score is a risk assessment model (RAM) based on simple variables, that has been proposed for the prediction of these adverse outcomes in patients with COPDE. If showed to be accurate, the BAP-65 RAM might be used to guide the patients management, in terms of destination and treatment. We conducted a retrospective, multicentre, chart-review study, on patients attending the ED for a COPDE during 2014. The aim of the study was the validation of the BAP-65 RAM for the prediction of in-hospital death or use of IMV (composite primary outcome). We assessed the discrimination and the prognostic performance of the BAP-65 RAM. We enrolled 2908 patients from 20 centres across Italy. The mean (standard deviation) age was 76 (11) years, and 38% of patients were female. The composite outcome occurred in 5.3% of patients. The AUROC of BAP-65 for the composite outcome was 0.64 (95%CI 0.59-0.68). The sensitivity of BAP-65 score>/=4 to predict in-hospital mortality was 44% (95% CI 34%-55%), the specificity was 84% (95% CI 82%-85%), the positive predictive value was 9% (95% CI 6%-12%), and the negative predictive value was 98% (95% CI 97%-98%). CONCLUSIONS: In

patients attending Italian EDs with a COPDE, we found that the BAP-65 score did not have sufficient accuracy to stratify patients upon their risk of severe in-hospital outcomes.

https://www.ejinme.com/article/S0953-6205(18)30411-4/fulltext

Ghosh, S., W. H. Anderson, et al. (2019). **"Alignment of Inhaled Chronic Obstructive Pulmonary Disease Therapies with Published Strategies. Analysis of the Global Initiative for Chronic Obstructive Lung Disease Recommendations in SPIROMICS."** Ann Am Thorac Soc **16**(2): 200-208.

RATIONALE: Despite awareness of chronic obstructive pulmonary disease (COPD) treatment recommendations, uptake is poor. The Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) spans 2010-2016, providing an opportunity to assess integration of 2011 Global Initiative for Obstructive Lung Disease (GOLD) treatment strategies over time in a large observational cohort study. OBJECTIVES: To evaluate how COPD treatment aligns with 2011 GOLD strategies and determine factors associated with failure to align with recommendations. METHODS: Information on inhaled medication use collected via questionnaire annually for 4 years was compiled into therapeutic classes (long-acting antimuscarinic agent, long-acting beta-agonist, inhaled corticosteroids [ICS], and combinations thereof). Medications were not modified by SPIROMICS investigators. 2011 GOLD COPD categories A, B, C, and D were assigned. Alignment of inhaler regimen with first-/second-line GOLD recommendations was determined, stratifying into recommendation aligned or nonaligned. Recommendation-nonaligned participants were further stratified into overuse and underuse categories. RESULTS: Of 1,721 participants with COPD, at baseline, 52% of regimens aligned with GOLD recommendations. Among participants with nonaligned regimens, 46% reported underuse, predominately owing to lack of long-acting inhalers in GOLD category D. Of the 54% reporting overuse, 95% were treated with nonindicated ICS-containing regimens. Among 431 participants with 4 years of follow-up data, recommendation alignment did not change over time. When we compared 2011 and 2017 recommendations, we found that 47% did not align with either set of recommendations, whereas 35% were in alignment with both recommendations. CONCLUSIONS: Among SPIROMICS participants with COPD, nearly 50% reported inhaler regimens that did not align with GOLD recommendations. Nonalignment was driven largely by overuse of ICS regimens in milder disease and lack of long-acting inhalers in severe disease.

Ghosh, S., R. A. Pleasants, et al. (2019). **"Prevalence and factors associated with suboptimal peak inspiratory flow rates in COPD."** Int J Chron Obstruct Pulmon Dis **14**: 585-595.

Purpose: Adequate peak inspiratory flow rate (PIFR) is required for drug dispersion with dry powder inhalers (DPIs). Prevalence of PIFR discordance (suboptimal PIFR with prescribed inhalers) and factors influencing device-specific PIFR are unclear in COPD. The objective of this study was to determine the prevalence of PIFR discordance and associated clinical factors in a stable COPD population. Patients and methods: An observational, single-center, cohort study was conducted including 66 outpatients with COPD. PIFR was measured using the In-Check Dial with applied resistance of prescribed inhalers. Participants were defined as discordant if measured PIFR was <30 L/min and <60 L/min for high and low-medium resistance devices, respectively, using an inspiratory effort the participant normally used with their prescribed DPI. Results: The median age of the COPD participants was 69.4 years, 92% were white and 47% were female. A total of 48% were using low-medium resistance DPIs (Diskus((R))/Ellipta((R))) and 76% used high-resistance DPI (Handihaler((R))). A total of 40% of COPD participants were discordant to prescribed inhalers. Female gender was the only factor consistently associated with lower PIFR. Shorter height was associated with reduced PIFR for low-medium resistance (r=0.44; P=0.01), but not high resistance (r=0.20; P=0.16). There was no correlation between PIFR by In-Check dial and PIFR measured by standard spirometer. Conclusion: PIFR is reduced in stable COPD patients, with female gender being the only factor consistently associated with reduced PIFR. Discordance with prescribed inhalers was seen in 40% of COPD patients, suggesting that many COPD patients do not generate adequate inspiratory force to overcome prescribed DPIs resistance in the course of normal use.

https://www.dovepress.com/getfile.php?fileID=48357

Gillissen, A., C. Gessner, et al. (2019). **"Patient Satisfaction and Clinical Outcomes with Budesonide plus Formoterol Spiromax for Asthma and Chronic Obstructive Pulmonary Disease: A Real-World, Observational Trial."** Respiration **97**(4): 292-301.

BACKGROUND: The fixed-dose combination of budesonide/formoterol (B/F) has been available in the Spiromax(R) dry powder inhaler since 2014. OBJECTIVES: To assess patient satisfaction, inhaler use errors, and disease control in patients with asthma or chronic obstructive pulmonary disease (COPD) treated with B/F Spiromax. METHODS: This non-interventional, prospective, 12-week study enrolled consecutive asthma or COPD patients who had recently begun treatment with B/F Spiromax or were switched from another inhaled corticosteroid/long-acting beta2-agonist combination to B/F Spiromax in routine clinical practice. Patients recruited from 243 specialist respiratory clinics or general practices in Germany were assessed for patient satisfaction (Satisfaction with Inhalers and Preference questionnaire), inhaler application errors (modified Easy Low Instruction over Time checklist), disease control, and safety. RESULTS: The population included 3,943 patients: asthma n = 2,707 (68.7%); COPD n = 1,236 (31.3%). At baseline, 60.1% of patients were "satisfied" or "very satisfied" with their previous inhaler, and this increased to 88.8% at week 12 of B/F Spiromax use. Overall, 62.1% of pre-treated patients preferred B/F Spiromax to their old inhaler. The frequency of any handling error observed with B/F Spiromax at week 12 was lower than at baseline (11.9 vs. 25.5% of patients, respectively). After 12 weeks, 77.4% were assessed as having improved (minimally, much, or very much) overall health status versus baseline. Guideline-defined disease severity (as rated by physicians) and patient-reported symptom severity improved during the study in both asthma and COPD patients. B/F Spiromax was well tolerated. CONCLUSION: B/F Spiromax was associated with high patient satisfaction, low device handling error rate, and improvements in clinical outcomes in real-world clinical practice.

https://www.karger.com/Article/Abstract/493860

Gilowska, I., E. Majorczyk, et al. (2019). **"The role of MMP-12 gene polymorphism - 82 A-to-G (rs2276109) in immunopathology of COPD in polish patients: a case control study."** BMC Med Genet **20**(1): 19.

BACKGROUND: Major symptoms of chronic obstructive pulmonary disease (COPD) are chronic bronchitis and emphysema leading from lung tissue destruction, that is an effect of an imbalance between metalloproteinases (MMPs) and their tissue inhibitors activity. As potential factor involved in this COPD pathogenesis, MMP-12 is considered. We investigated the role of genetic polymorphism and protein level of MMP-12 in the COPD development among Poles. METHODS: We analyzed - 82 A > G SNP in the promoter region of MMP-12 gene (rs2276109) among 335 smoked COPD patients and 309 healthy individuals, including 110 smokers. Additionally, 60 COPD patients and 61 controls (23 smokers) were tested for serum levels of MMP-12 using ELISA. All subjects were analyzed for lung function using spirometry (FEV1% and FEV1/FVC parameters). RESULTS: We observed that -82G allele and -82GG homozygous genotype frequencies of the SNP rs2276109 were significantly lower in COPD patients than in controls (12.5% vs 16.9%, respectively; chi(2) = 4.742, p = 0.02 for allele and 0.5% vs 3.9%, respectively; chi(2) = 9.0331, p = 0.01 for genotype). Moreover, -82G allele was more frequent in controls smokers than in non-smokers (22.3% vs 14.1%, chi(2) = 6.7588, p = 0.01). Serum level of MMP-12 was significantly higher in COPD patients than in controls groups (6.8 ng/ml vs 3.3 ng/ml, respectively; F = 7.433, p < 0.0001), although independently of analyzed gene polymorphisms. Additionally, no correlation between parameters of lung function (FEV1% and FEV1/FVC) and protein level was found. CONCLUSIONS: We found that -82G allele of SNP rs2276109 was associated with reduced risk of COPD, and COPD patients released more MMP-12 than healthy individuals, but independently on this SNP.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6339316/pdf/12881_2019_Article_751.pdf

Gompelmann, D., N. Benjamin, et al. (2019). **"Survival after Endoscopic Valve Therapy in Patients with Severe Emphysema."** Respiration **97**(2): 145-152.

BACKGROUND: Endoscopic valve therapy leads to an improvement of lung function, exercise tolerance, and quality of life in a selected cohort of patients with advanced emphysema. So far, only few data exist on the long-term outcome. OBJECTIVES: This analysis evaluated the impact of valve therapy on the survival of emphysema patients. METHODS: Survival rates of emphysema patients who underwent valve therapy were assessed according to their radiological outcome following valve placement. RESULTS: From 2005 to 2013, 449 emphysema patients (mean age 64 +/- 7 years) underwent valve therapy and were followed for a mean time of 37.3 +/- 21.3 months. A total of 128 patients (29%) developed complete lobar atelectasis, 34 out of these also experienced a pneumothorax; 50 patients (11%) developed pneumothorax without lobar atelectasis, and 261 patients (58%) target lobe volume reduction or no volume change. Patients with atelectasis showed significantly better baseline forced expiratory volume in 1 second (%), residual volume (L), total lung capacity (L), and transfer factor for carbon monoxide (%; all $p < 0.05$), but there was no significant difference in the BODE score ($p = 0.195$). Patients with valve-induced lobar atelectasis had a significant survival benefit compared to patients without atelectasis ($p = 0.009$; 5-year survival rate 65.3 vs. 43.9%). The advent of pneumothorax in 84 patients did not influence survival ($p = 0.52$). CONCLUSIONS: Lobar atelectasis following endoscopic valve therapy is associated with a survival benefit.

https://www.karger.com/Article/Abstract/492274

Gu, B. H., J. C. Choi, et al. (2019). **"Elastin-Specific Autoimmunity in Smokers With Thoracic Aortic Aneurysm and Dissection is Independent of Chronic Obstructive Pulmonary Disease."** J Am Heart Assoc **8**(8): e011671.

Background Thoracic aortic aneurysm (TAA) and dissection (TAD) are characterized by progressive disorganization of the aortic wall matrix, including elastin, a highly immunogenic molecule. Whether acquired autoimmune responses can be detected in TAA / TAD patients who are smokers is unknown. The objectives of this study were to determine whether TAA / TAD smokers have increased T-cell responses to human elastin fragments, and to determine whether autoimmune responses in TAA / TAD smokers are dependent on chronic obstructive pulmonary disease. Methods and Results In a cross-sectional study (N=86), we examined peripheral blood CD 4(+) T cell responses to elastin fragments in never-, former-, or current-smokers with or without TAA / TAD . CD 4(+) T cells were co-cultured with irradiated autologous peripheral blood CD 1a(+)/ CD 14(+) antigen presenting cells pulsed with or without elastin fragments to measure cytokine production. Baseline plasma concentration of anti-elastin antibodies and elastin-degrading enzymes (eg, matrix metalloproteinase-9, and -12, and neutrophil elastase) were measured in the same cohort. elastin fragment-specific CD 4(+) T cell expression of interferon-gamma, and anti-elastin antibodies were dependent on history of smoking in TAA / TAD patients but were independent of chronic obstructive pulmonary disease. Matrix metalloproteinase-9, and -12, and neutrophil elastase plasma concentrations were also significantly elevated in ever-smokers with TAA / TAD . Conclusions Cigarette smoke is associated with loss of self-tolerance and induction of elastin-specific autoreactive T- and B-cell responses in patients with TAA / TAD . Development of peripheral blood biomarkers to track immunity to self-antigens could be used to identify and potentially prognosticate susceptibility to TAA / TAD in smokers.

Gulbas, G., O. Turan, et al. (2019). **"Carotid intima-media thickness in chronic obstructive pulmonary disease and survival: A Multicenter Prospective Study."** Clin Respir JINTRODUCTION: Chronic obstructive pulmonary disease (COPD) is associated with increased cardiovascular morbidity and mortality. Carotid intima-media thickness (CIMT) is a non-invasive method assessing atherosclerosis. OBJECTIVE: It was

aimed to determine relationship and survival between COPD and CIMT. METHODS: CIMT was measured using Doppler ultrasound(USG) in 668 stable COPD patients at 24 centers. Patients were followed-up for two years. RESULTS: There were 610 patients who completed the study. There were 200 patients CIMT with<0.78 mm (group 1), and 410 with CIMT>/=0.78 mm (group 2). There was a significant difference at the parameters of age, gender, smoking load, biomass exposure, GOLD groups and degree of airway obstruction (FEV1) between group 1 and 2. Our results revealed positive correlations between mean CIMT and age, smoking load (pack-years), biomass exposure(years), exacerbation rate(last year), duration of hypertension(years) and cholesterol level; negative correlations between CIMT and FEV1 (p<0.05). According to logistic regression model,compared with Group A, risk of CIMT increase was 2.2 folds in Group B, 9.7 folds in Group C, and 4.4 folds in Group D(p<0.05). Risk of CIMT increase was also related with cholesterol level (p<0.05). Compared with infrequent exacerbation, it was 2.8 folds in the patients with frequent exacerbation(p<0.05). The mean survival time was slightly higher in Group 1,but not significant(23.9 versus 21.8 months) (p>0.05). CONCLUSION: This study is the first regarding CIMT with combined GOLD assessment groups. It has revealed important findings supporting the increase in atherosclerosis risk in COPD patients. We recommend Doppler USG of the carotid artery in COPD patients at severe stages.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13024

Guo, Y. l., Y. Qian, et al. (2015). **"A predictive model for the development of chronic obstructive pulmonary disease."** Biomed Rep **3**(6): 853-863.

The screening of a person at risk for chronic obstructive pulmonary disease (COPD) and timely treatment may provide opportunities to delay the progressive destruction of lung function. Therefore, a model to predict the disease is required. We hypothesized that demographic and clinical information in combination with genetic markers would aid in the prediction of COPD development, prior to its onset. The aim of the present study was to create a predictive model for COPD development. Demographic, clinical presentation and genetic polymorphisms were recorded in COPD patients and control subjects. Nighty-six single-nucleotide polymorphisms of 46 genes were selected for genotyping in the case-control study. A predictive model was produced using logistic regression with a stepwise model-building approach and was validated. A total of 331 patients and 351 control subjects were included. The logistic regression identified the following predictors: Gender, respiratory infection in early life, low birth weight, smoking history and genotype polymorphisms (rs2070600, rs10947233, rs1800629, rs2241712 and rs1205). The model was established using the following formula: COPD = 1/[1 + exp (-2.4933-1.2197 gender + 1.1842 respiratory infection in early life + 2.4350 low birth weight + 1.8524 smoking - 1.1978 rs2070600 + 2.0270 rs10947233 + 1.1913 rs10947233 + 0.6468 rs1800629 + 0.5272 rs2241712 + 0.4024 rs1205)] (when the value is >0.5). The Hosmer-Lemeshow test showed no significant deviations between the observed and predicted events. Validation of the model in 50 patients showed a modest sensitivity and specificity. Therefore, a predictive model based on demographic, clinical and genetic information may identify COPD prior to its onset.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4660625/pdf/br-03-06-0853.pdf

Hao, W., M. Li, et al. (2019). **"High Serum Fractalkine/CX3CL1 in Patients with Chronic Obstructive Pulmonary Disease: Relationship with Emphysema Severity and Frequent Exacerbation."** Lung **197**(1): 29-35.

OBJECTIVE: The purpose of this study was to investigate the relationship between serum fractalkine (CX3CL1/FKN) level and the multi-slice spiral computed tomography (MSCT) emphysema index in Chinese patients with chronic obstructive pulmonary disease (COPD). METHODS: We detected chemokine CX3CL1 in serum from 95 Chinese patients with COPD by using an enzyme-linked immunosorbent assay. According to the MSCT emphysema index, the selected cases were divided into an emphysema-dominant group (n = 25) and a non-emphysema-dominant group (n = 70). RESULTS: There were significant differences in body mass index and lung function between the two groups. The serum level of CX3CL1 in the emphysema-

dominant group was significantly higher than that in the non-emphysema-dominant group. Through multivariate logistic regression analysis, it was found that high serum CX3CL1 levels were independently associated with emphysema, with a relative risk of 2.617 (95% CI 1.018-6.121; P = 0.029). The percentage of frequent acute exacerbations during the first year of follow-up was significantly higher in the high-level serum CX3CL1 group (P = 0.039). After 3 years of follow-up, there was no significant difference in the CT emphysema index between the high and low serum CX3CL1 groups (P = 0.503). CONCLUSION: Our results suggest that the serum level of CX3CL1 is related to the MSCT emphysema index. Chemokine CX3CL1 might be a useful predictor for identifying frequent exacerbation and emphysema severity in patients with COPD.

https://link.springer.com/article/10.1007%2Fs00408-018-0176-9

Hayes Watson, C., H. Nuss, et al. (2018). **"Health beliefs associated with poor disease self-management in smokers with asthma and/or COPD: a pilot study."** J Asthma: 1-8.

BACKGROUND: Compared to nonsmokers, smokers with chronic disease are less likely to adhere to self-management recommendations for the management of their chronic conditions. Although the literature notes poor adherence trends in smokers, actual influences of adherence in these patients require further study. This study examines the health beliefs that influence self-management behaviors in smokers with chronic lung disease. METHODS: This prospective, cross-sectional study surveyed patients (n = 83) seen in the pulmonary outpatient clinics of the University Medical Center of New Orleans between November 2015 and February 2016. Eligible patients included those between 40-64 years old diagnosed with asthma and/or chronic obstructive pulmonary disease (COPD). Primary measures included perceived beliefs related to the susceptibility to asthma and/or COPD becoming worse, perceived barriers to adherence, and perceived benefits to adherence. Patient characteristics under-study included smoking status, race, gender, and diagnosis. Descriptive and chi-square analyses were performed to characterize the sample. Student's t and and regression analyses were conducted to examine the relationships between perceptions, smoking status, race, gender, and diagnosis. RESULTS: Compared to nonsmokers, smokers perceived their asthma and/or COPD becoming worse (p = 0.0023). Smokers also perceived more barriers (p < 0.0001), and fewer benefits to adherence than nonsmokers (p = 0.0021). CONCLUSION: The health beliefs of smokers may influence their self-management behaviors. Results of this study can inform the development of services that target smokers in order to improve adherence to self-management behaviors and health outcomes.

https://www.tandfonline.com/doi/full/10.1080/02770903.2018.1509990

He, C., S. Ren, et al. (2018). **"Adjuvant Therapy: YiqiDitanTongfu Decoction With External Diaphragm Pacer for Chronic Obstructive Pulmonary Disease Patients With Difficulty Weaning From Mechanical Ventilation."** Altern Ther Health MedContext * Global morbidity from chronic obstructive pulmonary disease (COPD) is high worldwide. Diaphragm pacing (DP) can maintain the natural, negative pressure breathing of COPD patients with diaphragmatic muscle dysfunction. The YiqiDitanTongfu (YDTF) decoction has been used clinically with COPD patients to help them to wean from mechanical ventilation, with their ventilation functions being improved and the success rate of weaning being largely increased. Objective * The study intended to investigate the combined therapeutic effects of external DP and the YDTF decoction for COPD patients who have had difficulty weaning from mechanical ventilation. Design * This study was a retrospective cohort study. Setting * The study occurred at the Hebei General Hospital and Hebei Province Chest Hospital (Hebei Province, Shijiazhuang, China). Participants * Participants were 90 patients with COPD + type 1 respiratory failure, 101 patients with COPD + Type 2 respiratory failure, and 96 patients with COPD at the compensated stage. INTERVENTION: The participants were randomly divided into 3 groups: (1) traditional treatment (control group), (2) traditional treatment plus treatment with a diaphragm pacemaker (DP group), and (3) traditional treatment plus treatment with a DP and a YDTF decoction (DP + YDTF group). All treatments occurred for 12 d. Outcome Measures * Relevant outcomes were measured and compared at baseline

and postintervention, including the rapid shallow breathing index, tidal volume, maximum inspiratory pressure, degree of diaphragmatic muscle activity, maximum expiratory pressure, the successful rates of weaning from mechanical ventilation, the potential of hydrogen, the partial pressure of oxygen, partial pressure of carbon dioxide, and oxygen saturation. Results * The patients treated with the DP plus the YDTF decoction were more successful in weaning from mechanical ventilation than those treated with DP. Of the patients with COPD + type 1 respiratory failure, 86.67% succeeded vs 70.00% of the DP patients. Of patients with COPD + type 2 respiratory failure, 87.88% succeeded vs 79.41% of the DP patients. Conclusion * The DP plus the YDTF concoction acted as a successful treatment for heart failure caused by CPOD in comparison with the DP or YDTF alone, providing evidence that the DP + YDTF concoction can serve as a competitive method for helping COPD patients to wean from mechanical ventilation.

He, N., B. H. Rosen, et al. (2018). **"Generation of Alpha-1 Antitrypsin Knockout and PI*ZZ Ferrets Using Crispr/Cas9. A Genetic Model of Emphysema."** Ann Am Thorac Soc **15**(Supplement_4): S292-s293.

RATIONALE: The most prevalent genetic cause of chronic obstructive pulmonary disease is alpha-1 antitrypsin (A1AT) deficiency, a disorder that has yet to be widely modeled in animals because of species-specific differences between rodents and humans. OBJECTIVES: To address these challenges, we engineered two A1AT ferret models using zygote gene editing to test the hypothesis that unopposed protease activity within the lung leads to emphysema and bronchitis. METHODS: Guide RNAs targeting exon 2 (for knockout) and exon 5 (for Z-allele mutation, Pi*Z) of the ferret A1AT gene were injected into ferret zygotes with Cas9 mRNA. For PI*Z targeting, a short oligonucleotide carrying the mutation was included. Offspring were genotyped and plasma levels of A1AT determined by Western blot before entry into a longitudinal study. Adult A1AT ferrets underwent bronchoscopy and FlexiVent over time to characterize lung disease. Control animals were wild-type (WT) and age, sex, and size matched. RESULTS: A1AT-deficient ferrets spontaneously develop hallmarks of emphysema as early as 3 months when compared with matched WT control ferrets. Over time, A1AT-KO ferrets reached an inspiratory capacity of 117% +/- 5% (WT, 57.4 ml; A1AT, 67.5 ml) and compliance of 111% +/- 4% (WT, 5.5 ml/cm H2O; A1AT, 6.1 ml/cm H2O; N = 8 pairs A1AT/WT, $P < 0.05$). Progression of these disease parameters and pressure-volume loop disturbances increased with age (oldest are approximately 2 yr). The bronchoalveolar lavage (BAL) proteome of KO animals confirmed absence of A1AT protein along with elevated soluble Muc5AC (Log2 fold change, 6.74; $P < 0.001$). Active neutrophil elastase was elevated in A1AT-KO versus WT BAL (292 +/- 82 vs. 179 +/- 17 ng/ml) but did not reach significance; in one experiment, active NE was sixfold higher in the upper lobe of the A1AT than the lower (1,240 vs. 209 ng/ml). Quantitative alveolar morphometry in one A1AT was 121% of its matched WT control. The PI*ZZ animals are entering studies at several months of age. CONCLUSIONS: Our findings suggest that A1AT-deficient ferrets spontaneously develop anatomic and physiologic aspects of progressive lung disease consistent with emphysema and chronic bronchitis.

Heintzman, J., J. Kaufmann, et al. (2019). **"Asthma/COPD Disparities in Diagnosis and Basic Care Utilization Among Low-Income Primary Care Patients."** J Immigr Minor Health **21**(3): 659-663.

Obstructive pulmonary disease outcomes in the United States differ between Latinos and non-Hispanic whites. There is little objective data about diagnosis prevalence and primary care visit frequency in these disease processes. We used electronic health record data to perform a retrospective cohort analysis of 34,849 low-income patients seen at Oregon community health centers between 2009 and 2013 to assess joint racial/ethnic and insurance disparities in diagnosis and visit rates between Latino and non-Hispanic white patients. The overall study prevalence of obstructive lung disease was 18%. Latinos had lower odds of obstructive lung disease diagnosis (OR 0.37, 95% CI 0.30-0.44). Among those diagnosed prior to 2009, the uninsured (regardless of race/ethnicity) had lower visit rates during 2009-2013 than the insured. This

study identified racial/ethnic disparities in the diagnosis of obstructive pulmonary disease between Latinos and non-Hispanic Whites, confirming trends observed in survey research but controlling for important confounders. Health insurance was associated with basic care utilization, suggesting that lack of health insurance could lessen the quality of care for obstructive pulmonary disease in Latino and non-Hispanic white patients.

https://link.springer.com/article/10.1007%2Fs10903-018-0798-2

Herbert, J., H. Thiermann, et al. (2019). **"COPD and asthma therapeutics for supportive treatment in organophosphate poisoning."** Clin Toxicol (Phila): 1-8.

CONTEXT: Nerve agents like sarin or VX have repeatedly been used in military conflicts or homicidal attacks, as seen in Syria or Malaysia 2017. Together with pesticides, nerve agents assort as organophosphorus compounds (OP), which inhibit the enzyme acetylcholinesterase. To counteract subsequent fatal symptoms due to acetylcholine (ACh) accumulation, oximes plus atropine are administered, a regimen that lacks efficacy in several cases of OP poisoning. New therapeutics are in development, but still need evaluation before clinical employment. Supportive treatment with already approved drugs presents an alternative, whereby compounds from COPD and asthma therapy are likely options. A recent pilot study by Chowdhury et al. included beta2-agonist salbutamol in the treatment of OP-pesticide poisoned patients, yielding ambiguous results concerning the addition. Here, we provide experimental data for further investigations regarding the value of these drugs in OP poisoning. METHODS: By video-microscopy, changes in airway area were analyzed in VX-poisoned rat precision cut lung slices (PCLS) after ACh-induced airway contraction and subsequent application of selected anticholinergics/beta2-agonists. RESULTS: Glycopyrrolate and ipratropium efficiently antagonized an ACh-induced airway contraction in VX-poisoned PCLS (EC50 glycopyrrolate 15.8 nmol/L, EC50 ipratropium 2.3 nmol/L). beta2-agonists formoterol and salbutamol had only negligible effects when solely applied in the same setting. However, combination of formoterol or salbutamol with low dosed glycopyrrolate or atropine led to an additive effect compared to the sole application [50.6 +/- 8.8% airway area increase after 10 nmol/L formoterol +1 nmol/L atropine versus 11.7 +/- 9.2% (10 nmol/L formoterol) or 8.6 +/- 5.9% (1 nmol/L atropine)]. DISCUSSION: We showed antagonizing effects of anticholinergics and beta2-agonists on ACh-induced airway contractions in VX-poisoned PCLS, thus providing experimental data to support a prospective comprehensive clinical study. CONCLUSIONS: Our results indicate that COPD and asthma therapeutics could be a valuable addition to the treatment of OP poisoning.

https://www.tandfonline.com/doi/full/10.1080/15563650.2018.1540785

Ho, T. W., C. T. Huang, et al. (2019). **"Metformin use mitigates the adverse prognostic effect of diabetes mellitus in chronic obstructive pulmonary disease."** Respir Res **20**(1): 69.

BACKGROUND AND OBJECTIVE: Among patients with chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) is a common comorbidity and is probably associated with increased systemic inflammation and worse prognosis. Metformin, with its pleiotropic anti-inflammatory and antioxidant actions, may offer theoretical benefits in COPD patients with DM. Thus, this study aimed to investigate the effects of DM and metformin use on mortality in the clinical trajectory of COPD. METHODS: This was a retrospective cohort study comprising patients with spirometry-confirmed COPD and an age of >/=40 years from 2008 to 2014. The primary outcome of interest was all-cause mortality. We evaluated the effects of DM on mortality through the clinical course of COPD and we also assessed the impact of metformin use on survival of the COPD population. RESULTS: Among 4231 COPD patients, 556 (13%) had DM, and these patients had 1.62 times higher hazards of 2-year mortality than those without DM (95% confidence interval [CI], 1.15-2.28) after adjusting for age, gender, COPD stage, comorbidities and prior COPD hospitalization. Over a 2-year period, metformin users had a significantly lower risk of death (hazard ratio, 0.46; 95% CI, 0.23-0.92) compared with non-metformin users in patients with coexistent COPD and DM. Moreover, metformin users had similar survival to COPD patients without DM. CONCLUSIONS: This study shows that DM is associated with an increased risk of death in COPD patients

and metformin use seems to mitigate the hazard. Our findings suggest a potential role of metformin in the management of DM in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6451256/pdf/12931_2019_Article_1035.pdf

Hong, Y., M. M. Graham, et al. (2019). **"The Association between Chronic Obstructive Pulmonary Disease and Coronary Artery Disease in Patients Undergoing Coronary Angiography."** Copd: 1-6.

Chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) are leading causes of morbidity and mortality. There are conflicting results regarding the association between COPD and CAD. We sought to measure the association between COPD and angiographically diagnosed CAD in a population-based cohort. We performed a retrospective analysis using data from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH), a prospectively collected registry capturing all patients undergoing coronary angiography in Alberta, Canada, since 1995. We included adult patients who had undergone coronary angiogram between April 1, 2007 and March 31, 2014. CAD was present if at least one coronary artery had a significant stenosis >/=50%. COPD was present if the patient had a documented COPD history and was prescribed bronchodilators or inhaled steroids. We evaluated the association between COPD and CAD using univariable and multivariable logistic regression. There were 26,137 patients included with a mean age of 63.3 +/- 12.2 years, and 19,542 (74.8%) were male. The crude odds ratio (OR) of having CAD was 0.83 (95% CI 0.74-0.92) for patients with COPD compared to those without COPD. The adjusted OR was 0.75 (95% CI 0.67-0.84) after controlling for age, sex, smoking history, body mass index, hypertension, diabetes, hyperlipidemia, peripheral artery disease and cardiac family history. In patients undergoing coronary angiography, COPD was negatively associated with CAD with and without the adjustment for classic risk factors. COPD patients should be properly examined for heart disease to reduce premature mortality.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1566894

Hu, Y., Y. Cheng, et al. (2019). **"A New-Designed Lung-Bending Device for Bronchoscopic Lung Volume Reduction of Severe Emphysema: A Feasibility Study in Pigs."** Respiration: 1-7.

BACKGROUND: Bronchoscopic therapies are less invasive alternatives of surgical lung volume reduction for severe emphysema. Bending of lung tissue by implanting metallic coils into bronchi is one of the procedures. A new-designed device with a similar rationale, Reverser, has been developed with some improvements. OBJECTIVES: The aim of the study was to evaluate the safety and feasibility of the Reversers. METHODS: Twelve healthy pigs were randomly divided into 3 groups (groups A, B, and C). The Reversers were implanted bronchoscopically into the selected airways using a proprietary delivery system. Physical examination, chest fluoroscopy, computed tomography (CT) scans, and bronchoscopic observations were performed before implantation and during the follow-up period. Necropsy was performed respectively at 1 month (group A), 3 months (group B), and 6 months (group C) after implantation. RESULTS: A total of 47 Reversers were implanted successfully. The procedure was feasible and well tolerated by all pigs. No severe complications, such as pneumothorax, abscesses, and airway hemorrhage, were found. No unintended injuries or death occurred. Mild granulation and inflammation were observed in the airway wall. Opacities around Reversers were shown on CT scans in some pigs. In the pigs with opacities, histological evaluation revealed widened alveolar septa due to inflammatory cell infiltration in the vicinity of the Reversers. On the analysis of CT data, there was a trend for volume reduction of the treated lung at 1 and 3 months after treatment compared with baseline. CONCLUSIONS: This study showed that Reversers were safe and feasible for bronchoscopic lung volume reduction in pigs.

https://www.karger.com/Article/Abstract/495142

Huang, H. H., S. J. Chen, et al. (2019). **"Influenza vaccination and risk of respiratory failure in patients with chronic obstructive pulmonary disease: A nationwide population-based case-cohort study."** J Microbiol Immunol Infect **52**(1): 22-29.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease which causes a considerable disease burden. Patients with COPD are at a higher risk for influenza infection and influenza vaccination are recommended at this high risk patient group. In the current study, we aimed to evaluate the association between influenza vaccination and the risk of respiratory failure (RF) in COPD patients. METHODS: From 2001 to 2005, patients with newly diagnosed COPD were identified from the NHIRD, and were followed until 2010. We explored the influenza vaccination rate among this COPD cohort. Furthermore, patients who experienced RF were defined as case group, whereas the others were defined as control group. Baseline characteristic were compared and association between influenza vaccination and RF were evaluated. RESULTS: The rate of influenza vaccination was significantly higher in patients age >/=65 years than those age <65 years (54.8% vs. 4%, p < 0.001). The vaccine cohort had more comorbidities, more health care utilization and more frequent acute exacerbations as compared with nonvaccine cohort. In multivariable logistic regression, influenza vaccination was associated with a reduced risk of respiratory failure (adjusted odds ratio [aOR] 0.87, 95% confidence interval [CI] 0.79-0.96). In subgroup analysis, we found that the association was insignificant in patients age <65 years, patients with relatively unstable disease status and patient did not receive influenza vaccination annually. CONCLUSIONS: Influenza vaccination was associated with a decreased risk of RF in patients with COPD. Recommendation of annual influenza vaccination should be made when managing this high-risk patient group.

https://www.sciencedirect.com/science/article/pii/S1684118217301974?via%3Dihub

Iyer, A. S., K. E. Holm, et al. (2019). **"Symptoms of anxiety and depression and use of anxiolytic-hypnotics and antidepressants in current and former smokers with and without COPD - A cross sectional analysis of the COPDGene cohort."** J Psychosom Res **118**: 18-26.

OBJECTIVES: To compare the frequency of anxiety/depressive symptoms and use of anxiolytic-hypnotics/antidepressants in smokers with and without COPD and to identify characteristics associated with having unmedicated symptoms. METHODS: Cross-sectional analysis of ambulatory, current/former smokers >/=10 pack years enrolled in the COPDGene study. We measured anxiety/depressive symptoms using the Hospital Anxiety and Depression Scale (subscales >/=8), recorded anxiolytic-hypnotic/antidepressant use, and defined unmedicated symptoms as elevated anxiety/depressive symptoms and not on medications. Regression analysis identified characteristics associated with having unmedicated symptoms. KEY RESULTS: Of 5331 current/former smokers (45% with and 55% without COPD), 1332 (25.0%) had anxiety/depressive symptoms. Anxiety symptoms were similar in frequency in smokers with and without COPD (19.7% overall), while depressive symptoms were most frequent in severe-very severe COPD at 20.7% (13.1% overall). In the entire cohort, 1135 (21.2%) were on medications. Anxiolytic-hypnotic use was highest in severe-very severe COPD (range 7.6%-12.0%), while antidepressant use showed no significant variation in smokers with and without COPD (range 14.7%-17.1%). Overall, 881 (66% of those with symptoms) had unmedicated symptoms, which was associated with African American race (adjusted OR 2.95, 95% CI 2.25-3.87), male gender (adjusted OR 1.93, 95% CI 1.57-2.36), no health insurance (adjusted OR 2.38, 95% CI 1.30-4.35), severe-very severe COPD (adjusted OR 1.48, 95% CI 1.04-2.11), and higher respiratory symptoms/exacerbation history (adjusted OR 2.21, 95% CI 1.62-3.02). CONCLUSIONS: Significant unmet mental health care needs exist in current and former smokers with and without COPD. One in five have unmedicated symptoms, identified by key demographic and clinical characteristics. PRIMARY FUNDING SOURCE: National Institutes of Health and The COPD Foundation.

Janssens, J. P., C. Weber, et al. (2019). **"Can Early Introduction of Palliative Care Limit Intensive Care, Emergency and Hospital Admissions in Patients with Severe Chronic Obstructive Pulmonary Disease? A Pilot Randomized Study."** Respiration: 1-10.

BACKGROUND: Despite their poor prognosis, patients with severe chronic obstructive pulmonary disease (COPD) have little access to palliative care and tend to have a high rate of hospital and intensive care unit (ICU) admissions during their last year of life. OBJECTIVES: To determine the feasibility of a home palliative care intervention during 1 year versus usual care, and the possible impact of this intervention on emergency, hospital and ICU admissions, survival, mood, and health-related quality of life (HRQL). METHODS: Prospective controlled study of patients with severe COPD (GOLD stage III or IV) and long-term oxygen therapy and/or home noninvasive ventilation and/or one or more hospital admissions in the previous year for acute exacerbation, randomized to usual care versus usual care with add-on monthly intervention by palliative care specialists at home for 12 months. RESULTS: Of 315 patients screened, 49 (15.5%) were randomized (26 to early palliative care; 23 to the control group); aged (mean +/- SD) 71 +/- 8 years; FEV1 was 37 +/- 14% predicted; 88% with a COPD assessment test score > 10; 69% on long-term oxygen therapy or home noninvasive ventilation. The patients accepted the intervention and completed the assessment scales. After 1 year, there was no difference between groups in symptoms, HRQL and mood, and there was a nonsignificant trend for higher admission rates to hospital and emergency wards in the intervention group. CONCLUSION: Although this pilot study was underpowered to formally exclude a benefit from palliative care in severe COPD, it raises several questions as to patient selection, reluctance to palliative care in this group, and modalities of future trials.

https://www.karger.com/Article/Abstract/495312

Jerng, J. S., C. H. Tang, et al. (2019). **"Healthcare utilization, medical costs and mortality associated with malnutrition in patients with chronic obstructive pulmonary disease: a matched cohort study."** Curr Med Res Opin: 1-9.

OBJECTIVE: Although disease-related malnutrition has prognostic implications for patients with chronic obstructive pulmonary disease (COPD), its health-economic impact and clinical burdens are uncertain. We conducted a population-level study to investigate these questions. METHODS: We excerpted data relevant to malnutrition, prolonged mechanical ventilation and medications from claims by 1,197,098 patients which were consistent with COPD and registered by the Taiwan National Health Insurance Administration between 2009 and 2013. These patients were separated into cohorts with or without respiratory failure requiring long-term mechanical ventilation, and each cohort was divided to compare cases who developed malnutrition after their first diagnosis consistent with COPD, versus non-malnourished propensity-score matched controls. RESULTS: The prevalence of malnutrition was 3.8% overall (10,259/287,000 non-ventilator-dependent; 1198/15,829 ventilator-dependent). Propensity-score matched non-ventilator-dependent patients who became malnourished (N = 10,242) had comparatively more hospitalizations, emergency room and outpatient visits, longer hospitalization (all $p < .01$), and higher mortality (HR = 2.26, 95% CI 2.18-2.34) than non-malnourished controls (N = 40,968). Malnourished ventilator-dependent patients (N = 1197) had higher rates of hospitalization, emergency room and outpatient visits, but shorter hospitalization (all $p < .001$) and lower mortality (HR = 0.85, 95% CI 0.80-0.93) than matched non-malnourished controls (N = 4788). Total medical expenditure on malnourished non-ventilator-dependent COPD patients was 75% higher than controls ($p < .001$), whereas malnourished ventilator-dependent patients had total costs 7% lower than controls ($p < .001$). CONCLUSIONS: Malnourishment among COPD patients who were not dependent on mechanical ventilation was associated with greater healthcare resource utilization and higher aggregate medical costs.

https://www.tandfonline.com/doi/full/10.1080/03007995.2019.1574460

Jimenez, D., A. Agusti, et al. (2019). **"The rationale, design, and methods of a randomized, controlled trial to evaluate the efficacy and safety of an active strategy for the diagnosis and treatment of acute pulmonary embolism during exacerbations of chronic obstructive pulmonary disease."** Clin Cardiol **42**(3): 346-351.

INTRODUCTION: Some previous studies have suggested a high prevalence of pulmonary embolism (PE) during exacerbations of chronic obstructive pulmonary disease (ECOPD). The SLICE trial aims to assess the efficacy and safety of an active strategy for the diagnosis and treatment of PE (vs usual care) in patients hospitalized because of ECOPD. METHODS: SLICE is a phase III, prospective, international, multicenter, randomized, open-label, and parallel-group trial. A total of 746 patients hospitalized because of ECOPD will be randomized in a 1:1 fashion to receive either an active strategy for the diagnosis and anticoagulant treatment of PE or usual care (ie, standard care without any diagnostic test for diagnosing PE). The primary outcome is a composite of all-cause death, non-fatal (recurrent) venous thromboembolism (VTE), or readmission for ECOPD within 90 days after enrollment. Secondary outcomes are (a) death from any cause within 90 days after enrollment, (b) non-fatal (recurrent) VTE within 90 days after enrollment, (c) readmission within 90 days after enrollment, and (d) length of hospital stay. RESULTS: Enrollment started in September 2014 and is expected to proceed until 2020. Median age of the first 443 patients was 71 years (interquartile range, 64-78), and 26% were female. CONCLUSIONS: This multicenter trial will determine the value of detecting PEs in patients with ECOPD. This has implications for COPD patient morbidity and mortality. TRIAL REGISTRATION NUMBER: NCT02238639.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/clc.23161

Jo, Y. S., Y. I. Hwang, et al. (2019). **"Comparing the different diagnostic criteria of Asthma-COPD overlap."** Allergy **74**(1): 186-189.

https://onlinelibrary.wiley.com/doi/abs/10.1111/all.13577

Jo, Y. S., S. K. Kim, et al. (2019). **"Longitudinal change of FEV1 and inspiratory capacity: clinical implication and relevance to exacerbation risk in patients with COPD."** Int J Chron Obstruct Pulmon Dis **14**: 361-369.

Background and objective: FEV1 is the gold standard for assessment of COPD. We compared efficacy of FEV1, inspiratory capacity (IC), and IC to total lung capacity (TLC) ratio in the evaluation of COPD and their association with exacerbation. Methods: We analyzed the association of dyspnea severity, quality of life status, and lung function with lung function measurements and exacerbation risk in 982 patients enrolled in the Korea COPD Subgroup Registry and Subtype Research study. Exacerbation and longitudinal lung function change were evaluated in 3 years' follow-up. Results: The FEV1, IC, and IC to TLC ratio showed comparable negative correlations with dyspnea severity and quality of life status, and positive correlation with exercise capacity. In patients with >2 events/year, annual rate of change in FEV1 and IC tended to decline more rapidly in those with FEV1 <50% than in those with FEV1 >50% (-14.46+/-19.40 mL/year vs 12.29+/-9.24 mL/year, P=0.213; -4.75+/-17.28 mL/year vs -78.05+/-34.16 mL/year, P=0.056 for FEV1 and IC, respectively), without significance. Conclusion: Longitudinal changes in IC and FEV1 were not significantly associated with exacerbation risk.

https://www.dovepress.com/getfile.php?fileID=47855

Kaireit, T. F., A. Voskrebenzev, et al. (2019). **"Comparison of quantitative regional perfusion-weighted phase resolved functional lung (PREFUL) MRI with dynamic gadolinium-enhanced regional pulmonary perfusion MRI in COPD patients."** J Magn Reson Imaging **49**(4): 1122-1132.

BACKGROUND: Perfusion-weighted noncontrast-enhanced proton lung MRI during free breathing is maturing as a novel technique for assessment of regional lung perfusion, but has not yet been validated in chronic obstructive pulmonary disease (COPD) patients. PURPOSE: To compare pulmonary parenchymal perfusion assessed by noncontrast-enhanced perfusion-weighted phase-resolved functional lung (PREFUL)-MRI with lung perfusion determined with dynamic gadolinium-enhanced (DCE)-MRI and with lung function test parameters. STUDY TYPE: Prospective. POPULATION: A single-center subset of the COPD cohort "COPD and SYstemic consequenzes-COmorbidities NETwork" (COSYCONET). Forty-seven patients with COPD (median age 66 [57-70] years) were studied. FIELD STRENGTH/SEQUENCE: For PREFUL-MRI a spoiled gradient echo sequence and for DCE-MRI, a 3D time-resolved spoiled gradient echo sequence was used at 1.5T. ASSESSMENT: PREFUL-MRI coronal slices were acquired in free breathing. DCE-MRI was performed in breath-hold with administration of 0.025 mmol/kg bodyweight of gadobutrol i.v. at a rate of 4 ml/s and pulmonary blood flow (PBF) maps were calculated. Slices of PREFUL and DCE-MRI were matched by their ventrodorsal position and corresponding slices were coregistered for evaluation. Perfusion defect percentages (QDP) were calculated for both methods. STATISTICAL TESTS: The obtained parameters were correlated using Spearman's correlation coefficient (r) and Bland-Altman plot analysis. RESULTS: PREFUL-QDP showed an absolute and spatial agreement with PBF-QDP on a global (39.3 (31.8-45.5)% vs. 44.7 (35.4-50.0)% with a spatial overlap of 62.2 (57.2-67.2)%)) as well as on a lobar level and correlated with lung function test parameters (PREFUL-QDP vs. FEV1 , r = -0.75, P < 0.0001). There was a systematic overestimation of PREFUL-QDP compared with PBF-QDP, mainly in the lower lobes, resulting in an overall overestimation for the whole lung with a mean difference of 5% (95% confidence interval [CI]: 3.0%; 7.0%; STD 6.8%). DATA CONCLUSION: PREFUL-MRI is a promising noninvasive, radiation-free tool for quantification of regional perfusion in COPD patients. LEVEL OF EVIDENCE: 1 Technical Efficacy: Stage 2 J. Magn. Reson. Imaging 2019;49:1122-1132.

https://onlinelibrary.wiley.com/doi/abs/10.1002/jmri.26342

Kalter-Leibovici, O., M. Benderly, et al. (2018). **"Disease Management Plus Recommended Care versus Recommended Care Alone for Ambulatory COPD Patients."** Am J Respir Crit Care MedRATIONALE: The efficacy of disease management programs in the treatment of patients with chronic obstructive pulmonary disease (COPD) remains uncertain. OBJECTIVE: To study the effect of disease management (DM) added to recommended care (RC) in ambulatory COPD patients. MEASUREMENTS AND MAIN RESULTS: In this trial, 1,202 COPD patients (age >40 years), with moderate to very severe airflow limitation were randomly assigned either to DM plus RC (study intervention) or to RC alone (control intervention). RC included follow-up by pulmonologists; inhaled long-acting bronchodilators and corticosteroids; smoking cessation intervention; nutritional advice and psychosocial support when indicated, and supervised physical activity sessions. DM, delivered by trained nurses during patients' visits to the designated COPD centers and remote contacts with the patients between these visits, included patient self-care education; monitoring patients' symptoms and adherence to treatment; provision of advice in case of acute disease exacerbation, and coordination of care vis-a-vis other healthcare providers. The primary composite endpoint was first hospital admission for respiratory symptoms or death from any cause. During 3,537 patient-years, 284 (47.2%) patients in the control group and 264 (44.0%) in the study intervention group had a primary endpoint event. The median (range) time elapsed until a primary endpoint event was 1.0 (0-4.0) years among patients assigned to the study intervention and 1.1 (0-4.1) years among patients assigned to the control intervention; adjusted hazard ratio, 0.92 (95%CI: 0.77 to 1.08). CONCLUSIONS: DM added to RC was not superior to RC alone in delaying first hospital admission or death among ambulatory COPD patients. Clinical trial registration available at www.clinicaltrials.gov, ID NCT00982384.

Kaluza, J., H. Harris, et al. (2019). **"Long-term unprocessed and processed red meat consumption and risk of chronic obstructive pulmonary disease: a prospective cohort study of women."** Eur J Nutr **58**(2): 665-672.

PURPOSE: Limited studies have examined red meat consumption in relation to risk of chronic obstructive pulmonary disease (COPD), and none have examined the impact of long-term diet on COPD risk. We sought to investigate the association between long-term red meat consumption and risk of COPD. METHODS: The population-based prospective Swedish Mammography Cohort included 34,053 women, aged 48-83 years, followed for the current analyses from 2002 to 2014. Unprocessed and processed red meat consumption was assessed with a self-administered questionnaire in 1987 and 1997. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). RESULTS: Over a mean follow-up of 11.6 years (2002-2014; 393,831 person-years), 1488 COPD cases were ascertained via linkage to the Swedish health registers. A positive association between long-term processed red meat (average from 1987 to 1997) and risk of COPD was observed. In contrast, no association was observed with unprocessed red meat with corresponding HRs of 1.36 (95% CI 1.03-1.79) for processed and 0.87 (95% CI 0.74-1.02) for unprocessed red meat among women who consumed >/= 50 g/day compared to < 25 g/day. The observed association with processed meat was confined to ex-smokers (P for interaction = 0.30); women consuming of >/= 50 g/day of processed meat had a 2.3-fold (95% CI 1.24-4.12) higher risk of COPD than those consuming < 25 g/day. No similar associations were observed among current or never smokers. CONCLUSION: In this prospective cohort of women with moderate red meat consumption, long-term processed red meat consumption was associated with an increased risk of COPD particularly among ex-smokers.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6437121/pdf/394_2018_Article_1658.pdf

Kaluza, J., H. R. Harris, et al. (2019). **"Alcohol Consumption and Risk of Chronic Obstructive Pulmonary Disease: A Prospective Cohort Study of Men."** Am J EpidemiolStudies indicate an inverse association between moderate alcohol consumption and chronic inflammatory diseases; however, the association between alcohol consumption and chronic obstructive pulmonary disease (COPD) incidence has not been widely studied. We investigated the associations of total alcohol consumption and intake of specific alcoholic beverages with risk of COPD in a population-based prospective cohort study, the Cohort of Swedish Men (n = 44,254). Alcohol consumption was assessed with a self-administered questionnaire in 1997. During follow-up (1998-2014), 2,177 COPD cases were ascertained. Moderate alcohol consumption was associated with the lowest risk of COPD. A J-shaped association was observed for ethanol consumption (P for nonlinearity = 0.003) and beer consumption (P for nonlinearity < 0.001); for wine consumption, a U-shaped association was observed (P for nonlinearity < 0.001). Defining a "standard drink" as 12 g of ethanol, the multivariable-adjusted hazard ratios were 0.77 (95% confidence interval (CI): 0.66, 0.90) and 0.92 (95% CI: 0.81, 1.05) for beer consumption of 4.1-6.0 and >6.0 standard drinks/week (SDW) versus <1.0 SDW, respectively; 0.80 (95% CI: 0.69, 0.93) and 1.00 (95% CI: 0.83, 1.21) for wine consumption of 2.0-4.0 and >4.0 SDW versus <1.0 SDW, respectively; and 1.10 (95% CI: 0.98, 1.24) and 1.20 (95% CI: 0.99, 1.44) for liquor consumption of 2.0-4.0 and >4.0 SDW versus <1.0 SDW, respectively. In conclusion, our findings suggest that moderate beer and wine consumption, but not liquor consumption, may decrease risk of COPD. Additional studies are needed to confirm these associations.

https://academic.oup.com/aje/advance-article-abstract/doi/10.1093/aje/kwz020/5381971?redirectedFrom=fulltext

Kameyama, N., S. Chubachi, et al. (2019). **"Predictive and modifying factors of bone mineral density decline in patients with COPD."** Respir Med **148**: 13-23.

RATIONALE: Various determinants of osteoporosis have been previously identified. However, only a few longitudinal studies have examined related factors. We aimed to investigate factors predicting and modifying rapid decline of bone mineral density in patients with chronic obstructive pulmonary disease.

METHODS: We analyzed patients with chronic obstructive pulmonary disease whose bone mineral density were measured at least three times over three years (n=111). We divided annual per cent changes of bone mineral density in different body parts into tertiles. Rapid decliners (n=33) were defined as those with the largest decline in at least two parts; all other participants were defined as non-rapid decliners (n=78). RESULTS: At enrollment, bone mineral density did not differ between the two groups. However, rapid decliners had a significantly greater rate of new vertebral fractures over 3 years compared with non-rapid decliners. On multivariate logistic regression analysis, age, moderate to severe emphysema, no daily exercise habits, and anemia increased the likelihood of rapid decliners. Furthermore, patients who newly started and continued bisphosphonate exhibited higher annual per cent changes of bone mineral density than did those without bisphosphonate use. CONCLUSIONS: A rapid decline in bone mineral density correlates to a higher likelihood of vertebral fracture. We clarified the predictors of bone mineral density decline and demonstrated that bisphosphonate use might modify bone mineral density in patients with chronic obstructive pulmonary disease.

https://www.resmedjournal.com/article/S0954-6111(19)30014-9/fulltext

Kao, Y. H., T. S. Tseng, et al. (2019). **"Association between continuity of care and emergency department visits and hospitalization in senior adults with asthma-COPD overlap."** Health Policy **123**(2): 222-228.

OBJECTIVE: To investigate associations between continuity of care (COC) and emergency department (ED) visits and hospitalization for chronic obstructive pulmonary disease (COPD) or asthma among elderly adults with asthma-COPD overlap (ACO). METHODS: A retrospective cohort study was performed using the Taiwan National Health Insurance research database. A total of 1141 ACO patients aged >/=65 years during 2005-2011 were observed and followed for 2 years. The Bice and Boxerman COC index (COCI) was used to evaluate COC by considering ambulatory care visits duo to COPD or asthma in the first year; ED visits and hospitalization for COPD or asthma were identified in the subsequent year, respectively. The COCI was divided into three levels (COCI < 0.3= low, 0.3 </= COCI<1=medium, COCI = 1=high). The Cox model was used to estimate the hazard ratio (HR) for ED visits and hospital admissions due to COPD or asthma. RESULTS: The average COCI was 0.55. 21.3% patients received outpatient care from a single physician. Compared to patients with high COC, those with low and medium COC had a higher risk of ED visits (aHR = 2.80 and 2.69, P < .01) and admissions (aHR = 1.80 and 1.72, P < .05). CONCLUSION: Increasing COC is beneficial for elderly patients with ACO in disease management. Policymakers could create effective pay-for-performance programs for the elderly ACO population to enhance COC and improve care outcomes.

Kaplan, A., K. R. Chapman, et al. (2019). **"Real-life effectiveness of indacaterol-glycopyrronium after switching from tiotropium or salmeterol/fluticasone therapy in patients with symptomatic COPD: the POWER study."** Int J Chron Obstruct Pulmon Dis **14**: 249-260.

Purpose: In contrast to randomized controlled trials (RCTs), changes in maintenance pharmacotherapy in clinical practice occur without a washout period. The Prospective cohort study for the real-life effectiveness evaluation of glycOpyrronium With indacatERol combination in the management of COPD in Canada (POWER) study evaluated the real-life effectiveness of indacaterol/glycopyrronium (IND/GLY) following a direct switch from a long-acting muscarinic antagonist (LAMA, tiotropium) or long-acting beta2-agonist (LABA)/inhaled corticosteroid (ICS) maintenance treatment (salmeterol/fluticasone [SFC]). Methods: POWER was a single-cohort, prospective, multicenter, interventional study in which patients with moderate-to-severe COPD, who remained symptomatic on their current treatment of once-daily (od) tiotropium 18 microg or twice-daily (bid) SFC (any dose), were switched to treatment with open-label IND/GLY 110/50 microg od for 16 weeks. Effectiveness end points were change from baseline in trough FEV1, transition dyspnea index (TDI) total scores, and COPD assessment test (CAT) scores at 16 weeks. Results: Trough FEV1 improved by 175 mL at Week 16 in patients who switched to IND/GLY. The change

was 176 mL (95% CI: 135-217) when switched from tiotropium and 172 mL (95% CI: 85-258) when switched from SFC fixed-dose combination (FDC). At Week 16, significant improvements were observed in the mean TDI total scores (Delta=2.5) and CAT scores (Delta=-6.5) after the switch to IND/GLY treatment (both P<0.0001). Additionally, IND/GLY was well tolerated in patients with moderate-to-severe COPD, and no safety signal was observed. Conclusion: In clinical practice settings, a direct switch from previous treatment with either tiotropium or SFC to IND/GLY was safe and provided superior clinically significant improvements in lung function and patient-related outcomes in patients with moderate-to-severe COPD. Clinical trial registration: NCT02202616.

https://www.dovepress.com/getfile.php?fileID=47617

Kauczor, H. U., M. O. Wielputz, et al. (2019). **"Computed Tomography Imaging for Novel Therapies of Chronic Obstructive Pulmonary Disease."** J Thorac Imaging **34**(3): 202-213.

Novel therapeutic options in chronic obstructive pulmonary disease (COPD) require delicate patient selection and thus demand for expert radiologists visually and quantitatively evaluating high-resolution computed tomography (CT) with additional functional acquisitions such as paired inspiratory-expiratory scans or dynamic airway CT. The differentiation between emphysema-dominant and airway-dominant COPD phenotypes by imaging has immediate clinical value for patient management. Assessment of emphysema severity, distribution patterns, and fissure integrity are essential for stratifying patients for different surgical and endoscopic lung volume reduction procedures. This is supported by quantitative software-based postprocessing of CT data sets, which delivers objective emphysema and airway remodelling metrics. However, the significant impact of scanning and reconstruction parameters, as well as intersoftware variability still hamper comparability between sites and studies. In earlier stage COPD imaging, it is less clear as to what extent quantitative CT might impact decision making and therapy follow-up, as emphysema progression is too slow to realistically be useful as a mid-term outcome measure in an individual, and longitudinal data on airway remodelling are still very limited.

Kelly, A. M., O. Van Meer, et al. (2019). **"Get With The Guidelines - Management Of COPD In EDs In Europe And Australasia is sub-optimal."** Intern Med JOBJECTIVES: Exacerbations of chronic obstructive pulmonary disease (COPD) are common in emergency departments (ED). Guidelines recommend administration of inhaled bronchodilators, systemic corticosteroids and antibiotics along with non-invasive ventilation (NIV) for patients with respiratory acidosis. We aimed to determine compliance with guideline recommendations for patients with treated for COPD in ED in Europe (EUR) and South East Asia/Australasia (SEA) and to compare management and outcomes. METHODS: In each region, an observational prospective cohort study was performed that included patients presenting to EDs with the main complaint of dyspnoea during three 72-hour periods. This planned sub-study included those with an ED primary discharge diagnosis of COPD. Data were collected on demographics, clinical features, treatment, disposition and in-hospital mortality. We determined overall compliance with guideline recommendations and compared treatments and outcome between regions. RESULTS: 801 patients were included from 122 EDs (66 EUR and 46 SEA). Inhaled bronchodilators were administered to 80.3% of patients, systemic corticosteroids to 59.5%, antibiotics to 44% and 60.6% of patients with pH <7.3 received NIV. The proportion administered systemic corticosteroids was higher in SEA (EUR vs. SEA for all comparisons; 52% vs. 66%, p<0.001) as was administration of antibiotics (40% vs. 49%, p=0.02). Rates of NIV and mechanical ventilation were similar. Overall in-hospital mortality was 4.2% (SEA 3.9% vs. EUR 4.5%, p=0.77). CONCLUSION: Compliance with guideline recommended treatments, in particular administration of corticosteroids and NIV, was sub-optimal in both regions. Improved compliance has the potential to improve patient outcome.

https://onlinelibrary.wiley.com/doi/abs/10.1111/imj.14323

Kim, J., C. H. Lee, et al. (2019). **"Acute Exacerbation According to GOLD 2017 Categories in Patients with Chronic Obstructive Pulmonary Disease."** Arch BronconeumolINTRODUCTION: The association between GOLD categorizations and future exacerbations has not been fully investigated. This study elucidates whether the GOLD 2017 classification is associated with different future exacerbation risk in patients with chronic obstructive pulmonary disease (COPD) compared with the previous GOLD categorization. Another objective was to investigate the impacts of the symptoms and FEV1 on the predicted future exacerbation independently of previous exacerbation history. METHODS: We analyzed patients from three prospective COPD cohorts (SNUH, KOCOSS, and KOLD) and evaluated the risk of moderate to severe exacerbation among different models, including GOLD grade (FEV1), GOLD 2011, and GOLD 2017. RESULTS: In total, 611 COPD patients were included (36 from SNUH, 257 from KOCOSS, and 318 from KOLD). GOLD 2017 classification, excluding FEV1% for categorization criteria, showed no differences in future exacerbation risk compared with GOLD grade and GOLD 2011 based on c-statistics. Among those with no frequent exacerbation history and FEV1 >/=50%, the group with more symptoms was significantly associated with future exacerbations than the group with less symptoms. A lower FEV1 (FEV1 <50%) was not associated with a higher future exacerbation risk than a higher FEV1 (FEV1 >/=50%), regardless of prior exacerbation history and symptom group. CONCLUSION: The GOLD 2017 classification was not different from GOLD grade and GOLD 2011 regarding the association with future exacerbation risk, and there were no significant differences in exacerbation risk according to FEV1%. This suggests that FEV1 might not be an important factor in future exacerbation risk. These results partly support the GOLD 2017 assessment tool.

Kim, Y. W., C. H. Lee, et al. (2019). **"Resting hyperinflation and emphysema on the clinical course of COPD."** Sci Rep **9**(1): 3764.

The aim of this study is to clarify whether the combined evaluation of resting hyperinflation and emphysema confers any additional advantages in terms of predicting clinical outcomes in chronic obstructive pulmonary disease (COPD) patients. We included COPD patients from the Korean Obstructive Lung Disease (KOLD) cohort. Patients with a residual volume/total lung capacity (RV/TLC) over the upper limit of normal were defined as having resting hyperinflation, and those with an emphysema index >10% were defined as having emphysema. We investigated the impacts of resting hyperinflation and emphysema on exacerbations and mortality. A total of 310 COPD patients were analyzed over a mean of 61.1 months. After adjustment for covariates, resting hyperinflation was an independent predictor of earlier exacerbation (HR = 1.66, CI = 1.24-2.22), more frequent exacerbation (IRR = 1.35, CI = 1.01-1.81), and higher mortality (HR = 2.45, CI = 1.16-5.17) risk. Emphysema was also significantly associated with earlier exacerbation (HR = 1.64, CI = 1.15-2.35), and higher mortality (HR = 3.13, CI = 1.06-9.27) risk. Participants with both resting hyperinflation and emphysema had an additively higher risk of earlier exacerbations (HR = 1.71, 95% CI = 1.26-2.33) and mortality (HR = 3.75, 95% CI = 1.81-7.73) compared with those in other groups. In conclusion, resting hyperinflation and emphysema had additional worse impacts on exacerbations and mortality in COPD patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6403229/pdf/41598_2019_Article_40411.pdf

Kiser, T. H., P. M. Reynolds, et al. (2019). **"Impact of Macrolide Antibiotics on Hospital Readmissions and Other Clinically Important Outcomes in Critically Ill Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Propensity Score-Matched Cohort Study."** Pharmacotherapy **39**(3): 242-252.

STUDY OBJECTIVE: To assess whether a macrolide-based antibiotic treatment strategy reduces in-hospital mortality, decreases hospital readmissions, or improves other clinically important outcomes compared

with a non-macrolide antibiotic treatment strategy in critically ill patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). DESIGN: Propensity score-matched pharmacoepidemiologic cohort study. DATA SOURCE: Premier's Perspective Hospital Database. PATIENTS: A total of 28,700 adults aged 40 years or older who were admitted to one of 566 United States intensive care units and had the primary diagnosis of AECOPD between January 2010 and December 2014 and received antibiotic treatment within 2 days of hospital admission were included. Patients were divided into macrolide (11,602 patients [40%]) or non-macrolide (17,098 patients [60%]) antibiotic treatment groups. Propensity score analysis successfully matched 8660 patients in each treatment group. MEASUREMENTS AND MAIN RESULTS: In the matched cohort, the macrolide treatment group was not associated with decreased hospital mortality after day 2 (3.0% vs 3.3%, p=0.28), intensive care unit length of stay (2 days vs 2 days, p=0.12), hospital length of stay (6 days vs 6 days, p=0.86), or length of assisted ventilation (3 days vs 3 days, p=0.71), compared with the non-macrolide treatment group. However, a macrolide-based antibiotic regimen was associated with an overall reduction in 30-day hospital readmissions (7.3% vs 8.8%, p<0.01), increased time to next all-cause (159 vs 130 days, p<0.01) or AECOPD (200 vs 175 days, p=0.03) readmission, and decreased hospital costs ($32,730 vs $34,021, p<0.01). CONCLUSION: The results of this study suggest that inclusion of a macrolide antibiotic in the treatment regimen may have both acute and sustained benefits in critically ill patients admitted to the intensive care unit with an AECOPD, including reductions in hospital readmissions and improvements in time to next readmission.

https://accpjournals.onlinelibrary.wiley.com/doi/abs/10.1002/phar.2221

Koseoglu, C., O. Kurmus, et al. (2016). **"Association between carotid intima-media thickness and presence of coronary artery disease in chronic obstructive pulmonary disease patients."** Anatol J Cardiol **16**(8): 601-607.

OBJECTIVE: Chronic obstructive pulmonary disease (COPD) is a risk factor for cardiovascular disease (CVD). Carotid intima-media thickness (CIMT) is the sign of subclinical atherosclerosis. Therefore, the aim of this study was to evaluate whether CIMT measurement is related with significant coronary artery disease (CAD) in patients with COPD, similar to those without COPD. METHODS: One hundred and eight patients with previously diagnosed COPD and 78 patients without COPD who underwent coronary angiography (CAG) were enrolled in this prospective cross-sectional study. Carotid artery ultrasonography was performed on all patients after coronary angiography by another operator who was blind to the CAG results. The patients were divided into four subgroups as follows: group 1: COPD (-) and CAD (-); group 2: COPD (-) and CAD (+); group 3: COPD (+) and CAD (+); and group 4: COPD (+) and CAD (-). Patients with previous coronary revascularization, carotid artery disease, and lung disease other than COPD were not enrolled in this study. The student's t-test, chi-square analysis, multiple logistic regression analysis, and receiver operating characteristic (ROC) curve were used for statistical analysis. RESULTS: CIMT was found to be highest in patients with both significant CAD and COPD (group 3) (p<0.05). Among the 108 COPD patients, the odds ratio associated with the CIMT >1.25 mm to predict CAD was 12.4. The area under the ROC curve for a cut-off value of 1.25 mm for CIMT to predict CAD in COPD patients was calculated as 0.913, with a sensitivity of 89.7% and specificity of 86.7%. CONCLUSION: CIMT has a predictive value for the presence of CAD in patients with COPD. Further studies are needed to validate our results.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5368517/pdf/AJC-16-601.pdf

Koul, P. A., A. A. Nowshehr, et al. (2019). **"Cost of Severe Chronic Obstructive Pulmonary Disease Exacerbations in a High Burden Region in North India."** Ann Glob Health **85**(1)BACKGROUND: Data on costs of acute exacerbations of COPD (AECOPD) in low-income countries are sparse. We conducted a prospective survey to assess direct and indirect costs of severe AECOPD in a tertiary care setting in a high prevalence area of North India. METHODS: We conducted face-to-face surveys using a semi-structured questionnaire among a convenience sample of 129 consenting patients admitted with

AECOPD. Data were collected on out-of-pocket costs of hospitalization, consultation, medications, diagnostics, transportation, lodging, and missed work days for self and their attendants. Out-of-pocket costs were supplemented with World Health Organization-CHOICE estimates. Missed work-days were valued on per capita national income (Indian Rupees [INR] 68,748, US$1,145.8). Median total cost per exacerbation episode was INR 44,390 (Inter-quartile range [IQR]: INR 33,354-63,642; US$739.8, IQR: 555.9-1060.7). Hospital costs constituted the largest component of the costs (71%) followed by other costs directly borne by the patient himself (29%), medicine costs (14%), transportation charges (2%) and diagnostic tests (3%). Indirect costs to caregivers (median INR 1,544, IQR: INR 0-17,370 INR; US$25.7, IQR: US$0-289.5), calculated as financial loss due to missed work days, accounted for 4% of the total cost. Expenses were covered by family members in all but 11 patients. CONCLUSIONS: AECOPD in India are associated with substantial costs and strategies to reduce the burden of disease such as smoking cessation, influenza and pneumococcal vaccination, etc should be aggressively pursued.

https://agh.ubiquitypress.com/articles/10.5334/aogh.2423/

Kunisaki, S. M., J. M. Saito, et al. (2019). **"Current operative management of congenital lobar emphysema in children: A report from the Midwest Pediatric Surgery Consortium."** J Pediatr SurgPURPOSE: The purpose of this study was to evaluate the clinical presentation and operative outcomes of patients with congenital lobar emphysema (CLE) within a large multicenter research consortium. METHODS: After central reliance IRB-approval, a retrospective cohort study was performed on all operatively managed lung malformations at eleven participating children's hospitals (2009-2015). RESULTS: Fifty-three (10.5%) children with pathology-confirmed CLE were identified among 506 lung malformations. A lung mass was detected prenatally in 13 (24.5%) compared to 331 (73.1%) in non-CLE cases (p<0.0001). Thirty-two (60.4%) CLE patients presented with respiratory symptoms at birth compared to 102 (22.7%) in non-CLE (p<0.0001). The most common locations for CLE were the left upper (n=24, 45.3%), right middle (n=16, 30.2%), and right upper (n=10, 18.9%) lobes. Eighteen (34.0%) had resection as neonates, 30 (56.6%) had surgery at 1-12months of age, and five (9.4%) had resections after 12months. Six (11.3%) underwent thoracoscopic excision. Median hospital length of stay was 5.0days (interquartile range, 4.0-13.0). CONCLUSIONS: Among lung malformations, CLE is associated with several unique features, including a low prenatal detection rate, a predilection for the upper/middle lobes, and infrequent utilization of thoracoscopy. Although respiratory distress at birth is common, CLE often presents clinically in a delayed and more insidious fashion. LEVEL OF EVIDENCE: Level III.

https://www.jpedsurg.org/article/S0022-3468(19)30184-8/fulltext

Kuo, L. C., J. H. Chen, et al. (2019). **"End-of-Life Health Care Utilization Between Chronic Obstructive Pulmonary Disease and Lung Cancer Patients."** J Pain Symptom ManageCONTEXT: At the end of life, chronic obstructive pulmonary disease (COPD) and lung cancer (LC) patients exhibit similar symptoms; however, a large-scale study comparing end-of-life health care utilization between these two groups has not been conducted in East Asia. OBJECTIVES: To explore and compare end-of-life resource use during the last six months before death between COPD and LC patients. METHODS: Using data from the Taiwan National Health Insurance Research Database, we conducted a nationwide retrospective cohort study in COPD (n = 8640) and LC (n = 3377) patients who died between 1997 and 2013. RESULTS: The COPD decedents were more likely to be admitted to intensive care units (57.59% vs 29.82%), to have longer intensive care unit stays (17.59 vs 9.93 days), and to undergo intensive procedures than the LC decedents during their last six months; they were less likely to receive inpatient (3.32% vs 18.24%) or home-based palliative care (0.84% vs 8.17%) and supportive procedures than the LC decedents during their last six months. The average total medical cost during the last six months was approximately 18.42% higher for the COPD decedents than for the LC decedents. CONCLUSION: Higher intensive health care resource use, including intensive procedure use, at the end of life suggests a focus on prolonging life in COPD patients; it also indicates an unmet demand for palliative care in these patients.

Avoiding potentially inappropriate care and improving end-of-life care quality by providing palliative care to COPD patients are necessary.

https://www.jpsmjournal.com/article/S0885-3924(19)30044-2/fulltext

Kwak, M. J., V. Bhise, et al. (2019). **"National trend of utilization, clinical and economic outcomes of transcatheter aortic valve replacement among patients with chronic obstructive pulmonary disease."** Curr Med Res Opin: 1-9.

OBJECTIVES: We aimed to trend the utilization of transcatheter aortic valve replacement (TAVR) among COPD patients, compare its outcomes to surgical aortic valve replacement (SAVR) and assess any social disparities in its outcomes. BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) have been increasingly undergoing TAVR, but studies to evaluate the national trend of TAVR utilization and outcomes are still lacking. METHODS: We conducted a retrospective observational study using a nationally representative database, the National Inpatient Sample (NIS). RESULTS: From 2010 to 2014, the proportion of TAVR among COPD patients has increased from <1% to >50%. Patients who underwent TAVR were older, more likely to be women or white, carried more public insurance and had more comorbidities. There was no overall difference in mortality between TAVR and SAVR (2.74% vs. 2.59%, p = .860), and it has been consistently similar over time. However, patients with TAVR had shorter length of stay in the hospital after the procedure and were more likely to be discharged home than the SAVR group. Among the TAVR group, there were no gender, race or insurance disparities for in-hospital mortality, but female gender was related to lower discharge home rate, higher cost and longer stay in hospital. CONCLUSIONS: The rate of TAVR among COPD patients has been increasing nationally since 2011. In spite of higher comorbidities, TAVR did not show a difference in hospital mortality compared to SAVR but demonstrated shorter length of stay and more home discharges. This suggests that TAVR is a viable and potentially better option for patients with COPD.

https://www.tandfonline.com/doi/full/10.1080/03007995.2019.1583024

Ladziak, N. and N. P. Albanese (2019). **"Effect of changing COPD triple-therapy inhaler combinations on COPD symptoms."** Am J Manag Care **25**(4): 201-204.

OBJECTIVES: To determine if symptoms changed after changing chronic obstructive pulmonary disease (COPD) triple-therapy inhalers to a less expensive regimen. STUDY DESIGN: Retrospective observational case-series analysis. METHODS: A quality improvement program was instituted to reduce drug costs associated with COPD inhalers between fall 2016 and spring 2017. Patients identified as taking an inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) inhaler and a long-acting muscarinic agonist (LAMA) inhaler were changed to a LAMA/LABA inhaler and an ICS inhaler. Symptoms were assessed at baseline and subsequent follow-up using the COPD Assessment Test (CAT), with lower scores representing better symptom control. Then, a retrospective observational case-series analysis of 118 patient charts was completed. The primary outcome was mean difference in CAT score. Data were analyzed using a paired t test with an alpha value of 0.05. RESULTS: Of 118 patients included in the quality improvement program, 19 met the inclusion and exclusion criteria. The mean (SD) CAT score prior to the change was 15.53 (5.36), and the mean (SD) CAT score after the change was 14.68 (6.98). Symptom scores improved after the change, with an average difference in postchange and prechange CAT scores of -0.84, although this difference was not statistically significant (95% CI, -3.57 to 1.89; P = .525). CONCLUSIONS: Based on the results of this observational review, changing COPD triple-therapy inhalers did not result in a significant change in patient-reported symptom scores. Patients may use triple-therapy inhalers that are most affordable without a significant change in symptom control.

Lainscak, M., S. von Haehling, et al. (2011). **"Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease."** J Cachexia Sarcopenia Muscle **2**(2): 81-86.

BACKGROUND: Nutritional status, weight loss and cachexia have important prognostic implications in patients with chronic obstructive pulmonary disease (COPD). Body mass index (BMI) has been implicated in COPD risk assessment, but information is mostly limited to composite scores or to patients with stable disease. We aimed to analyse the association between BMI and mortality in acute exacerbation of COPD. METHODS: This retrospective survey included 968 patients hospitalized due to acute exacerbation of COPD at the University Clinic Golnik from February 2002 to June 2007. Vital status was ascertained with Central Population Registry, and database was censored on November 1, 2008. RESULTS: Median BMI was 25.08 kg/m(2) (interquartile range, 21.55-29.05 kg/m(2)) and 210 patients (22%) had BMI < 21 kg/m(2). During median follow-up of 3.26 years (1.79-4.76 years), 430 patients (44%) died. Lowest mortality was found for BMI 25.09-29.05 kg/m(2). When divided per BMI decile, mortality was lowest for BMI 25.09-26.56 kg/m(2) (33%). In univariate analysis, BMI per quartile and BMI per unit increase were predictive for all-cause mortality. In an adjusted model, BMI per 1 kg/m(2) unit increase was associated with 5% less chance of death (hazard ratio 0.95, 95% confidence interval 0.93-0.97). CONCLUSIONS: Low BMI < 21 kg/m(2) is frequent in patients hospitalized due to acute exacerbation of COPD. Higher BMI was independently predictive of better long-term survival. A better outcome in obese patients compared to normal weight is in contrast to primary prevention data but concurs with observations of an obesity paradox in other cardiovascular diseases.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3118008/pdf/13539_2011_Article_23.pdf

Lanclus, M., J. Clukers, et al. (2018). **"Machine Learning Algorithms Utilizing Functional Respiratory Imaging May Predict COPD Exacerbations."** Acad RadiolRATIONALE AND OBJECTIVES: Acute chronic obstructive pulmonary disease exacerbations (AECOPD) have a significant negative impact on the quality of life and accelerate progression of the disease. Functional respiratory imaging (FRI) has the potential to better characterize this disease. The purpose of this study was to identify FRI parameters specific to AECOPD and assess their ability to predict future AECOPD, by use of machine learning algorithms, enabling a better understanding and quantification of disease manifestation and progression. MATERIALS AND METHODS: A multicenter cohort of 62 patients with COPD was analyzed. FRI obtained from baseline high resolution CT data (unenhanced and volume gated), clinical, and pulmonary function test were analyzed and incorporated into machine learning algorithms. RESULTS: A total of 11 baseline FRI parameters could significantly distinguish ($p < 0.05$) the development of AECOPD from a stable period. In contrast, no baseline clinical or pulmonary function test parameters allowed significant classification. Furthermore, using Support Vector Machines, an accuracy of 80.65% and positive predictive value of 82.35% could be obtained by combining baseline FRI features such as total specific image-based airway volume and total specific image-based airway resistance, measured at functional residual capacity. Patients who developed an AECOPD, showed significantly smaller airway volumes and (hence) significantly higher airway resistances at baseline. CONCLUSION: This study indicates that FRI is a sensitive tool (PPV 82.35%) for predicting future AECOPD on a patient specific level in contrast to classical clinical parameters.

https://www.academicradiology.org/article/S1076-6332(18)30487-2/fulltext

Law, S., P. Kumar, et al. (2016). **"Malnutrition screening in patients admitted to hospital with an exacerbation of chronic obstructive pulmonary disease and its association with patient outcomes."** Hosp Pract (1995) **44**(4): 207-212.

OBJECTIVES: There is a paucity of information on the prevalence and clinical implications of malnutrition in patients hospitalised for management of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). This study aimed to fill this gap in knowledge. METHODS: We performed a retrospective

observational cohort study of 100 hospitalised AECOPD patients. The Malnutrition Screening Tool (MST) was used to identify patients at risk of malnutrition (MST >/=2). Patient characteristics, length of stay, readmission rate, 12-month survival and overall survival were collected using a proforma. RESULTS: MST scores were available in 90 patients, of whom 22% of patients had a MST score of >/=2. There were no significant differences in COPD severity, treatment received and biochemical parameters between the groups of patients 'at risk of malnutrition' and those 'not at risk of malnutrition'. Length of stay in hospital was longer in patients 'at risk of malnutrition' (median (IQR): 3.5 (2-7.5) vs. 3.0 (1-5), p = 0.048). Overall survival was significantly reduced in patients with 'at risk of malnutrition' compared to those patients 'not at risk of malnutrition' (337 +/- 245 vs. 670 +/- 292, p < 0.001). CONCLUSIONS: Using the MST we found that one-fifths of our hospitalised AECOPD patients are at 'at risk of malnutrition'. Moreover, this cohort of patients had worse outcomes both during and extending beyond hospitalisation compared to patients 'not at risk of malnutrition'. Our study illustrates the need for routine malnutrition screening for hospitalised AECOPD patients because it has implications for potentially reducing morbidity and mortality in COPD.

https://www.tandfonline.com/doi/full/10.1080/21548331.2016.1224007

Lee, C. M., J. Heo, et al. (2019). **"Inhaled Corticosteroid-Related Tuberculosis in the Real World Among Patients with Asthma and COPD: A 10-Year Nationwide Population-Based Study."** J Allergy Clin Immunol Pract **7**(4): 1197-1206.e3.

BACKGROUND: There have been concerns about the risk of inhaled corticosteroid (ICS)-related tuberculosis (TB) development. OBJECTIVE: We investigated the occurrence of TB among ICS users according to underlying respiratory diseases and type of ICS. METHODS: A 12-year population cohort comprising approximately 1 million subjects collected from the Korean claims database were used. Adult ICS users (budesonide or fluticasone) were enrolled. The temporal relationship between TB development and the last ICS prescription before TB development was evaluated. A nested case-control study was performed with 1:4 matching for age, sex, and the initiation date of the ICS. RESULTS: There were 17,991 ICS users, and 175 developed TB during the study period. Approximately 80% (140/175) of patients who developed TB were diagnosed within 3 years after the last ICS prescription. In the nested case-control study, the occurrence of TB was not related to the type of ICS, but was related to a higher annual admission rate and a higher comorbidity score. The risk of TB was higher in patients with chronic obstructive pulmonary disease (COPD) than in those with asthma (odds ratio: 2.31; CI 95%: 1.39-3.38; P = .0011) after adjusting for covariates. The subgroup analysis revealed no difference between budesonide and fluticasone with respect to the risk of developing TB in patients with asthma, COPD, or asthma-COPD overlap syndrome. CONCLUSION: An increased risk of TB development may persist for 3 years after stopping the ICS and the risk is higher in patients with COPD regardless of the type of ICS used.

https://www.sciencedirect.com/science/article/pii/S2213219818306640?via%3Dihub

Lee, J. H., K. L. Hailey, et al. (2019). **"Cigarette Smoke Triggers IL-33-Associated Inflammation in a Model of Late Stage COPD."** Am J Respir Cell Mol BiolChronic Obstructive Pulmonary Disease (COPD) is a worldwide threat. Cigarette smoke (CS) exposure causes cardiopulmonary disease, COPD and increases the risk for pulmonary tumors. In addition to poor lung function, those with COPD are susceptible to bouts of dangerous inflammation triggered by pollutants or infection. These severe inflammatory episodes can lead to additional exacerbations, hospitalization, further deterioration of lung function and reduced survival. Suitable models of the inflammatory conditions associated with CS, which potentiate the downward spiral in COPD patients, are lacking and the underlying mechanisms that trigger exacerbations are not well understood. While initial CS exposure activates a protective role for vascular endothelial growth factor (VEGF) functions in barrier integrity, chronic exposure depletes pulmonary VEGF guard function in severe COPD. Thus, we hypothesized that mice with compromised VEGF production and challenged with CS would trigger human-like severe inflammatory progressions of COPD. In this model, we discovered that CS exposure promotes an amplified Interleukin-33 (IL-33)

cytokine response and severe disease progression. Our VEGF knockout model combined with CS recapitulates severe COPD with an influx of IL-33-expressing macrophages and neutrophils. Normally, IL-33 is quickly inactivated by a post-translational disulfide bond (DSB) formation. Our results reveal that bronchoalveolar lavage fluid (BALF) from the CS-exposed, VEGF-deficient cohort promotes a significantly prolonged lifetime of active pro-inflammatory IL-33. Taken together, our data demonstrate that with the loss of a VEGF-mediated protective barrier, the CS response switches from a localized danger to an uncontrolled long-term and long-range amplified IL-33-mediated inflammatory response that ultimately destroys lung function.

Lee, S. H., J. H. Lee, et al. (2019). **"Change in inhaled corticosteroid treatment and COPD exacerbations: an analysis of real-world data from the KOLD/KOCOSS cohorts."** Respir Res **20**(1): 62.

BACKGROUND: This cohort study of patients with chronic obstructive pulmonary disease (COPD) was performed to evaluate the status of inhaled corticosteroid (ICS) prescriptions following the 2017 revision of the Global Initiative for Chronic Obstructive Lung Disease guidelines. METHODS: A total of 1144 patients from the Korean Obstructive Lung Disease and Korea Chronic Obstructive Pulmonary Disorders Subgroup Study cohorts, with final follow-up visits completed between 2017 and 2018, were analyzed. Features indicative of ICS usage were as follows: a history of asthma, blood eosinophils of >/=300 cells/mul, or >/= 2 exacerbations in the year prior to enrollment. Among baseline ICS users, we compared annual total and severe exacerbation rates, based on ICS continuation or withdrawal. RESULTS: ICS-containing regimens were prescribed to 46.3% of the enrolled of patients in 2014; this decreased to 38.8% in 2017, and long-acting dual bronchodilators were used instead. Among ICS users in 2017, 47.5% did not exhibit features indicative of ICS usage; 478 used ICS at baseline, and ICS was withdrawn in 77 (16.1%) during the study period. The proportion of patients with asthma and the baseline annual exacerbation rate were greater in the ICS withdrawal groinup than in the ICS continued group (56.6% vs. 41%, p = 0.01; 0.79 vs. 0.53, p < 0.001). Annual exacerbation rates during the follow-up period were similar between the ICS-withdrawal and ICS -continued groups (0.48 vs. 0.47, p = 0.84); however, former exhibited a significantly higher rate of severe exacerbation (0.22 vs. 0.12, p = 0.03). CONCLUSIONS: Prescriptions of ICS to treat COPD decreased with increased use of long-acting dual bronchodilators. ICS withdrawal might impact severe exacerbation; the potential risks and benefits of withdrawing ICS should therefore be considered based on patients' characteristics.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6437901/pdf/12931_2019_Article_1029.pdf

Lee, Y. S., K. H. Min, et al. (2019). **"The Economic Effect of Early Management in Patients with Early Chronic Obstructive Pulmonary Disease: Results from a Population-Based Nationwide Survey."** LungPURPOSE: The economic effect of regular follow-up and early management in patients with early chronic obstructive pulmonary disease (COPD) has not yet been clarified. Therefore, this study aimed to estimate the economic effect of regular follow-up and early management in these patients. METHODS: Patients with early COPD were identified from the Korea National Health and Nutrition Examination Survey. We analyzed medical utilization and cost for 2 years without any missing data by using the Korean National Health Insurance data. Patients with routine healthcare maintenance were defined as, after diagnosis, those with regular visits to the hospital and receiving early management of COPD. RESULTS: Among 1204 patients with early COPD, the patients who were classified as the group with routine healthcare maintenance (69/146; 47.3%) and the group with intermittent healthcare user (79/1058; 7.5%) visited to hospital for the next 2 years. The patients with routine healthcare maintenance had lower cost of inpatient service and frequencies of emergency room (ER) visit and intensive care unit (ICU) admission than intermittent healthcare users (cost of inpatient service, $4595 vs. $4953 per person; ER visit, 7.2 vs. 11.5; ICU admission, 4.3 vs. 7.7). Even in patients with COPD and FEV1 >/= 80, early intervention through follow-up reduced the cost of inpatient service because these patients could have had less severe acute exacerbations than intermittent healthcare users. CONCLUSION: Patients with early

COPD, even those with FEV1 >/= 80, need regular follow-up for early management and disease control as well as for reducing the socioeconomic burden of the disease.

https://link.springer.com/article/10.1007%2Fs00408-019-00208-5

Leitao Filho, F. S., N. M. Alotaibi, et al. (2018). **"Sputum Microbiome is Associated with 1-Year Mortality Following COPD Hospitalizations."** Am J Respir Crit Care MedRATIONALE: Lung dysbiosis promotes airway inflammation and decreased local immunity, potentially playing a role in the pathogenesis of acute exacerbations of COPD (AECOPD). We determined the relationship between sputum microbiome at the time of AECOPD hospitalization and 1-year mortality in a COPD cohort. METHODS: We used sputum samples from 102 patients hospitalized due to AECOPD. All subjects were followed for one year after discharge. The microbiome profile was assessed through sequencing of 16S rRNA gene. Microbiome analyses were performed according to 1-year mortality status. To investigate the effect of alpha diversity measures and taxa features on time to death, we applied Cox proportional-hazards regression models and obtained hazard ratios (HR) associated with these variables. MEASUREMENTS AND MAIN RESULTS: We observed significantly lower values of alpha diversity (Richness, Shannon Index, Evenness, and Faith's Phylogenetic Diversity) among non-survivors (n=19, 18.6%) compared to survivors (n=83, 81.4%). Beta diversity analysis also demonstrated significant differences between both groups (adj. PERMANOVA, p=0.010). The survivors had a higher relative abundance of Veillonella; in contrast, non-survivors had a higher abundance of Staphylococcus. The adjusted HRs for 1-year mortality increased significantly with decreasing alpha diversity. We also observed lower survival among patients in whom sputum samples were negative for Veillonella (HR: 13.5, 95% CI: 4.2 - 43.9, p<0.001) or positive for Staphylococcus (HR: 7.3, 95% CI: 1.6 - 33.2, p=0.01). CONCLUSION: The microbiome profile of sputum in AECOPD is associated with 1-year mortality and may be used to identify subjects with a poor prognosis at the time of hospitalization.

Leong, P., M. I. Macdonald, et al. (2019). **"Coexisting chronic obstructive pulmonary disease and cardiovascular disease in clinical practice: a diagnostic and therapeutic challenge."** Med J AustChronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) frequently coexist but combined disease is often not recognised. Since symptoms overlap significantly, it is common for patients' presentations to be attributed to one disease alone, and for the other to be overlooked. The effect of COPD and CVD goes beyond the shared risk factors of smoking and advancing age. The presence of COPD adversely affects cardiac disease and vice versa. In comparison to individuals with one disease alone, those with both conditions have a higher mortality rate, experience more frequent exacerbations with more hospitalisations and have worse quality of life. More patients with mild and moderate COPD die from CVD than from COPD, and there is a higher rate of arrhythmias, particularly atrial fibrillation. Accurate and timely diagnosis is therefore crucial. Retrospective evidence indicates that individuals with COPD and CVD may have better outcomes with appropriate CVD pharmacotherapy, yet robust prospective evidence is lacking. Inhaled medications for patients with stable COPD improve quality of life and reduce exacerbations, but there is limited evidence that they reduce mortality. A low threshold for investigation and treatment of CVD in COPD and COPD in CVD is essential.

https://onlinelibrary.wiley.com/doi/abs/10.5694/mja2.50120

Leung, R. W. M., J. A. Alison, et al. (2019). **"Inter-rater and intra-rater reliability of the Brief-BESTest in people with chronic obstructive pulmonary disease."** Clin Rehabil **33**(1): 104-112.

OBJECTIVE:: To investigate the inter-rater and intra-rater reliability of the Brief Balance Evaluation System Test (Brief-BESTest) in people with chronic obstructive pulmonary disease and its correlation between the Brief-BESTest score and lung function, functional exercise capacity, functional lower limb strength, and fear of falling. DESIGN:: Prospective, single-group, observational study. SETTING:: Outpatient pulmonary rehabilitation program. SUBJECTS:: People with chronic obstructive pulmonary disease who were attending a pulmonary rehabilitation program. INTERVENTION:: Participants performed three Brief-BESTests on two separate days, assessed by two independent physiotherapists. Participants also performed a lung function test, two 6-minute walk tests, the five sit-to-stand test and completed the Fall Efficacy Scale International questionnaire. RESULTS:: Thirty participants (mean (SD) age was 72 (7), forced expiratory volume in 1 second % predicted was 47 (16%), and baseline 6-minute walk distance was 427 (90) meters) completed the study. The interclass coefficients of the inter-rater and intra-rater reliability were 0.86 and 0.96, respectively. The Brief-BESTest score was moderately correlated with the 6-minute walk distance (r = 0.49, P < 0.01) and the five sit-to-stand test time (r =-0.54, P < 0.01). No adverse events were reported after the completion of 90 tests in this study. CONCLUSION:: The Brief-BESTest was shown to have good inter- and intra-rater reliability for measuring balance in people with chronic obstructive pulmonary disease. A moderate correlation was demonstrated between the Brief-BESTest balance score with functional exercise capacity and functional lower limb strength in this population.

Levesque, J., A. Antoniadis, et al. (2019). **"Minimal clinically important difference of 3-minute chair rise test and the DIRECT questionnaire after pulmonary rehabilitation in COPD patients."** Int J Chron Obstruct Pulmon Dis **14**: 261-269.

Background: The 3-minute chair rise test (3-minute CRT) and the Disability Related to COPD Tool (DIRECT) are two reproducible and valid short tests that can assess the benefit of pulmonary rehabilitation (PR) in terms of functional capacity and dyspnea in everyday activities. Methods: We determined the minimal clinically important difference (MCID) of the DIRECT questionnaire and 3-minute CRT using distribution methods and anchor encroaches with a panel of eight standard tests in a cohort of 116 COPD patients who completed a PR program in real-life settings. Results: The estimated MCID for the 3-minute CRT and DIRECT scores was five repetitions and two units, respectively, using separate and combined independent anchors. The all-patient (body mass index-obstruction-dyspnea-exercise [BODE] scores 0-7), BODE 0-2 (n=42), and BODE 3-4 (n=50) groups showed improvements greater than the MCID in most tests and questionnaires used. In contrast, the BODE 5-7 group (n=24) showed improvements greater than MCID in only the 3-minute CRT, 6-minute walk test, endurance exercise test, and DIRECT questionnaire. Discussion and conclusion: This study demonstrates that the short and simple DIRECT questionnaire and 3-minute CRT are responsive to capture the beneficial effects of a PR program in COPD patients, including those with severe disease. Trial registration number: NCT03286660.

https://www.dovepress.com/getfile.php?fileID=47663

Li, Q., P. Larivee, et al. (2019). **"Greater eosinophil counts at first COPD hospitalization are associated with more readmissions and fewer deaths."** Int J Chron Obstruct Pulmon Dis **14**: 331-341.

Purpose: The impacts of high blood eosinophil count (HBEC) at admission for COPD exacerbation on posthospitalization outcomes are still unclear. Previous studies have focused on its associations with first readmission rates; yet, its impacts on longitudinal outcomes such as subsequent readmissions still have to be explored. The main objective of this study is to investigate outcomes associated with HBEC following a first hospitalization for COPD exacerbation. Patients and methods: This is an observational cohort study design. We retrospectively analyzed data of patients with a first hospitalization within 5 years for COPD exacerbation between April 2006 and March 2013. Patients were stratified into the HBEC group if the blood eosinophil count at admission was >/=200 cells/microL and/or >/=2% of the total white blood cells. With information on exact dates of subsequent hospitalizations and death, we modeled readmissions and death as states in a multi-state Markov model and estimated transition

probabilities to the next states. Sensitivity analyses were performed by varying thresholds for the definition of HBEC (>/=300 cells/microL and/or >/=3%). Results: A total of 479 patients were included, of which 173 had HBEC. The transition probabilities for a first readmission was 74% (95% CI, 66%-83%) for patients with HBEC vs 70% (95% CI, 63%-77%) for patients with normal blood eosinophil count (NBEC). The transition probabilities for a second readmission were 91% (95% CI, 84%-100%) for HBEC patients in contrast with 83% (95% CI, 74%-92%) for NBEC patients. Meanwhile, transition probability for death was lower in patients with HBEC. The differences enlarged in sensitivity analyses with higher cutoff. Conclusion: Greater blood eosinophil cell counts during a first hospitalization for COPD predict increased susceptibility to up to two readmissions. These patients may however have a lower risk of death.

https://www.dovepress.com/getfile.php?fileID=47784

Li, S., G. Wang, et al. (2018). **"The REACH Trial: A Randomized Controlled Trial Assessing the Safety and Effectiveness of the Spiration(R) Valve System in the Treatment of Severe Emphysema."** Respiration: 1-12.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) has become a leading cause of morbidity and mortality in China, with tobacco smoke, air pollution, and occupational biohazards being the major risk factors. OBJECTIVES: The REACH trial is a multicenter, prospective, randomized controlled trial undertaken in China to assess the safety and effectiveness of the Spiration(R) Valve System (SVS) compared to standard medical care in COPD patients with severe emphysema. METHODS: Patients with severe airflow obstruction, hyperinflation, and severe dyspnea with interlobar fissure integrity were evaluated for enrollment. A total of 107 subjects were randomized in a 2: 1 allocation ratio to either the treatment group (SVS valves and medical management) or the control group (medical management alone). RESULTS: The 3-month primary endpoint showed statistically significant improvement in forced expiratory volume in 1 s in the treatment group compared to the control group (0.104 +/- 0.18 vs. 0.003 +/- 0.15 L, p = 0.001), with the difference being durable through 6 months. Statistically significant target lobe volume reduction was achieved at 3 months (mean change 684.4 +/- 686.7 mL) and through 6 months (757.0 +/- 665.3 mL). Exercise function and quality of life measures improved in the treatment group, but showed a deterioration in the control group. The serious adverse event (SAE) rate was 33% in the treatment group and 24.2% in the control group. The predominance of SAEs were acute exacerbations of COPD in both groups. There was 1 death in the control group and no deaths in the treatment group. CONCLUSION: The SVS represents a novel approach for the treatment of severe emphysema with a clinically acceptable risk-benefit profile.

https://www.karger.com/Article/Pdf/494327

Liacos, A., C. F. McDonald, et al. (2019). **"The Pulmonary Rehabilitation Adapted Index of Self-Efficacy (PRAISE) tool predicts reduction in sedentary time following pulmonary rehabilitation in people with chronic obstructive pulmonary disease (COPD)."** Physiotherapy **105**(1): 90-97.

OBJECTIVES: To examine the predictive validity, minimal important difference (MID) and responsiveness of the PRAISE tool. DESIGN: Retrospective data analysis from HomeBase trial of home vs centre-based pulmonary rehabilitation. SETTING: Tertiary health service. PARTICIPANTS: One hundred and sixty-six participants with COPD (100 men) with mean age 69 (SD 9) years, FEV1% predicted 50% (19). INTERVENTIONS: Eight-week pulmonary rehabilitation program, conducted at the hospital or at home. MAIN OUTCOME MEASURES: The 15-item PRAISE tool comprising 10 general and five pulmonary rehabilitation-specific self-efficacy questions. Predictive validity was examined by exploring the relationship between baseline PRAISE score and objective change in physical activity following pulmonary rehabilitation using the SenseWear Armband. The MID was evaluated using anchor-based and distribution-based methods. Responsiveness was assessed with effect sizes. RESULTS: A higher baseline PRAISE score (indicating better self-efficacy) was an independent predictor of reduced sedentary time following pulmonary rehabilitation (P=0.03). A one point increase in PRAISE was

associated with a decrease in sedentary time of 4minutes/day (95% confidence interval -7.8 to -0.4minutes/day). Anchor-based estimates of the MID were 0.5 to 1.5 points; however sensitivity and specificity were modest (area under the curve <0.70). Change in PRAISE score following pulmonary rehabilitation had an effect size of 0.21. CONCLUSIONS: The PRAISE tool has predictive validity and may be useful to identify those with high self-efficacy who are more likely to achieve important health behaviour changes with pulmonary rehabilitation. The small effect size suggests that the PRAISE tool was not responsive to changes following pulmonary rehabilitation. TRIAL REGISTRATION NUMBER: NCT01423227, clinicaltrials.gov.

https://www.physiotherapyjournal.com/article/S0031-9406(18)30168-8/pdf

Lim, B. L., S. O. Cheah, et al. (2019). **"Most impactful predictors for hyperoxaemia in exacerbation of chronic obstructive pulmonary disease managed by Emergency Medical Services and Emergency Department."** Clin Respir J **13**(4): 256-266.

INTRODUCTION: Hyperoxemia in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) leads to adverse outcomes. It remains prevalent in the pre-hospital Emergency Medical Services (EMS) and Emergency Department (ED). OBJECTIVE: To determine the key predictors for hyperoxemia in AECOPD in EMS and ED. METHODS: This was a prospective observational study of AECOPD patients in EMS and two EDs. Hyperoxemia was defined as PaO2 > 65 mm Hg (corresponds to SpO2 > 92%). We determined apriori candidate factors in Patient, Organization and Staff domains. Primary outcomes were the key predictors for hyperoxemia. Secondary outcomes were in-hospital mortality and mechanical ventilation rates in hyperoxemic versus non-hyperoxemic groups. We generated a logistic regression model for each domain. We reported the adjusted odds ratios (AORs), 95% CIs and p values. We selected the output factors using AOR >/=2.0 and >/=2.5 for modifiable and non-modifiable factors, respectively. These selected factors were fed into a final model with eventual factors selected based on: threshold AORs as stated above and/or 95% CIs including these AORs. RESULTS: Three hundred and twenty-six patients were analysed; 60.7% had hyperoxemia. We found three eventual modifiable factors; first, ED SpO2 > 95% [AOR 2.62 (95% CIs: 1.61-4.33); P < 0.001], EMS non-rebreathing mask [AOR 2.01 (95% CIs: 1.06-3.97); P = 0.04]; and ED nasal cannula [AOR 1.69 (95% CIs: 1.05-2.72); P = 0.03]. Secondary outcomes did not differ between groups. CONCLUSION: We identified three key modifiable predictors. We intend to conduct an interventional study using them to reduce hyperoxemia rate in AECOPD.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13007

Lin, W. C., C. W. Chen, et al. (2019). **"The association between recent hospitalized COPD exacerbations and adverse outcomes after percutaneous coronary intervention: a nationwide cohort study."** Int J Chron Obstruct Pulmon Dis **14**: 169-179.

Purpose: COPD is associated with coronary artery disease, and exacerbations are major events in COPD. However, the impact of recent hospitalized exacerbations on outcomes of percutaneous coronary intervention (PCI) remains underdetermined. Patients and methods: Using the National Health Insurance Research Database of Taiwan, we identified 215,275 adult patients who underwent first-time PCI between 2000 and 2012. Among these patients, 15,485 patients had COPD. The risks of hospital mortality, overall mortality, and adverse cardiovascular outcomes after PCI (ie, ischemic events, repeat revascularization, cerebrovascular events, and major adverse cardiac and cerebrovascular events [MACCEs]) in relation to COPD, and the frequency and timing of recent hospitalized exacerbations within 1 year before PCI were estimated. Results: COPD was independently associated with increased risks of hospital mortality, overall mortality, ischemic events, cerebrovascular events, and MACCE during follow-up after PCI. Among cerebrovascular events, ischemic rather than hemorrhagic stroke was more likely to occur. In COPD patients, recent hospitalized exacerbations further increased the risks of overall mortality, ischemic events, and MACCE following PCI. Notably, patients with more frequent or more recent hospitalized exacerbations had a trend toward higher risks of these adverse events (all P-values for trend <0.0001), especially those with >/=2 exacerbations within 1 year or any exacerbation within 1 month before PCI.

Conclusion: Integrated care is urgently needed to alleviate COPD-related morbidity and mortality after PCI, especially for patients with a recent hospitalized exacerbation.

https://www.dovepress.com/getfile.php?fileID=47335

Lozo Vukovac, E., K. Mise, et al. (2019). **"Bronchoalveolar pH and inflammatory biomarkers in patients with acute exacerbation of chronic obstructive pulmonary disease."** J Int Med Res **47**(2): 791-802.

OBJECTIVES: This study aimed to directly measure pH in the lungs, determine lactate dehydrogenase (LDH), C-reactive protein (CRP), and glucose levels in serum and bronchoalveolar aspirate, and identify bacterial pathogens from bronchoalveolar fluid during acute exacerbation of chronic obstructive pulmonary disease (AECOPD). METHODS: We performed an observational, analytical case-control study from February 2015 to March 2017. We included 84 patients with AECOPD and 42 with stable chronic obstructive pulmonary disease (COPD). All participants underwent detailed medical anamnesis, a clinical examination, chest radiography, spirometry, an arterial blood gas test, bronchoscopy, bacterial culture, and serum/bronchiolar aspirate laboratory testing. RESULTS: The mean pH of bronchoalveolar fluid was significantly higher in patients with AECOPD than in patients with stable COPD. The mean lung pH value, bronchoalveolar and serum LDH levels, and serum CRP levels in patients with isolated bacteria were higher than those in patients without isolated bacteria in the AECOPD patient group. Lung pH values in patients with AECOPD were significantly correlated with bronchoalveolar LDH and glucose levels. CONCLUSIONS: AECOPD is associated with local cell and tissue injury in the lungs, especially in the presence of bacterial pathogens, which is accompanied by a low systemic inflammatory response.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6381468/pdf/10.1177_0300060518811560.pdf

Luehrs, R. E., J. D. Newell, Jr., et al. (2018). **"CT-Measured Lung Air-Trapping is Associated with Higher Carotid Artery Stiffness in Individuals with Chronic Obstructive Pulmonary Disease."** J Appl Physiol (1985)Early stages of chronic obstructive pulmonary disease (COPD) are characterized by the loss and narrowing of terminal bronchioles in the lung resulting in 'air-trapping,' often occurring before overt emphysema manifests. Individuals with an airway-predominant phenotype of COPD display extensive lung air-trapping and are at greater cardiovascular disease (CVD) risk than COPD patients with an emphysema-predominant phenotype. We hypothesized that the degree of computed tomography (CT)-quantified lung air-trapping would be associated with greater aortic and carotid artery stiffness and lower endothelial function, known biomarkers of CVD risk. Lung air-trapping was associated with greater aortic stiffness (carotid femoral pulse wave velocity, CFPWV) ($r=0.60$, $p=0.007$) and carotid beta-stiffness ($r=0.75$, $p=0.0001$) among adults with ($n=10$) and without ($n=9$) a clinical diagnosis of COPD and remained significant after adjusting for blood pressure (BP) and smoking history (pack-years) (carotid beta-stiffness $r=0.68$, $p<0.01$; CFPWV $r=0.53$, $p=0.03$). The association between lung air-trapping and carotid beta-stiffness remained significant after additionally adjusting for age and FEV1 ($r=0.64$, $p=0.01$). In the COPD group only ($n=10$), lung air-trapping remained associated with carotid beta-stiffness ($r=0.82$, $p=0.05$) after adjustment for age, pack-years and FEV1. In contrast, no association was observed between CFPWV and lung air-trapping after adjustment for BP, pack-years, age and FEV1 ($r=0.12$, $p=0.83$). Lung air-trapping was not associated with endothelial function (brachial artery flow mediated dilation) in the entire cohort ($p=0.80$) or in patients with COPD only ($p=0.71$). These data suggest that carotid artery stiffness may be a mechanism explaining the link between airway- predominant phenotypes of COPD and high CVD risk.

https://www.physiology.org/doi/abs/10.1152/japplphysiol.00580.2018

Lutz, S. M., B. Frederiksen, et al. (2018). **"Common and rare variants genetic association analysis of cigarettes per day among ever smokers in COPD cases and controls."** Nicotine Tob ResIntroduction: Cigarette smoking is a major environmental risk factor for many diseases, including chronic obstructive pulmonary disease (COPD). There are shared genetic influences on cigarette smoking and COPD. Genetic risk factors for cigarette smoking in cohorts enriched for COPD are largely unknown. Methods: We performed genome-wide association analyses for average cigarettes per day (CPD) across the COPDGene Non-Hispanic White (NHW) (n=6,659) and African American (AA) (n=3,260), GenKOLS (n=1,671), and ECLIPSE (n=1,942) cohorts. In addition, we performed exome array association analyses across the COPDGene NHW and AA cohorts. We considered analyses across the entire cohort and stratified by COPD case-control status. Results: We identified genome-wide significant associations for CPD on chromosome 15q25 across all cohorts (lowest p=1.78x10-15), except in the COPDGene AA cohort alone. Previously reported associations on chromosome 19 had suggestive and directionally consistent associations (RAB4 p=1.95x10-6; CYP2A7 p=7.50x10-5; CYP2B6 4.04x10-4). When we stratified by COPD case-control status, single nucleotide polymorphisms (SNPs) in chromosome 15q25 were nominally associated in both NHW COPD cases (Beta=0.11, p=5.58x10-4) and controls (Beta=0.12, p=3.86x10-5). For the gene-based exome array association analysis of rare variants, there were no exome-wide significant associations. For these previously replicated associations, the most significant results were among COPDGene NHW subjects for CYP2A7 (p=5.2x10-4). Conclusions: In a large genome-wide association study of both common variants and a gene-based association of rare coding variants in ever smokers, we found genome-wide significant associations on chromosome 15q25 with CPD for common variants, but not for rare coding variants. These results were directionally consistent among COPD cases and controls. IMPLICATIONS: We examined both common and rare coding variants associated with CPD in a large population of heavy smokers with and without COPD of NHW and AA descent. We replicated genome-wide significant associations on chromosome 15q25 with CPD for common variants among NHW subjects, but not for rare variants. We demonstrated for the first time that common variants on chromosome 15q25 associated with CPD are similar among COPD cases and controls. Previously reported associations on chromosome 19 showed suggestive and directionally consistent associations among common variants (RAB4, CYP2A7, and CYP2B6) and for rare variants (CYP2A7) among COPDGene NHW subjects. While the genetic effect sizes for these SNPs on chromosome 15q25 are modest, we show that this creates a substantial smoking burden over the lifetime of a smoker.

https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/nty095/4996129?redirectedFrom=fulltext

Lytras, T., M. Kogevinas, et al. (2019). **"Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey."** Occup Environ Med **76**(4): 222-229.

OBJECTIVES: Chronic bronchitis (CB) is an important chronic obstructive pulmonary disease (COPD)-related phenotype, with distinct clinical features and prognostic implications. Occupational exposures have been previously associated with increased risk of CB but few studies have examined this association prospectively using objective exposure assessment. We examined the effect of occupational exposures on CB incidence in the European Community Respiratory Health Survey. METHODS: Population samples aged 20-44 were randomly selected in 1991-1993, and followed up twice over 20 years. Participants without chronic cough or phlegm at baseline were analysed. Coded job histories during follow-up were linked to the ALOHA Job Exposure Matrix, generating occupational exposure estimates to 12 categories of chemical agents. Their association with CB incidence over both follow-ups was examined with Poisson models using generalised estimating equations. RESULTS: 8794 participants fulfilled the inclusion criteria, contributing 13 185 observations. Only participants exposed to metals had a higher incidence of CB (relative risk (RR) 1.70, 95% CI 1.16 to 2.50) compared with non-exposed to metals. Mineral dust exposure increased the incidence of chronic phlegm (RR 1.72, 95% CI 1.43 to 2.06). Incidence of chronic phlegm was increased in men exposed to gases/fumes and to solvents and in women exposed to pesticides. CONCLUSIONS: Occupational exposures are associated with chronic phlegm and CB, and the evidence is strongest for metals and mineral dust exposure. The observed differences between men and women warrant further investigation.

https://oem.bmj.com/content/76/4/222.long

Machado, F. V. C., L. P. Schneider, et al. (2019). **"Clinical impact of body composition phenotypes in patients with COPD: a retrospective analysis."** Eur J Clin NutrBACKGROUND/OBJECTIVES: Abnormal body composition is an independent determinant of COPD outcomes. To date, it is already known that patient stratification into body composition phenotypes are associated with important outcomes, such as exercise capacity and inflammation, but there are no data comparing physical activity and muscle strength among these phenotypes. Thus, the aim of this study was to compare clinical characteristics and physical function in patients with COPD stratified into body composition phenotypes. SUBJECTS/METHODS: Two-hundred and seventy stable COPD patients were classified according to the 10th and 90th percentiles of sex-age-BMI-specific reference values for fat-free and fat mass indexes into four groups: Normal body composition (NBC), Obese, Sarcopenic, and Sarcopenic-obese (SO). Patients underwent assessment of exercise capacity, peripheral and respiratory muscle strength, physical activity, dyspnea severity, functional status, and symptoms of anxiety and depression. RESULTS: The prevalence of patients classified as NBC, Obese, Sarcopenic, and SO was 39%, 13%, 21%, or 27%, respectively. SO presented lower 6MWT compared with NBC ($P < 0.05$). Sarcopenic and SO groups presented worse muscle strength compared with NBC ($P < 0.05$). Sarcopenic group presented more time in moderate-to-vigorous physical activity compared to all other groups ($P < 0.05$) and less sedentary time when compared with NBC and obese groups ($P < 0.05$). There were no differences regarding dyspnea severity, functional status, and symptoms of anxiety and depression ($P > 0.16$). Sarcopenic and SO groups had, respectively, 7.8 [95% CI: 1.6-37.7] and 9.5 [2.2-41.7] times higher odds to have a 6MWT equal or lower to 350 meters. CONCLUSIONS: Body composition phenotypes are associated with physical function in patients with COPD. Sarcopenic-obese patients were the most impaired.

https://www.nature.com/articles/s41430-019-0390-4

Maestri, R., C. Bruschi, et al. (2019). **"Physiological and clinical characteristics of patients with COPD admitted to an inpatient pulmonary rehabilitation program: A real-life study."** Pulmonology **25**(2): 71-78.
BACKGROUND AND OBJECTIVE: Patient selection criteria and experimental interventions of randomized controlled trials may not reflect how things work in practice. The aim of this study was to describe the characteristics of chronic obstructive pulmonary disease (COPD) patients undergoing an inpatient pulmonary rehabilitation program (PRP) and the correlates of success. METHODS: Retrospective database review of 975 consecutive patients transferred from acute care hospitals after an acute exacerbation (group A: 14.6%) or admitted from home (group B: 75.4%), from 2010 to 2017. Patients were also divided according to the associated registered main diagnosis: COPD (group 1: 30.6%); COPD and respiratory failure (group 2: 51.7%); COPD and obstructive sleep apnea (group 3: 17.6%). Baseline correlates of post-PRP changes in six minute walking test (6MWT) were also evaluated. RESULTS: Global Initiative for Chronic Obstructive Lung Disease stages 3 and 4 were the most commonly represented in group 2 (p=0.0001). Comorbidity Index of all patients was 3.9+/-1.8. The overall in-hospital mortality rate was 1.3% (5.6% vs 0.6%, in groups A and B, respectively; p=0.0001). Hypertension, cardiac diseases and obesity were observed in 65.2, 52.2 and 29.6% of patients, respectively. Post-PRP 6MWT increased in all groups. Age, male gender, airway obstruction and baseline 6MWT were correlated with a post-PRP 30 meter increase in 6MWT. CONCLUSION: Confirming data of literature, this real-life study shows the characteristics of COPD patients undergoing an inpatient PRP with significant improvement in exercise capacity, independent of whether in stable state or after a recent exacerbation or of the associated main diagnosis.

https://www.sciencedirect.com/science/article/pii/S2531043718301107?via%3Dihub

Mahta, A., A. E. Merkler, et al. (2019). **"Emphysema: A Potential Risk Factor for Subarachnoid Hemorrhage and Ruptured Aortic Aneurysm."** Stroke **50**(4): 992-994.

Background and Purpose- Protease/antiprotease imbalance is implicated in the pathogenesis of emphysema and may also lead to vessel wall weakening, aneurysm development, and rupture. However, it is unclear whether emphysema is associated with cerebral and aortic aneurysm rupture. Methods- We performed a retrospective cohort study using outpatient and inpatient claims data from 2008 to 2014 from a nationally representative sample of Medicare beneficiaries >/=66 years of age. Our predictor variable was emphysema, and our outcome was hospitalization for either aneurysmal subarachnoid hemorrhage or a ruptured aortic aneurysm. All predictors and outcomes were defined using previously reported International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code algorithms. Survival statistics and Cox regression were used to compare risk between patients with and without emphysema. Results- We identified 1 670 915 patients, of whom 133 972 had a diagnosis of emphysema. During a mean follow-up period of 4.3 (+/-1.9) years, we identified 4835 cases of aneurysm rupture, 433 of which occurred in patients with emphysema. The annual incidence of aneurysm rupture was 6.5 (95% CI, 6.4-6.8) per 10 000 in patients without emphysema and 14.6 (95% CI, 13.3-16.0) per 10 000 in patients with emphysema. After adjustment for demographics and known risk factors for aneurysmal disease, emphysema was independently associated with aneurysm rupture (hazard ratio, 1.7; 95% CI, 1.5-1.9). Emphysema was associated with both aneurysmal subarachnoid hemorrhage (hazard ratio, 1.5; 95% CI, 1.3-1.7) and ruptured aortic aneurysm (hazard ratio, 2.3; 95% CI, 1.9-2.8). Conclusions- Patients with emphysema face an increased risk of developing subarachnoid hemorrhage and aortic aneurysm rupture, potentially consistent with shared pathways in pathogenesis.

Marco, E., D. Sanchez-Rodriguez, et al. (2018). **"Malnutrition according to ESPEN consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease."** Clin NutrBACKGROUND: Nutritional disorders are frequent in patients with chronic pulmonary obstructive disease (COPD) and have negative health impacts. This study aimed to explore the value of the European Society of Clinical Nutrition and Metabolism (ESPEN) definition of malnutrition (and/or its individual components) to predict hospitalizations and mortality at 2 years, and to determine the prevalence of malnutrition in COPD patients referred to pulmonary rehabilitation. METHODS: The study was a prospective analysis of 118 patients with COPD free of exacerbations and/or hospital admissions in the previous two months. Main outcome variables were mortality, hospital admissions, and length of stay at 2-year follow-up; main covariates were malnutrition assessment according to the ESPEN definition and its components: unintentional weight loss, body mass index, and fat-free mass index (FFMI). Body composition was assessed by bioimpedance analysis. Kaplan-Meier survival curves and linear regression analyses were performed, adjusting for age and airflow obstruction as potential confounders. RESULTS: The observed prevalence of malnutrition was 24.6%. Malnutrition was associated with increased mortality risk (HR = 3.9 [95% CI: 1.4-10.62]). FFMI was independently associated with increased mortality (HR = 17.0 [95% CI: 2.24-129.8]), which persisted after adjustment for age and lung function (adjusted HR = 13.0 [95% CI: 1.67-101.7]). Low age-related body mass index was associated with increased risk of hospital admissions. CONCLUSIONS: Malnutrition according to ESPEN criteria, highly prevalent in patients with stable COPD referred to pulmonary rehabilitation, was associated with 4 times greater mortality risk after 2 years. Low FFMI was associated with a 17-fold increase in mortality risk, suggesting independent predictive value.

https://www.clinicalnutritionjournal.com/article/S0261-5614(18)32452-X/fulltext

McGuire, K., J. A. Avina-Zubieta, et al. (2017). **"Risk of Incident Chronic Obstructive Pulmonary Disease in Rheumatoid Arthritis: A Population-Based Cohort Study."** Arthritis Care Res (Hoboken)OBJECTIVE: Studies have demonstrated a link between chronic obstructive pulmonary disease (COPD) and inflammation, raising the question whether chronic inflammatory conditions, such as rheumatoid

arthritis (RA), predispose to COPD. Our objective was to evaluate the risk of incident COPD hospitalization in RA compared to the general population. METHODS: We studied a population-based incident RA cohort with matched general population controls, using administrative health data. All incident RA cases in British Columbia who first met RA definition between January 1996 and December 2006 were selected using previously published criteria. General population controls were randomly selected, matched 1:1 to RA cases on birth year, sex, and index year. COPD outcome was defined as hospitalization with a primary COPD code. Incidence rates, 95% confidence intervals (95% CIs), and incidence rate ratios (IRRs) were calculated for RA and controls. Multivariable Cox proportional hazards models estimated the risk of COPD in RA compared to the general population after adjusting for potential confounders. Sensitivity analyses were performed to test the robustness of the results to the possible confounding effect of smoking, unavailable in administrative data, and to COPD outcome definitions. RESULTS: The cohorts included 24,625 RA individuals and 25,396 controls. The incidence of COPD hospitalization was greater in RA than controls (IRR 1.58, 95% CI 1.34-1.87). After adjusting for potential confounders, RA cases had a 47% greater risk of COPD hospitalization than controls. The increased risk remained significant after modeling for smoking and with varying COPD definitions. CONCLUSION: In our population-based cohort, individuals with RA had a 47% greater risk of COPD hospitalization compared to the general population.

https://onlinelibrary.wiley.com/doi/abs/10.1002/acr.23410

Mekki, M., T. Paillard, et al. (2019). **"Effect of adding neuromuscular electrical stimulation training to pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: randomized clinical trial."** Clin Rehabil **33**(2): 195-206.

OBJECTIVE:: To investigate the effectiveness of neuromuscular electrical stimulation added to pulmonary rehabilitation on walking tolerance and balance in patients with chronic obstructive pulmonary disease (COPD). DESIGN:: Randomized clinical trial. SETTING:: Outpatient, Faculty of Medicine of Sousse, Tunisia. SUBJECTS:: A total of 45 patients with COPD were assigned to an intervention group (n = 25) or a control group (n = 20). INTERVENTIONS:: The intervention group underwent a neuromuscular electrical stimulation added to pulmonary rehabilitation, and the control group underwent only a pulmonary rehabilitation, three times per week during six months. MAIN MEASURES:: Measures were taken at baseline and after six months of training. A stabilometric platform, time up and go, Berg balance scale tests, 6 minute walking test, and the maximal voluntary contraction were measured. RESULTS:: In the intervention group, an increase in an exercise tolerance manifested by a longer distance walked in 6 minute walking test 619.5 (39.6) m was observed in comparison to the control group 576.3 (31.5) m. The values of the time up and go, Berg balance scale, and maximal voluntary contraction in the intervention group at follow-up were significantly higher than those in the control group (P = 0.02, P = 0.01, P = 0.0002, respectively). The center of pressure in the mediolateral and in the anteroposterior directions, as well as the center of pressure area was significantly more improved in open eyes and closed eyes in the intervention group compared to the control group (P < 0.001). CONCLUSION:: The neuromuscular electrical stimulation added to pulmonary rehabilitation group benefited from better walking tolerance and greater balance improvement than the only pulmonary rehabilitation.

Melen, E., S. Guerra, et al. (2019). **"Linking COPD epidemiology with pediatric asthma care; implications for the patient and the physician."** Pediatr Allergy ImmunolA 10-year-old patient with asthma, diagnosed in early childhood, with a pre-bronchodilator forced expiratory volume in 1 second (FEV1) of 75% of predicted attends a routine follow-up visit. The patient and family perceive his asthma as 'well controlled', but should his physician be concerned about his reduced lung function? What are the implications of a lower than expected FEV1 in childhood on the respiratory health of this patient in adulthood? Lung function is known to track with age, and there is a high likelihood that this patient will

enter adulthood with a sub-optimal lung function. This article is protected by copyright. All rights reserved.

https://onlinelibrary.wiley.com/doi/abs/10.1111/pai.13054

Mendoza, C. S., G. R. Washko, et al. (2012). **"EMPHYSEMA QUANTIFICATION IN A MULTI-SCANNER HRCT COHORT USING LOCAL INTENSITY DISTRIBUTIONS."** Proc IEEE Int Symp Biomed Imaging: 474-477.

This article investigates the suitability of local intensity distributions to analyze six emphysema classes in 342 CT scans obtained from 16 sites hosting scanners by 3 vendors and a total of 9 specific models in subjects with Chronic Obstructive Pulmonary Disease (COPD). We propose using kernel density estimation to deal with the inherent sparsity of local intensity histograms obtained from scarcely populated regions of interest. We validate our approach by leave-one-subject-out classification experiments and full-lung analyses. We compare our results with recently published LBP texture-based methodology. We demonstrate the efficacy of using intensity information alone in multi-scanner cohorts, which is a simpler, more intuitive approach.

https://ieeexplore.ieee.org/document/6235587/

Menon, S., P. Nightingale, et al. (2019). **"Chronic Obstructive Pulmonary Disease and the Risk of Esophagitis, Barrett Esophagus, and Esophageal Adenocarcinoma: A Primary Care Case-Control Study."** J Clin GastroenterolBACKGROUND: Chronic gastroesophageal reflux predisposes to the development of esophageal adenocarcinoma (EAC). Asthma and medication to treat it are associated with gastroesophageal reflux and EAC. We studied subjects with chronic obstructive pulmonary disease (COPD) to examine the relationship between COPD and medication used to treat it, and the risk of reflux esophagitis, Barrett esophagus, and EAC. METHODS: A case-control study from the UK General Practice Research Database was conducted. Cases were aged 50 or above with a diagnosis of COPD and were matched with controls without a diagnosis of COPD by age, general practitioners practice, and time on the database. EAC was confirmed by cross-referencing cancer registry data. Cox-regression analysis was performed to assess the relationship between COPD, reflux esophagitis, Barrett esophagus, and EAC. RESULTS: A total of 45,141 cases were studied [24,464 male, age 75 (50 to 100) years]. Among COPD cases there were 55 esophageal cancers (30 EAC) and 506 Barrett esophagus, compared with 62 (34 EAC) and 329 Barrett esophagus among controls. COPD was not associated with EAC on univariable [0.92 (0.56 to 1.50), P=0.73] and multivariable analysis [0.85 (0.52 to 1.40), P=0.53]. COPD was however, associated with Barrett esophagus on univariable [0.92 (0.56 to 1.50), P=0.73] and multivariable [1.53 (1.31 to 1.78), P<0.001] analysis and reflux esophagitis on univariable [1.41 (1.36 to 1.48), P<0.001] and multivariable [1.33 (1.27 to 1.40), P<0.001] analysis. CONCLUSION: COPD is associated with an increased risk of reflux esophagitis and Barrett esophagus but not EAC.

Metin Okmen, B., O. Sengoren Dikis, et al. (2019). **"Investigation of the effect of kinesiotaping on the respiratory function and depression in male patients with chronic obstructive pulmonary disease: a prospective, randomized, controlled, and single-blind study."** Aging Male: 1-7.

OBJECTIVES: We aimed to investigate the effect of kinesiotaping (KT) on the respiratory parameters as measured by spirometry and depression in the chronic obstructive pulmonary disease (COPD) patients. METHODS: In this prospective, randomized, controlled, single-blind study 42 male patients with COPD diagnosis were randomized into two groups. In Group1 (n = 21) routine COPD medical treatment plus kinesiotaping and in Group2 (n = 21) only routine COPD medical treatment was given. KT was changed on every fifth day (for a total of three times and 15 days). The patients were assessed using Visual

Analog Scale (VAS) for difficulty experienced by the patients during respiration, respiratory function test (RFT), modified medical research council (mMRC) dyspnea scale and beck depression inventory (BDI). The data were obtained before treatment and posttreatment. RESULTS: In Group 1; statistically significant improvement was found in all parameters except for FVC and FVC % following treatment compared to pretreatment values. Comparison of the difference scores (the amount of recovery between posttreatment and pretreatment) of the two groups showed significantly superior improvement in Group1 for all parameters except for FVC, FVC % and FEV1% following the treatment ($p < .05$). CONCLUSIONS: The results of this study showed that supplementary kinesiotaping improved respiratory function and depression significantly compared to only routine medical treatment in COPD patients who were in stable condition.

https://www.tandfonline.com/doi/full/10.1080/13685538.2019.1567703

Minasian, A. G., F. J. van den Elshout, et al. (2014). **"Serial pulmonary function tests to diagnose COPD in chronic heart failure."** Transl Respir Med **2**(1): 12.

BACKGROUND: It is unknown whether serial pulmonary function tests are necessary for the correct diagnosis of chronic obstructive pulmonary disease (COPD) in patients with stable non-congested chronic heart failure (CHF). The aim of this study was to determine the prevalence of COPD in outpatients with stable CHF without pulmonary congestion using initial as well as confirmatory spirometry three months after treatment for COPD. METHODS: Spirometry was performed in 187 outpatients with stable CHF without pulmonary congestion on chest radiograph who had a left ventricular ejection fraction < 40% (mean age 69 +/- 10 years, 78% men). COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease guidelines. The diagnosis of COPD was confirmed three months after treatment with tiotropium in newly diagnosed COPD patients. RESULTS: Using a three month follow-up spirometry to confirm initial diagnosis of de novo COPD did not change COPD prevalence significantly: 32.6% initially versus 32.1% after three months of follow-up. Only 1 of 25 (4%) patients with newly diagnosed COPD was not reproducibly obstructed at follow-up. COPD was greatly under- (19%) and overdiagnosed (32%). CONCLUSIONS: Spirometry should be used under stable and euvolemic conditions to decrease the burden of undiagnosed or overdiagnosed COPD in patients with CHF. Under these conditions, a confirmatory spirometry is unnecessary, as it does not change a newly established diagnosis of COPD in the vast majority of patients with CHF. TRIAL REGISTRATION: ClinicalTrials.gov Identifier NCT01429376.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4177105/pdf/40247_2014_Article_12.pdf

Misu, S., M. Kaneko, et al. (2019). **"Exercise-Induced Oxygen Desaturation as a Predictive Factor for Longitudinal Decline in 6-Minute Walk Distance in Subjects With COPD."** Respir Care **64**(2): 145-152.

BACKGROUND: There are limited longitudinal studies reporting predictive factors for decline in 6-min walk distance (6MWD) in patients with COPD. While previous studies have confirmed the association between air-flow limitation and decline in 6MWD, other factors have not been clarified. The objective of this study was to investigate whether exercise-induced oxygen desaturation (EID) could be a predictive factor for decline in 6MWD in patients with COPD. The interactive effect of air-flow limitation on the association between EID and decline in 6MWD was also investigated. METHODS: A longitudinal observational study was conducted with 71 out-patients with COPD who were followed for 1 year. 6MWD, EID, spirometry, and clinical characteristics were assessed. The effect of EID on changes in 6MWD was examined using linear regression analyses. Furthermore, the subjects were categorized into 4 groups according to their EID and air-flow limitation status, and changes in 6MWD were compared among the groups. RESULTS: 51 subjects completed the follow-up assessments, and 29 (56.9%) experienced EID. Multiple linear regression model revealed that EID was the only predictive factor for changes in 6MWD after adjusting for confounders (beta = -38.9, P = .02). As results of multiple comparisons among the 4 groups based on EID and air-flow limitation status, changes in 6MWD in the EID and severe air-flow limitation group were the lowest. CONCLUSION: Our results revealed that EID was a predictive factor for decline in the

functional capacity of subjects with COPD. The assessment of EID and air-flow limitation would thus be useful in estimating the prognosis of decline in the functional capacity of patients with COPD.

http://rc.rcjournal.com/content/64/2/145.short

Miyazaki, T., K. Fukushima, et al. (2019). **"Efficacy and safety of cefditoren pivoxil for exacerbations of chronic obstructive pulmonary disease: A prospective multicenter interventional study."** J Infect ChemotherOral antibiotic therapy for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) usually involves an aminopenicillin with clavulanic acid, a macrolide, or a quinolone. To date, however, the clinical efficacy and safety of the oral cephalosporin cefditoren pivoxil has not been evaluated in Japanese patients with acute exacerbations of COPD. We conducted a prospective, multicenter, single arm, interventional study from January 2013 to March 2017 to determine the efficacy and safety of oral administration of 200 mg cefditoren pivoxil three times daily for 7 days in a cohort of 29 eligible patients from 15 hospitals. The mean age (SD) of participants was 73.1 (8.1) years and 28 had a smoking history (the mean [SD] of smoking index, 1426.7 [931.7]). The primary efficacy endpoint was clinical response (cure rate) at test of cure, which was set at 5-10 days after treatment ceased. Of the 23 patients finally analyzed, cure was achieved in 15 (65.2%), while 8 (34.8%) remained uncured. Previous experience of acute exacerbations significantly affected the cure rate: none of the three patients who had at least two prior exacerbations were cured, while 15 of the 20 patients with one or fewer prior exacerbations were cured (p = 0.032). The microbiological eradication rate was 88.9% at test of cure. During treatment, mild pneumonia was reported as an adverse event in one patient (3.4%) but resolved within 10 days of onset. We conclude that cefditoren pivoxil represents a viable alternative for antibiotic therapy in patients with few prior exacerbations.

https://www.jiac-j.com/article/S1341-321X(19)30082-0/pdf

Moy, M. L., K. F. Harrington, et al. (2019). **"Characteristics at the time of oxygen initiation associated with its adherence: Findings from the COPD Long-term Oxygen Treatment Trial."** Respir Med **149**: 52-58.
RATIONALE: Characteristics associated with adherence to long-term oxygen therapy (LTOT) in COPD remain unclear. OBJECTIVES: To identify patient characteristics at the time of oxygen initiation associated with its adherence. METHODS: We conducted a secondary analysis of data from 359 COPD participants assigned to oxygen in the Long-term Oxygen Treatment Trial. Participants were prescribed continuous (n=214) or intermittent (n=145) oxygen based on desaturation patterns at study entry. At the time of initial prescription, participants rated their perceived readiness, confidence, and importance to use oxygen on a 0-10 scale (0=not at all, 10=very much). During follow-up, they self-reported average hours per day of use (adherence). Adherence was averaged over short-term (0-30 days), medium-term (months 9-12), and long-term (month 13 to last follow-up) intervals. Multivariable logistic regression models explored characteristics associated with high adherence (>/=16h/day [continuous] or >/=8h/day [intermittent]) during each time interval. RESULTS: Participant readiness, confidence, and importance at the time of oxygen initiation were associated with high short- and medium-term adherence. For each unit increase in baseline readiness, the odds of high short-term adherence increased by 21% (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.05-1.40) and 94% (OR 1.94, 95% CI 1.45-2.59) in the continuous and intermittent groups, respectively. In both groups, high adherence in the medium-term was associated with high adherence in the long-term (continuous, OR 12.49, 95% CI 4.90-31.79; intermittent, OR 38.08, 95% CI 6.96-208.20). CONCLUSIONS: Readiness, confidence, and importance to use LTOT at initiation, and early high adherence, are significantly associated with long-term oxygen adherence.

https://www.resmedjournal.com/article/S0954-6111(19)30040-X/fulltext

Mullerova, H., B. Hahn, et al. (2019). **"Exacerbations and health care resource use among patients with COPD in relation to blood eosinophil counts."** Int J Chron Obstruct Pulmon Dis **14**: 683-692.

Purpose: Current understanding of the relationship between COPD phenotype and health care resource utilization (HCRU) is limited. This real-world study evaluated disease burden and HCRU for COPD subgroups prone to exacerbation as defined by blood eosinophil (EOS) count and multiple inhaler triple therapy (MITT) use. Methods: This was a large-scale, retrospective, longitudinal, observational cohort study using data from the US IBM Watson Explorys real-world database (GSK Study HO-17-18395). The population of interest comprised patients with COPD >/=40 years of age with >/=2 moderate or >/=1 severe exacerbations (prior year) while on inhaled maintenance therapy, with >/=1 blood EOS count. Data were analyzed during the year prior to index date (last COPD encounter between January 1, 2011 and December 31, 2016). Four subgroups were analyzed based on a combination of EOS counts (<150 and >/=150 cells/muL) and MITT use (receiving or not receiving). Among these groups, clinical characteristics, exacerbations, and HCRU were described. A sensitivity analysis that further stratified EOS into four categories (<150, >/=150-<300, >/=300-<500, and >/=500 cells/muL) was also performed. Results: The COPD population of interest comprised 34,268 patients. Subgroups with EOS >/=150 cells/muL vs <150 cells/muL had more comorbidities and experienced significantly higher mean numbers of moderate exacerbations (not receiving MITT, >/=150 cells/muL vs <150 cells/muL: 1.93 vs 1.82, P<0.0001; receiving MITT 2.26 vs 2.16, P=0.0062) and COPD-related emergency visits (not receiving MITT, >/=150 cells/muL vs <150 cells/muL: 3.0 vs 2.5, P<0.001; receiving MITT 3.4 vs 3.1, P=0.0011). Increasing EOS category was associated with higher HCRU. Conclusion: Blood EOS >/=150/muL cells were associated with increased HCRU and higher exacerbation rates compared with EOS <150 cells/muL, irrespective of MITT use. COPD phenotyping using blood EOS could help identify candidates for additional therapies that target eosinophilic inflammatory pathways.

https://www.dovepress.com/getfile.php?fileID=48689

Myers, L. C., M. K. Faridi, et al. (2019). **"ICU Utilization for Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease Receiving Noninvasive Ventilation."** Crit Care Med **47**(5): 677-684.

OBJECTIVES: We investigated whether patients with chronic obstructive pulmonary disease could safely receive noninvasive ventilation outside of the ICU. DESIGN: Retrospective cohort study. SETTING: Twelve states with ICU utilization flag from the State Inpatient Database from 2014. PATIENTS: Patients greater than or equal to 18 years old with primary diagnosis of acute exacerbation of chronic obstructive pulmonary disease and secondary diagnosis of respiratory failure who received noninvasive ventilation. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Multilevel logistic regression models were used to obtain hospital-level ICU utilization rates. We risk-adjusted using both patient/hospital characteristics. The primary outcome was in-hospital mortality; secondary outcomes were invasive monitoring (arterial/central catheters), hospital length of stay, and cost. We examined 5,081 hospitalizations from 424 hospitals with ICU utilization ranging from 0.05 to 0.98. The overall median in-hospital mortality was 2.62% (interquartile range, 1.72-3.88%). ICU utilization was not significantly associated with in-hospital mortality (beta = 0.01; p = 0.05) or length of stay (beta = 0.18; p = 0.41), which was confirmed by Spearman correlation (rho = 0.06; p = 0.20 and rho = 0.02; p = 0.64, respectively). However, lower ICU utilization was associated with lower rates of invasive monitor placement by linear regression (beta = 0.05; p < 0.001) and Spearman correlation (rho = 0.28; p < 0.001). Lower ICU utilization was also associated with significantly lower cost by linear regression (beta = 14.91; p = 0.02) but not by Spearman correlation (rho = 0.09; p = 0.07). CONCLUSIONS: There is wide variability in the rate of ICU utilization for noninvasive ventilation across hospitals. Chronic obstructive pulmonary disease patients receiving noninvasive ventilation had similar in-hospital mortality across the ICU utilization spectrum but a lower rate of receiving invasive monitors and probably lower cost when treated in lower ICU-utilizing hospitals. Although the results suggest that noninvasive ventilation can be delivered safely outside of the ICU, we advocate for hospital-specific risk assessment if a hospital were considering changing its noninvasive ventilation delivery policy.

Nishio, M., T. Kubo, et al. (2019). **"Estimation of lung cancer risk using homology-based emphysema quantification in patients with lung nodules."** PLoS One **14**(1): e0210720.

The purpose of this study was to assess whether homology-based emphysema quantification (HEQ) is significantly associated with lung cancer risk. This retrospective study was approved by our institutional review board. We included 576 patients with lung nodules (317 men and 259 women; age, 66.8 +/- 12.3 years), who were selected from a database previously generated for computer-aided diagnosis. Of these, 283 were diagnosed with lung cancer, whereas the remaining 293 showed benign lung nodules. HEQ was performed and percentage of low-attenuation lung area (LAA%) was calculated on the basis of computed tomography scans. Statistical models were constructed to estimate lung cancer risk using logistic regression; sex, age, smoking history (Brinkman index), LAA%, and HEQ were considered independent variables. The following three models were evaluated: the base model (sex, age, and smoking history); the LAA% model (the base model + LAA%); and the HEQ model (the base model + HEQ). Model performance was assessed using receiver operating characteristic analysis and the associated area under the curve (AUC). Differences in AUCs among the models were evaluated using Delong's test. AUCs of the base, LAA%, and HEQ models were 0.585, 0.593, and 0.622, respectively. HEQ coefficient was statistically significant in the HEQ model (P = 0.00487), but LAA% coefficient was not significant in the LAA% model (P = 0.199). Delong's test revealed significant difference in AUCs between the LAA% and HEQ models (P = 0.0455). In conclusion, after adjusting for age, sex, and smoking history (Brinkman index), HEQ was significantly associated with lung cancer risk.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6342309/pdf/pone.0210720.pdf

Nyberg, A., M. Tistad, et al. (2019). **"Can the COPD web be used to promote self-management in patients with COPD in swedish primary care: a controlled pragmatic pilot trial with 3 month- and 12 month follow-up."** Scand J Prim Health Care **37**(1): 69-82.

OBJECTIVE: Evaluate the feasibility of the COPD Web and its study design and study procedures and to increase the understanding of the potential effect of the tool in order to provide guidance for a future large scale trial. DESIGN: Parallel-group controlled pragmatic pilot trial. SUBJECTS: There was a total of 83 patients with COPD (mean age 70 +/- 8 years with a forced expiratory volume in first second percent predicted of 60 +/- 17%). The intervention group (n = 43) was introduced to and had access to the COPD Web in addition to usual care, while the control group (n = 40) received usual care alone. MAIN OUTCOME MEASURES: The feasibility of the COPD Web (i.e., if and how the COPD Web was used) was automatically collected through the website, while outcomes on health, conceptual knowledge, and physical activity (PA) were collected through questionnaires at baseline, 3 months and 12 months. RESULTS: At 3 months, 77% of the intervention group was considered users, and the majority of time spent on the site was related to PA and exercises and was spent during the first month (>80%). In addition, the intervention group reported increased PA (odds ratio [OR] = 4.4, P < .001), increased conceptual knowledge in five domains (OR = 2.6-4.2, all P < .05), and altered disease management strategies (e.g., increased PA) (OR >/= 2.7 P < .05) in comparison to the control group. The latter was also different between groups at 12 months (OR = 3.7, P = .044). Knowledge of PA was correlated with level of PA (rho = .425-.512, P < .05) as well as to the use of PA as a strategy to manage their disease (chi(2) = 11.2-32.9, P < .05). CONCLUSION: Giving patients with COPD access to the COPD Web in addition to their ordinary primary care might be an effective shorter term (3 month) strategy to promote self-management. However, these results needs to be confirmed in a definitive large-scale trial. Key points Even though self-management strategies are an important part of chronic obstructive pulmonary disease (COPD) management, access to support for such strategies are limited for a large part of the COPD-population. Promoting self-management through the COPD Web might increase short-term levels of physical activity, promote conceptual knowledge and alter disease management strategies. The primary care COPD population in this study experienced limited impact of the disease in daily life, limited exertional dyspnea, and high generic quality-of-life, but vastly reduced levels of physical activity. A future large scale study should include strategies to encourage greater exposures to the COPD Web, including an extended analysis of factors associated with using or not using the tool over time and its impact on

outcome measures, objective measures of conceptual knowledge, and physical activity, and it should include a large enough sample size to enable sub-group analyses and strategies to enhance recruitment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6452803/pdf/ipri-37-1569415.pdf

O'Conor, R., K. Muellers, et al. (2019). **"Effects of health literacy and cognitive abilities on COPD self-management behaviors: A prospective cohort study."** Respir MedINTRODUCTION: Low rates of adherence to self-management behaviors are common among patients with COPD. Health literacy and cognitive abilities may influence engagement in self-management behaviors. We sought to assess the association between health literacy and cognitive abilities with self-management behaviors in patients with COPD. METHODS: We conducted an observational cohort study among American adults with COPD in New York, New York, and Chicago, Illinois. Outcomes included adherence to COPD medication, metered dose inhaler (MDI) and dry powder inhaler (DPI) technique, receipt of vaccination, and routine healthcare appointments. Health literacy was measured with the Short Test of Functional Health Literacy in Adults. Cognitive function was assessed in terms of global, fluid (working memory, processing speed, executive function) and crystallized (verbal) ability. RESULTS: Adequate health literacy was associated with adequate adherence to COPD medications (OR 1.46; 95% CI, 1.02-2.08), correct MDI (OR 1.66; 95% CI, 1.13-2.44) and DPI (OR 2.17; 95% CI, 1.30-3.64) technique. Fluid abilities were also associated with medication behaviors and visiting a regular healthcare provider, while crystalized abilities were not. Global cognitive abilities were associated with correct inhaler technique. No other associations were found with non-medication self-management behaviors. CONCLUSIONS: COPD patients with limited health literacy and deficits in fluid cognitive abilities have lower rates of adherence and poorer inhaler technique than individuals with adequate health literacy and greater fluid cognitive abilities. These findings highlight the importance of considering the health literacy level and cognitive ability when caring for and educating patients with COPD.

https://www.resmedjournal.com/article/S0954-6111(19)30042-3/fulltext

Odeyemi, Y. E., O. Lewis, et al. (2019). **"Does Low FEV1 in Addition to Fixed Ratio and/or Lower Limit of Normal of FEV1/FVC Improve Prediction of Mortality in COPD? The NHANES-III-linked-mortality Cohort."** J Natl Med Assoc **111**(1): 94-100.

PURPOSE: There is presently an ongoing debate on the relative merits of suggested criteria for spirometric airway obstruction. This study tests the null hypothesis that no superiority exists with the use of fixed ratio (FR) of forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) < 0.7 versus less than lower limit predicted (LLN) criteria with or without FEV1 <80% predicted in regards to future mortality. METHODS: In 1988-1994 the Third National Health and Nutrition Examination Survey (NHANES III) measured FEV1 and FVC with mortality follow-up data through December 31, 2011. For this survival analysis 7472 persons aged 40 and over with complete data formed the analytic sample. RESULTS: There were a total of 3554 deaths. Weighted Cox proportional hazards regression revealed an increased hazard ratio in persons with both fixed ratio and lower limit of normal with a low FEV1 (1.79, $p < 0.0001$), in those with fixed ratio only with a low FEV1 (1.77, $p < 0.0001$), in those with abnormal fixed ratio only with a normal FEV1 (1.28, $p < 0.0001$) compared with persons with no airflow obstruction (reference group). These remained significant after adjusting for demographic variables and other confounding variables. CONCLUSIONS: The addition of FEV1 < 80% of predicted increased the prognostic power of the fixed ratio <0.7 and/or below the lower limit of predicted criteria for airway obstruction.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6349529/pdf/nihms-987519.pdf

O'Doherty, B., J. Dorman, et al. (2019). **"Improvement in health status with once-daily indacaterol/glycopyrronium 110/50 mug in COPD patients: real-world evidence from an observational study in Ireland."** Ir J Med SciAIMS: Indacaterol/glycopyrronium (IND/GLY) 110/50 mug is a once-daily (o.d.) fixed-dose combination of long-acting beta2-agonist/long-acting muscarinic antagonist approved in over 90 countries, including Ireland, for the management of COPD. The present study was conducted to evaluate health status of COPD patients, initiated on IND/GLY 110/50 mug o.d., using the Clinical COPD Questionnaire (CCQ) tool in a real-world primary care setting in Ireland. METHODS: This was a real-world, prospective, open-label study. COPD patients aged > 40 years and with a smoking history of > 10 pack-years were included and switched to once-daily IND/GLY 110/50 mug. Enrolment of patients into the study occurred only after the decision had been made by the physician to prescribe IND/GLY 110/50 mug. Data were collected at baseline and Week 26. Health status was assessed using the validated CCQ. RESULTS: A total of 200 patients were included in study. The mean CCQ total score decreased from 2.36 at baseline to 1.44 at Week 26 (Delta, 0.92; P < 0.0005). Of the 156 patients who completed study, 113 (72.4%) achieved minimum clinically important difference in CCQ total score with IND/GLY 110/50 mug. CCQ domain scores also decreased during the study. Improvement in health status was observed across all GOLD groups and irrespective of prior COPD treatment. Adverse events were reported by 20% of patients with COPD exacerbation/infected COPD being the most common AE, reported by 11 patients. CONCLUSIONS: In real-life clinical practice in Ireland, IND/GLY 110/50 mug o.d. demonstrated statistically significant and clinically important improvement in health status in patients with COPD.

https://link.springer.com/content/pdf/10.1007%2Fs11845-019-02001-y.pdf

Oelsner, E. C., P. P. Balte, et al. (2019). **"Albuminuria, Lung Function Decline, and Risk of Incident Chronic Obstructive Pulmonary Disease. The NHLBI Pooled Cohorts Study."** Am J Respir Crit Care Med **199**(3): 321-332.

RATIONALE: Chronic lower respiratory diseases (CLRDs), including chronic obstructive pulmonary disease (COPD) and asthma, are the fourth leading cause of death. Prior studies suggest that albuminuria, a biomarker of endothelial injury, is increased in patients with COPD. OBJECTIVES: To test whether albuminuria was associated with lung function decline and incident CLRDs. METHODS: Six U.S. population-based cohorts were harmonized and pooled. Participants with prevalent clinical lung disease were excluded. Albuminuria (urine albumin-to-creatinine ratio) was measured in spot samples. Lung function was assessed by spirometry. Incident CLRD-related hospitalizations and deaths were classified via adjudication and/or administrative criteria. Mixed and proportional hazards models were used to test individual-level associations adjusted for age, height, weight, sex, race/ethnicity, education, birth year, cohort, smoking status, pack-years of smoking, renal function, hypertension, diabetes, and medications. MEASUREMENTS AND MAIN RESULTS: Among 10,961 participants with preserved lung function, mean age at albuminuria measurement was 60 years, 51% were never-smokers, median albuminuria was 5.6 mg/g, and mean FEV1 decline was 31.5 ml/yr. For each SD increase in log-transformed albuminuria, there was 2.81% greater FEV1 decline (95% confidence interval [CI], 0.86-4.76%; P = 0.0047), 11.02% greater FEV1/FVC decline (95% CI, 4.43-17.62%; P = 0.0011), and 15% increased hazard of incident spirometry-defined moderate-to-severe COPD (95% CI, 2-31%, P = 0.0021). Each SD log-transformed albuminuria increased hazards of incident COPD-related hospitalization/mortality by 26% (95% CI, 18-34%, P < 0.0001) among 14,213 participants followed for events. Asthma events were not significantly associated. Associations persisted in participants without current smoking, diabetes, hypertension, or cardiovascular disease. CONCLUSIONS: Albuminuria was associated with greater lung function decline, incident spirometry-defined COPD, and incident COPD-related events in a U.S. population-based sample.

Oelsner, E. C., V. E. Ortega, et al. (2019). **"A Genetic Risk Score Associated with COPD Susceptibility and Lung Structure on Computed Tomography."** Am J Respir Crit Care MedRATIONALE: Chronic obstructive pulmonary disease (COPD) has been associated with numerous genetic variants, yet the extent to which its genetic risk is mediated by variation in lung structure remains unknown. OBJECTIVES: To characterize associations between a genetic risk score (GRS) associated with COPD susceptibility and lung structure on computed tomography (CT). METHODS: We analyzed data from the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study, a US general population-based cohort, and SPIROMICS, a study of COPD. A weighted GRS was calculated from 83 single nucleotide polymorphisms previously associated with lung function. Lung density, spatially-matched airway dimensions, and airway counts were assessed on full-lung CT. Generalized linear models were adjusted for age, age-squared, sex, height , principal components of genetic ancestry, smoking status, pack-years, CT model, milliamperes, and total lung volume. MEASUREMENTS AND MAIN RESULTS: MESA Lung and SPIROMICS contributed 2,517 and 2,339 participants, respectively. Higher GRS was associated with lower lung function and increased COPD risk, as well as lower lung density, smaller airway lumens, and fewer small airways, without effect modification by smoking. Adjustment for CT lung structure, particularly small airways measures, attenuated associations between the GRS and FEV1/FVC by 100% and 60% in MESA and SPIROMICS, respectively. Lung structure (P<.0001), but not the GRS (P>.10), improved discrimination of moderate-to-severe COPD cases relative to clinical factors alone. CONCLUSIONS: A GRS associated with COPD susceptibility was associated with CT lung structure. Lung structure may be an important mediator of heritability and determinant of personalized COPD risk.

Olofson, J., B. Bake, et al. (2018). **"Prediction of COPD and Related Events Improves by Combining Spirometry and the Single Breath Nitrogen Test."** Copd **15**(5): 424-431.

Chronic obstructive pulmonary disease (COPD) develops in small airways. Severity of small airway pathology relates to progression and mortality. The present study evaluated the prediction of COPD of a validated test for small airway disease, i.e. a slope of the alveolar plateau of the single breath nitrogen test (N2-slope). The N2-slope, spirometry, age, smoking habits, and anthropometric variables at baseline were obtained in a population-based sample (n = 592). The cohort was followed for first COPD events (first hospital admission of COPD or related conditions or death from COPD) during 38 years. During follow-up, 52 subjects (8.8%) had a first COPD event, of which 18 (3.0%) died with a first COPD diagnosis. In the proportional hazard regression analysis adjusted for age and smoking habits, the cumulative COPD event incidence increased from 5% among those with high forced expired volume in one second (FEV1) to 25% among those with low FEV1, while increasing from 4% among those with the lowest N2-slope to 26% among those with the highest. However, combining the N2-slope and FEV1 resulted in considerable synergy in the prediction of first COPD event and even more so when taking account of smoking habits. The cumulative COPD event incidence rate was 75% among heavy smokers with the highest N2-slope and lowest FEV1, and less than 1% among never smokers with the lowest N2-slope and highest FEV1. Thus, combining the results of the single breath N2-slope and FEV1 considerably improved the prediction of COPD events as compared to either test alone.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2018.1538330?needAccess=true

Pacileo, G., V. D. Tozzi, et al. (2019). **"Administrative databases and clinical governance: The case of COPD."** Int J Health Plann Manage **34**(1): 177-186.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. However, COPD is still underdiagnosed, undertreated, and not sufficiently prevented. Health administrative databases provide a powerful way of studying COPD in the population. METHODS: This retrospective study used administrative data, collected during 2011 and 2012, retrieved from 3 Italian local health authorities (LHAs). RESULTS: The analysis through administrative databases allowed firstly to identify patients with COPD receiving services by the 3 LHAs: The estimated average is ~3% of the

population aged >/=40 years. Furthermore, it was also possible to stratify patients by investigating the health consumption in hospitalization for COPD and use of respiratory drugs. In all 3 LHA patients with moderate COPD were the majority of the population with COPD. Finally, it was possible to distinguish patients who made an appropriate use of SABA (76% of the total), patients who had a potentially inappropriate use (20%), and those with an overuse of SABA (4%). CONCLUSION: The use of SABA consumption patterns can be a reliable proxy variable to detect subgroups who may necessitate therapy revision. Health administrative databases seem beneficial for planning health care interventions, including the COPD field. They are robust information systems subjected to regular data quality controls remaining the prevalent data source, reliable because of the amount of data and the population coverage, especially in countries with a National Health Service System.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/hpm.2609

Pahwa, P., M. Rana, et al. (2019). **"Incidence and Longitudinal Changes in Prevalence of Chronic Bronchitis in Farm and Non-Farm Rural Residents of Saskatchewan."** J Occup Environ Med **61**(4): 347-356.

OBJECTIVE: To assess the predictors associated with incidence and longitudinal changes in the prevalence of chronic bronchitis (CB) among farm and non-farm residents of rural Saskatchewan, Canada. METHODS: The Saskatchewan Rural Health Study was a prospective study of the lung health of rural dwellers. We obtained information on 4624 households, 8261 individuals (2797 households, 4867 individuals) at baseline (follow-up). RESULTS: Incidence of CB was 4.3% over 4 years. The prevalence was 6.4% and 5.3% (baseline) and 12.1% and 9.2% (follow-up) in non-farm and farm residents, respectively. The prevalence of CB was associated with current smokers; father ever had lung trouble; obesity; mother smoked during pregnancy; allergic reaction to cats and to pollen; household income inadequacy and age. CONCLUSION: Prevalence and incidence of CB in rural people appear to be a complex mix of personal and contextual factors.

Papakonstantinou, E., I. Bonovolias, et al. (2019). **"Serum levels of hyaluronic acid are associated with COPD severity and predict survival."** Eur Respir J **53**(3)Hyaluronic acid (HA) and its degradation products play an important role in lung pathophysiology and airway remodelling in chronic obstructive pulmonary disease (COPD).We investigated if HA and its degrading enzyme hyaluronidase (HYAL)-1 are associated with COPD severity and outcome.Serum HA was assessed in a discovery cohort of 80 COPD patients at stable state and exacerbations. HA, HYAL-1 and HYAL-1 enzymatic activity were evaluated at stable state, exacerbations and 4 weeks after exacerbations in 638 COPD patients from the PROMISE validation cohort.In the discovery cohort, serum HA was higher at exacerbations compared with the stable state ($p=0.015$). In the validation cohort, HA was higher at moderate and severe exacerbations than at baseline ($p<0.001$), and remained higher after 4 weeks ($p<0.001$). HA was strongly predictive for overall survival since it was associated with time to death ($p<0.001$) independently of adjusted Charlson score, annual exacerbation rate and BODE (body mass, airflow obstruction, dyspnoea, exercise capacity) index. Serum HYAL-1 was increased at moderate ($p=0.004$) and severe ($p=0.003$) exacerbations, but decreased after 4 weeks ($p<0.001$). HYAL-1 enzymatic activity at stable state was inversely correlated with FEV1 % pred ($p=0.034$) and survival time ($p=0.017$).Serum HA is associated with COPD severity and predicts overall survival. Degradation of HA is associated with airflow limitation and impairment of lung function.

https://erj.ersjournals.com/content/53/3/1801183

Park, H. J., S. M. Lee, et al. (2019). **"Prediction of Treatment Response in Patients with Chronic Obstructive Pulmonary Disease by Determination of Airway Dimensions with Baseline Computed Tomography."** Korean J Radiol **20**(2): 304-312.

OBJECTIVE: To determine the predictive factors for treatment responsiveness in patients with chronic obstructive pulmonary disease (COPD) at 1-year follow-up by performing quantitative analyses of baseline CT scans. MATERIALS AND METHODS: COPD patients (n = 226; 212 men, 14 women) were recruited from the Korean Obstructive Lung Disease cohort. Patients received a combination of inhaled long-acting beta-agonists and corticosteroids twice daily for 3 months and subsequently received medications according to the practicing clinician's decision. The emphysema index, air-trapping indices, and airway parameter (Pi10), calculated using both full-width-half-maximum and integral-based half-band (IBHB) methods, were obtained with baseline CT scans. Clinically meaningful treatment response was defined as an absolute increase of >/= 0.225 L in the forced expiratory volume in 1 second (FEV(1)) at the one-year follow-up. Multivariate logistic regression analysis was performed to investigate the predictors of an increase in FEV(1), and receiver operating characteristic (ROC) analysis was performed to evaluate the performance of the suggested models. RESULTS: Treatment response was noted in 47 patients (20.8%). The mean FEV(1) increase in responders was 0.36 +/- 0.10 L. On univariate analysis, the air-trapping index (ATI) obtained by the subtraction method, ATI of the emphysematous area, and IBHB-measured Pi10 parameter differed significantly between treatment responders and non-responders (p = 0.048, 0.042, and 0.002, respectively). Multivariate analysis revealed that the IBHB-measured Pi10 was the only independent variable predictive of an FEV(1) increase (p = 0.003). The adjusted odds ratio was 1.787 (95% confidence interval: 1.220-2.619). The area under the ROC curve was 0.641. CONCLUSION: Measurement of standardized airway dimensions on baseline CT by using a recently validated quantification method can predict treatment responsiveness in COPD patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6342755/pdf/kjr-20-304.pdf

Park, S. Y., H. Jung, et al. (2019). **"Longitudinal analysis to better characterize Asthma-COPD overlap syndrome: Findings from an adult asthma cohort in Korea (COREA)."** Clin Exp AllergyBACKGROUND: Asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), which has received much attention, has not been unanimously defined. OBJECTIVE: In this study, we tried to demonstrate that longitudinally defined ACOS is more useful in the real world than blending patients with asthma and COPD. METHODS: The study patients had undergone two consecutive pulmonary function tests measured at least 3 months apart (n = 1889). We selected the patients who had positive bronchodilator response or methacholine provocation tests (n = 959). Next, we defined ACOS as a patient with a persistent airflow obstruction [forced expiratory volume in 1 second (FEV1)/forced vital capacity <0.7] that was identified twice consecutively by an interval of at least 3 months (n = 228). RESULTS: The proportions of patients who were older, male and smokers were significantly higher, and baseline lung function was lower in patients with ACOS. In the longitudinal analysis, the mean change in lung function was high, and a greater decline in FEV1 was observed in patients with ACOS. In addition, we compared ACOS and severe asthma, and we also performed a cluster analysis and compared the results with our definition of ACOS. According to our definition, ACOS is an independent subtype with distinctive characteristics. Finally, a genome-wide association study (GWAS) was performed to identify genetic variations associated with ACOS, but no significant single nucleotide polymorphisms were identified. CONCLUSION: Our findings suggest that ACOS should be defined longitudinally and considered as an independent subgroup distinguished by inherited environmental factors rather than as a genetically distinct independent group.

https://onlinelibrary.wiley.com/doi/abs/10.1111/cea.13339

Pasquale, C. B., J. Vietri, et al. (2019). **"Patient-Reported Consequences of Community-Acquired Pneumonia in Patients with Chronic Obstructive Pulmonary Disease."** Chronic Obstr Pulm Dis **6**(2)Community acquired pneumonia (CAP) carries high morbidity, mortality, and economic burden, which is even higher

in adults diagnosed with chronic obstructive pulmonary disease (COPD). While several studies have assessed the clinical burden and mortality risk of CAP and COPD, very few studies focus on CAP burden from a COPD patient perspective. Individuals recently diagnosed with CAP and with pre-existing COPD were recruited through the COPD Foundation. The CAP Burden of Illness Questionnaire (CAP-BIQ), a content validated questionnaire assessing CAP symptomatology, duration of symptoms and CAP impact on work, activities and family, was administered at baseline and at 30-days follow-up. Of the 490 participants recruited, 481 had data sufficient for analysis. The prevalence of respiratory-related symptoms was very high (>90%) at the time of diagnosis with other generalized symptoms such as fatigue, trouble sleeping, headaches and confusion present in more than 60% of participants. Mean duration of symptoms varied from approximately 2 weeks for headaches and fever to more than a month for fatigue, wheezing, dyspnea, and cough. Employed participants missed an average of 21 days of work and those not employed missed 36 days of usual activities. Over 84% required help from family, friends or care givers. CAP is a serious and burdensome condition for people with COPD, a condition that can impair activities for weeks, frequently requires care from family or friends, and includes lingering symptoms. The patient-reported impact of CAP reported in this study underscores the need for prevention strategies in this population.

https://journal.copdfoundation.org/Portals/0/JCOPDF/Files/Volume6-Issue2/JCOPDF-2018-0144-Pasquale.pdf

Petite, S. E. and J. A. Murphy (2019). **"Systemic Corticosteroid and Antibiotic Use in Hospitalized Patients With Chronic Obstructive Pulmonary Disease Exacerbation."** Ann Pharmacother **53**(2): 144-150.

BACKGROUND: Effective inpatient chronic obstructive pulmonary disease (COPD) exacerbation management is critical to appropriately manage health care resources. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines provide recommendations on appropriate systemic corticosteroid and antibiotic use, in select patients, for COPD exacerbation. OBJECTIVE: To determine the impact of GOLD guideline-recommended systemic corticosteroid and antibiotic therapy in the hospital setting on clinical outcomes in patients with COPD exacerbation. METHODS: This was a noninterventional, retrospective, single-center study. Adults admitted to a non-intensive care unit internal medicine service with documented COPD exacerbation were included. Two analyses were conducted evaluating systemic corticosteroid and antibiotic therapy. RESULTS: A total of 220 patients were included in the systemic corticosteroid cohort. No difference in 30-day readmission rates was demonstrated for the standard (200 mg prednisone equivalents [PEs] for exacerbation course) and high-dose groups (>200 mg PEs; 20.5% vs 13.1%, respectively; P = 0.15). Hospital length of stay (LOS) was significantly shorter for patients prescribed standard-dose therapy (3 days [2-4.5] vs 4 days [2-6]; P < 0.001). A total of 174 patients were included in the antibiotic cohort. For the appropriate and inappropriate antibiotic use groups, no significant differences were observed between 30-day readmission rates (15% vs 18.4%, respectively; P = 0.57) and hospital LOS (4 days [2-5] in both groups; P = 0.97). Conclusion and Relevance: Hospital LOS was shorter for patients prescribed standard-dose systemic corticosteroids; however, no differences in other clinical outcomes were found in either cohort. Use of guideline-recommended systemic corticosteroid and antibiotic therapy is recommended for hospitalized patients with COPD exacerbation.

Pichl, A., N. Sommer, et al. (2019). **"Riociguat for treatment of pulmonary hypertension in COPD - a translational study."** Eur Respir JChronic obstructive pulmonary disease (COPD) which comprises the phenotypes of chronic bronchitis and emphysema is often associated with pulmonary hypertension (PH). However, currently no approved therapy exists for PH-COPD. Signalling of the nitric oxide/cyclic guanoside monophosphate (NO-cGMP) axis plays an important role in PH and COPD.We investigated the treatment effect of riociguat, which promotes the NO-cGMP pathway, in the mouse model of smoke-induced PH and emphysema in a curative approach and retrospectively analysed the effect of riociguat treatment on PH in single patients with PH-COPD.In mice with established PH and emphysema (after 8 months of cigarette smoke exposure) riociguat treatment for another 3 months fully reversed

PH. Moreover, histological hallmarks of emphysema were decreased. Microarray analysis revealed involvement of different signalling pathways, e.g. related to matrix metalloproteinases (MMPs). MMP activity was decreased in vivoby riociguat. In PH-COPD patients treated with riociguat (n=7) the pulmonary vascular resistance, airway resistance and circulating MMP levels decreased, while oxygenation at rest was not significantly changed.Conclusions: Riociguat may be beneficial for treatment of PH-COPD. Further long-term prospective studies are necessary to investigate the tolerability, efficacy on functional parameters and the effect specifically on pulmonary emphysema in COPD patients.

https://erj.ersjournals.com/content/early/2019/03/27/13993003.02445-2018

Pikoula, M., J. K. Quint, et al. (2019). **"Identifying clinically important COPD sub-types using data-driven approaches in primary care population based electronic health records."** BMC Med Inform Decis Mak **19**(1): 86.

BACKGROUND: COPD is a highly heterogeneous disease composed of different phenotypes with different aetiological and prognostic profiles and current classification systems do not fully capture this heterogeneity. In this study we sought to discover, describe and validate COPD subtypes using cluster analysis on data derived from electronic health records. METHODS: We applied two unsupervised learning algorithms (k-means and hierarchical clustering) in 30,961 current and former smokers diagnosed with COPD, using linked national structured electronic health records in England available through the CALIBER resource. We used 15 clinical features, including risk factors and comorbidities and performed dimensionality reduction using multiple correspondence analysis. We compared the association between cluster membership and COPD exacerbations and respiratory and cardiovascular death with 10,736 deaths recorded over 146,466 person-years of follow-up. We also implemented and tested a process to assign unseen patients into clusters using a decision tree classifier. RESULTS: We identified and characterized five COPD patient clusters with distinct patient characteristics with respect to demographics, comorbidities, risk of death and exacerbations. The four subgroups were associated with 1) anxiety/depression; 2) severe airflow obstruction and frailty; 3) cardiovascular disease and diabetes and 4) obesity/atopy. A fifth cluster was associated with low prevalence of most comorbid conditions. CONCLUSIONS: COPD patients can be sub-classified into groups with differing risk factors, comorbidities, and prognosis, based on data included in their primary care records. The identified clusters confirm findings of previous clustering studies and draw attention to anxiety and depression as important drivers of the disease in young, female patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6472089/pdf/12911_2019_Article_805.pdf

Plutinsky, M., K. Brat, et al. (2019). **"Prognostic Accuracy of Three COPD Classification Systems in Relation to Long-Term Mortality of COPD Patients: A Prospective Multicenter Study."** LungRecent research showed group B patients express higher mortality compared to group C patients when GOLD A-D grouping is used. We aimed to compare the prognostic accuracy of three GOLD classification systems, I-IV ("pre-2011"), A-D ("2011-2016") and A-D ("2017-present") in relation to mortality, exacerbation risk, quality of life (QoL) assessment and specific treatments use in a real-life COPD cohort. We used the data of 720 patients from the Czech Multicenter Research Database of COPD. Four-year mortality and time-to-exacerbation using the GOLD "pre-2011", "2011-2016" and "2017-present" classification schemes were assessed. Moreover, distribution of specific treatments use and QoL measures were analyzed. The GOLD I-IV classification system showed gradual increase in 4-year mortality across the stages (GOLD II 18.8%, III 28.5%, IV 38.7%) ($p = 0.001$). Using the A-D "2011-2016" classification scheme, group C patients had lower mortality (16.7%) than group B (18.7%) ($p = 0.009$). The A-D "2017-present" classification showed higher mortality in group B (25.5%) compared to group C (20%) ($p = 0.05$). For additional outcomes, the GOLD I-IV scheme showed highest match between the calculated 4-year exacerbation risk and QoL measures and GOLD stage/grouping. In terms of specific treatment distributions, various patterns for each GOLD classification system were observed with best match of GOLD "2017-present" system to the layout of GOLD groups and categories. We conclude the GOLD I-IV

classification system had the highest accuracy related to mortality, QoL measures and exacerbation risk prediction, while the A-D "2017-present" scheme was most accurate within severity of symptoms prediction reflected also by more frequent specific treatments use.

https://link.springer.com/article/10.1007%2Fs00408-019-00196-6

Polke, M., M. Rotting, et al. (2019). **"Interventional therapy in patients with severe emphysema: evaluation of contraindications and their incidence."** Ther Adv Respir Dis **13**: 1753466619835494.

BACKGROUND: Endoscopic and surgical interventions may be beneficial for selected patients with emphysema. Rates of treatment failure decrease when the predictors for successful therapy are known. The aim of the study was to evaluate the number of patients with severe emphysema who were not eligible for any intervention, and the reasons for their exclusion. METHODS: The study was a retrospective analysis of 231 consecutive patients with advanced emphysema who were considered for interventional therapy in 2016 at the Thoraxklinik, Heidelberg, Germany. The reasons for not receiving valve or coil therapy were assessed for all patients who did not receive any therapy. RESULTS: Of the 231 patients, 50% received an interventional therapy for lung volume reduction (LVR) (82% valve therapy, 6% coil therapy, 4.3% polymeric LVR or bronchial thermal vapour ablation, 4.3% total lung denervation, and 3.4% lung volume reduction surgery [LVRS]). A total of 115 patients did not undergo LVR. Out of these, valve or coil therapy was not performed due to one or more of the following reasons: incomplete fissure in 37% and 0%; missing target lobe in 31% and 30%; personal decision in 18% and 28%; pulmonary function test results in 8% and 15%; ventilatory failure in 4% and 4%; missing optimal standard medical care and/or continued nicotine abuse in 4% and 3%; general condition too good in less than 1% and 3%; cardiovascular comorbidities in 0% and 3%; age of patient in 0% and less than 1%. Both techniques were not performed due to one or more of the following reasons: solitary pulmonary nodule(s)/consolidation in 27%; bronchopathy in 7%; neoplasia in 2%; destroyed lung in 2%; prior LVRS in less than 1%. CONCLUSIONS: The main reason for not placing valves was an incomplete fissure and for coils a missing target lobe. Numerous additional contraindications that may exclude a patient from interventional emphysema therapy should be respected.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6421604/pdf/10.1177_1753466619835494.pdf

Poon, T., D. G. Paris, et al. (2017). **"Extended Versus Short-Course Corticosteroid Taper Regimens in the Management of Chronic Obstructive Pulmonary Disease Exacerbations in Critically Ill Patients."** J Intensive Care Med: 885066617741470.

BACKGROUND: Previous literature has suggested that a short course of corticosteroids is similarly effective as an extended course for managing an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). However, there are limited data regarding the optimal corticosteroid regimen in critically ill patients and the dosing strategies remain highly variable in this population. METHODS: This retrospective cohort study evaluated patients with AECOPD admitted to the intensive care unit within a 2-year period. Patients were divided into short-course (</=5 days) or extended-course (>5 days) corticosteroid taper groups. The primary end point was treatment failure, defined as the need for intubation, reintubation, or noninvasive mechanical ventilation. Secondary end points included the duration of mechanical ventilation, hospital and intensive care unit length of stay, and adverse events. RESULTS: Of the 151 patients who met the inclusion criteria, 94 received an extended taper and 57 received a short taper. Treatment failure occurred in 3 patients, who were all in the extended taper group (P = .17). In a propensity score-matched cohort, the hospital length of stay was 7 days in the short taper group compared to 11 days in the extended taper group (P < .0001). No differences in adverse events were observed. CONCLUSION: A short-course corticosteroid taper in critically ill patients with AECOPD is associated with reduced hospital length of stay and decreased corticosteroid exposure without increased risk of treatment failure. A prospective randomized trial is warranted.

Proietti, M., P. Agosti, et al. (2019). **"Hospital Care of Older Patients With COPD: Adherence to International Guidelines for Use of Inhaled Bronchodilators and Corticosteroids."** J Am Med Dir AssocOBJECTIVES: We aimed to analyze the prevalence and impact of COPD in older patients hospitalized in internal medicine or geriatric wards, and to investigate adherence to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, associated clinical factors, and outcomes. DESIGN: Data were obtained from REgistro POliterapie SIMI (REPOSI), a prospective multicenter observational registry that enrolls inpatients aged >/=65 years. SETTING AND PARTICIPANTS: Older hospitalized patients enrolled from 2008 to 2016 with a diagnosis of COPD. MEASURES: We evaluated adherence to the 2018 GOLD guidelines at admission and discharge, by examining the prescription of inhaled bronchodilators and corticosteroids in COPD patients. We also evaluated the occurrence of outcomes and its association with COPD and guideline adherence. RESULTS: At hospital admission, COPD was diagnosed in 1302 (21.5%) of 6046 registered patients. COPD patients were older, with more impaired clinical and functional status and multiple comorbidities. Overall, 34.3% of COPD patients at admission and 35.6% at discharge were adherent to the GOLD guidelines. Polypharmacy (>/=5 drugs) at admission [odds ratio (OR): 3.28, 95% confidence interval (CI): 2.24-4.81], a history of acute COPD exacerbation (OR: 2.65, 95% CI: 1.44-4.88) at admission, smoking habit (OR: 1.45, 95% CI: 1.08-1.94), and polypharmacy at discharge (OR: 6.76, 95% CI: 4.15-11.0) were associated with adherence to guidelines. COPD was independently associated with the risk of cardiovascular and respiratory death and rehospitalization occurrence compared to patients without COPD during follow-up. Adherence to guidelines was inversely associated with the occurrence of death from all causes (OR: 0.12, 95% CI: 0.02-0.90). CONCLUSIONS/IMPLICATIONS: COPD was common in older patients acutely hospitalized, showing an impaired functional and clinical status. Prescriptions for older COPD patients were often not adherent to GOLD guidelines. Poor adherence to guidelines was associated with a worse clinical status. There is a need to improve adherence to guidelines in treating COPD patients, with the ultimate goal of reducing clinical events.

https://www.jamda.com/article/S1525-8610(19)30159-8/fulltext

Pulido Herrero, E., S. Garcia Gutierrez, et al. (2019). **"Chronic obstructive pulmonary disease assessment test: usefulness for monitoring recovery and predicting poor course of disease after exacerbations."** Emergencias **31**(1): 21-26.

OBJECTIVES: To assess the usefulness of the chronic obstructive pulmonary disease (COPD) assessment test (CAT) for evaluating recovery from an acute exacerbation of chronic COPD. To assess whether the CAT score used along with a COPD exacerbation severity scale can better predict risk of a poor course of disease. MATERIAL AND METHODS: Prospective multicenter cohort study enrolling patients who attended hospital emergency departments with symptoms of exacerbated COPD. We recorded sociodemographic and clinical data and information from 2 questionnaires: the CAT and the modified dyspnea scale of the Medical Research Council (mMRC). Measures of clinical outcome in this study were the CAT score 2 months after the COPD exacerbation and poor course of disease during the hospital stay or 1 week after discharge from the emergency department if patients were not hospitalized. RESULTS: The cohort included 501 patients. The median (interquartile range) CAT score was 13 (7-18) on the day before the exacerbation, 25 (19-30) during emergency care for the exacerbation, and 13 (7-18) 2 months later. The difference between the CAT scores before the exacerbation and 2 months later was not statistically significant when the cohort was stratified by severity of baseline COPD (mild, moderate, and severe/very severe) (P=.585, P=.419, and P=.4357). The short-term course of disease was poor for 91 patients (18.16%). Combining the mMRC and the CAT scores to predict poor short-term outcome gave an area under the receiver operating characteristic curve (AUC) of 0.701 (95% CI, 0.640-0.762). The AUC for the mMRC score without the CAT score was 0.667 (95% CI, 0.616- 0.737). The difference between the AUCs was not statistically significant (P=.088). CONCLUSION: The CAT score may be useful for monitoring recovery from a COPD exacerbation. Combining the CAT score and a COPD severity score may be useful for predicting clinical course after an exacerbation.

Putcha, N., A. Fawzy, et al. (2018). **"Anemia and Adverse Outcomes in a Chronic Obstructive Pulmonary Disease Population with a High Burden of Comorbidities. An Analysis from SPIROMICS."** Ann Am Thorac Soc **15**(6): 710-717.

RATIONALE: Chronic obstructive pulmonary disease (COPD) is a common cause of morbidity and associated with a significant burden of comorbidities. Although anemia is associated with adverse outcomes in COPD, its contribution to outcomes in individuals with other comorbid chronic diseases is not well understood. OBJECTIVES: This study examines the association of anemia with outcomes in a large, well-characterized COPD cohort, and attempts to understand the contribution of anemia to outcomes and phenotypes in individuals with other comorbidities. METHODS: Participants with COPD from SPIROMICS (the Subpopulations and Intermediate Outcome Measures in COPD Study) were analyzed in adjusted models to determine the associations of normocytic anemia with clinical outcomes, computed tomographic measures, and biomarkers. Analysis was additionally performed to understand the independence and possible interactions related to cardiac and metabolic comorbidities. RESULTS: A total of 1,789 individuals with COPD from SPIROMICS had data on hemoglobin, and of these 7.5% (n = 135) were found to have normocytic anemia. Anemic participants were older with worse airflow obstruction, a higher proportion of them were African Americans, and they had a higher burden of cardiac and metabolic comorbidities. Anemia was strongly associated with 6-minute walk distance (beta, -61.43; 95% confidence interval [CI], -85.11 to -37.75), modified Medical Research Council dyspnea questionnaire (beta, 0.27; 95% CI, 0.11-0.44), and St. George's Respiratory Questionnaire (beta, 3.90; 95% CI, 1.09-6.71), and these adjusted associations were stronger among those with two or more cardiac and metabolic comorbidities. Anemia was associated with higher levels of serum C-reactive protein, soluble receptor for advanced glycosylation end-products, and epithelial cadherin-1, findings that persisted when in those with a high burden of comorbidities. CONCLUSIONS: Anemia is associated with worse exercise capacity, greater dyspnea, and greater disease severity among adults with COPD, particularly among those with comorbid chronic cardiac and metabolic diseases. The biomarkers found in anemic individuals suggest inflammation, lung tissue injury, and oxidative stress as possible pathways for the adverse correlations of anemia with outcomes in COPD; however, substantial further study is required to better understand these potential mechanisms. Clinical trial registered with www.clinicaltrials.gov (NCT01969344).

Quiros-Roldan, E., M. C. Pezzoli, et al. (2019). **"A COPD Case-Finding Program in a Large Cohort of HIV-Infected Persons."** Respir Care **64**(2): 169-175.

BACKGROUND: COPD screening guidelines in patients with HIV are lacking, and data about its under-diagnosis are still limited. This study aimed to determinate the feasibility of a case-finding program and the prevalence of COPD under-diagnosis in a large cohort of HIV-infected subjects. METHODS: All out-patients attending their routine visit for HIV monitoring at Spedali Civili General Hospital in Brescia, Italy, from February 2015 to January 2016, were enrolled. The case-finding program was structured in three steps: questionnaire administration, pre-bronchodilator spirometry testing measured with a portable spirometer, and post-bronchodilator diagnostic spirometry during a pulmonology appointment. RESULTS: A total of 1,463 subjects were included; the average age was 46.2 +/- 10.3 y. Two hundred eighty-two subjects had a positive questionnaire; 190 completed portable spirometry, and approximately 34% (65 of 190 subjects) reported respiratory impairment; of these 65 subjects, 33 completed diagnostic spirometry, and 66.7% (22 of 33) showed evidence of COPD, including 2 subjects with severe airway obstruction (GOLD stage 3, according to the Global Initiative for Chronic Obstructive Lung Disease). High dropout rates were observed in our program. Individuals with COPD exacerbations showed lower CD4+ cell counts at screening compared to those without acute worsening of symptoms (534 cells/mm(3) for subjects with GOLD 1 exacerbations and 495 cells/mm(3) for subjects with GOLD 2

exacerbations vs 781 cells/mm(3) for those without acute worsening of symptoms). The positive predictive value of the COPD screening questionnaire and portable spirometry was 33.8%. CONCLUSIONS: COPD may be under-diagnosed in HIV-infected people, and case-finding programs are an urgent issue to address as part of routine practice in these individuals.

http://rc.rcjournal.com/content/64/2/169.short

Ragland, M. F., C. J. Benway, et al. (2019). **"Genetic Advances in COPD: Insights from COPDGene."** Am J Respir Crit Care MedChronic obstructive pulmonary disease (COPD) is a common and progressive disease that is influenced by both genetic and environmental factors. For many years, knowledge of the genetic basis of COPD was limited to Mendelian syndromes, such as alpha-1 antitrypsin deficiency and cutis laxa, caused by rare genetic variants. Fortunately, over the past decade, the proliferation of genome-wide association studies (GWAS), the accessibility of whole genome sequencing, and the development of novel methods for analyzing genetic variation data have led to a substantial increase in our understanding of genetic variants that play a role in COPD susceptibility and COPD-related phenotypes. COPDGene, a multicenter, longitudinal study of over 10,000 current and former cigarette smokers, has been pivotal to these breakthroughs in understanding the genetic basis of COPD. To date, over 20 genetic loci have been convincingly associated with COPD affection status, with additional loci demonstrating association with COPD-related phenotypes such as emphysema, chronic bronchitis, and hypoxemia. In this review, we discuss the contributions of the COPDGene study to the discovery of these genetic associations as well as the ongoing genetic investigations of COPD subtypes, protein biomarkers, and post-GWAS analysis.

Rai, R. S., M. A. Rowlands, et al. (2019). **"Posttraumatic Emphysema of the Optic Nerve Sheath."** Ophthalmic Plast Reconstr Surg **35**(2): e43-e45.

The authors describe the case of a 19-year-old female who suffered posttraumatic emphysema of the optic nerve sheath. She suffered massive head trauma requiring emergent neurosurgery and was incidentally found to have air in her optic nerve sheath on CT scan. At 6 weeks follow up, her visual acuity (20/25 uncorrected) and color perception in the affected eye were excellent. Her examination was notable for an afferent pupillary defect, mild disc pallor, and optic nerve atrophy on optical coherence tomography. This is a case of a patient with posttraumatic optic nerve sheath emphysema who recovered excellent visual function and received follow-up ophthalmic imaging.

Raymakers, A. J. N., M. Sadatsafavi, et al. (2019). **"Inhaled corticosteroids and the risk of lung cancer in chronic obstructive pulmonary disease (COPD): a population-based cohort study."** Eur Respir JInhaled corticosteroids are often prescribed in patients with chronic obstructive pulmonary disease (COPD). Their impact on the risk of lung cancer, a leading cause of mortality in COPD patients, is unknown.Population-based linked administrative data between the years 1997-2007 from the province of British Columbia, Canada were used to evaluate the association between lung cancer risk and ICS use in COPD patients. COPD was defined on the basis of receipt of three COPD-related prescriptions in subjects 50 years of age or greater. Exposure to ICS was incorporated into multivariable Cox regression models using several time-dependent methods ("ever" exposure, cumulative duration of use, cumulative dose, weighted cumulative duration of use, and weighted cumulative dose).There were 39,676 patients who met the inclusion criteria. The mean age of the cohort was 70.7 (sd: 11.1) years and 53% were female. There were 994 (2.5%) cases of lung cancer during follow-up. In the reference-case analysis (time-dependent "ever"

exposure), ICS exposure was associated with a 30% reduced risk of lung cancer (HR: 0.70 (95% CI: 0.61-0.80)). ICS exposure was associated with a decrease in the risk of lung cancer diagnosis over all five methods of quantifying exposure.This population-based study suggests that ICS use reduces the risk of lung cancer in COPD patients.

https://erj.ersjournals.com/content/early/2019/03/15/13993003.01257-2018

Rebordosa, C., E. Plana, et al. (2019). **"GOLD assessment of COPD severity in the Clinical Practice Research Datalink (CPRD)."** Pharmacoepidemiol Drug Saf **28**(2): 126-133.

PURPOSE: To evaluate availability of spirometry and symptom data in the Clinical Practice Research Datalink (United Kingdom) to assess COPD severity using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 definition and comparing it with an algorithm used in other studies. METHODS: This was a descriptive, noninterventional, secondary database cohort study of patients with COPD aged 40 years or older, who initiated treatment with specific COPD medications. Patients were classified according to COPD severity (1) in GOLD 2016 "ABCD" categories based on symptoms (Medical Research Council dyspnea grade, COPD Assessment Test, breathlessness), percent predicted FEV1, and exacerbation history and (2) as mild, moderate, severe, or very severe based on treatment and exacerbation history. RESULTS: The study included 63 900 patients with COPD aged 40 years or older that were new users of 1 or more COPD medication of interest. Percent predicted FEV1 was available for 80.9% of patients; symptoms for 75.6% of patients. Classification into GOLD 2016 ABCD categories was possible for 75.6% of the patients. The GOLD 2016 ABCD definition classified more patients under the high-risk categories (22.1%, A; 18.8%, B; 21.3%, C; 37.9%, D) than did the adapted algorithm (7.9%, mild; 48.6%, moderate; 42.1%, severe; 1.4%, very severe). CONCLUSION: Using our adaptation of the GOLD 2016 COPD severity classification, the information in the Clinical Practice Research Datalink allowed us to ascertain COPD severity in approximately 75% of patients with COPD. Algorithms that include medication use tend to misclassify patients with the extreme COPD severity categories.

https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4448

Reilev, M., K. B. Kristensen, et al. (2019). **"Discontinuation of therapy among COPD patients who experience an improvement in exacerbation status."** Eur J Clin PharmacolPURPOSE: A subset of patients with chronic obstructive pulmonary disease (COPD) experience a decrease in exacerbation frequency, leading to a diminished need for treatment with inhaled corticosteroids (ICS). We investigated prescribing and discontinuation patterns of long-acting bronchodilators and ICS in COPD patients according to exacerbation frequency. METHODS: Using the nationwide Danish health registries, we conducted a drug utilization study among patients who had at least two exacerbations or one hospitalization due to an exacerbation during 2011-2012. This study population was stratified according to consistency of exacerbation occurrence after 12, 24, 36, and 48 months of follow-up and the groups were described according to use of ICS, long-acting beta2-agonists (LABA), and long-acting anticholinergics (LAMA), and combinations thereof. RESULTS: We identified 29,010 COPD exacerbators during 2011-2012. Upon inclusion, 70% received ICS-containing regimens, in combination with LABA (23%) or both LABA and LAMA (41%). The proportion of prevalent users of ICS-containing regimens decreased to 56% during follow-up among exacerbation-free individuals, while it increased to 86% in individuals who experienced at least one exacerbation annually. Persistence to ICS-containing regimens was 58% after 4 years in individuals without exacerbations compared to 74% among those with annual exacerbations. Similar patterns were observed for triple therapy which was the most extensively used drug combination regardless of consistency of exacerbation occurrence. CONCLUSIONS: The extensive use of ICS and the relatively high persistence to ICS-containing regimens in individuals who had a decrease in exacerbation occurrence highlight a need for the development and implementation of de-escalation strategies in clinical practice.

https://link.springer.com/article/10.1007%2Fs00228-019-02667-4

Ricci, F., P. Wollmer, et al. (2018). **"Markers of cardiovascular autonomic dysfunction predict COPD in middle-aged subjects."** Eur Respir JAutonomic dysfunction is commonly observed in chronic obstructive pulmonary disease (COPD) and may relate to the known comorbidity with coronary artery disease (CAD). We hypothesised that clinical markers of cardiovascular autonomic dysfunction predict COPD in the population, independently of CAD.In a population-based cohort of 24 768 subjects (mean age 45 years) without baseline airflow obstruction, we analysed the cross-sectional relationship of one-minute orthostatic systolic (SBP) and diastolic (DBP) blood pressure changes, and resting heart rate with forced vital capacity (FVC) and forced expiratory volume (FEV1). Cox-regression-models were used to analyse the association of orthostatic SBP and DBP changes (SBP/DBP-decrease) and resting heart rate with incident COPD over 32-year follow-up.Baseline orthostatic SBP-decrease (p=0.020) and DBP-decrease (p=0.001) associated with reduced FVC, whereas resting heart rate associated with reduced FVC and FEV1 (p<0.001). After adjustment for smoking and baseline lung function, SBP-decrease predicted COPD (Hazard ratio [HR] 1.10 per 10 mmHg; 95% confidence interval [CI]:1.03-1.18). Resting heart rate predicted COPD among smokers (HR 1.11 per 10 beats-per-minute increase; 95%CI:1.05-1.18). Results were similar in subjects without CAD.Subtle signs of cardiovascular autonomic dysfunction may precede development of COPD in middle-aged subjects. This association is independent of the relationship between cardiovascular autonomic dysfunction and CAD.

https://erj.ersjournals.com/content/51/3/1702481

Rio Ramirez, M. T., M. A. Juretschke Moragues, et al. (2018). **"Value of Exhaled Nitric Oxide (FeNO) And Eosinophilia During the Exacerbations of Chronic Obstructive Pulmonary Disease Requiring Hospital Admission."** Copd **15**(4): 369-376.

The aim of this study was to analyze whether FeNO levels in acute exacerbation of COPD (AECOPD) with hospital admission have better diagnostic value than eosinophilia in blood, and to evaluate its usefulness in predicting a better clinical response. An observational prospective study of patients with AECOPD was carried out. FeNO determinations were made on arrival at the emergency room (ER), at discharge and during stability 3-6 months after discharge. Co-morbidities, bronchodilators, inhaled (IGC) and systemic (SGC) glucocorticoids, eosinophils, systemic inflammation markers (procalcitonin, C-reactive protein), eosinophil cationic protein, and total IgE were collected. Fifty consecutive patients (92% men, mean age 75 +/- 6 years) were included in this study. Phenotypes were 26% Asthma-COPD Overlap Syndrome (ACOS), 42% chronic bronchitis (CB) and 32% emphysema. ACOS patients showed significantly higher levels of FeNO (73 ppb) and eosinophils (508 cells/mm(3)) than the rest (CB: 23 ppb, 184 cells/mm(3), emphysema: 27 ppb, 159 cells/mm(3); $p < 0.05$). A significant correlation between FeNO levels measured in ER and eosinophils was observed ($r = 0.7$; $p < 0.001$), but not at discharge or in stable phase. No significant association was found with parameters of systemic inflammation and mean stay. In conclusion, the determination of FeNO in AECOPD does not offer advantages over the evaluation of eosinophilia. These parameters rise at arrival in ER, descend at discharge, and remain unchanged in the stable phase. Both present similar diagnostic utility and are able to better identify the ACOS phenotype, which helps select a population that could benefit from a glucocorticoids therapy.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1482532

Rodriguez-Manero, M., E. Lopez-Pardo, et al. (2019). **"A prospective study of the clinical outcomes and prognosis associated with comorbid COPD in the atrial fibrillation population."** Int J Chron Obstruct Pulmon Dis **14**: 371-380.

Background: Patients with COPD are at higher risk of presenting with atrial fibrillation (AF). Information about clinical outcomes and optimal medical treatment of AF in the setting of COPD remains missing. We

aimed to describe the prevalence of COPD in a sizeable cohort of real-world AF patients belonging to the same healthcare area and to examine the relationship between comorbid COPD and AF prognosis. Methods: Prospective analysis performed in a specific healthcare area. Data were obtained from several sources within the "data warehouse of the Galician Healthcare Service" using multiple analytical tools. Statistical analyses were completed using SPSS 19 and STATA 14.0. Results: A total of 7,990 (2.08%) patients with AF were registered throughout 2013 in our healthcare area (n=348,985). Mean age was 76.83+/-10.51 years and 937 (11.7%) presented with COPD. COPD patients had a higher mean CHA2DS2-VASc (4.21 vs 3.46; P=0.02) and received less beta-blocker and more digoxin therapy than those without COPD. During a mean follow-up of 707+/-103 days, 1,361 patients (17%) died. All-cause mortality was close to two fold higher in the COPD group (28.3% vs 15.5%; P<0.001). Independent predictive factors for all-cause mortality were age, heart failure, diabetes, previous thromboembolic event, dementia, COPD, and oral anticoagulation (OA). There were nonsignificant differences in thromboembolic events (1.7% vs 1.5%; P=0.7), but the rate of hemorrhagic events was significantly higher in the COPD group (3.3% vs 1.9%; P=0.004). Age, valvular AF, OA, and COPD were independent predictive factors for hemorrhagic events. In COPD patients, age, heart failure, vasculopathy, lack of OA, and lack of beta-blocker use were independent predictive factors for all-cause mortality. Conclusion: AF patients with COPD have a higher incidence of adverse events with significantly increased rates of all-cause mortality and hemorrhagic events than AF patients without COPD. However, comorbid COPD was not associated with differences in cardiovascular death or stroke rate. OA and beta-blocker treatment presented a risk reduction in mortality while digoxin use exerted a neutral effect.

https://www.dovepress.com/getfile.php?fileID=47998

Ronnow, S. R., L. L. Langholm, et al. (2019). **"Specific elastin degradation products are associated with poor outcome in the ECLIPSE COPD cohort."** Sci Rep **9**(1): 4064.

Chronic obstructive pulmonary disease (COPD) is characterized by a slow heterogeneous progression. Therefore, improved biomarkers that can accurately identify patients with the highest likelihood of progression and therefore the ability to benefit from a given treatment, are needed. Elastin is an essential structural protein of the lungs. In this study, we investigated whether elastin degradation products generated by the enzymes proteinase 3, cathepsin G, neutrophil elastase, MMP7 or MMP9/12 were prognostic biomarkers for COPD-related outcomes. The elastin degradome was assessed in a subpopulation (n = 1307) of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort with 3 years of clinical follow-up. Elastin degraded by proteinase 3 could distinguish between COPD participants and non-smoking controls (p = 0.0006). A total of 30 participants (3%) died over the 3 years of observation. After adjusting for confounders, plasma levels of elastin degraded by proteinase 3 and cathepsin G were independently associated with mortality outcome with a hazard ratio per 1 SD of 1.49 (95%CI 1.24-1.80, p < 0.0001) and 1.31 (95%CI 1.10-1.57, p = 0.0029), respectively. Assessing the elastin degradome demonstrated that specific elastin degradation fragments have potential utility as biomarkers identifying subtypes of COPD patients at risk of poor prognosis and supports further exploration in confirmatory studies.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6412140/pdf/41598_2019_Article_40785.pdf

Ronnow, S. R., J. M. B. Sand, et al. (2019). **"Type IV collagen turnover is predictive of mortality in COPD: a comparison to fibrinogen in a prospective analysis of the ECLIPSE cohort."** Respir Res **20**(1): 63.

BACKGROUND: Identifying subjects with chronic obstructive pulmonary disease (COPD) at high risk of exacerbation and mortality is key to aid individual management of COPD. The only FDA approved blood-based drug development biomarker for patients at high risk of mortality, is plasma fibrinogen. In this study, we benchmarked two biomarkers of basement membrane remodeling, a characteristic of COPD, against plasma fibrinogen alone and as a combination. The biomarkers of basement membrane remodeling are two neoepitopes from of the alpha 3 chain of type IV collagen (COL4A3). MATERIALS AND METHODS: COL4A3 degradation was assessed by the biomarkers C4Ma3 and tumstatin (TUM) in

year 1 plasma samples in 984 COPD subjects, 95 non-smoking controls and 95 smoking controls from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort. They were measured by competitive ELISA using monoclonal antibodies recognizing two specific MMP-generated cleavage site within COL4A3. The level of fibrinogen was previously assessed in year 1 plasma. RESULTS: In COPD subjects, plasma C4Ma3 levels were significantly correlated with plasma fibrinogen levels (0.389 (P < 0.0001)). Cox proportional-hazards regression adjusted for relevant confounders showed that high levels of plasma C4Ma3, but not TUM, were related to a higher risk of mortality (hazard ratio 5.12 (95% CI 2.28-11.50), P < 0.0001). High levels of plasma fibrinogen were not associated with all-cause mortality in this subpopulation, contradictory to published results. Whereas plasma C4Ma3 multiplied by fibrinogen showed to be related to a higher risk of mortality (hazard ratio 5.74 (95% CI 2.65-12.41), P < 0.0001). Plasma C4Ma3 levels were related to the number of hospitalizations due to COPD exacerbations in the year before study start (P = 0.0375). Fibrinogen levels were related to hospitalized exacerbations prior to study start (P = 0.0058) and were also related to future exacerbations (P < 0.0001). CONCLUSION: We compared herein fibrinogen, C4Ma3 and TUM as biomarkers for COPD prognosis. Fibrinogen was related to future exacerbation, whereas C4Ma3 and the combination of C4Ma3 with fibrinogen were superior to fibrinogen alone in predicting mortality. This pilot study suggests that the assessment of plasma C4Ma3 could be important for identifying COPD patients with a poor prognosis. TRIAL REGISTRATION: NCT00292552 , GSK Study No. SCO104960.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6444812/pdf/12931_2019_Article_1026.pdf

Rubinsztajn, R., T. Przybylowski, et al. (2019). **"Comorbidities in chronic obstructive pulmonary disease: Results of a national multicenter research project."** Adv Clin Exp Med **28**(3): 319-324.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is associated with various comorbidities, which influence the course of COPD and worsen prognosis. OBJECTIVES: The aim of this study was to analyze the comorbidities in a cohort of COPD patients in Poland during 12 months of observation. MATERIAL AND METHODS: A total of 444 COPD patients (median age: 66.1 years) in all stages of airflow limitation severity were enrolled. Medical histories and a questionnaire concerning comorbidities were analyzed at baseline and after 12 months (data of 267 patients available). Anthropometric data, pulmonary function, and body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE index) were assessed. RESULTS: No comorbidities were reported in 9 patients (2.0%), 101 patients (22.7%) had 1-2 comorbidities, 243 (54.7%) had 3-5, and 91 (20.6%) had more than 5 comorbidities. Cardiovascular diseases (CVDs) were the most frequent ones, followed by peptic ulcer, obstructive sleep apnea (OSA), diabetes, gastroesophageal reflux disease (GERD), and osteoporosis; 11 patients had a history of lung cancer. Cachexia was observed in 11 cases, overweight in 136 cases and obesity in 139 cases. The incidence of CVDs increased with time. The number of comorbidities correlated with the body mass index (BMI) and the number of hospitalizations for extra-pulmonary causes, but not with airflow limitation. The BODE index score increased with the number of comorbidities. CONCLUSIONS: In a cohort of Polish COPD patients, the most frequent comorbidities were CVDs. The number of comorbidities affected the BODE index, but not airflow limitation. The BODE index is better than forced expiratory volume in 1 s (FEV1) in the rating of COPD patients' condition. The BMI correlated with the number of comorbidities as well as the number of hospitalizations for extra-pulmonary causes.

Sandberg, J., G. Engstrom, et al. (2019). **"Breathlessness and incidence of COPD, cardiac events and all-cause mortality: A 44-year follow-up from middle age throughout life."** PLoS One **14**(3): e0214083.

BACKGROUND: Breathlessness is prevalent in the general population and may be associated with adverse health outcomes. This study aimed to evaluate the association of breathlessness with Chronic Obstructive Pulmonary Disease (COPD) events, cardiac events and all-cause mortality from middle-age throughout life. METHODS: Breathlessness was measured in 699, 55-year old men residing in Malmo, Sweden using modified Medical Research Council (mMRC). COPD events (hospitalisation, death or diagnosis) cardiac

events and all-cause mortality was assessed using The Swedish Causes of Death Register and Hospital Discharge Register. Data was analyzed using Cox- and competing risks (Fine-Gray) regression analysis. RESULTS: 695 (99%) of 699 participants died and four emigrated during follow up. Eighty-seven (12%) had mMRC = 1 and 19 (3%) had mMRC>/=2. Breathlessness was associated with COPD events; adjusted Sub-Hazard Ratio 2.1 (95% CI, 1.2-3.6) for mMRC = 1 and 7.5 (2.6-21.7) for mMRC >/= 2 but not associated with cardiac events when adjusting for competing events and confounding. Breathlessness was associated increased all- cause mortality (Hazard Ratios of 1.4 (1.1-1.7) (mMRC = 1) and 3.4 (2.1-5.6) (mMRC >/= 2)). CONCLUSION: Breathlessness is associated with increased risk of COPD events and increase in all-cause mortality from age 55 until death.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6422305/pdf/pone.0214083.pdf

Sato, S., M. Nakamura, et al. (2019). **"The impact of emphysema on surgical outcomes of early-stage lung cancer: a retrospective study."** BMC Pulm Med **19**(1): 73.

BACKGROUND: The presence of emphysema on computed tomography (CT) is associated with an increased frequency of lung cancer, but the postoperative outcomes of patients with pulmonary emphysema are not well known. The objective of this study was to investigate the association between the extent of emphysema and long-term outcomes, as well as mortality and postoperative complications, in early-stage lung cancer patients after pulmonary resection. METHODS: The clinical records of 566 consecutive lung cancer patients who underwent pulmonary resection in our department were retrospectively reviewed. Among these, the data sets of 364 pathological stage I patients were available. The associations between the extent of lung emphysema and long-term outcomes and postoperative complications were investigated. Emphysema was assessed on the basis of semiquantitative CT. Surgery-related complications of Grade >/= II according to the Clavien-Dindo classification were included in this study. RESULTS: Emphysema was present in 63 patients. The overall survival and relapse-free survival of the non-emphysema and emphysema groups at 5 years were 89.0 and 61.3% (P < 0.001), respectively, and 81.0 and 51.7%, respectively (P < 0.001). On multivariate analysis, significant prognostic factors were emphysema, higher smoking index, and higher histologic grade (p < 0.05). Significant risk factors for poor recurrence-free survival were emphysema, higher smoking index, higher histologic grade, and presence of pleural invasion (P < 0.05). Regarding Grade >/= II postoperative complications, pneumonia and supraventricular tachycardia were more frequent in the emphysema group than in the non-emphysema group (P = 0.003 and P = 0.021, respectively). CONCLUSION: The presence of emphysema affects the long-term outcomes and the development of postoperative complications in early-stage lung cancer patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6449985/pdf/12890_2019_Article_839.pdf

Sato, Y., A. Yoshihisa, et al. (2019). **"Prognostic impact of chronic obstructive pulmonary disease on adverse prognosis in hospitalized heart failure patients with preserved ejection fraction - A report from the JASPER registry."** J Cardiol **73**(6): 459-465.

BACKGROUND: The prognostic impact of chronic obstructive pulmonary disease (COPD) on heart failure (HF) with preserved ejection fraction (HFpEF) patients and its clinical characteristics have not yet been fully examined. METHODS: The Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry is a nationwide, observational, prospective registration of consecutive Japanese hospitalized HFpEF patients with left ventricular ejection fraction (LVEF) of >/=50%. Among 535 patients enrolled in the registry, 10 lacking COPD data, and seven who died during the first hospitalization, were excluded. Finally, 518 patients were enrolled in this analysis. We divided these patients into two groups: the COPD group (n=40, 7.7%) and the non-COPD group (n=478, 92.3%). This analysis had two primary endpoints: (1) all-cause death and (2) all-cause death or rehospitalization for HF. RESULTS: The COPD group showed a higher prevalence of male sex (70.0% vs. 48.1%, p=0.008), history of prior hospitalization for HF (63.2% vs. 35.1%, p=0.001), smoking history (71.8% vs. 43.3%, p=0.001), and a higher usage of loop diuretics (70.0% vs. 50.0%, p=0.015). In the follow-up period after discharge (median 733 days), there

were 82 all-cause deaths and 127 rehospitalizations for HF. In the Kaplan-Meier analysis, the COPD group showed higher all-cause death and reached the composite endpoint more often than in the non-COPD group (all-cause death, log-rank 0.035; all-cause death or rehospitalization for HF, log-rank 0.025). In the Cox proportional hazard analysis, COPD was a predictor of all-cause death (hazard ratio 1.957, 95% confidence interval 1.037-3.694, p=0.038) and the composite endpoint (hazard ratio 1.694, 95% confidence interval 1.064-2.697, p=0.026). CONCLUSIONS: COPD is associated with adverse prognosis in hospitalized patients with HFpEF.

https://www.journal-of-cardiology.com/article/S0914-5087(19)30010-3/fulltext

Schreuder, A., C. Jacobs, et al. (2019). **"Predicting all-cause and lung cancer mortality using emphysema score progression rate between baseline and follow-up chest CT images: A comparison of risk model performances."** PLoS One **14**(2): e0212756.

PURPOSE: Normalized emphysema score is a protocol-robust CT biomarker of mortality. We aimed to improve mortality prediction by including the emphysema score progression rate-its change over time-into the models. METHOD AND MATERIALS: CT scans from 6000 National Lung Screening Trial CT arm participants were included. Of these, 1810 died (445 lung cancer-specific). The remaining 4190 survivors were sampled with replacement up to 24432 to approximate the full cohort. Three overlapping subcohorts were formed which required participants to have images from specific screening rounds. Emphysema scores were obtained after resampling, normalization, and bullae cluster analysis of the original images. Base models contained solely the latest emphysema score. Progression models included emphysema score progression rate. Models were adjusted by including baseline age, sex, BMI, smoking status, smoking intensity, smoking duration, and previous COPD diagnosis. Cox proportional hazard models predicting all-cause and lung cancer mortality were compared by calculating the area under the curve per year follow-up. RESULTS: In the subcohort of participants with baseline and first annual follow-up scans, the analysis was performed on 4940 participants (23227 after resampling). Area under the curve for all-cause mortality predictions of the base and progression models 6 years after baseline were 0.564 (0.564 to 0.565) and 0.569 (0.568 to 0.569) when unadjusted, and 0.704 (0.703 to 0.704) to 0.705 (0.704 to 0.705) when adjusted. The respective performances predicting lung cancer mortality were 0.638 (0.637 to 0.639) and 0.643 (0.642 to 0.644) when unadjusted, and 0.724 (0.723 to 0.725) and 0.725 (0.725 to 0.726) when adjusted. CONCLUSION: Including emphysema score progression rate into risk models shows no clinically relevant improvement in mortality risk prediction. This is because scan normalization does not adjust for an overall change in lung density. Adjusting for changes in smoking behavior is likely required to make this a clinically useful measure of emphysema progression.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6383935/pdf/pone.0212756.pdf

Scrutinio, D., P. Guida, et al. (2019). **"Acutely decompensated heart failure with chronic obstructive pulmonary disease: Clinical characteristics and long-term survival."** Eur J Intern Med **60**: 31-38.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is among the most common comorbidities in patients hospitalized with heart failure and is generally associated with poor outcomes. However, the results of previous studies with regard to increased mortality and risk trajectories were not univocal. We sought to assess the prognostic impact of COPD in patients admitted for acutely decompensated heart failure (ADHF) and investigate the association between use of beta-blockers at discharge and mortality in patients with COPD. METHODS: We studied 1530 patients. The association of COPD with mortality was examined in adjusted Fine-Gray proportional hazard models where heart transplantation and ventricular assist device implantation were treated as competing risks. The primary outcome was 5-year all-cause mortality. RESULTS: After adjusting for establisked risk markers, the subdistribution hazard ratios (SHR) of 5-year mortality for COPD patients compared with non-COPD patients was 1.25 (95% confidence intervals [CIs] 1.06-1.47; p=.007). The relative risk of death for COPD patients increased steeply from 30 to 180days, and remained noticeably high throughout the entire follow-up. Among patients with comorbid COPD, the use of beta-blockers at discharge was associated with a significantly

reduced risk of 1-year post-discharge mortality (SHR 0.66, 95%CIs 0.53-0.83; p</=.001). CONCLUSIONS: Our data indicate that ADHF patients with comorbid COPD have a worse long-term survival than those without comorbid COPD. Most of the excess mortality occurred in the first few months following hospitalization. Our data also suggest that the use of beta-blockers at discharge is independently associated with improved survival in ADHF patients with COPD.

https://www.ejinme.com/article/S0953-6205(18)30447-3/fulltext

Seifer, F. D., G. Hansen, et al. (2019). **"Health-care utilization and expenditures among patients with comorbid bronchiectasis and chronic obstructive pulmonary disease in US clinical practice."** Chron Respir Dis **16**: 1479973119839961.

Recent research suggests that bronchiectasis (BE) may be more common than previously believed and that comorbid chronic obstructive pulmonary disease (COPD) is widespread in this patient population. Little is known about the economic burden among patients with BE, and less is known about the burden among those with comorbid BE + COPD. A retrospective matched-cohort design and data from a US health-care claims repository were employed. From the source population comprising adults who had comprehensive medical/drug benefits for >/=1 day in 2013 (i.e. the referent year) and evidence of BE and/or COPD at any time from 2009 to 2013, patients with BE + COPD were age/sex-matched (1:1:1) to patients with BE only and patients with COPD only. For each matched subgroup, annualized levels of respiratory-related and all-cause health-care utilization and expenditures in 2013 were summarized. Source population included 679,679 patients; among those with BE (n = 31,027), 50% had comorbid COPD. Mean (95% CI) annual levels of respiratory-related utilization and expenditures among matched patients with BE + COPD (n = 11,685) were higher by 2.4-3.5 times versus patients with BE only and 2.0-2.5 times versus patients with COPD only: hospitalizations, 0.39 (0.37-0.41) versus 0.11 (0.09-0.12) and 0.16 (0.14-0.17); ambulatory encounters, 16.5 (16.1-16.9) versus 6.8 (6.6-7.0) and 8.2 (7.9-8.4); and total expenditures, US$15,685 (14,693-16,678) versus US$5605 (5059-6150) and US$6262 (5655-6868). Respiratory-related utilization and expenditures are high among patients with BE or COPD receiving medical care in US clinical practice and are especially high among those with comorbid BE + COPD receiving medical care, emphasizing the importance of identifying and treating this unique patient population. Funding for this research was provided by RespirTech to Policy Analysis Inc. (PAI).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6456842/pdf/10.1177_1479973119839961.pdf

Senthilselvan, A. and J. Beach (2018). **"Characteristics of asthma and COPD overlap syndrome (ACOS) in the Canadian population."** J Asthma: 1-9.

OBJECTIVE: Asthma is a chronic disease affecting both children and adults, whereas chronic obstructive pulmonary disease (COPD) is a respiratory disease most commonly related to smoking and is usually seen in adults. When the airway disease shares features of both asthma and COPD, the phenotype is referred to as asthma and COPD overlap syndrome (ACOS). The objective of this cross-sectional study is to characterize ACOS in the Canadian population. METHODS: Data from the first three cycles of the Canadian Health Measures Survey (CHMS) were used in this study. The study included 9059 subjects aged 30 years and above. The CHMS included a detailed interviewer-administered questionnaire and spirometry measurements. Based on the self-report, subjects were categorized into control, ACOS, COPD only and asthma only groups. RESULTS: The prevalence of ACOS, COPD and asthma groups was 1.59%, 2.21% and 6.65%, respectively. The proportion of females was significantly greater than males in the ACOS group. The proportion of wheeze was highest in the ACOS group (64.93%) whereas the prevalence of shortness of breath was the highest in the COPD group (46.25%). Heart disease, cancer, arthritis and liver disease were more prevalent in the ACOS group than in COPD, asthma and control groups. Severity of airway obstruction was the highest in the ACOS group and was followed by COPD, asthma and control groups, respectively. CONCLUSIONS: Characteristics of ACOS in the Canadian population were similar to those observed in the developed countries and longitudinal studies are required to determine the incidence and risk factors of ACOS.

https://www.tandfonline.com/doi/full/10.1080/02770903.2018.1531997

Sievi, N. A., M. Kohler, et al. (2019). **"No impact of exacerbation frequency and severity on the physical activity decline in COPD: a long-term observation."** Int J Chron Obstruct Pulmon Dis **14**: 431-437.

Introduction: COPD exacerbations are associated with a concomitant profound reduction in daily physical activity (PA). Thereby, exacerbation frequency and severity may have an amplifying effect. Whether the reduced level of PA returns to the level prior to exacerbation or has a sustained negative impact on activity behavior over time is unclear. Methods: The number of steps per day over 1 week, as a measure of daily PA, was assessed annually in a cohort of patients with COPD. Exacerbation frequency and severity were documented. Uni- and multivariate mixed effect models were used to investigate associations between change in number of steps per day (dependent variable) and exacerbations. Stratification by possible confounders was performed. Results: One hundred and eighty one COPD patients (median [quartile] age 64 [59/69] years, 65% male, median [quartiles] FEV1 % pred. 46 [33/65]) suffered a total of 273 exacerbations during the observation period (median [quartiles] follow-up time of 2.1 [1.6/3.1] years). Neither the frequency nor the severity of exacerbations was significantly related to the overall decline in PA over time. Stratification by different possible confounders such as age, sex and disease severity did not yield a subgroup in which exacerbations enhance the decrease in PA over time. Conclusion: The drop in PA during the phase of an acute exacerbation seems not to be a lasting phenomenon leading to a fundamental change in activity behavior. Trial registration: www.ClinicalTrials.gov, NCT01527773.

https://www.dovepress.com/getfile.php?fileID=48075

Singh, G., A. Agarwal, et al. (2019). **"Impact of PAP therapy on hospitalization rates in Medicare beneficiaries with COPD and coexisting OSA."** Sleep Breath **23**(1): 193-200.

OBJECTIVE: Growing evidence supports that patients with chronic obstructive pulmonary disease (COPD) and coexisting obstructive sleep apnea (OSA) have poor prognosis. This association is described as overlap syndrome. Positive airway pressure (PAP) therapy is now the preferred treatment for OSA. We hypothesized that use of PAP therapy in elderly patients with overlap syndrome would be associated with lower healthcare utilization. METHODS: In this retrospective cohort study, we analyzed data from 5% national sample of fee-for-service Medicare beneficiaries with a diagnosis of COPD who were newly started on PAP therapy in 2011. We examined the effect of PAP therapy on emergency room (ER) visits and hospitalizations for all-cause and COPD-related conditions in the 1 year pre- and 1 year post-initiation of PAP therapy. RESULTS: In year 2011, we identified 319 patients with overlap syndrome who were new users of PAP therapy. In this cohort of patients, hospitalization rates for COPD-related conditions were significantly lower in the 1 year post-initiation of PAP therapy compared to the 1-year pre-initiation period (19.4 vs 25.4%, P value = 0.03). However, ER visits (for any cause or COPD-related conditions) and hospitalization rates for any cause did not differ significantly in the pre- and post-initiation periods. PAP therapy was more beneficial in older adults, those with higher COPD complexity, and those with three or more comorbidities. CONCLUSION: Initiation of PAP therapy in elderly patients with overlap syndrome is associated with a reduction in hospitalization for COPD-related conditions, but not for all-cause hospitalizations and ER visits.

https://link.springer.com/article/10.1007%2Fs11325-018-1680-0

Slebos, D. J., J. Cicenia, et al. (2019). **"Predictors of Response to Endobronchial Coil Therapy in Patients With Advanced Emphysema."** ChestBACKGROUND: The Lung Volume Reduction Coil Treatment in Patients With Emphysema (RENEW) trial reported improvements in quality of life, pulmonary function, and exercise performance following endobronchial coil treatment. OBJECTIVES: The purpose of this post hoc

analysis was to identify baseline predictors, including quantitative CT measures, that identify patients most likely to significantly benefit from endobronchial coil therapy. METHODS: Quantitative CT analysis by an independent radiology laboratory and a qualitative evaluation by five blinded experts of the baseline thoracic CT imaging were performed. Univariate and multivariate logistic regression analyses were performed to elucidate characteristics associated with clinical response. RESULTS: In total, 125 patients underwent coil treatment and had evaluable 12-month follow-up results. Of these, 78 patients received treatment of lobes with the highest emphysematous destruction determined by quantitative CT analysis (quantitative visual match [QVM]+), and 47 received treatment in at least one lobe that was not the most destroyed (QVM-). From the 78 patients with QVM+ treatment, a subgroup of 50 patients (64%) was identified with baseline residual volume > 200% predicted, emphysema score > 20% low attenuation area, and absence of airway disease. In this subgroup, greater lobar residual volume reduction in the treated lobes was achieved, which was associated with significant mean +/- SE improvement in FEV1 (15.2 +/- 3.1%), St. George's Respiratory Questionnaire (-12 +/- 2 points), and residual volume (-0.57 +/- 0.13 L). DISCUSSION: This post hoc analysis found that both significant hyperinflation (residual volume >/= 200% predicted) and CT analysis are critical for patient selection and treatment planning for endobronchial coil therapy. Quantitative CT analysis is important to identify optimal lobar treatment and to exclude patients with insufficient emphysema (< 20% low attenuation area), whereas visual assessment identifies patients with signs of airway disease associated with worse outcomes. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01608490; URL: www.clinicaltrials.gov.

https://journal.chestnet.org/article/S0012-3692(19)30188-6/fulltext

Smallwood, N., L. Ross, et al. (2018). **"A Palliative Approach is Adopted for Many Patients Dying in Hospital with Chronic Obstructive Pulmonary Disease."** Copd **15**(5): 503-511.

Severe chronic breathlessness in advanced chronic obstructive pulmonary disease (COPD) is undertreated and few patients access specialist palliative care in the years before death. This study aimed to determine if symptom palliation or a palliative approach were delivered during the final hospital admission in which death occurred. Retrospective medical record audits were completed at two Australian hospitals, with all patients who died from COPD over 12 years between 1 January 2004 and 31 December 2015 included. Of 343 patients included, 217 (63%) were male with median age 79 years (IQR 71.4-85.0). Median respiratory function: FEV1 0.80L (42% predicted), FVC 2.02L (73% predicted) and DLco 9 (42% predicted). 164 (48%) used domiciliary oxygen. Sixty (18%) patients accessed specialist palliative care and 17 (5%) wrote an advance directive prior to the final admission. In the final admission, 252 (74%) patients had their goal of care changed to aim for comfort (palliation) and 99 (29%) were referred to specialist palliative care. Two hundred and eighty-six (83%) patients received opioids and 226 (66%) received benzodiazepines, within 1 or 2 days respectively after admission to palliate symptoms. Median starting and final opioid doses were 10 mg (IQR = 5-20) and 20 mg (IQR = 7-45) oral morphine equivalent/24 h. Hospital site and year of admission were significantly associated with palliative care provision. Respiratory and general physicians provided a palliative approach to the majority of COPD patients during their terminal admission, however, few patients were referred to specialist palliative care. Similarly, there were missed opportunities to offer symptom palliation and a palliative approach in the years before death.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1549210

Spannella, F., F. Giulietti, et al. (2019). **"Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Oldest Adults: Predictors of In-Hospital Mortality and Need for Post-acute Care."** J Am Med Dir AssocOBJECTIVES: Older age is associated with higher risk of death during acute exacerbations of chronic obstructive pulmonary disease (AE-COPD). Older patients hospitalized for AE-COPD often require post-acute care after acute phase. The aim of this study was to evaluate components of a comprehensive geriatric assessment and clinical/laboratory parameters, in order to find predictors of in-hospital mortality and need for post-acute care in patients aged 80 and older hospitalized for AE-COPD.

DESIGN: Prospective observational study. SETTING: Hospital assessment. PARTICIPANTS: 121 patients consecutively admitted to an internal medicine and geriatrics department for AE-COPD. MEASURES: Activities of Daily Living (ADL) Hierarchy scale, Geriatric Index of Comorbidity, cognitive impairment, and clinical and laboratory parameters were collected. RESULTS: Mean age: 87.0 +/- 4.9 years; male: 54.5%. In-hospital mortality (18.2% of patients) was significantly associated with functional disability, high comorbidity, cognitive impairment, anemia, older age, lower albumin, higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) and white blood cell levels, oral corticosteroids taken before admission, and no angiotensin-converting enzyme inhibitors or angiotensin receptor blockers taken before admission. In a stepwise logistic regression, functional dependence (P = .006), cognitive impairment (P = .038), and oral corticosteroids therapy before hospitalization (P = .035) were independently associated with a higher risk of in-hospital mortality. Among laboratory parameters, only NT-proBNP remained significantly associated with in-hospital mortality (P = .026). The need for post-acute care (18.2% of survivors) was associated with older age, higher admission Pco2, greater comorbidity, and cognitive impairment. In a stepwise logistic regression, only cognitive impairment (P = .016) and ln_Pco2 (P = .056) confirmed their association with the need for post-acute care. CONCLUSIONS/IMPLICATIONS: Preadmission functional dependence, cognitive impairment, and corticosteroid use, plus elevated NT-proBNP at admission are risk factors for mortality during an AE-COPD in the oldest old. Therefore, medical providers should consider these, as well as the patient's advance directives, in planning hospital care. Furthermore, providers should arrange especially careful posthospitalization monitoring and frequent follow-up of individuals with cognitive impairment and baseline hypercapnia.

https://www.jamda.com/article/S1525-8610(19)30152-5/fulltext

Spece, L. J., L. M. Donovan, et al. (2018). **"Quality of Care Delivered to Veterans with COPD Exacerbation and the Association with 30-Day Readmission and Death."** Copd **15**(5): 489-495.

Quality of chronic obstructive pulmonary disease (COPD) care is thought to be an important intermediate process to improve the well-being of patients admitted to hospital for exacerbation. We sought to examine the quality of inpatient COPD care and the associations with readmission and mortality. We performed a cohort study of 2,364 veterans aged over 40 and hospitalized for COPD between 2005 and 2011 at five Department of Veterans Affairs hospitals. We examined whether patients received six guideline recommended care items including short-acting bronchodilators, corticosteroids, antibiotics, positive-pressure ventilation (in cases of acute hypercarbic respiratory failure), chest imaging, and arterial blood gas measurement. Our primary outcome was all-cause hospital readmission or death within 30 days. Overall quality of care was not significantly associated with readmission or death (acute care aOR 0.98; 95% CI 0.87-1.11; ICU aOR 0.89; 95% CI 0.71-1.13). Delivery of corticosteroids and antibiotics was associated with reduced odds of readmission and death (aOR 0.77; 95% CI 0.61-0.92). Few patients received all of the recommended care items (18% of acute care, 38% of ICU patients). Quality of care did not vary by race or sex but did vary significantly across sites and did not improve over time. Our composite measure of COPD care quality was not associated with readmission or death. Further efforts are needed to improve care delivery to patients hospitalized with COPD.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1543390

Sprooten, R. T. M., G. G. U. Rohde, et al. (2019). **"Risk stratification for short-term mortality at hospital admission for acute exacerbations of COPD."** RespirologyBACKGROUND AND OBJECTIVE: Exacerbations of chronic obstructive pulmonary disease (ECOPD) are associated with increased in-hospital and short-term mortality. Developing an easy-to-use model to predict adverse outcomes will be useful in daily clinical practice and will facilitate management decisions. We aimed to assess mortality rates and potential predictors for short-term mortality after severe ECOPD. Classification and Regression Tree (CART) model was used to identify predictors of adverse outcome. METHODS: A retrospective observational cohort study, including all patients admitted to Maastricht University Medical Center with ECOPD between June 2011 and December 2014 was performed. The last admission was taken into

account, and its demographic, clinical and biochemical data were recorded. RESULTS: A total of 364 hospitalized patients were enrolled. Mean (SD) age was 70.5 (10.2) years, 54.4% were male and mean FEV1 45.2% (17.7) of predicted. The in-hospital and 90-day mortality were, respectively, 8.5 and 16.2%. Independent risk factors for 90-day mortality were: PaC02 (odds ratio (OR): 1.31; 95% confidence interval (CI): 1.00-0.35), age (OR: 1.09; CI: 0.06-0.11), body mass index (BMI) < 18.5 kg/m(2) (OR: 2.72; 95% CI: 0.53-1.47) and previous admission for ECOPD in last 2 years (OR: 1.29; 95% CI: -0.14, -0.65). The CART model selected PaCO2 >/= 9.1 kPa, age > 80 years, BMI < 18.5 kg/m(2) and previous admission for ECOPD as the most discriminatory factors. CONCLUSION: According CART analysis, high PaCO2 and age, low BMI and previous admission for ECOPD in last 2 years were the strongest predictors of 90-day mortality in patients with severe ECOPD. In absence of any of these factors, no patients died, suggesting that this model indeed enables risk stratification.

https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13538

Stanford, R. H., E. D. Parker, et al. (2019). **"Assessment of COPD-related outcomes in patients initiating a once daily or twice daily ICS/LABA."** Respir Med **150**: 1-7.

BACKGROUND: Use of inhaled corticosteroids and long acting beta agonist (ICS/LABA) combination therapy has been shown to decrease the frequency of exacerbations in patients with chronic obstructive pulmonary disease (COPD). In this population, adherence to treatment is associated with better disease control and lower risk of COPD-related exacerbations in the future. Using a treatment with a more convenient regimen or easier-to-use device could improve patient adherence, improve disease control, decrease the frequency of exacerbations and minimize the COPD-related economic burden. Real-world information on the impact on healthcare costs and exacerbation risk of initiating once-daily or twice daily ICS/LABA in this patient population is limited. The objective of this study was to assess COPD-related healthcare costs, adherence, and exacerbations in COPD patients initiating treatment with fluticasone furoate/vilanterol 100/25 (FF/VI) or budesonide/formoterol 160/4.5 (BUD/F) using a large managed care database in the US. METHODS: This was a retrospective cohort study among COPD patients initiating FF/VI or BUD/F between January 01, 2014 and June 30, 2016. The analysis used the Optum Research Database (ORD) which contains patients from commercial and Medicare Advantage Prescription Drug (MAPD) plans. The study included new initiators of ICS/LABA as either FF/VI or BUD/F for COPD, >/=40 years of age at index, >/=15 months of continuous enrollment (12 months pre-index and >/=3 months post-index). New users of FF/VI or BUD/F were matched on baseline characteristics using propensity score matching (PSM) methods. Multivariate models including ordinary least squares regression, Lin's regression, logistic regression, and Cox proportional hazards were used to assess differences between the cohorts on outcomes of interest. RESULTS: A total of 18,652 subjects met all inclusion and exclusion criteria with 5044 initiating FF/VI and 13,608 initiating BUD/F. Of these, 9026 subjects were matched at a 1:1 ratio (4513 patients in each cohort) and were included in the final analyses. Proportion of days covered (PDC), was significantly better for FF/VI (mean PDC [SD]: FF/VI: 0.46 [0.31], BUD/F: 0.41 [0.29], p<0.001) while FF/VI was associated with a 9% lower risk (adj. hazard ratio (HR): 0.91, 95% CI: 0.85-0.96) of having a moderate or severe COPD-related exacerbation. However, COPD-related healthcare costs were not significantly different, $11,521 vs $10,986, p=0.41 for FF/VI and BUD/F, respectively. CONCLUSIONS: Patients initiating once-daily FF/VI were more adherent, and were associated with a lower risk of subsequent COPD-related exacerbations compared with twice-daily BUD/F, however this was not associated with a significant difference in costs. (GSK Study HO1617333/206702).

https://www.resmedjournal.com/article/S0954-6111(19)30036-8/fulltext

Su, T. H., S. H. Chang, et al. (2019). **"beta-blockers after acute myocardial infarction in patients with chronic obstructive pulmonary disease: A nationwide population-based observational study."** PLoS One **14**(3): e0213187.

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) less often receive beta-blockers after acute myocardial infarction (AMI). This may influence their outcomes after AMI. This study evaluated the

efficacy of beta-blockers after AMI in patients with COPD, compared with non-dihydropyridine calcium channel blockers (NDCCBs) and absence of these two kinds of treatment. METHODS AND RESULTS: We conducted a nationwide population-based cohort study using data retrieved from Taiwan National Health Insurance Research Database. We collected 28,097 patients with COPD who were hospitalized for AMI between January 2004 and December 2013. After hospital discharge, 24,056 patients returned to outpatient clinics within 14 days (the exposure window). Those who received both beta-blockers and NDCCBs (n = 302) were excluded, leaving 23,754 patients for analysis. Patients were classified into the beta-blocker group (n = 10,638, 44.8%), the NDCCB group, (n = 1,747, 7.4%) and the control group (n = 11,369, 47.9%) based on their outpatient prescription within the exposure window. The beta-blockers group of patients had lower overall mortality risks (adjusted hazard ratio [95% confidence interval]: 0.91 [0.83-0.99] versus the NDCCB group; 0.88 [0.84-0.93] versus the control group), but the risk of major adverse cardiac events within 1 year was not statistically different. beta-blockers decreased risks of re-hospitalization for COPD and other respiratory diseases by 12-32%. CONCLUSIONS: The use of beta-blockers after AMI was associated with a reduced mortality risk in patients with COPD. beta-blockers did not increase the risk of COPD exacerbations.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6400336/pdf/pone.0213187.pdf

Suissa, S., S. Dell'Aniello, et al. (2019). **"Comparative Effectiveness and Safety of LABA-LAMA vs LABA-ICS Treatment of COPD in Real-World Clinical Practice."** ChestBACKGROUND: Long-acting beta2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are recommended as initial maintenance treatments for COPD, with their combination (LABA-LAMA) advocated as the disease progresses. Randomized trials comparing the effectiveness of this combination with the alternative combination of LABA with inhaled corticosteroid (LABA-ICS) have reported conflicting data, while there are no real-world comparative effectiveness and safety studies of these regimens in clinical practice settings. METHODS: We identified a cohort of patients with COPD during 2002-2015, age 55 years or older, from the United Kingdom's Clinical Practice Research Datalink. Patients initiating LABA-LAMA on the same day (no ICS) were matched on time-conditional high-dimensional propensity scores with patients initiating LABA-ICS on the same day (no LAMA), and monitored for 1 year for the occurrence of a moderate or severe COPD exacerbation and severe pneumonia. RESULTS: The cohort included 1,977 initiators of LABA-LAMA matched with 1,977 initiators of LABA-ICS. The hazard ratio (HR) of moderate or severe COPD exacerbation associated with LABA-LAMA initiation, relative to LABA-ICS initiation, was 1.04 (95% CI, 0.90-1.20), while for a severe exacerbation it was 0.94 (95% CI, 0.65-1.36). The incidence of severe pneumonia requiring hospitalization was lower with LABA-LAMA initiation (HR, 0.66; 95% CI, 0.41-1.05), particularly in the on-treatment analysis (HR, 0.66; 95% CI, 0.50-0.87). CONCLUSIONS: In a real-world clinical practice setting of COPD treatment, combined LABA-LAMA inhalers appear to be as effective as combined LABA-ICS inhalers in preventing COPD exacerbations. However, a LABA-LAMA combination may be preferred because it is associated with fewer severe pneumonias.

https://journal.chestnet.org/article/S0012-3692(19)30696-8/fulltext

Suissa, S., M. Hudson, et al. (2019). **"Comparative safety of abatacept in rheumatoid arthritis with COPD: A real-world population-based observational study."** Semin Arthritis RheumOBJECTIVE: The ASSURE randomized trial of abatacept safety in rheumatoid arthritis (RA) reported more frequent respiratory adverse events with abatacept among the subgroup of 54 patients with chronic obstructive pulmonary disease (COPD), leading to a label warning. We assessed the risk of adverse respiratory events associated with abatacept, compared with other biologic DMARDs (bDMARDs), among patients with RA and COPD in a real-world observational setting. METHODS: We formed a prevalent new-user cohort of patients with RA and COPD treated with bDMARDs within the US-based MarketScan databases from 2007 to 2014. Abatacept users were matched on time-conditional propensity scores to users of other bDMARDs. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of adverse respiratory events comparing abatacept with other bDMARDs were estimated using the Cox model. RESULTS: The cohort included

1807 patients initiating abatacept and 3547 matched patients initiating another bDMARD. The HR of the combined endpoint of hospitalized COPD exacerbation, bronchitis and hospitalized pneumonia or influenza with abatacept relative to other bDMARDs was 0.87 (95% CI: 0.68-1.12). For hospitalized COPD exacerbation it was 0.60 (95% CI: 0.32-1.11), 0.80 (95% CI: 0.56-1.14) for bronchitis, while for pneumonia or influenza it was 1.39 (95% CI: 0.91-2.13) if hospitalized and 1.05 (95% CI: 0.86-1.29) as outpatient. CONCLUSION: This large safety study from a real world setting finds no increased risk of adverse respiratory events with abatacept compared with other bDMARDs in patients with RA and COPD. This study does not substantiate the safety signal raised by the smaller ASSURE trial.

Suzuki, A., Y. Kondoh, et al. (2019). **"Performance of the COPD Assessment Test in patients with connective tissue disease-associated interstitial lung disease."** Respir Med **150**: 15-20.

BACKGROUND: Patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) often experience impaired health status. In daily clinical practice, a short and easy instrument for assessing health status would be useful to help better understand the patient's condition. The COPD Assessment Test (CAT) is a simple questionnaire about respiratory symptoms and their impact. We aimed to examine the CAT's performance characteristics and to generate data to support its reliability and validity in patients with CTD-ILD. METHODS: We used data from 132 CTD-ILD patients evaluated at Tosei General Hospital from July 2011 to July 2016 to assess the cross-sectional and longitudinal validity of the CAT. RESULTS: The mean age of the patients was 64.5 years and 87 (66%) were women. There were no significant differences in CAT score between any of the CTD subgroups. Internal consistency (Cronbach's alpha=0.881) and repeatability (intraclass correlation coefficient [ICC]=0.803) for the CAT score were acceptable. At baseline, CAT score was significantly associated with clinically meaningful measures of physiologic function, exercise capacity, and dyspnea. Change in CAT score over 6-12 months was also associated with change in other measures. In the distribution- and anchor-based analyses, the estimated minimal clinically important difference of CAT score was 1-4 points. CONCLUSION: These data support the validity and reliability of CAT as a sensitive measure for assessing health status in patients with CTD-ILD.

https://www.resmedjournal.com/article/S0954-6111(19)30033-2/fulltext

Takeuchi, K., K. Matsumoto, et al. (2019). **"Periodontitis Is Associated with Chronic Obstructive Pulmonary Disease."** J Dent Res **98**(5): 534-540.

Although they are known to share pathophysiological processes, the relationship between periodontitis and chronic obstructive pulmonary disease (COPD) is not fully understood. The aim of the present study was to test the hypothesis that periodontitis is associated with a greater risk of development of COPD, when smoking is taken into account. The analysis in a 5-y follow-up population-based cohort study was based on 900 community-dwelling Japanese adults (age: 68.8 +/- 6.3 [mean +/- SD], 46.0% male) without COPD aged 60 or older with at least 1 tooth. Participants were classified into 3 categories according to baseline periodontitis severity (no/mild, moderate, and severe). COPD was spirometrically determined by a fixed ratio of <0.7 for forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) and by FEV1/FVC below the lower limit of normal. Poisson regression was used to calculate the relative risk (RR) of developing COPD according to the severity of periodontitis. The population attributable fraction (PAF) was also calculated. During follow-up, 22 (2.4%) subjects developed COPD. Compared with no/mild periodontitis subjects, a significantly increased risk of COPD occurred among severe periodontitis subjects (RR = 3.55; 95% confidence interval [CI], 1.18 to 10.67), but no significant differences were observed between the no/mild and moderate categories (RR = 1.48; 95% CI, 0.56 to 3.90). After adjustment for potential confounders, including smoking intensity, the relationship between severe periodontitis and risk of COPD remained significant (RR = 3.51; 95% CI, 1.15 to 10.74). Likewise, there was a positive association of periodontitis severity with risk of COPD (P for trend = 0.043). The PAF for

COPD due to periodontitis was 22.6%. These data highlight the potential importance of periodontitis as a risk factor for COPD.

Taverner, J., L. Ross, et al. (2019). **"Antimicrobial prescription in patients dying from chronic obstructive pulmonary disease."** Intern Med J **49**(1): 66-73.

BACKGROUND: Despite rising antimicrobial resistance, treatment guidelines for chronic obstructive pulmonary disease (COPD) exacerbations are frequently ignored. Patients with terminal conditions are often prescribed antimicrobials despite the goal of care to reduce burdensome treatments. The appropriate use of antimicrobials in patients who die from an exacerbation of COPD is unknown. AIM: To review antimicrobial prescription during the final admission in patients who died from an acute exacerbation of COPD. METHODS: A retrospective medical record audit was performed for 475 patients who died over 12 years (2004-2015). Patients were analysed within three groups: Group 1 - pneumonia on chest radiograph, Group 2 - infective exacerbation of COPD +/- raised inflammatory markers (white cell count, C-reactive protein) and Group 3 - non-infective exacerbation of COPD. RESULTS: A total of 221 patients died from COPD. The median age was 80 years, and 136 (60%) were male. Median respiratory function: forced expiratory volume in 1 s 0.8 L (41.0%), forced vital capacity 2.0 L (74.0%) and diffusing capacity for carbon monoxide 8 (40.5%). A total of 109 (49.3%) patients used home oxygen and 156 (70.6%) were ex-smokers. Of the cohort, 90.5% received antimicrobials. In Groups 1, 2 and 3, 68 (94.4%), 108 (92.3%) and 24 (75.0%) patients received antimicrobials respectively. Guideline-concordant therapy was administered to 31.7% of patients (Group 1: 79.2%, Group 2: 4.3%, Group 3: 25.0%), 60.2% of patients received ceftriaxone and 44.8% received azithromycin. The median duration of therapy was 4 days and 27.1% received antimicrobials at the time of death. CONCLUSION: Antimicrobials are overprescribed, and non-guideline antimicrobials are overused in patients who die from COPD. Further education of medical staff, regular medication reviews and the use of disease severity scores or clinical pathways may improve antimicrobial stewardship.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/imj.13959

Thiboutot, J., W. Yuan, et al. (2019). **"Current Advances in COPD Imaging."** Acad Radiol **26**(3): 335-343.

OBJECTIVE: To review the recent advances in available technologies for imaging COPD and present the novel optical coherence tomography (OCT) airway imaging technology. MATERIALS AND METHODS: This is an unstructured review of published evidence of available pulmonary imaging technologies along with a demonstration of state-of-the-art OCT imaging technology of in vivo human and animal airways. RESULTS: Advanced imaging techniques such as Magnetic Resonance (MR) imaging using hyperoloarized noble gases, micro-Computed Tomography (micro-CT), and OCT aim to further our understanding of COPD. Lung densitometry can aid in identifying an exacerbation prone phenotype which may have implications for targeting specific therapies to these individuals. MR ventilation scans have the ability to provide a functional and regional distribution of airflow obstruction offering insight into the airway and parenchymal changes induced by COPD. Micro-CT gives a near microscopic view of the terminal bronchioles and alveoli permitting study of the microarchitecture of the lung ex vivo. Optical coherence tomography can visualize the microstructure of the airway walls (epithelium, smooth muscle, blood vessels, cartilage) permitting real time in vivo as well as longitudinal evaluation of airway changes in patients with COPD. CONCLUSION: Advanced imaging techniques play a vital role in expanding our current understanding of COPD.

https://www.academicradiology.org/article/S1076-6332(18)30272-1/fulltext

Thuppal, S., S. Markwell, et al. (2019). **"Comparison between the EQ-5D-3L and the SF-6D quality of life (QOL) questionnaires in patients with chronic obstructive pulmonary disease (COPD) undergoing lung volume reduction surgery (LVRS)."** Qual Life ResPURPOSE: Lung volume reduction surgery (LVRS) has been shown to improve lung function, but also improve the overall quality of life (QOL). The aim of this study is to compare two QOL questionnaires-EuroQol Questionnaire (EQ-5D-3L) and 36-item Short Form Health Survey (SF-36) in patients post-LVRS. METHODS: All patients undergoing LVRS for severe chronic obstructive pulmonary disease (COPD) at a single center of excellence were analyzed (n = 94). Baseline demographic and clinical outcomes were characterized. Both EQ-5D-3L and SF-36 questionnaires were administered to all patients at baseline (n = 94) and at the end of 1 year (n = 89) post-surgery. SF-36 was converted to Short Form six-dimensions (SF-6D) using standard algorithm. Correlation, discrimination, responsiveness and differences across the two questionnaires were examined. RESULTS: The mean age of patients enrolled in the cohort was 66 years. There was significant increase in forced expiratory volume (FEV1, 43%), forced vital capacity (FVC 46%), diffusion capacity (DLCO 15%), 6 min walk distance test (6MWD 21%) and a significant decrease in residual volume (RV 23%) at the end of 1-year follow-up. The overall mean utility index significantly improved for both SF-6D and EQ-5D-3L questionnaires at the end of follow-up (p = 0.0001). However, the magnitude of percentage increase was higher with EQ-5D-3L compared to SF-6D (32% vs. 13%). Stronger correlations confirmed convergent validity at the end of 1-year follow-up between similar domains. Both questionnaires failed to discriminate between different levels of disease severity post-LVRS in patients with severe COPD. CONCLUSIONS: Both questionnaires responded similarly in patients with COPD post-LVRS. Combining results from QOL questionnaire(s) along with symptoms of disease and history of exacerbation may be a possible solution for identifying disease severity in old and sick patients unwilling/unable to come to hospital for a pulmonary function test post-LVRS.

https://link.springer.com/article/10.1007%2Fs11136-019-02123-x

Tomioka, T., K. Fukui, et al. (2019). **"Influence of atrial fibrillation on cardiac prognosis in chronic obstructive pulmonary disease."** Indian Heart J **71**(1): 7-11.

BACKGROUND: Chronic obstructive pulmonary disease (COPD), a known risk factor for the development of congestive heart failure (CHF), was recently shown to predict the prevalence of atrial fibrillation (AF). Here, we explore the influence of AF on cardiac prognosis in COPD patients. METHODS: A total of 339 consecutive patients who underwent spirometry from 2010 to 2013 for various reasons were retrospectively examined. Based on the diagnostic criteria, patients were stratified into COPD and non-COPD groups, which were both further divided into those with AF (chronic AF or paroxysmal AF) or sinus rhythm (SR) based on previous electrocardiography results. Significances of differences in cardiac events were assessed by the chi-square test. Multivariate logistic regression analyses and Cox proportional hazard models were applied to evaluate the influence of AF on cardiac events. RESULTS: Of the 339 patients, 190 were diagnosed with COPD, with 42 of these were having AF. During the mean follow-up period of 7.4 +/- 0.8 years, CHF developed more frequently in COPD patients with AF than in COPD patients without AF [50% vs 7%; odds ratio (OR) 12.4, 95% confidence interval (CI): 5.25-29.49, $p < 0.05$]. AF was an independent predictor of CHF development (OR 20.4, 95% CI: 6.55-79.80, $p < 0.05$) and cardiac mortality (OR 2.8, 95% CI: 1.79-4.72, $p < 0.05$). Moreover, positive correlations were found between the severity of pulmonary obstruction with AF and CHF development ($R = 0.69$, $p < 0.05$), as well as cardiac mortality ($R = 0.78$.$p < 0.05$). CONCLUSIONS: These results suggest that AF may be strongly associated with cardiac mortality and CHF in COPD patients.

https://www.sciencedirect.com/science/article/pii/S0019483218304280?via%3Dihub

Trantham, L., M. V. Sikirica, et al. (2019). **"Healthcare costs and utilization associated with muscle weakness diagnosis codes in patients with chronic obstructive pulmonary disease: a United States claims analysis."** J Med Econ **22**(4): 319-327.

AIMS: Muscle weakness (MW)-attributable healthcare resource utilization (HCRU) and costs in patients with chronic obstructive pulmonary disease (COPD) have not been well-characterized in US insurance claims databases. The primary objective of this study was to estimate HCRU in patients with evidence of COPD with and without MW diagnosis codes. MATERIALS AND METHODS: This retrospective analysis used the MarketScan((R)) Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases. Between January 2007 and March 2016, we identified patients aged >/=40 years with diagnosis codes for COPD (>/=1 emergency department or inpatient claim or >/=2 outpatient claims within 1 year). The cohort was divided into patients with and without >/=1 MW diagnosis code. Propensity score matching was used to generate pairs of patients with and without MW (1:1). Multivariable regression analyses were used to estimate adjusted incremental costs and utilization attributable to the presence of MW diagnosis codes among patients with COPD. RESULTS: Of 427,131 patients who met the study inclusion criteria, 14% had evidence of MW. After matching, 107,420 unique patients remained equally distributed across MW status. Patients with MW diagnosis codes had greater predicted annual HCRU, $2,465 greater total predicted annual COPD-related costs, and $15,179 greater total all-cause costs than those without MW diagnosis codes. Overall, <1% of patients received COPD-related pulmonary rehabilitation services. LIMITATIONS: Study limitations include the potential for undercoding of MW and lack of information on severity of MW in claims data. CONCLUSION: The presence of MW diagnosis codes yielded higher HCRU in this COPD population and suggests that the burden of MW affects both all-cause and COPD-related care. However, utilization of pulmonary rehabilitation, a known effective treatment for MW, remains low. Future research should expand on our results by assessing data sources that allow for clinical confirmation of MW among patients with COPD.

https://www.tandfonline.com/doi/full/10.1080/13696998.2018.1563414

Trethewey, S. P., R. G. Edgar, et al. (2019). **"Temporal trends in survival following ward-based NIV for acute hypercapnic respiratory failure in patients with COPD."** Clin Respir J **13**(3): 184-188.

INTRODUCTION: Non-invasive ventilation (NIV) is recommended for treatment of acute hypercapnic respiratory failure (AHRF) in acute exacerbations of COPD. National UK audit data suggests that mortality rates are rising in COPD patients treated with NIV. OBJECTIVE: To investigate temporal trends in in-hospital mortality in COPD patients undergoing a first episode of ward-based NIV for AHRF. METHODS: Retrospective study of hospitalised COPD patients treated with a first episode of ward-based NIV at a large UK teaching hospital between 2004 and 2017. Patients were split into two cohorts based on year of admission, 2004-2010 (Cohort 1) and 2013-2017 (Cohort 2), to facilitate comparison of patient characteristics. RESULTS: In total, 547 unique patients were studied. There was no difference in in-hospital mortality rate between the time periods studied (17.6% vs 20.5%, P = .378). In Cohort 2 there were more females, a higher rate of co-morbid bronchiectasis and pneumonia on admission and more severe acidosis, hypercapnia and hypoxia. More patients in Cohort 2 had NIV as the ceiling of treatment. Patients in Cohort 2 experienced a longer time from AHRF diagnosis to application of NIV, higher maximum inspiratory positive airway pressure, lower maximum oxygen and shorter duration of NIV. Finally, patients in Cohort 2 experienced a shorter hospital length of stay (LOS), with no differences observed in rate of transfer to critical care or intubation. CONCLUSION: In-hospital mortality remained stable and LOS decreased over time, despite greater comorbidity and more severe AHRF in COPD patients treated for the first time with ward-based NIV.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12994

Trikalinos, T. A., G. Raman, et al. (2006). **AHRQ Technology Assessments**. Pulmonary Rehabilitation for COPD and Other Lung Diseases. Rockville (MD), Agency for Healthcare Research and Quality (US).

The Center for Medicare and Medicaid Services (CMS) has requested a technology assessment through the Agency for Healthcare Research and Quality (AHRQ) on pulmonary rehabilitation (PR) primarily for COPD and conditions such as asthma, bronchiectasis, ventilator dependency, and other relevant respiratory illness. The objective is to address specific questions about safety and effectiveness of PR. There seems to be limited evidence on safety and effectiveness of PR for other conditions of interest, apart from COPD. Also, the evidence of PR effectiveness in the elderly has not been systematically evaluated.

Specific components of PR and subgroups of patients eligible for PR are also of interest to CMS. The overarching question of interest to CMS is: What is the evidence for safety and effectiveness of PR for patients >/=65 years old with COPD, asthma, bronchiectasis and other relevant conditions? CMS is also interested in a description of the outcomes measures reported in the studies, a summary of the evidence on complications, harms, and adverse events associated with PR that have been reported, and an assessment on whether conditions prevalent in the older Medicare population increase the risk for these events with PR. Specific factors of interest to CMS include: a. Internal and external validity of the studies (includes inclusion and exclusion criteria of the studies). b. Length of follow-up. c. Intensity of treatment, number and frequency of sessions. d. Patient characteristics (i.e., gender, comorbidity) and disease characteristics (i.e., disease severity). Age of patients and generalizability to Medicare population. e. Concurrent treatment with beta-agonists and/or hormonal treatments and/or new therapies (e.g., spiriva) and/or concurrent treatment with supplementary oxygen. f. Concurrent PR in disease management programs. g. Place of delivery (e.g., home, inpatient, outpatient). h. Physician supervision. i. Components of the PR and whether components were individually tailored or generalized. j. Persistence of benefits/harms over time. k. Repeated course of PR.

Tseng, C. H. (2019). **"Metformin and risk of chronic obstructive pulmonary disease in diabetes patients."** Diabetes Metab **45**(2): 184-190.

PURPOSE: This study aimed to investigate whether metformin can affect risk of chronic obstructive pulmonary disease (COPD) in type 2 diabetes (T2D) patients. METHODS: T2D patients newly diagnosed during 1999-2005 were enrolled from the reimbursement database of Taiwan's National Health Insurance system and followed up to 31 December 2011. Analyses were conducted in an unmatched cohort (92,272 ever-users and 10,697 never-users of metformin) and a propensity score (PS) matched pair cohort (10,697 ever-users and 10,697 never-users). Cox regression incorporated into the inverse probability of treatment weighting using the PS was used to estimate hazard ratios (HRs). RESULTS: In the unmatched cohort, 2573 never-users and 13,840 ever-users developed COPD with respective incidences of 5994.64 and 3393.19 per 100,000 person-years. The overall HR was 0.560 (95% confidence interval [CI]: 0.537-0.584). HRs for the first (<25.27months), second (25.27-55.97months) and third (>55.97months) tertiles of cumulative duration were 1.021 (0.975-1.070), 0.575 (0.548-0.603) and 0.265 (0.252-0.280), respectively. Analyses of the matched cohort showed an overall HR of 0.643 (0.605-0.682), with HRs of 1.212 (1.122-1.309), 0.631 (0.578-0.689) and 0.305 (0.273-0.340) for the respective tertiles. CONCLUSION: A reduced risk of COPD is observed in metformin users with T2D.

Turan Sonmez, F. and R. Eroz (2018). **"The role of argyrophilic nucleolar organizing region-associated proteins in clinical exacerbation of chronic obstructive pulmonary disease."** J Int Med Res **46**(12): 4995-5003.

OBJECTIVE: To investigate whether argyrophilic nucleolar organizing region-associated protein (AgNOR) parameters can be used as a biomarker that could potentially help with the management and clinical prognosis of chronic obstructive pulmonary disease (COPD) exacerbation. METHODS: This case-control study enrolled patients with COPD who were admitted to the Emergency Department and healthy sex- and age-matched control subjects. Peripheral blood samples were collected at hospital admission and the peripheral lymphocytes were silver-stained to investigate the quantity and distribution of AgNOR proteins. Fifty nuclei per patient were viewed and the total AgNOR area/total nuclear area (TAA/TNA) ratio and the mean AgNOR number for each patient were calculated. RESULTS: A total of 20 patients with COPD exacerbation and 17 healthy control subjects were recruited to the study. The TAA/TNA ratio and the mean AgNOR number were significantly higher in the patients with COPD exacerbation compared with the healthy control subjects. The mean AgNOR number showed a positive correlation with the pCO2 levels on admission. CONCLUSION: AgNOR protein levels were elevated during a COPD exacerbation compared with healthy control subjects and there was a positive correlation between pCO2 levels and mean AgNOR number.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6300929/pdf/10.1177_0300060518788751.pdf

Turcotte, D. A., S. Woskie, et al. (2019). **"Asthma, COPD, and home environments: Interventions with older adults."** Ann Allergy Asthma ImmunolBACKGROUND: We describe a multifaceted home environmental intervention project involving low-income older adults with asthma who have a greater risk of asthma-related respiratory impacts because they spend up to 90% of their time in the home where many allergens and respiratory irritants are found. Although sufficient evidence suggests that home interventions are effective in improving health of children with asthma, the Task Force on Community Preventive Services has stated that evidence is insufficient for the effectiveness of home interventions on adults with asthma. OBJECTIVE: To evaluate the hypothesis that multifaceted home environmental interventions improve the respiratory health and reduce asthma triggers for older adults with asthma. METHODS: We conducted community health worker-led interventions in the homes of 86 low-income older adults (age 62 or older) diagnosed with asthma, residing in public and private subsidized housing in Lowell, Massachusetts, from 2014 to 2017. Health and environmental assessment at baseline and follow-up 1 year later included collecting data on respiratory health, quality of life, medication use, doctor/emergency room/hospital visits, using the St. George Respiratory Questionnaire and Asthma Control Test and evaluation of asthma trigger activities and exposures through questionnaires and home surveys. Interventions included education on asthma and environmental triggers and environmental remediation. RESULTS: Statistically significant reductions in self-reported environmental asthma triggers and health improvements were found in the following areas: doctor visits, use of antibiotics for chest problems, respiratory symptoms and quality of life indicators, and asthma control (ACT score). CONCLUSION: Our results provide evidence that multifaceted home interventions are effective in improving the environmental quality and respiratory health of an older adult population with asthma.

https://www.annallergy.org/article/S1081-1206(19)30142-5/fulltext

Uemasu, K., S. Sato, et al. (2019). **"Annual decline in arterial blood oxygen predicts development of chronic respiratory failure in COPD with mild hypoxaemia: A 6-year follow-up study."** Respirology **24**(3): 262-269.

BACKGROUND AND OBJECTIVE: Chronic respiratory failure (CRF) with hypoxaemia is an important pathophysiology in patients with chronic obstructive pulmonary disease (COPD), and existing mild hypoxaemia may be a sign of future CRF development. However, little is known about the trajectory of partial arterial pressure of oxygen (PaO2) decline in patients with COPD. We assessed decline in PaO2 and the impact of short-term reductions in PaO2 to predict future decline in PaO2 . METHODS: A total of 172 outpatients with COPD from a prospective cohort study were enrolled. Pulmonary function tests and arterial blood gas (ABG) analyses were conducted at baseline and 1 year after enrolment and changes in PaO2 (DeltaPaO2) and other parameters were calculated. Survival and incidence of CRF (as assessed by prescription of long-term home oxygen therapy) were monitored for 6 years. RESULTS: A total of 164 patients completed the observation period and 101 patients had mild hypoxaemia (PaO2 < 80 Torr) at baseline. No patients with normal PaO2 (>/=80 Torr) developed CRF, and 10 patients with mild hypoxaemia developed CRF in 6 years. Baseline airflow limitation and diffusion capacity were significantly associated with development of CRF. Receiver-operating characteristic curve analysis showed that DeltaPaO2 of -3.05 Torr/year is a useful cut-off value to predict development of CRF in 6 years (hazard ratio (HR): 12.6, 95% CI: 3.48-58.73, P < 0.0001). CONCLUSION: Patients with COPD and mild hypoxaemia may benefit from repeat ABG after 1 year. Although PaO2 trajectories widely varied, significant annual changes in PaO2 of at least -3.0 Torr/year were predictive of CRF development.

https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13402

van Beers, M., D. J. A. Janssen, et al. (2018). **"Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions."** Expert Rev Respir Med: 1-14.

INTRODUCTION: Cognitive impairment (CI) is an important but an under-recognized extra-pulmonary feature of chronic obstructive pulmonary disease (COPD). It is related to the burden of disability, worse health outcomes, and impaired self-management. Areas covered: CI includes deterioration of a wide range of cognitive functions, such as memory and various executive functions. Risk of hospitalization might be higher in patients with COPD compared to those without, with CI negatively impacting the wellbeing of patients with COPD. Disease-specific factors such as hypoxemia and inflammation, lifestyle factors such as dietary insufficiencies and lack of physical activity, and comorbidities such as obstructive sleep apnea and depression are likely to synergistically contribute to the development of CI in COPD. Tailored interventions can possibly improve CI in COPD, but this needs further investigation. Expert commentary: Further research is warranted involving the optimization of neuropsychological testing for screening and outcome assessment, longitudinal studies to investigate the development of CI in COPD over time, and randomized clinical trials to test the feasibility and efficacy of promising interventions.

https://www.tandfonline.com/doi/full/10.1080/17476348.2018.1533405

van Beers, M., M. Rutten-van Molken, et al. (2019). **"Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: The randomized controlled NUTRAIN trial."** Clin NutrBACKGROUND AND AIMS: The efficacy of nutritional intervention to enhance short- and long-term outcomes of pulmonary rehabilitation in COPD is still unclear, hence this paper aims to investigate the clinical outcome and cost-effectiveness of a 12-month nutritional intervention strategy in muscle-wasted COPD patients. METHODS: Prior to a 4-month pulmonary rehabilitation programme, 81 muscle-wasted COPD patients (51% males, aged 62.5 +/- 0.9 years) with moderate airflow obstruction (FEV1 55.1 +/- 2.2% predicted) and impaired exercise capacity (Wmax 63.5 +/- 2.4% predicted) were randomized to 3 portions of nutritional supplementation per day (enriched with leucine, vitamin D and polyunsaturated fatty acids) [NUTRITION] or PLACEBO (phase 1). In the unblinded 8-month maintenance phase (phase 2), both groups received structured feedback on their physical activity level assessed by accelerometry. NUTRITION additionally received 1 portion of supplemental nutrition per day and motivational interviewing-based nutritional counselling. A 3-month follow-up (phase 3) was included. RESULTS: After 12 months, physical capacity measured by quadriceps muscle strength and cycle endurance time were not different, but physical activity was higher in NUTRITION than in PLACEBO (Delta1030 steps/day, $p = 0.025$). Plasma levels of the enriched nutrients ($p < 0.001$) were higher in NUTRITION than PLACEBO. Trends towards weight gain in NUTRITION and weight loss in PLACEBO led to a significant between-group difference after 12 months (Delta1.54 kg, $p = 0.041$). The HADS anxiety and depression scores improved in NUTRITION only (Delta-1.92 points, $p = 0.037$). Generic quality of life (EQ-5D) was decreased in PLACEBO but not in NUTRITION (between-group difference after 15 months 0.072 points, $p = 0.009$). Overall motivation towards exercising and healthy eating was high and did not change significantly after 12 months; only amotivation towards healthy eating yielded a significant between-group difference (Delta1.022 points, $p = 0.015$). The cost per quality-adjusted life-year after 15 months was EUR 16,750. CONCLUSIONS: Nutritional intervention in muscle-wasted patients with moderate COPD does not enhance long-term outcome of exercise training on physical capacity but ameliorates plasma levels of the supplemented nutrients, total body weight, physical activity and generic health status, at an acceptable increase of costs for patients with high disease burden.

https://www.clinicalnutritionjournal.com/article/S0261-5614(19)30114-1/pdf

van Dam van Isselt, E. F., M. van Eijk, et al. (2019). **"A Prospective Cohort Study on the Effects of Geriatric Rehabilitation Following Acute Exacerbations of COPD."** J Am Med Dir AssocOBJECTIVES: Older patients with chronic obstructive pulmonary disease (COPD), hospitalized for an acute exacerbation,

often do not receive recommended post-acute pulmonary rehabilitation. This underuse might be related to the impaired clinical and functional status of these patients, who are more likely to present with frailty, comorbidities, and disability. Having developed and implemented a geriatric rehabilitation program for these patients (GR_COPD), the primary aim of this study was to investigate the effectiveness of this program. DESIGN AND INTERVENTION: A prospective cohort study with a 3-month follow-up period. Patients who declined the GR_COPD program were considered as controls. SETTING AND PARTICIPANTS: The study was conducted at the pulmonary department of 2 hospitals. Patients were eligible when hospitalized as a result of an acute exacerbation of COPD and indicated for the GR_COPD program based on standardized criteria. METHODS: Primary outcome was defined as change in disease-specific health status measured with the clinical COPD questionnaire (CCQ), secondary outcome as the exacerbation rate ratio during follow-up. To balance potential confounders between the intervention and control group, propensity score-based weighted linear regression analyses were performed. RESULTS: Of the 158 included patients [78 (49.4%) male, mean age 70.8 (+/-8.1) years, mean forced expiratory volume in 1 second: 35.5 (+/-12.8) as % of predicted], 78 received the GR_COPD program. The results of the CCQ showed a significant and clinically relevant treatment effect of -0.56 points [95% confidence interval (CI) -0.89, -0.23; P = .001). Patients in the control group had 2.77 times more exacerbations compared with the intervention group (95% CI 2.13, 3.58; P < .001). CONCLUSIONS/IMPLICATIONS: This study shows a clinically relevant effect of the GR_COPD program on disease-specific health status and exacerbation rate. Implementation of the program for older patients with severe COPD hospitalized for an acute exacerbation is recommended.

https://www.jamda.com/article/S1525-8610(19)30251-8/fulltext

Van de Moortele, T., U. Goerke, et al. (2017). **"Airway morphology and inspiratory flow features in the early stages of Chronic Obstructive Pulmonary Disease."** Clin Biomech (Bristol, Avon)BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of death worldwide. Inhaled pollutants are the prime risk factor, but the pathogenesis and progression of the diseased is poorly understood. Most studies on the disease onset and trajectory have focused on genetic and molecular biomarkers. Here we investigate the role of the airway anatomy and the consequent respiratory fluid mechanics on the development of COPD. METHODS: We segmented CT scans from a five-year longitudinal study in three groups of smokers (18 subjects each) having: (i) minimal/mild obstruction at baseline with declining lung function at year five; (ii) minimal/mild obstruction at baseline with stable function, and (iii) normal and stable lung function over the five year period. We reconstructed the bronchial trees up to the 7th generation, and for one subject in each group we performed MRI velocimetry in 3D printed models. FINDINGS: The subjects with airflow obstruction at baseline have smaller airway diameters, smaller child-to-parent diameter ratios, larger length-to-diameter ratios, and smaller fractal dimensions. The differences are more significant for subjects that develop severe decline in pulmonary function. The secondary flows that characterize lateral dispersion along the airways are found to be less intense in the subjects with airflow obstruction. INTERPRETATION: These results indicate that morphology of the conducting airways and inspiratory flow features are correlated with the status and progression of COPD already at an early stage of the disease. This suggests that imaging-based biomarkers may allow a pre-symptomatic diagnosis of disease progression.

https://www.clinbiomech.com/article/S0268-0033(17)30286-3/fulltext

van der Does, A. M., M. Heijink, et al. (2019). **"Dynamic differences in dietary polyunsaturated fatty acid metabolism in sputum of COPD patients and controls."** Biochim Biophys Acta Mol Cell Biol Lipids **1864**(3): 224-233.

INTRODUCTION: Disturbances in onset and resolution of inflammation in chronic obstructive pulmonary disease (COPD) are incompletely understood. Dietary polyunsaturated fatty acids (PUFAs) can be converted into lipid mediators here collectively named oxylipins. These include classical eicosanoids, but also pro-resolving mediators. A balanced production of pro-inflammatory and pro-resolving oxylipins is of

importance for adequate inflammatory responses and subsequent return to homeostasis. OBJECTIVES: Here we investigated if PUFA metabolism is disturbed in COPD patients. METHODS: Free PUFA and oxylipin levels were measured in induced sputum samples from the Bergen COPD cohort and COPD exacerbation study using liquid chromatography-mass spectrometry. Additionally, effects of whole cigarette smoke on PUFA metabolism in air-liquid interface cultures of primary bronchial epithelial cells were assessed. RESULTS: Significantly lower levels of free alpha-linolenic acid, linoleic acid and eicosapentaenoic acid (EPA) were detected in sputum from stable COPD patients compared to controls. During acute exacerbation (AE), levels of free arachidonic acid and docosapentaenoic acid were higher than in stable COPD patients. Furthermore, levels of omega-3 EPA- and docosahexaenoic acid-derived oxylipins were lower in sputum from stable COPD patients compared to controls. Cyclooxygenase-2-converted mediators were mostly increased during AE. In vitro studies additionally showed that cigarette smoke exposure may also directly contribute to altered epithelial PUFA metabolism, and indirectly by causing airway epithelial remodelling. CONCLUSIONS: Our findings show significant differences in PUFA metabolism in COPD patients compared to controls, further changed during AE. Airway epithelial remodelling may contribute to these changes. These findings provide new insight in impaired inflammatory resolution in COPD.

https://www.sciencedirect.com/science/article/pii/S1388198118303688?via%3Dihub

van der Leest, S. and M. L. Duiverman (2019). **"High-intensity non-invasive ventilation in stable hypercapnic COPD: Evidence of efficacy and practical advice."** Respirology **24**(4): 318-328.

Patients with end-stage chronic obstructive pulmonary disease (COPD) frequently develop chronic hypercapnic respiratory failure (CHRF), with disabling symptoms and poor survival. The use of long-term nocturnal non-invasive ventilation (NIV) to treat CHRF in COPD has long been subject of debate due to conflicting evidence. However, since the introduction of high-intensity NIV (HI-NIV) in COPD, physiological and clinical benefits have been shown. HI-NIV refers to specific ventilator settings used for NIV aimed at achieving normocapnia or the lowest partial arterial carbon dioxide pressure ($PaCO_2$) values as possible. This review will provide an overview of existing evidence of the efficacy of HI-NIV stable COPD patients with CHRF. Secondly, we will discuss hypotheses underlying NIV benefit in stable hypercapnic COPD, providing insight into better patient selection and hopefully more individually titrated HI-NIV. Finally, we will provide practical advice on how to initiate and follow-up patients on HI-NIV, with special emphasis on monitoring that should be available during the initiation and follow-up of HI-NIV, and will discuss more extended monitoring techniques that could improve HI-NIV treatment in the future.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/resp.13450

van der Plas, A. G. M., M. G. Oosterveld-Vlug, et al. (2018). **"Continuity of GP care after the last hospitalization for patients who died from cancer, chronic obstructive pulmonary disease or heart failure: a retrospective cohort study using administrative data."** Fam PractBackground: Discharge from hospital to home can be a stressful experience for patients and carers. Contact with the GP is important to ensure continuity of care. Objectives: To investigate timing of contact with the GP and locum after the last hospitalization in the last year of life and to investigate patient and care characteristics related to contact with the GP within 2 days after discharge. Methods: Health insurance data were combined with data from Statistics Netherlands on patients who mainly received care at home in the last 4 months of life. Patients who died from cancer (n = 3014), chronic obstructive pulmonary disease (COPD, n = 195) or heart failure (n = 171) were compared. Results: First contact after hospital discharge was within 2 days for 51.7% of patients and within a week for 77.8% of patients. Patients who died from COPD or heart failure had contact less often than patients with cancer. Characteristics related to having contact within 2 days after discharge were older age, cause of death cancer, home death, timing of last hospitalization closer to death and contact with a locum in the week after discharge. Conclusion: Results may indicate that the GP is likely to visit patients with more care needs sooner. This would be in accordance with the finding that contact with the GP was more likely after a hospitalization closer to death and that contact

within 2 days was related to contact with a locum within a week after discharge. Proactive care is necessary. This is a joint responsibility of GPs and medical specialists.

https://academic.oup.com/fampra/advance-article-abstract/doi/10.1093/fampra/cmy065/5047161?redirectedFrom=fulltext

Vaughan, A., S. Stevanovic, et al. (2019). **"The effect of diesel emission exposure on primary human bronchial epithelial cells from a COPD cohort: N-acetylcysteine as a potential protective intervention."** Environ Res **170**: 194-202.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) will be the third leading cause of death world-wide by 2020. Prolonged exposure to particulate matter is associated with COPD progression and mortality. Diesel emissions are a major contributor to particulate matter pollution. In this study we test a therapeutic antioxidant, N-acetylcysteine (NAC), for its ability to protect bronchial epithelial cells (pHBECs) from patients with COPD from adverse effects of diesel emission exposure. METHODS: pHBECs from patients with or without COPD were cultured at air-liquid interface (ALI). Cells were exposed to diesel emissions for 30min with or without 3-h post-exposure treatment with 5mM N-acetylcysteine (NAC). Filtered laboratory air was tested as a negative control. Cell responses (cell viability, inflammation and oxidative stress) and gene expression profiles for intracellular and immune signaling were assessed. RESULTS: Diesel emissions exposure increased IL-8 secretion and production, antioxidant production, and cytochrome P450 1a1 (CYP1a1) mRNA expression and suppressed superoxide dismutase-1 (SOD1) mRNA expression in bronchial epithelial cells from COPD patients. Treatment with N-acetyl cysteine attenuated the suppression of SOD1. Nanostring gene expression profiling of the filtered air controls showed COPD epithelial cells have increased expression of MHC class II and an interferon signaling profile. CONCLUSIONS: This study indicates that bronchial epithelial cells from COPD patients may be vulnerable to diesel emission exposure due to reduced antioxidant capacity, and elevated CYP1a1 mRNA expression. NAC did not appear to offer protection. Future research will be needed to explore other means of recovering oxidant capacity in COPD airways.

von Siemens, S. M., R. A. Jorres, et al. (2019). **"Effect of COPD severity and comorbidities on the result of the PHQ-9 tool for the diagnosis of depression: results from the COSYCONET cohort study."** Respir Res **20**(1): 30.

The diagnosis of depression, a frequent comorbidity of chronic obstructive pulmonary disease (COPD), is often supported by questionnaires, such as the Patient Health Questionnaire 9 (PHQ-9). It is unknown to which extent its single questions are affected by the clinical characteristics of COPD patients.We addressed this question in 2255 GOLD grade 1-4 patients from the COSYCONET (COPD and Systemic Consequences - Comorbidities Network) COPD cohort. The dependence on COPD severity was assessed using symptoms, exacerbation risk (GOLD A-D; modified Medical Research Council dyspnoea scale (mMRC)), and frequent comorbidities as predictors of PHQ-9 results, while including age, gender, body mass index (BMI) and smoking habits as covariates.Symptoms and exacerbation risk were associated with depression in an additive manner, with mean elevations in the PHQ-9 sum score by 2.75 and 1.44 points, respectively. Asthma, sleep apnoea, gastrointestinal disorders, osteoporosis and arthritis were linked to increases by 0.8 to 1.3 points. Overall, the COPD characteristics contributed to the mean PHQ-9 score by increases from 4.5 or 5.2 to 6.3 points, respectively, when either taking GOLD A as reference or the absence of comorbidities. This finding was independent of the diagnosis of mental disorder or the intake of antidepressants. The presence of COPD led to an increase in the proportion of scores indicating depression from 12 to 22%. Single item analysis revealed homogenous effects regarding GOLD groups, but heterogeneous effects regarding GOLD grades.These findings indicate specific effects of COPD severity on the PHQ-9 depression score, especially symptoms and exacerbation risk, explaining the high prevalence of depression in COPD. Alternative explanations like an overlap of COPD severity and PHQ-9 items are discussed. Of note, we also found COPD treatment effects on depression scores.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6371561/pdf/12931_2019_Article_997.pdf

Wang, J. and B. Cao (2019). **"Procalcitonin and other markers to guide antibiotic use in chronic obstructive pulmonary disease exacerbations in the era of antimicrobial resistance."** Curr Opin Pulm Med **25**(2): 158-164.

PURPOSE OF REVIEW: This review summarizes the latest discoveries regarding the use of clinical indicators and biomarkers to guide antibiotic use in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and it analyzes the advantages and disadvantages of various indicators and markers. RECENT FINDINGS: For AECOPD patients admitted to emergency departments and medical wards, procalcitonin (PCT)-guided antibiotic therapy reduced antibiotic use without adverse outcomes. In contrast, for severe AECOPD patients admitted to ICUs, PCT-guided antibiotic therapy increased the overall mortality in a 3-month follow-up period, and antibiotic use was not decreased. SUMMARY: PCT is the most promising biomarker to guide antibiotic use in patients with AECOPD. However, patients with severe AECOPD admitted in ICU may not benefit from PCT-guided antibiotic therapy.

Wang, W. H., C. C. Cheng, et al. (2019). **"Improving outcomes in chronic obstructive pulmonary disease by taking beta-blockers after acute myocardial infarction: a nationwide observational study."** Heart Vesselsbeta-Blockers are a standard therapy for acute myocardial infarction (AMI) due to their better short-term and long-term outcomes. However, beta-blockers are often under-prescribed in chronic obstructive pulmonary disease (COPD) patients with AMI, since they are thought be related to bronchospasm. The aim of this study was to investigate the association between the usage of beta-blockers and the risk of mortality in COPD patients after first AMI via a nationwide, population-based cohort study. In this retrospective study, we identified 186,326 patients with AMI diagnosed between January 2000 and December 2012, 23,116 of whom had COPD, from the National Health Insurance Research Database. A total of 7609 patients (32.92%) were prescribed beta-blockers, while 15,507 were not. The beta-blocker patients were stratified into selective and non-selective beta-blocker groups. Multivariate Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) with 95% confidence intervals (95% CI). Selective beta-blocker use showed a reduced risk of mortality, as compared with patients without beta-blockers (HR 0.93; 95% CI 0.89-0.98; $p < 0.01$) while non-selective beta-blocker groups did not increase the risk of mortality compared to the patients without beta-blockers (HR 0.98; 95% CI 0.94-1.02; $p = 0.38$). In addition, the use of beta-blockers was found to be associated with a reduced risk of mortality in most stratified analyses which was seen particularly in males, patients aged 65 years and above, and in individuals with an array of comorbidities. These findings suggest that beta-blockers improve overall survival among COPD patients after first AMI.

https://link.springer.com/article/10.1007%2Fs00380-019-01341-0

Wells, J. M., M. M. Parker, et al. (2018). **"Elevated circulating MMP-9 is linked to increased COPD exacerbation risk in SPIROMICS and COPDGene."** JCI Insight **3**(22)BACKGROUND: Matrix metalloprotease 9 (MMP-9) is associated with inflammation and lung remodeling in chronic obstructive pulmonary disease (COPD). We hypothesized that elevated circulating MMP-9 represents a potentially novel biomarker that identifies a subset of individuals with COPD with an inflammatory phenotype who are at increased risk for acute exacerbation (AECOPD). METHODS: We analyzed Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) and Genetic Epidemiology of COPD (COPDGene) cohorts for which baseline and prospective data were available. Elevated MMP-9 was defined based on >95th percentile plasma values from control (non-COPD) sample in SPIROMICS. COPD subjects were classified

as having elevated or nonelevated MMP-9. Logistic, Poisson, and Kaplan-Meier analyses were used to identify associations with prospective AECOPD in both cohorts. RESULTS: Elevated MMP-9 was present in 95/1,053 (9%) of SPIROMICS and 41/140 (29%) of COPDGene participants with COPD. COPD subjects with elevated MMP-9 had a 13%-16% increased absolute risk for AECOPD and a higher median (interquartile range; IQR) annual AECOPD rate (0.33 [0-0.74] versus 0 [0-0.80] events/year and 0.9 [0.5-2] versus 0.5 [0-1.4] events/year for SPIROMICS and COPDGene, respectively). In adjusted models within each cohort, elevated MMP-9 was associated with increased odds (odds ratio [OR], 1.71; 95%CI, 1.00-2.90; and OR, 3.03; 95%CI, 1.02-9.01), frequency (incidence rate ratio [IRR], 1.45; 95%CI, 1.23-1.7; and IRR, 1.24; 95%CI, 1.03-1.49), and shorter time-to-first AECOPD (21.7 versus 31.7 months and 14 versus 21 months) in SPIROMICS and COPDGene, respectively. CONCLUSIONS: Elevated MMP-9 was independently associated with AECOPD risk in 2 well-characterized COPD cohorts. These findings provide evidence for MMP-9 as a prognostic biomarker and potential therapeutic target in COPD. TRIAL REGISTRATION: ClinicalTrials.gov: NCT01969344 (SPIROMICS) and NCT00608764 (COPDGene). FUNDING: This work was funded by K08 HL123940 to JMW; R01HL124233 to PJC; Merit Review I01 CX000911 to JLC; R01 (R01HL102371, R01HL126596) and VA Merit (I01BX001756) to AG. SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) is funded by contracts from the NHLBI (HHSN268200900013C, HHSN268200900014C,HHSN268200900015C HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, and HHSN268200900020C) and a grant from the NIH/NHLBI (U01 HL137880), and supplemented by contributions made through the Foundation for the NIH and the COPD Foundation from AstraZeneca/MedImmune; Bayer; Bellerophon Therapeutics; Boehringer-Ingelheim Pharmaceuticals Inc.; Chiesi Farmaceutici; Forest Research Institute Inc.; GlaxoSmithKline; Grifols Therapeutics Inc.; Ikaria Inc.; Novartis Pharmaceuticals Corporation; Nycomed GmbH; ProterixBio; Regeneron Pharmaceuticals Inc.; Sanofi; Sunovion; Takeda Pharmaceutical Company; and Theravance Biopharma and Mylan. COPDGene is funded by the NHLBI (R01 HL089897 and R01 HL089856) and by the COPD Foundation through contributions made to an Industry Advisory Board composed of AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, Siemens, and Sunovion.

https://df6sxcketz7bb.cloudfront.net/manuscripts/123000/123614/jci.insight.123614.v1.pdf

Wong, E. K. C., P. C. S. Lee, et al. (2018). **"Role of venous blood gases in hypercapnic respiratory failure chronic obstructive pulmonary disease patients presenting to the emergency department."** Intern Med JBACKGROUND: Many patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have type 2 respiratory failure. Often arterial blood gases (ABG) are not performed and correlation with venous blood gases (VBG) is controversial. The venous pH and bicarbonate ($HCO3^-$) are useful,(1) but VBG $PCO2$ ($PvCO2$) is considered too unpredictable. We examined the utility of VBGs in this cohort of patients. PATIENTS AND METHODS: A prospective study of AECOPD patients with type 2 respiratory failure presenting to ED was performed. Patients being considered for non-invasive ventilation (NIV) and who required an ABG were invited to participate. A subsequent VBG was also taken and Bland Altman plots were used for analysis. RESULTS: Sixty-three patients were included in this study. The limits of agreement for pH and $HCO3^-$ were narrow. Wider limits of agreement with a systematic bias of 7.7mmHg were noted with $pCO2$. CONCLUSIONS: The utility of VBG pH and $HCO3^-$ was again demonstrated. VBG $pCO2$ in this cohort of patients may have a role in the assessment of AECOPD patients. Further study is needed on the possible role of VBGs in the management of such patients with type 2 respiratory failure particularly those using NIV.

https://onlinelibrary.wiley.com/doi/abs/10.1111/imj.14186

Xia, C., M. Rook, et al. (2019). **"Early imaging biomarkers of lung cancer, COPD and coronary artery disease in the general population: rationale and design of the ImaLife (Imaging in Lifelines) Study."** Eur J EpidemiolLung cancer, chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD)

are expected to cause most deaths by 2050. State-of-the-art computed tomography (CT) allows early detection of lung cancer and simultaneous evaluation of imaging biomarkers for the early stages of COPD, based on pulmonary density and bronchial wall thickness, and of CAD, based on the coronary artery calcium score (CACS), at low radiation dose. To determine cut-off values for positive tests for elevated risk and presence of disease is one of the major tasks before considering implementation of CT screening in a general population. The ImaLife (Imaging in Lifelines) study, embedded in the Lifelines study, is designed to establish the reference values of the imaging biomarkers for the big three diseases in a well-defined general population aged 45 years and older. In total, 12,000 participants will undergo CACS and chest acquisitions with latest CT technology. The estimated percentage of individuals with lung nodules needing further workup is around 1-2%. Given the around 10% prevalence of COPD and CAD in the general population, the expected number of COPD and CAD is around 1000 each. So far, nearly 4000 participants have been included. The ImaLife study will allow differentiation between normal aging of the pulmonary and cardiovascular system and early stages of the big three diseases based on low-dose CT imaging. This information can be finally integrated into personalized precision health strategies in the general population.

https://link.springer.com/content/pdf/10.1007%2Fs10654-019-00519-0.pdf

Xiao, X., H. Han, et al. (2019). **"Prevalence of Atrial Fibrillation in Hospital Encounters With End-Stage COPD on Home Oxygen: National Trends in the United States."** ChestBACKGROUND: This study aimed to evaluate the prevalence of atrial fibrillation (AF) in hospital encounters with end-stage COPD on home oxygen admitted for COPD exacerbation. METHODS: We used the 2003 to 2014 Nationwide Inpatient Sample to conduct a retrospective analysis. This study included all patients >/= 18 years of age with a primary diagnosis of COPD on home oxygen who were hospitalized for COPD exacerbation. We used multivariate-adjusted models to evaluate the association of AF with clinical factors, cost, length of stay, and hospital outcomes. RESULTS: In total, 1,345,270 patients were included; of these, 244,488 (18.2%) had AF. The AF prevalence increased from 12.9% in 2003 to 21.3% in 2014 (P < .0001) and varied by age, sex, race, income, insurance type, and hospital region. Advancing age, female sex, white race, high income, and large hospital size were associated with increased odds of AF. Presence of AF was a risk predictor for in-hospital death (OR, 1.54; 95% CI, 1.45-1.65), acute respiratory failure (OR, 1.09; 95% CI, 1.06-1.12), invasive mechanical ventilation (OR, 1.37; 95% CI, 1.29-1.47), noninvasive mechanical ventilation (OR, 1.14; 95% CI, 1.09-1.18), acute kidney injury (OR, 1.09; 95% CI, 1.04-1.13), sepsis (OR, 1.23; 95% CI, 1.10-1.37), and stroke (OR, 1.80; 95% CI, 1.40-2.32). AF was also associated with increased cost and length of stay. CONCLUSIONS: AF prevalence in hospital encounters with end-stage COPD increased from 2003 to 2014. Better management strategies for patients with end-stage COPD comorbid with AF are needed, especially in elderly individuals.

https://journal.chestnet.org/article/S0012-3692(19)30029-7/fulltext

Xie, F. and L. Xie (2019). **"COPD and the risk of mild cognitive impairment and dementia: a cohort study based on the Chinese Longitudinal Health Longevity Survey."** Int J Chron Obstruct Pulmon Dis **14**: 403-408.

Background: COPD may lead to cognitive impairment or even dementia. However, the current conclusions are inconsistent with little evidence from prospective, large-sample studies. This study was designed to explore the association of COPD with mild cognitive impairment (MCI) and dementia risk based on a cohort study. Patients and methods: All participants were from the Chinese Longitudinal Health Longevity Survey (CLHLS) 2011/2012 waves. The follow-up survey was conducted in 2014 and the incidence of MCI and dementia were recorded. Results: During the 3-year follow-up period, 712 new cases of MCI and 83 new cases of dementia were diagnosed. The incidence of MCI and dementia were higher in those with COPD than those without COPD at baseline. Cox analysis showed that the HRs of COPD for MCI and dementia incidence were 1.486 (95% CI: 1.207-1.855) and 1.896 (95% CI: 1.079-3.330), respectively after adjusting for related covariates. For different baseline smoking status, those who were

current smokers had the highest HRs of COPD for MCI and dementia. Conclusion: Baseline COPD was independently associated with increased risk of MCI and dementia incidence among Chinese elderly, and the association was more pronounced among those who were current smokers.

https://www.dovepress.com/getfile.php?fileID=48022

Xie, J., F. Li, et al. (2018). **"Prevalence of pulmonary embolism in patients with obstructive sleep apnea and chronic obstructive pulmonary disease: The overlap syndrome."** Heart LungOBJECTIVE: Growing evidence indicates that both obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) may be closely associated with the prevalence of pulmonary embolism (PE). However, the relationship of overlap syndrome (OS) (coexistence of OSA and COPD) with PE is unclear. The purpose of this study was to investigate whether OS were associated with increased PE prevalence. METHODS: We performed a retrospective chart review of patients who underwent sleep study at Beijing An Zhen Hospital from 2011 to 2014. The association of OS with PE prevalence was estimated by using logistic regression models. RESULTS: In contrast to control patients (neither OSA nor COPD), those subjects with OS had higher odds of PE (OR9.61; 95%CI 4.02-21.31, p<0.001) with significance persisting after adjusting for covariates (OR 5.66; 95%CI 1.80-16.18, p=0.004). Meanwhile, patients with OS compared with those with isolated OSA also had significantly higher odds of PE in univariate (OR 4.79; 95%CI 2.04-10.33, p=0.0007) and adjusted models (OR 3.89; 95%CI 1.27-10.68, p=0.019). In subgroup analysis, patients with OS had higher odds of PE than control group among male subjects (OR 8.12, 95%CI1.86-31.87, p=0.007) and patients>/=58 years (OR 5.50, 95%CI 1.51-18.14, p=0.012) in multivariable models. Percentage of total sleep time with saturation lower than 90% (T90)>/=2.6% was significantly associated with prevalence of PE (OR 4.72, 95%CI1.34-19.83, p=0.015) in subgroup of patients older than 58. CONCLUSIONS: OS is independently associated with PE prevalence. Longitudinal studies are needed to better understand the relationship with incident PE.

https://www.heartandlung.org/article/S0147-9563(18)30275-9/fulltext

Xie, S., P. Yan, et al. (2019). **"Efficacy and safety of Xuebijing injection and its influence on immunomodulation in acute exacerbations of chronic obstructive pulmonary disease: study protocol for a randomized controlled trial."** Trials **20**(1): 136.

BACKGROUND: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the leading cause of mortality in chronic obstructive pulmonary disease (COPD). Traditional Chinese medicine (TCM) has been widely used in Asia as an adjunct treatment for AECOPD to improve the patients' symptoms. Xuebijing (XBJ) injection is one of the major herbal medicines used in TCM. Previous small-sample clinical trials have proven its efficacy and safety in the treatment of AECOPD; however, the current data on XBJ as an adjunct therapy are insufficient. The present study will be a multi-center randomized clinical trial (RCT) to evaluate the efficacy and safety of XBJ injection in AECOPD and explore its influence on the immune function based on the altered levels of T cells. METHODS: This study will be a prospective, randomized, placebo-controlled, blinded, multi-center trial. A total of 300 eligible patients will be randomly assigned to the treatment or placebo control group in a 1:1 ratio using a central randomization system. The treatment group will receive routine medication plus XBJ injection, and the control group will receive routine medication plus 0.9% NaCl injection. The patients will receive the corresponding treatment for 5 days starting within 24 h of enrollment. The primary outcome, the of rate endotracheal intubation, will be evaluated on day 28 after treatment. The secondary outcomes will include changes in immune and inflammatory indicators, respiratory support, mortality rate after 28 days, blood gas analysis, improvement in Acute physiology and chronic health evaluation (APACHE) II scores and clinical symptoms, and the length and cost of intensive care unit stay and hospitalization. The safety of the interventions will be assessed throughout the trial. DISCUSSION: This is the first and largest randomized, controlled, blinded trial that evaluates the efficacy of XBJ injection as adjuvant therapy for AECOPD. The results of this trial will provide valuable clinical evidence for recommendations on the management of the disease and identify the underlying mechanisms. TRIAL REGISTRATION: ClinicalTrials.gov,

NCT02937974 . Registered on 13 October 2016. Chinese clinical trial registry, ChiCTR-IPR-17011667. Registered on 15 June 2017.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6380049/pdf/13063_2019_Article_3204.pdf

Xu, J., Y. Shang, et al. (2019). **"Correlation between lung cancer and the HHIP polymorphisms of chronic obstructive pulmonary disease (COPD) in the Chinese Han population."** Genes Immun **20**(4): 273-280.

To further investigate the relationship between lung cancer and hedgehog interacting protein (HHIP) polymorphisms of chronic obstructive pulmonary disease (COPD) patients, we conducted a case-control study in a Chinese Han population. Six HHIP SNPs with minor allele frequencies >5% (rs1489758, rs1489759, rs10519717, rs13131837, rs1492820, and rs7689420) were analyzed in 1,017 COPD patients (767 males and 246 females) and 430 non-COPD patients. Using logistic regression analysis, we found that rs7689420 was significantly associated with lung cancer in COPD patients in the Chinese Han population ($P < 0.001$). The recessive allele of rs7689420 was associated with the occurrence of lung cancer in all COPD patients (odds ratios [OR] of 0.609 and 0.424 for the CT and TT genotypes, respectively) as well as in serious COPD patients (OR of 0.403 and 0.305 for CT and TT, respectively). Additionally, rs1489759 and rs3131837 were associated with lung cancer in various genetic models. rs1489758, rs1489759, and rs10519717 were also associated with lung cancer in serious COPD patients. However, none of the SNPs were significantly associated with lung cancer in mild COPD patients or healthy subjects. Therefore, the HHIP SNPs of COPD patients likely play a role in lung cancer pathology in the Chinese Han population.

https://www.nature.com/articles/s41435-018-0033-0

Yamaguchi, Y., S. Shiota, et al. (2019). **"Polysomnographic features of low arousal threshold in overlap syndrome involving obstructive sleep apnea and chronic obstructive pulmonary disease."** Sleep BreathPURPOSE: In patients with overlap syndrome (OVS), the pathophysiologies of obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease can interact with one another. Focusing on low arousal threshold, the authors evaluated polysomnographic features of OVS patients. METHODS: This retrospective, multicenter study was conducted at three hospitals in Japan. Patients aged >/= 60 years who underwent polysomnography and pulmonary function testing were reviewed. Severity of airflow limitation (AFL) was classified according to the Global Initiative for Chronic Obstructive Lung Disease criteria. Low arousal threshold was predicted based on the following polysomnography features: lower apnea-hypopnea index (AHI); higher nadir oxygen saturation, and larger hypopnea fraction of total respiratory events. These features were compared among patients with only OSA (n = 126), OVS with mild AFL (n = 16), and OVS with moderate/severe AFL (n = 22). RESULTS: A low arousal threshold was more frequently exhibited by OVS patients with moderate/severe AFL than by those with OSA only (p = 0.016) and OVS with mild AFL (p = 0.026). As forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) decreased in OVS patients, the mean length of apnea decreased (r = 0.388, p = 0.016), hypopnea fractions increased (r = - 0.337, p = 0.039), and AHI decreased (r = 0.424, p = 0.008). FEV1/FVC contributed to low arousal threshold independent of age, sex, smoking history, hospital, or body mass index in all subjects (OR 0.946 [95% CI 0.909-0.984]) and in OVS patients (OR 0.799 [95% CI 0.679-0.940]). CONCLUSIONS: This study first described peculiar polysomnographic features in OVS patients with moderate/severe AFL, suggesting a high prevalence of low arousal threshold.

https://link.springer.com/article/10.1007%2Fs11325-019-01786-7

Ye, L., Y. Zhang, et al. (2019). **"Emphysema quantification on computed tomography and its value in predicting radiation pneumonitis in lung cancer treated by stereotactic body radiotherapy."** J Radiat ResA large portion of patients with early-stage non-small-cell lung cancer (NSCLC) who are receiving stereotactic body radiation therapy (SBRT) are medically inoperable due to compromised pulmonary function, and among these patients pulmonary emphysema (PE) is common. However, the relationship between PE and radiation-induced lung injuries remains unclear. In this study, we aimed to describe the full spectrum of computed tomography (CT) features after SBRT for NSCLC, and to explore their relationship with variables, including PE and dosimetric factors. In all, 71 patients were enrolled. PE was quantified as the percentage of low attenuation area [attenuation values of <-860 Hounsfield units (HU)] within the radiation field (%LAA-860). Spearman's correlation and logistic regression were used to explore factors related to radiological features and radiation pneumonitis (RP). At the 1-year follow-up, acute radiological changes included: (i) diffuse consolidation, 11.3%; (ii) patchy consolidation and ground-glass opacities, 42.3%; and (iii) patchy ground-glass opacity, 14.1%. Late morphological changes occurred in 61.9% of patients (50.7% with a modified conventional pattern, 5.6% with a mass-like pattern and 5.6% with a scar-like pattern). Lower %LAA-860 was the only factor that was significantly associated with consolidation changes at 6 months after SBRT [odds ratio (OR), 0.008; P = 0.009], and it was also a significant predictor for Grade >/= 2 RP (OR, 0.003; P = 0.04). Our study showed that patients with PE can benefit from SBRT on the condition that good control of dose-volume constraints is achieved.

https://watermark.silverchair.com/rrz007.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAmMwggJfBgkqhkiG9w0BBwagggJQMIICTAIBADCCAkUGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMnbe_mTJ8-IM3GQklAgEQgIICFrTv3NYX8nJSsWPr4ogZ3iWoswO1CWR2ZpxqGr47bw1iWfU-Q1rGm777ryf6ZMusDdZudK87VqoWcCluTvEn5r3pu0XEB80b13pg4GbwXcEf7SfTn5ZjeusKT3upKu0Xiia4g6spOP2QSTzSxS0VkXoAcahcsmJ_GMojpmhrZ5QNrkMaZpqp4wLDyCA_NYIYAGX_hGopdJabE5bxj55Dli21Kg5P8pGzDB84bh6VVnYC6PIrL796XKd2KGDRyCNTX_GkBd45zCL_gW-kGtLTojw9p2pz5uWDHV0jy4RynGDzR6PupXu9N36vAac0kZVYJQZdOE-mzvcd2xqUzGJk1KGJ6qSM1vHJsaYsl0MT4qmdKqhwy1NNung2DOS9qbs-A8plO72YmPYNEoSek2tcetLJjKgz6M1Ow--mqE4k5LCF0SMG8bAN_T0-RqXitqzYj_TV1usCONXamC-SFtOzk_-7PhUN9dWJCy6ZMctYIZme0PhypADbg5tkPmytpPvkpVtZs4OzUxgpWpfr45nVMD4E3vD9juw38GD6V1NIPcuqsEk00k3E2KOa-Ld8cFJd2TAXqP8pxoie-A3UqnptE3-ry8OmTJBO15SKNFUsjkmDmyKVCzauC2MiJUgiWT-PaP7tTX4XKhnVfiSEhSn4M3B4KBFlEr1pDzdLAE1oBALQg7ehJUKgHhVU4cKCWk6tjIkwnud0RQ

Yii, A. C. A., C. H. Loh, et al. (2019). **"A clinical prediction model for hospitalized COPD exacerbations based on "treatable traits"."** Int J Chron Obstruct Pulmon Dis **14**: 719-728.

Background: Assessing risk of future exacerbations is an important component in COPD management. History of exacerbation is a strong and independent predictor of future exacerbations, and the criterion of >/=2 nonhospitalized or >/=1 hospitalized exacerbation is often used to identify high-risk patients in whom therapy should be intensified. However, other factors or "treatable traits" also contribute to risk of exacerbation. Objective: The objective of the study was to develop and externally validate a novel clinical prediction model for risk of hospitalized COPD exacerbations based on both exacerbation history and treatable traits. Patients and methods: A total of 237 patients from the COPD Registry of Changi General Hospital, Singapore, aged 75+/-9 years and with mean post-bronchodilator FEV1 60%+/-20% predicted, formed the derivation cohort. Hospitalized exacerbation rate was modeled using zero-inflated negative binomial regression. Calibration was assessed by graphically comparing the agreement between predicted and observed annual hospitalized exacerbation rates. Predictive (discriminative) accuracy of the model for identifying high-risk patients (defined as experiencing >/=1 hospitalized exacerbations) was assessed with area under the curve (AUC) and receiver operating characteristics analyses, and compared to other existing risk indices. We externally validated the prediction model using a multicenter dataset comprising 419 COPD patients. Results: The final model included hospitalized exacerbation rate in the previous year, history of acute invasive/noninvasive ventilation, coronary artery disease, bronchiectasis, and sputum nontuberculous mycobacteria isolation. There was excellent agreement between predicted and observed annual hospitalized exacerbation rates. AUC was 0.789 indicating good discriminative accuracy, and was significantly higher than the AUC of the Global Initiative for Chronic

Obstructive Lung Disease (GOLD) risk assessment criterion (history of >/=1 hospitalized exacerbation in the previous year) and the age, dyspnea, and obstruction index. When applied to the independent multicenter validation cohort, the model was well-calibrated and discrimination was good. Conclusion: We have derived and externally validated a novel risk prediction model for COPD hospitalizations which outperforms several other risk indices. Our model incorporates several treatable traits which can be targeted for intervention to reduce risk of future hospitalized exacerbations.

https://www.dovepress.com/getfile.php?fileID=48767

Yong, P. C., K. Sigel, et al. (2019). **"The effect of radiographic emphysema in assessing lung cancer risk."** ThoraxPURPOSE: Lung cancer risk models optimise screening by identifying subjects at highest risk, but none of them consider emphysema, a risk factor identifiable on baseline screen. Subjects with a negative baseline low-dose CT (LDCT) screen are at lower risk for subsequent diagnosis and may benefit from risk stratification prior to additional screening, thus we investigated the role of radiographic emphysema as an additional predictor of lung cancer diagnosis in participants with negative baseline LDCT screens of the National Lung Screening Trial. METHODS: Our cohorts consist of participants with a negative baseline (T0) LDCT screen (n=16 624) and participants who subsequently had a negative 1-year follow-up (T1) screen (n=14 530). Lung cancer risk scores were calculated using the Bach, PLCOm2012 and Liverpool Lung Project models. Risk of incident lung cancer diagnosis at the end of the study and number screened per incident lung cancer were compared between participants with and without radiographic emphysema. RESULTS: Radiographic emphysema was independently associated with nearly double the hazard of lung cancer diagnosis at both the second (T1) and third (T2) annual LDCT in all three risk models (HR range 1.9-2.0, p<0.001 for all comparisons). The number screened per incident lung cancer was considerably lower in participants with radiographic emphysema (62 vs 28 at T1 and 91 vs 40 at T2). CONCLUSION: Radiographic emphysema is an independent predictor of lung cancer diagnosis and may help guide decisions surrounding further screening for eligible patients.

https://thorax.bmj.com/content/early/2019/02/05/thoraxjnl-2018-212457

Yoshimatsu, Y., K. Tobino, et al. (2019). **"Repetitive saliva swallowing test and water swallowing test may identify a COPD phenotype at high risk of exacerbation."** Clin Respir JINTRODUCTION: Patients with chronic obstructive pulmonary disease (COPD) are known to present with dysphagia from an early stage. Dysphagia leads to swallowing-related complications, in turn leading to COPD exacerbation. Dysphagia screening is recommended; however little is known of its utility in detecting a COPD phenotype at risk for exacerbation. The simple swallowing provocation test (SSPT), considered to be a standard screening test, requires specific equipment, physician skill and patient discomfort. OBJECTIVES: The aim of this study was to find an easier and less invasive measure to screen for dysphagia in patients with COPD. METHODS: We retrospectively reviewed patients with COPD who were screened for dysphagia [Repetitive saliva swallowing test (RSST), water swallowing test (WST), SSPT and a questionnaire] from June to November 2016. The patients were classified into two groups according to the presence of COPD exacerbation in the past 3 years (ie, exacerbation and non-exacerbation group), and the dysphagia screening results were compared between the groups. RESULTS: Of the 80 cases included, 42 had 1 or more exacerbations in the past 3 years (exacerbation group), and 38 had none (non-exacerbation group). Statistically significant differences between the groups were observed in the RSST, and vocal change in the WST ($P < 0.05$). There were no significant differences between the groups in the results of SSPT, COPD stage and other clinical status. CONCLUSIONS: Compared to the SSPT, RSST and WST may be more appropriate screening methods in patients with COPD. A prospective study is necessary for further assessment.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13014

Yu, X. Q., M. H. Wang, et al. (2017). **"Effect of comprehensive therapy based on Chinese medicine patterns on self-efficacy and effectiveness satisfaction in chronic obstructive pulmonary disease patients."** Chin J Integr MedOBJECTIVE: To evaluate the effect of comprehensive therapy based on Chinese medicine (CM) patterns on self-efficacy and satisfaction with its effectiveness in patients with chronic obstructive pulmonary disease (COPD). METHODS: A total of 216 patients were randomly divided into the trial group (n =108) and the control group (n =108) based on the stratified and block randomization design. Patients in the trial group were treated with conventional Western medicine combined with Bufei Jianpi Granules (), Bufei Yishen Granules (), and Yiqi Zishen Granules () according to the CM patterns respectively, and patients in the control group were treated with conventional Western medicine. The COPD Self-Efficacy Scale (CSES) and the Effectiveness Satisfaction Questionnaire for COPD (ESQ-COPD) were employed in a 6-month treatment and in further 6 month follow-up visit. RESULTS: Among the 216 patients, 191 patients (97 in the trial group and 94 in the control group) fully completed the study. After 12-month treatment and follow-up, the mean scores of the trial group all continued to increase over time, which were significantly higher than those of the control group (P <0.05), and the improvement in the following trial group domain: negative affect domain (12.13%), intense emotional arousal domain (12.21%), physical exertion domain (11.72%), weather/environmental domain (13.77%), behavioral risk domain (7.67%) and total score (10.65%). The trial group also exhibited significantly higher mean scores in the ESQ-COPD (P <0.05) and the improvement in the following domain: capacity for life and work domain (30.59%), clinical symptoms domain (53.52%), effect of therapy domain (35.95%), convenience of therapy domain (35.54%), and whole effect domain (52.47%). CONCLUSIONS: Bufei Jianpi Granules, Bufei Yishen Granules and Yiqi Zishen Granules can improve the self-efficacy and satisfaction of COPD patients.

https://link.springer.com/article/10.1007%2Fs11655-017-2417-9

Zhang, X., Y. Guo, et al. (2019). **"A functional variant alters binding of activating protein 1 regulating expression of FGF7 gene associated with chronic obstructive pulmonary disease."** BMC Med Genet **20**(1): 33.

BACKGROUND: Genome-wide association studies (GWASs) of a large cohort of subjects with chronic obstructive pulmonary disease (COPD) have successfully identified multiple risk genes, including fibroblast growth factor 7 (FGF7). However, the underlying molecular mechanism influencing function of FGF7 and risk of COPD remains further study. METHODS: In this study, we replicated the genetic association of variants near the FGF7 gene in 258 Chinese Han patients with COPD and 311 healthy controls. Additionally, we functionally evaluated a candidate causal variant upstream of the FGF7 gene. RESULTS: The most significant association was observed at rs12905203 (P = 5.9 x 10(- 3), odd ratio, OR = 1.516) that explains associations of previously reported variants at the FGF7 locus. Electrophoretic mobility shift assay (EMSA) and chromatin immunoprecipitation-quantitative polymerase chain reaction (ChIP-qPCR) assays showed that the risk allele of the variant was bound to activator protein 1 transcription factors (c-Fos and c-Jun) with a significantly reduced affinity and associated with decreased mRNA expression of FGF7 in fibroblast cells at both resting and PMA/Ionomycin-stimulated conditions. Overexpression of c-Fos and c-Jun proteins or stimulation with PMA/Ionomycin significantly increases mRNA expression of FGF7 in fibroblast cells. Bioinformatic analysis showed that the variant overlaps with multiple genetic regulatory marks, suggesting the regulatory DNA element might function as an enhancer for the FGF7 gene. Luciferase enhancer activity assays demonstrated that the DNA sequences carrying the variant produce enhancer activity while the risk allele of the variant reduces its activity. CONCLUSIONS: In this study, we demonstrated a consistent association of the FGF7 gene with COPD and mechanistically characterized a candidate functional variant upstream of the FGF7 gene. These data highlighted the important role of the risk variant and the FGF7 gene in influencing risk for COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6380023/pdf/12881_2019_Article_761.pdf

Zhang, Z., J. Wang, et al. (2019). **"Impacts of event-specific air quality improvements on total hospital admissions and reduced systemic inflammation in COPD patients."** PLoS One **14**(3): e0208687.

There is limited evidence linking the impacts of reduced air pollution on hospital admissions. The potential biological mechanisms are still not completely understood. This study examined the effects of mitigated ambient pollution on hospital admissions and inflammatory biomarker levels in chronic obstructive pulmonary disease (COPD) COPD patients. Daily hospital admissions were compared over 51 days associated with the Asian Games period (Nov 1-Dec 21, 2010) with the identical calendar dates of baseline years (2004-2009 and 2011-2013). A three-year cohort study was conducted with 36 COPD patient participants. The daily particulate matter (PM10) decreased from 65.86 mug/m3 during the baseline period to 62.63 mug/m3 during the Asian Games period; the daily NO2 level decreased from 51.33 mug/m3 to 42.63 mug/m3. Between the baseline period and the Asian Games, daily hospital admissions from non-accidental diseases decreased from 116 to 93, respectively; respiratory diseases decreased from 20 to 17, respectively; and cardiovascular diseases decreased from 11 to 9 during the Asian Games period, respectively. No statistically significant reductions were seen in the remaining months of 2010 in Guangzhou, during the the Asian Games period in the control city, and two other control diseases. Furthermore, we identified significant improvement in CRP and fibrinogen by -20.4% and -15.4% from a pre-Asian game period to a during-Asian game period, respectively. For CRP, we found significant increases in NO2 at lag1-3 days after-Asian game period and significant increases in PM10 at lag1-2 days. Similar effects were also seen with fibrinogen. This discovery provides support for efforts to diminish air pollution and improve public health through human air pollutants intervention. Improved air pollution during the 2010 Asian games was correlated with decreases in biomarkers associated with systemic inflammation in COPD patient participants.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6426198/pdf/pone.0208687.pdf

Zhou, T., Y. Zhong, et al. (2019). **"A prospective study of salvational intervention with ICS/LABA for reducing chronic obstructive pulmonary disease exacerbation under severe air pollution (SIRCAP) in Beijing: protocol of a multi-center randomized controlled trial."** BMC Pulm Med **19**(1): 22.

BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality all over the world. Acute exacerbation of COPD (AECOPD) not only accelerates the progression of disease, but also causes hospital administration and death events. Epidemiologic studies have shown air pollution is a high risk factor of AECOPD. However, there are rare technics or treatment strategies recommended to reduce severe air pollution related AECOPD. METHODS: This is a multi-center, prospective, randomized and standard treatment parallel control clinical trial. Seven hundred sixty-four stable COPD patients in group B, C and D according to GOLD 2017 will be recruited and equally divided into two parallel groups, salvational intervention (SI group) and control group (CT group). Original treatments for participants include tiotropium (18mug once q.d), budesonide/formoterol (160mug/4.5mug once or twice b.i.d) or budesonide/formoterol (160mug/4.5mug once or twice b.i.d) with tiotropium (18mug once q.d). The savational intervention for SI group is routine treatment plus budesonide/formoterol (160mug/4.5mug once b.i.d) from the first day after severe air pollution (air quality index, AQI >/=200) to the third day after AQI < 200. CT group will maintain the original treatment. The intervention will last for 2 years. Primary outcome is the frequency of AECOPD per year and the secondary outcomes include the incidence of unplanned outpatient visits, emergency visits, hospitalization, medical cost and mortality associated with AECOPD per year. DISCUSSION: The salvational intervention is a novel strategy for COPD management under severe air pollution. Results of the present study will provide reference information to guide clinical practice in reducing the air pollution related exacerbation of COPD. TRIAL REGISTRATION: This study has been registered at www.ClinicalTrials.gov (registration identifier: NCT03083067) in 17 March, 2017.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6347780/pdf/12890_2018_Article_771.pdf