COPD/Emphysema PubMed search results covering the period 20/07/2019 – 25/10/19

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 ("2019/07/20"[CDAT] : "3000"[CDAT])

Almagro, P., A. De la Sierra, et al. (2018). **"Spirometrically Confirmed Chronic Obstructive Pulmonary Disease Worsens Long-Term Prognosis after Percutaneous Coronary Intervention."** Am J Respir Crit Care Med **197**(6): 824-826.

Alotaibi, N. M., V. Chen, et al. (2019). **"Phenotyping and outcomes of hospitalized COPD patients using rapid molecular diagnostics on sputum samples."** Int J Chron Obstruct Pulmon Dis **14**: 311-319.

Background: Etiologies of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are heterogeneous. We phenotyped severe AECOPD based on molecular pathogen detection of sputum samples collected at hospitalization of COPD patients and determined their outcomes. Methods: We phenotyped 72 sputum samples of COPD patients who were hospitalized with a primary diagnosis of AECOPD using a molecular array that detected common bacterial and viral respiratory pathogens. Based on these results, the patients were classified into positive or negative pathogen groups. The pathogen-positive group was further divided into virus or bacteria subgroups. Admission day 1 blood samples were assayed for N-terminal prohormone brain natriuretic peptide, CRP, and complete blood counts. Results: A total of 52 patients had a positive result on the array, while 20 patients had no pathogens detected. The most common bacterial pathogen detected was Haemophilus influenzae and the most common virus was rhinovirus. The pathogen-negative group had the worse outcomes with longer hospital stays (median 6.5 vs 5 days for bacteria-positive group, P=0.02) and a trend toward increased 1-year mortality (P=0.052). The bacteria-positive group had the best prognosis, whereas the virus-positive group had outcomes somewhere in between the bacteria-positive and pathogen-negative groups. Conclusion: Molecular diagnostics on sputum can rapidly phenotype serious AECOPD into bacteria-, virus-, or pathogen-negative groups. The bacteria-positive group appears to have the best prognosis, while pathogen-negative group has the worst. These data suggest that AECOPD is a heterogeneous event and that accurate phenotyping of AECOPD may lead to novel management strategies that are personalized and more precise.

https://www.dovepress.com/getfile.php?fileID=47694

Antus, B., C. Paska, et al. (2018). **"Monitoring Antioxidant Enzyme Activity during Exacerbations of Chronic Obstructive Pulmonary Disease."** Copd **15**(5): 496-502.

Superoxide dismutases (SODs) and catalase (CAT) have been implicated as major antioxidant enzymes of the human lungs. In this study, we investigated whether activities of these enzymes are altered in the airways of patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). SOD and CAT activities were measured in the sputum, exhaled breath condensate, and serum of 36 COPD patients experiencing a severe exacerbation. Measurements were performed using colorimetric assays in samples collected at the time of hospital admission and at the time of hospital discharge following treatment of AECOPD. For comparison, antioxidants were also assessed in 24 stable COPD patients and 23 healthy control subjects. SOD and CAT activities in sputum were significantly increased in patients with AECOPD compared to those with stable disease (SOD: 0.142 [0.053-0.81] vs. 0.038 [0.002-0.146] U/mL, $p < 0.01$; CAT: 48.7 [18.7-72.6] vs. 10.2 [2.9-40.6] nmol/min/mL, $p < 0.05$), while treatment of exacerbation led to a decrease in enzyme activities (SOD: 0.094 [0.046-0.45] U/mL, $p < 0.05$; CAT: 28.0 [7.3-60.4] nmol/min/mL, $p < 0.005$). No changes were observed in the serum ($p > 0.05$). Both

SOD and CAT activities significantly correlated with sputum neutrophil and lymphocyte cell counts in patients with AECOPD. Moreover, SOD and CAT values correlated with each other and also with sputum malondialdehyde, an established marker for oxidative stress. Our data demonstrate that sputum antioxidant activity is elevated during COPD exacerbation and suggest that activation of SODs and CAT is an integral part of the human defense mechanism against the increased oxidant production associated with AECOPD.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1535581

Ayora, A. F., L. M. Soler, et al. (2019). **"Analysis of two questionnaires on quality of life of Chronic Obstructive Pulmonary Disease patients."** Rev Lat Am Enfermagem **27**: e3148.

OBJECTIVE: to evaluate the efficacy of quality of life questionnaires St. George Respiratory Questionnaire and Chronic Obstructive Pulmonary Disease Assessment Test in patients with chronic obstructive pulmonary disease based on correlation and agreement analyses, and identify the most effective tool to assess their quality of life. METHOD: cross-sectional cohort study with patients hospitalized in a Spanish hospital for exacerbation of chronic obstructive pulmonary disease. Health-related quality of life was assessed with both questionnaires. The correlation and the agreement between the questionnaires were analyzed, as well as the internal consistency. Associations were established between the clinical variables and the results of the questionnaire. RESULTS: one hundred and fifty-six patients participated in the study. The scales had a correlation and agreement between them and high internal consistency. A higher sensitivity of the Chronic Obstructive Pulmonary Disease Assessment Test was observed for the presence of cough and expectoration. CONCLUSION: the questionnaires have similar reliability and validity to measure the quality of life in patients with acute chronic obstructive pulmonary disease, and the Chronic Obstructive Pulmonary Disease Assessment Test is more sensitive to detect cough and expectoration and requires a shorter time to be completed.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6687364/pdf/0104-1169-rlae-27-e3148.pdf

Barak, O. F., S. Mladinov, et al. (2017). **"Disturbed blood flow worsens endothelial dysfunction in moderate-severe chronic obstructive pulmonary disease."** Sci Rep **7**(1): 16929.

The aims of this study were: (1) to test whether oscillatory shear stress further exacerbates endothelial dysfunction in patients with moderate-severe COPD, and (2) to test whether low flow oxygen administration improves endothelial function and is protective against oscillatory shear stress-induced endothelial dysfunction in patients with moderate-severe COPD. In 17 patients and 10 age-matched non-smoking control subjects we examined brachial artery flow-mediated dilation (FMD) and circulating microparticles before and after 20 minutes of experimentally-induced oscillatory shear stress. COPD patients performed this intervention a second time following a 20-minute wash in period of low flow supplemental oxygen to normalize arterial oxygen saturation. COPD patients had ~six-fold greater baseline retrograde shear rate ($P < 0.05$) and lower FMD ($P < 0.05$). The oscillatory shear stress intervention induced significant decreases in brachial artery FMD of all groups ($P < 0.05$). Oscillatory shear stress elevated circulating markers of endothelial cell apoptosis (CD31+/CD41b- microparticles) in COPD patients, but not age-matched controls. Supplemental oxygen administration abrogated the oscillatory shear stress-induced increase in CD31+/CD41b- microparticles, and improved FMD after accounting for the shear stress stimulus. We have demonstrated that acutely disturbed blood flow with increased retrograde shear stress further deteriorates the already impaired endothelial function with attendant endothelial apoptosis in patients with moderate-severe COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5717042/pdf/41598_2017_Article_17249.pdf

Bianchi, L., M. Bezzi, et al. (2018). **"Additive effect on pulmonary function and disability of intensive pulmonary rehabilitation following bronchoscopy lung volume reduction (BLVR) for severe emphysema."** Respir Med **143**: 116-122.

BACKGROUND: Pulmonary rehabilitation (PR) is mandatory before bronchoscopy lung volume reduction (BLVR); there is scant information about its efficacy post-BLVR. We retrospectively evaluated pulmonary function (PF) and disability in patients pre/post-BLVR and its additive effect on an intensive PR program post-BLVR vs matched non-BLVR controls. We analyzed changes within BLVR patients according to presence or not of atelectasis. METHODS: We compared PF and exercise tolerance (6-min walk test, 6MWT) in 39 BLVR patients (FEV1% pred. 28.9+/-1.5; RV% pred. 236.1+/-7.7) pre-/post-BLVR, and vs. 32 controls (FEV1% pred. 32.7+/-1.5; RV % pred. 217.8+/-8.3) before and after PR. RESULTS: BLVR patients showed a greater improvement than controls in PF (difference between groups: 3.8 for FEV1% pred., p=0.043; -20.5 for RV % pred., p=0.02) and 6MWT response rate (12/39 vs. 1/39 subjects, p=0.003). Both groups further improved significantly 6MWT after PR without a significant difference between groups. Atelectasis after BLVR mainly accounted for the improvement in FEV1% pred, RV% pred. and 6MWT compared to both BLVR without atelectasis and controls. CONCLUSION: BLVR improves PF (particularly RV) and exercise tolerance, patients with lobar exclusion being the best improvers. PR following BLVR yields a further improvement in exercise tolerance in both (atelectasis and non-atelectasis) subgroups.

https://www.resmedjournal.com/article/S0954-6111(18)30288-9/fulltext

Biswas, N. and M. A. Sangma (2019). **"Factors Related to Noninvasive Ventilation Outcomes during an Episode of Hypercapnic Respiratory failure in Chronic Obstructive Pulmonary Disease."** Mymensingh Med J **28**(3): 605-619.

Non invasive ventilation (NIV) plays a vital role in the treatment of an episode of Hypercapnic respiratory failure (HRF) in Chronic obstructive pulmonary disease (COPD) patients. We wanted to investigate the possible effect on NIV outcomes of i) demographic factors, ii) the etiology of an episode of HRF and iii) the overall number and "individual" chronic and acute co-morbidities iv) biochemical parameters in COPD patients ventilated for an episode of HRF. This prospective study of 102(49.29%) COPD patients with HRF were eligible for NIV conducted in Respiratory care unit (RCU) and Intensive care unit (ICU) of National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh from July 2016 to December 2017. Among them 70(68.63%) patients were improved and 32(31.37%) were not improved. On the study, some variables were associated with NIV outcome. On gross difference, two sample Z test had been applied in variables - age ($p<0.01$), mean days hospital stays before introduction of NIV ($p<0.0001$), APACHE II (Acute Physiological And Chronic Health Evaluation II) ($p<0.001$), Charlson co-morbidity index (CCI) ($p=0.0212$), serum albumin ($p<0.001$), PH ($p=0.007$), serum potassium ($p<0.0001$) whereas chi(2) test had been applied in variables - nutritional status ($p<0.01$), pneumonia ($p=0.0003$), dementia ($p=0.0004$), connective tissue disease ($p=0.0094$), mild liver disease ($p=0.0355$), diabetes mellitus with end organ damage ($p=0.017$), renal disease ($p=0.0462$), fibrothorax ($p=0.0422$). Some variables were not associated ($p>0.05$) with NIV outcome- two sample Z test had been done in variables- smoking status, PaO(2) /FiO(2) ($p=0.7235$), HCO(3) - ($p=0.1552$), serum sodium ($p=0.0827$) whereas chi(2) test had been done in variables - sex, educational background, congestive heart failure ($p=0.06$), cardiogenic pulmonary oedema ($p=0.6358$) and pneumothorax ($p=0.06$), history of myocardial infarction ($p=0.1024$), congestive heart failure ($p=0.06$), peripheral vascular disease ($p=0.4636$), cerebrovascular disease ($p=0.1074$), peptic ulcer disease ($p=0.06$), hemiplegia ($p=0.4138$) , Diabetes without end organ damage ($p=0.1034$), tumour without metastasis ($p=0.42259$), solid tumour with metastasis ($p=0.0562$), leukaemia (0.1388), lymphoma ($p=0.9388$), obstructive sleep apnoea (0.9395), bed ridden patients (0.4984), history of pulmonary tuberculosis ($p=0.08$), kyphoscoliosis ($p=0.1388$), pneumenectomy ($p=0.1388$). On logistic regression analysis, eight variables had been shown association with NIV outcome among the seventeen variables which had association with NIV outcome in two sample Z test and chi(2) tests. Presence of Dementia increased chance of NIV failure 19.32 times, diabetes with end organ damage 10.9375 times and pneumonia 5.3636 times, fibrothorax 3.8077 times, renal disease 2.7273 times. Serum potassium imbalance 1.4615 times and increased serum albumin 1g/dl increased chance of NIV success 1.79 times, PH had also association with NIV outcome. Variables that predict the outcome of NIV are some non modifiable and some modifiable. If special precaution is taken for non modifiable variables and necessary management to correct the abnormalities of

modifiable variables, improvements of patient's condition with NIV will be more satisfactory than the present condition.

Biton, J., H. Ouakrim, et al. (2018). **"Impaired Tumor-Infiltrating T Cells in Patients with Chronic Obstructive Pulmonary Disease Impact Lung Cancer Response to PD-1 Blockade."** Am J Respir Crit Care Med **198**(7): 928-940.

RATIONALE: Patients with chronic obstructive pulmonary disease (COPD) have a higher prevalence of lung cancer. The chronic inflammation associated with COPD probably promotes the earliest stages of carcinogenesis. However, once tumors have progressed to malignancy, the impact of COPD on the tumor immune microenvironment remains poorly defined, and its effects on immune-checkpoint blockers' efficacy are still unknown. OBJECTIVES: To study the impact of COPD on the immune contexture of non-small cell lung cancer. METHODS: We performed in-depth immune profiling of lung tumors by immunohistochemistry and we determined its impact on patient survival (n = 435). Tumor-infiltrating T lymphocyte (TIL) exhaustion by flow cytometry (n = 50) was also investigated. The effectiveness of an anti-PD-1 (programmed cell death-1) treatment (nivolumab) was evaluated in 39 patients with advanced-stage non-small cell lung cancer. All data were analyzed according to patient COPD status. MEASUREMENTS AND MAIN RESULTS: Remarkably, COPD severity is positively correlated with the coexpression of PD-1/TIM-3 (T-cell immunoglobulin and mucin domain-containing molecule-3) by CD8 T cells. In agreement, we observed a loss of CD8 T cell-associated favorable clinical outcome in COPD(+) patients. Interestingly, a negative prognostic value of PD-L1 (programmed cell death ligand 1) expression by tumor cells was observed only in highly CD8 T cell-infiltrated tumors of COPD(+) patients. Finally, data obtained on 39 patients with advanced-stage non-small cell lung cancer treated by an anti-PD-1 antibody showed longer progression-free survival in COPD(+) patients, and also that the association between the severity of smoking and the response to nivolumab was preferentially observed in COPD(+) patients. CONCLUSIONS: COPD is associated with an increased sensitivity of CD8 tumor-infiltrating T lymphocytes to immune escape mechanisms developed by tumors, thus suggesting a higher sensitivity to PD-1 blockade in patients with COPD.

Bonnefoy, V., M. Garnier, et al. (2018). **"Bronchial Dieulafoy's Disease: Visualization of Embolization Particles in Bronchial Aspirate."** Am J Respir Crit Care Med **198**(7): 954-955.

Boyer, L., S. Bastuji-Garin, et al. (2018). **"Are Systemic Manifestations Ascribable to COPD in Smokers? A Structural Equation Modeling Approach."** Sci Rep **8**(1): 8569.

Whether the systemic manifestations observed in Chronic Obstructive Pulmonary Disease (COPD) are ascribable to lung dysfunction or direct effects of smoking is in debate. Structural Equations Modeling (SEM), a causal-oriented statistical approach, could help unraveling the pathways involved, by enabling estimation of direct and indirect associations between variables. The objectives of the study was to investigate the relative impact of smoking and COPD on systemic manifestations, inflammation and telomere length. In 292 individuals (103 women; 97 smokers with COPD, 96 smokers without COPD, 99 non-smokers), we used SEM to explore the pathways between smoking (pack-years), lung disease (FEV1, KCO), and the following parameters: arterial stiffness (aortic pulse wave velocity, PWV), bone mineral density (BMD), appendicular skeletal muscle mass (ASMM), grip strength, insulin resistance (HOMA-IR), creatinine clearance (eGFR), blood leukocyte telomere length and inflammatory markers (Luminex assay).

All models were adjusted on age and gender. Latent variables were created for systemic inflammation (inflammatory markers) and musculoskeletal parameters (ASMM, grip strength, BMD). SEM showed that most effects of smoking were indirectly mediated by lung dysfunction: e.g. via FEV1 on musculoskeletal factor, eGFR, HOMA-IR, PWV, telomere length, CRP, white blood cells count (WBC) and inflammation factor, and via KCO on musculoskeletal factor, eGFR and PWV. Direct effects of smoking were limited to CRP and WBC. Models had excellent fit. In conclusion, SEM highlighted the major role of COPD in the occurrence of systemic manifestations while smoking effects were mostly mediated by lung function.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5988713/pdf/41598_2018_Article_26766.pdf

Burkart, K. M., T. Sofer, et al. (2018). **"A Genome-Wide Association Study in Hispanics/Latinos Identifies Novel Signals for Lung Function. The Hispanic Community Health Study/Study of Latinos."** Am J Respir Crit Care Med **198**(2): 208-219.

RATIONALE: Lung function and chronic obstructive pulmonary disease (COPD) are heritable traits. Genome-wide association studies (GWAS) have identified numerous pulmonary function and COPD loci, primarily in cohorts of European ancestry. OBJECTIVES: Perform a GWAS of COPD phenotypes in Hispanic/Latino populations to identify loci not previously detected in European populations. METHODS: GWAS of lung function and COPD in Hispanic/Latino participants from a population-based cohort. We performed replication studies of novel loci in independent studies. MEASUREMENTS AND MAIN RESULTS: Among 11,822 Hispanic/Latino participants, we identified eight novel signals; three replicated in independent populations of European Ancestry. A novel locus for FEV1 in ZSWIM7 (rs4791658; P = 4.99 x 10(-9)) replicated. A rare variant (minor allele frequency = 0.002) in HAL (rs145174011) was associated with FEV1/FVC (P = 9.59 x 10(-9)) in a region previously identified for COPD-related phenotypes; it remained significant in conditional analyses but did not replicate. Admixture mapping identified a novel region, with a variant in AGMO (rs41331850), associated with Amerindian ancestry and FEV1, which replicated. A novel locus for FEV1 identified among ever smokers (rs291231; P = 1.92 x 10(-8)) approached statistical significance for replication in admixed populations of African ancestry, and a novel SNP for COPD in PDZD2 (rs7709630; P = 1.56 x 10(-8)) regionally replicated. In addition, loci previously identified for lung function in European samples were associated in Hispanic/Latino participants in the Hispanic Community Health Study/Study of Latinos at the genome-wide significance level. CONCLUSIONS: We identified novel signals for lung function and COPD in a Hispanic/Latino cohort. Including admixed populations when performing genetic studies may identify variants contributing to genetic etiologies of COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6058984/pdf/rccm.201707-1493OC.pdf

Carney, C. and M. Benzeval (2019). **"The moderating effect of childhood disadvantage on the associations between smoking and occupational exposure and lung function; a cross sectional analysis of the UK Household Longitudinal Study (UKHLS)."** BMC Public Health **19**(1): 690.

BACKGROUND: Lung function is lower in people with disadvantaged socio-economic position (SEP) and is associated with hazardous health behaviours and exposures. The associations are likely to be interactive, for example, exposure to socially patterned environmental tobacco smoke (ETS) in childhood is associated with an increased effect of smoking in adulthood. We hypothesise that disadvantaged childhood SEP increases susceptibility to the effects of hazards in adulthood for lung function. We test whether disadvantaged childhood SEP moderates smoking, physical activity, obesity, occupational exposures, ETS and air pollution's associations with lung function. METHODS: Data are from the Nurse Health Assessment (NHA) in waves two and three of the United Kingdom Household Longitudinal Study (UKHLS). Analysis is restricted to English residents aged at least 20 for women and 25 for men, producing a study population of 16,339. Lung function is measured with forced expiratory volume in the first second (FEV1) and standardised to the percentage of expected FEV1 for a healthy non-smoker of equivalent age, gender, height and ethnicity (FEV1%). Using STATA 14, a mixed linear model was fitted with interaction terms between childhood SEP and health behaviours and occupational exposures. Cross level interactions tested whether childhood SEP moderated household ETS and neighbourhood air

pollution's associations with FEV1%. RESULTS: SEP, smoking, physical activity, obesity, occupational exposures and air pollution were associated with lung function. Interaction terms indicated a significantly stronger negative association between disadvantaged childhood SEP and currently smoking (coefficient -6.47 %, 95% confidence intervals (CI): 9.51 %, 3.42 %) as well as with formerly smoking and occupational exposures. Significant interactions were not found with physical activity, obesity, ETS and air pollution. CONCLUSION: The findings suggest that disadvantaged SEP in childhood may make people's lung function more susceptible to the negative effects of smoking and occupational exposures in adulthood. This is important as those most likely to encounter these exposures are at greater risk to their effects. Policy to alleviate this inequality requires intervention in health behaviours through public health campaigns and in occupational health via health and safety legislation.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6549314/pdf/12889_2019_Article_7039.pdf

Cazzola, M. and M. G. Matera (2018). **"Combining Dual Bronchodilation and beta-Blockade in Patients With an Overlap Between COPD and Cardiovascular Diseases."** Chest **153**(6): 1289-1291.

https://journal.chestnet.org/article/S0012-3692(18)30228-9/pdf

Cheng, T., Y. Li, et al. (2019). **"Emphysema extent on computed tomography is a highly specific index in diagnosing persistent airflow limitation: a real-world study in China."** Int J Chron Obstruct Pulmon Dis **14**: 13-26.

Objective: The diagnostic value of emphysema extent in consistent air flow limitation remains controversial. Therefore, we aimed to assess the value of emphysema extent on computed tomography (CT) on the diagnosis of persistent airflow limitation. Furthermore, we developed a diagnostic criterion for further verification. Materials and methods: We retrospectively enrolled patients who underwent chest CT and lung function test. To be specific, 671 patients were enrolled in the derivation group (Group 1.1), while 479 patients were in the internal validation group (Group 1.2). The percentage of lung volume occupied by low attenuation areas (LAA%) and the percentile of the histogram of attenuation values were calculated. Results: In patients with persistent airflow limitation, the LAA% was higher and the percentile of the histogram of attenuation values was lower, compared with patients without persistent airflow limitation. Using LAA% with a threshold of -950 HU >1.4% as the criterion, the sensitivity was 44.3% and 47.2%, and the specificity was 95.2% and 95.7%, in Group 1.1 and Group 1.2, respectively. The specificity was influenced by the coexistence of interstitial lung disease, pneumothorax, and post-surgery, rather than the coexistence of pneumonia, nodule, or mass. Multivariable models were also developed. Conclusion: The emphysema extent on CT is a highly specific marker in the diagnosis of persistent airflow limitation.

https://www.dovepress.com/getfile.php?fileID=46997

Chung, H., G. Deshpande, et al. (2019). **"Health Plan Enrollment and Disenrollment of Individuals With and Without Established Chronic Disease in a U.S. Commercially Insured and Medicare Advantage Population."** J Manag Care Spec Pharm **25**(5): 612-620.

BACKGROUND: Chronic disease is associated with increased health care resource utilization and costs. Effective development and implementation of health care management and clinical intervention programs require an understanding of health plan member enrollment and disenrollment behavior. OBJECTIVE: To examine the health plan enrollment and disenrollment behavior of commercially insured and Medicare Advantage members with established chronic disease compared with matched members without the disease of interest, using data from a large national health insurer in the United States. METHODS: This retrospective matched cohort study used administrative claims data from the HealthCore Integrated

Research Database from January 1, 2006, to November 30, 2015, to identify adults with chronic disease (type 2 diabetes mellitus [T2DM], cardiovascular disease [CVD], chronic obstructive pulmonary disease [COPD], rheumatoid arthritis [RA], and breast cancer [BC]). Members with no established chronic disease (controls) were directly matched to members with established chronic disease (cases) on demographic characteristics. The earliest date on which members met the criteria for a given disease was defined as the index date. Controls had the same index date as the matched cases. All members had >/= 12 months of continuous health plan enrollment before the index date. Outcomes included health plan member disenrollment and enrollment duration. Incidence rates per 1,000 member-years for member disenrollment were evaluated along with incidence rate ratios (relative risk) using a Poisson model. Time to disenrollment was analyzed by Cox proportional hazard models and Kaplan-Meier survival curves. Sensitivity analyses were conducted where death was included as a disenrollment event. RESULTS: 70,907 health plan members with BC (99.7% female, mean age 60.5 years); 28,883 members with COPD (52.3% female, mean age 66.7); 835,358 members with CVD (50.5% female, mean age 62.7 years); 210,936 members with T2DM (45.2% female, mean age 53.6 years); and 31,954 members with RA (72.0% female, mean age 55.5 years) were matched to controls and met the study criteria. The incidence rates of health plan disenrollment ranged from 155 to 192 members per 1,000 members per year. Compared with controls, members with chronic disease were 30%-40% less likely to disenroll from a health plan (P < 0.001 for all comparisons). Among those who disenrolled, enrollment duration ranged from 2.3 to 2.7 years among cases and 1.5 to 1.8 years among matched controls (P </= 0.001 for all comparisons). CONCLUSIONS: This real-world study demonstrated that members with chronic disease had a significantly lower rate of disenrollment and a longer duration of enrollment compared with matched controls and were continuously enrolled for almost a year longer than members without a diagnosed chronic disease. Understanding health plan enrollment and disenrollment behavior may provide a valuable context for determining the time frame for the effect of health care programs and initiatives. DISCLOSURES: Funding for this study was provided by HealthCore, a wholly owned subsidiary of Anthem. Chung, Deshpande, Zolotarjova, Quimbo, and Willey are employees of HealthCore. Kern and Cochetti are former employees of HealthCore. Quimbo, Cochetti, and Willey are shareholders of Anthem. HealthCore receives funding from multiple pharmaceutical companies to perform various research studies outside of the submitted work. The preliminary results of this study were presented at AMCP Nexus 2015; March 26-29, 2015; Orlando, FL, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2017 Conference; May 20-24, 2017; Boston, MA.

Collins, P. F., M. Elia, et al. (2018). **"The influence of deprivation on malnutrition risk in outpatients with chronic obstructive pulmonary disease (COPD)."** Clin Nutr **37**(1): 144-148.

BACKGROUND & AIMS: The social gradient in chronic obstructive pulmonary disease (COPD) is considerable, but the influence of deprivation on common clinical risk factors such as malnutrition is unclear. This study aimed to explore the relationship between COPD disease-severity, deprivation and malnutrition. METHODS: 424 outpatients with a confirmed diagnosis of COPD were routinely screened for malnutrition risk using the 'Malnutrition Universal Screening Tool' ('MUST') while attending respiratory clinics across two hospitals; a large city hospital (site A) and a smaller community hospital (site B). Deprivation was assessed for each outpatient according to their address (postcode) using the English governments' index of multiple deprivation (IMD) and related to malnutrition risk. Each postcode was attributed to both an IMD score and IMD rank, where a higher IMD score and a lower IMD ranking indicated increased deprivation. RESULTS: Overall prevalence of malnutrition was 22% (95% CI 18-26%; 9% medium risk, 13% high risk). It was significantly higher at site A (28% vs 17%; p = 0.004) where patients were also significantly more likely to reside in areas of more deprivation than those at site B (IMD rank: 15,510 SD 8137 vs 22,877 SD 6827; p < 0.001). COPD disease-severity was positively associated with malnutrition (p < 0.001) whilst a higher rank IMD was negatively associated with malnutrition (p = 0.014). CONCLUSIONS: Deprivation is a significant independent risk factor for malnutrition in outpatients with COPD. Consideration of deprivation is important in the identification of malnutrition and the nutritional management of patients with COPD.

https://www.clinicalnutritionjournal.com/article/S0261-5614(16)31319-X/fulltext

Corbellini, C., A. Boussuges, et al. (2018). **"Diaphragmatic Mobility Loss in Subjects With Moderate to Very Severe COPD May Improve After In-Patient Pulmonary Rehabilitation."** Respir Care **63**(10): 1271-1280.

BACKGROUND: The diaphragm changes in COPD lead to functional inefficiency correlated to lung function loss. Muscle-fiber shortening follows lung hyperinflation, which results in a chronic mechanical disadvantage that impairs diaphragmatic mobility that worsens in COPD exacerbations. OBJECTIVES: To correlate the diaphragmatic mobility loss to COPD severity by using M-mode ultrasonography and to verify if the diaphragmatic mobility can improve after in-patient pulmonary rehabilitation. METHODS: We used M-mode ultrasonography to access diaphragmatic mobility during normal breathing or breathing at rest and deep inspiration in 52 subjects with moderate to very severe COPD who underwent pulmonary rehabilitation and 16 healthy subjects. Lung function test, arterial blood gas analysis, and a 6-min walk test were also performed. The measurements were performed at rehabilitation admission and discharge. RESULTS: We screened 30 subjects with severe to very severe COPD who had completed pulmonary rehabilitation. At discharge, inspiratory capacity improved, from 1.58 +/- 0.5L to 1.7 +/- 0.6 L (P = .04). Diaphragmatic mobility during deep inspirations increased from (mean +/- SD) 4.58 +/- 1.83 cm to 5.45 +/- 1.56 cm (P = .05) after pulmonary rehabilitation. The diaphragmatic mobility during rest breathing was higher in the subjects with COPD (2.25 +/- 0.83 cm) than in the healthy subjects (1.27 +/- 0.3 cm) (P = .01). The diaphragmatic mobility for the rest breathing and deep inspirations were correlated to an FEV1 decrease (r = -0.74, P < .001; and r = 0.8, P < .001, respectively). CONCLUSIONS: Our findings demonstrated diaphragmatic mobility loss in the subjects with moderate to very severe COPD. These changes were correlated with COPD severity, and diaphragmatic mobility loss improved after in-patient pulmonary rehabilitation. (ClinicalTrial.gov registration NCT02838953.).

http://rc.rcjournal.com/content/respcare/63/10/1271.full.pdf

Coste, F., I. Benlala, et al. (2019). **"Quantitative CT assessment of bronchial and vascular alterations in severe precapillary pulmonary hypertension."** Int J Chron Obstruct Pulmon Dis **14**: 381-389.

Background: Little is known about in vivo alterations at bronchial and vascular levels in severe pulmonary hypertension (PH) of different etiologies. We aimed to compare quantitative computed tomography (CT) data from the following three groups of severe precapillary PH patients: COPD, idiopathic pulmonary arterial hypertension (iPAH), and chronic thromboembolic PH (CTEPH). Patients and methods: This study was approved by the institutional review board. Severe PH patients (mean pulmonary arterial pressure [mPAP] >/=35 mmHg) with COPD, iPAH, or CTEPH (n=24, 16, or 16, respectively) were included retrospectively between January 2008 and January 2017. Univariate analysis of mPAP was performed in each severe PH group. Bronchial wall thickness (WT) and percentage of cross sectional area of pulmonary vessels less than 5 mm(2) normalized by lung area (%CSA<5) were measured and compared using CT, and then combined to arterial partial pressure of oxygen (PaO2) to generate a "paw score" compared within the three groups using Kruskal-Wallis and its sensitivity using Fisher's exact test. Results: WT was higher and %CSA<5 was lower in the COPD group compared to iPAH and CTEPH groups. Mosaic pattern was higher in CTEPH group than in others. In severe PH patients secondary to COPD, mPAP was positively correlated to %CSA<5. By contrast, in severe iPAH, this correlation was negative, or not correlated in severe CTEPH groups. In the COPD group, "paw score" showed higher sensitivity than in the other two groups. Conclusion: Unlike in severe iPAH and CTEPH, severe PH with COPD can be predicted by "paw score" reflecting bronchial and vascular morphological differential alterations.

https://www.dovepress.com/getfile.php?fileID=47965

Cragg, L., S. Williams, et al. (2018). **"Fostering the exchange of real world data across different countries to answer primary care research questions: an UNLOCK study from the IPCRG."** NPJ Prim Care Respir Med **28**(1): 8.

There is growing awareness amongst healthcare planners, providers and researchers of the need to make better use of routinely collected health data by translating it into actionable information that improves efficiency of healthcare and patient outcomes. There is also increased acceptance of the importance of real world research that recruits patients representative of primary care populations and evaluates interventions realistically delivered by primary care professionals. The UNLOCK Group is an international collaboration of primary care researchers and practitioners from 15 countries. It has coordinated and shared datasets of diagnostic and prognostic variables for COPD and asthma to answer research questions meaningful to professionals working in primary care over a 6-year period. Over this time the UNLOCK Group has undertaken several studies using data from unselected primary care populations from diverse contexts to evaluate the burden of disease, multiple morbidities, treatment and follow-up. However, practical and structural constraints have hampered the UNLOCK Group's ability to translate research ideas into studies. This study explored the constraints, challenges and successes experienced by the UNLOCK Group and its participants' learning as researchers and primary care practitioners collaborating to answer primary care research questions. The study identified lessons for future studies and collaborations that require data sharing across borders. It also explored specific challenges to fostering the exchange of primary care data in comparison to other datasets such as public health, prescribing or hospital data and mechanisms that may be used to overcome these.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5843627/pdf/41533_2018_Article_75.pdf

Cushen, B., I. Sulaiman, et al. (2018). **"The Clinical Impact of Different Adherence Behaviors in Patients with Severe Chronic Obstructive Pulmonary Disease."** Am J Respir Crit Care Med **197**(12): 1630-1633.

Di Stefano, A., C. Sangiorgi, et al. (2018). **"TGF-beta Signaling Pathways in Different Compartments of the Lower Airways of Patients With Stable COPD."** Chest **153**(4): 851-862.

BACKGROUND: The expression and localization of transforming growth factor-beta (TGF-beta) pathway proteins in different compartments of the lower airways of patients with stable COPD is unclear. We aimed to determine TGF-beta pathway protein expression in patients with stable COPD. METHODS: The expression and localization of TGF-beta pathway components was measured in the bronchial mucosa and peripheral lungs of patients with stable COPD (n = 44), control smokers with normal lung function (n = 24), and control nonsmoking subjects (n = 11) using immunohistochemical analysis. RESULTS: TGF-beta1, TGF-beta3, and connective tissue growth factor expression were significantly decreased in the bronchiolar epithelium, with TGF-beta1 also decreased in alveolar macrophages, in patients with stable COPD compared with control smokers with normal lung function. TGF-beta3 expression was increased in the bronchial lamina propria of both control smokers with normal lung function and smokers with mild/moderate stable COPD compared with control nonsmokers and correlated significantly with pack-years of smoking. However, TGF-beta3(+) cells decreased in patients with severe/very severe COPD compared with control smokers. Latent TGF-beta binding protein 1 expression was increased in the bronchial lamina propria in subjects with stable COPD of all severities compared with control smokers with normal lung function. Bone morphogenetic protein and activin membrane-bound inhibitor expression (BAMBI) in the bronchial mucosa was significantly increased in patients with stable COPD of all severities compared with control subjects. No other significant differences were observed between groups for all the other molecules studied in the bronchial mucosa and peripheral lung. CONCLUSIONS: Expression of TGF-betas and their regulatory proteins is distinct within different lower airway compartments in stable COPD. Selective reduction in TGF-beta1 and enhanced BAMBI expression may be associated with the increase in autoimmunity in COPD.

http://spiral.imperial.ac.uk/bitstream/10044/1/55585/9/1-s2.0-S0012369217332853-main.pdf

Ehsani, H., M. J. Mohler, et al. (2019). **"Upper-extremity function prospectively predicts adverse discharge and all-cause COPD readmissions: a pilot study."** Int J Chron Obstruct Pulmon Dis **14**: 39-49.

Background: Frailty can inform management approaches for individuals with COPD. However, inpatient measures of frailty are seldom employed because they are time-consuming or inapplicable for bed-bound patients. We investigated the feasibility and potential of an innovative sensor-based upper-extremity function (UEF) test for frailty assessment in predicting adverse outcomes. Methods: Hospitalized patients with COPD-related exacerbations (aged >/=55 years) were recruited and performed the UEF test within 24 hours of admission. UEF parameters were obtained and fed into our previously developed frailty model to calculate frailty status (non-frail, pre-frail, and frail) and frailty score (0: extreme resilience to 1: extreme frailty). In-hospital (length of stay) and post-discharge (discharge disposition, 30-day exacerbation with treatment, and all-cause 30-day readmission) outcomes were collected. Associations between UEF frailty and outcomes were investigated using ANOVA and logistic models adjusted for demographic data. Results: In total, 42 patients were recruited. All participants were able to perform the UEF test. Based on UEF, participants were stratified into three groups of non-frail (n=6, frailty score =0.18+/-0.09), pre-frail (n=14, frailty score =0.45+/-0.09), and frail (n=22, frailty score =0.78+/-0.11). Both frailty status and frailty score were significantly associated with unfavorable discharge disposition (P<0.005) and all-cause 30-day readmission (P<0.05). On the other hand, UEF frailty measures were associated with neither hospital length of stay (P>0.5) nor 30-day exacerbation with treatment (P>0.70). Age was only significantly associated with unfavorable discharge disposition (P=0.048). Conclusion: In agreement with previous work, the current findings underline the importance of measuring frailty for risk-stratification of COPD patients. The UEF was feasible and easily performed among all hospitalized COPD patients. In this study, we have shown that, using our quick and objective frailty measures, COPD patients can be prospectively risk-stratified in terms of unfavorable discharge disposition and all-cause 30-day readmissions.

https://www.dovepress.com/getfile.php?fileID=47040

Elmussareh, M., P. C. Simonsen, et al. (2018). **"Correlation between organ-specific co-morbidities and complications in bladder cancer patients undergoing radical cystectomy."** Scand J Urol **52**(5-6): 395-400.

OBJECTIVE: To evaluate the association between patients' organ-specific co-morbidities and post-operative complications following radical cystectomy for bladder cancer. PATIENTS AND METHODS: All patients who underwent radical cystectomy at Aarhus University Hospital during the period from January 2006 to February 2014 were included retrospectively. A total of 40 comorbidities and 59 complications were registered meticulously. Univariate and multivariate analyses were used to detect associations between the individual comorbidities and specific post-operative complications. RESULTS: Ninety-two per cent (575/625) of patients experienced one or more complications following radical cystectomy. Clavien-Dindo grade 3-5 complications were observed in 40.8% of patients, and 6.2% had severe complications (Clavien-Dindo grade 4-5). The mortality rate was 2.2%. High BM, previous myocardial infarction and chronic obstructive pulmonary disease were noted to be associated with moderate-to-severe post-operative complications (Clavien-Dindo grade 3-5), while diabetes and lymphoproliferative disorders were significantly associated with severe complications (Clavien-Dindo grade 4-5). CONCLUSION: This study demonstrates that overall complications to radical cystectomy are high (92%). The associations between specific comorbidities and complications need to be further investigated in order to evaluate whether pre-operative assessment can be more optimally used in a prevention strategy tailored to the individual patient.

https://www.tandfonline.com/doi/full/10.1080/21681805.2018.1531921

Eriksson, B., H. Backman, et al. (2018). **"Pattern of Cardiovascular Comorbidity in COPD in a Country with Low-smoking Prevalence: Results from Two-population-based Cohorts from Sweden."** Copd **15**(5): 454-463.

Cardiovascular diseases are the most common comorbidities in COPD, due to common risk factors such as smoking. The prevalence of current smokers in Sweden has decreased over four decades to around 10%. The aim of the present study was to investigate the prevalence, distribution and associations of cardiovascular comorbidities in COPD by disease severity in two large areas of Sweden, both with low-smoking prevalence. Data from clinical examinations in 2009-2012, including spirometry and structured interview, from two large-scale population studies, the West Sweden Asthma Study (WSAS) and the OLIN Studies in Northern Sweden, were pooled. COPD was defined using post-bronchodilator spirometry according to the fixed ratio FEV1/FVC <0.70 and the lower limit of normal (LLN(5th) percentile) of the ratio of FEV1/FVC. Of the 1839 subjects included, 8.7% and 5.7% had COPD according to the fixed ratio and the LLN criterion. Medication for heart disease or hypertension among those with moderate-to-severe COPD was more common than among those without COPD (fixed ratio definition of COPD: 51% vs. 23%, p < 0.001; LLN definition: 42% vs. 24%, p = 0.002). After adjusting for known risk factors for COPD, including smoking, age, socio-economic status, and occupational exposure for gas, dust and fumes, only heart failure remained significantly, and independently, associated with COPD, irrespective of the definitions of COPD. Though a major decrease in smoking prevalence, the pattern of cardiovascular comorbidities in COPD still remains similar with previously performed studies in Sweden and in other Westernized countries as well.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2018.1535580?needAccess=true

Fazekas, A. S., M. Aboulghaith, et al. (2018). **"Long-term outcomes after acute hypercapnic COPD exacerbation : First-ever episode of non-invasive ventilation."** Wien Klin Wochenschr **130**(19-20): 561-568.

BACKGROUND: Non-invasive ventilation (NIV) is used to treat acute hypercapnic respiratory failure (AHRF) in patients with chronic obstructive pulmonary disease (COPD); however, long-term outcomes following discharge are largely unknown. This study aimed to characterize long-term outcomes and identify associated markers in patients with COPD after surviving the first episode of HRF requiring NIV. METHODS: This study retrospectively analyzed 122 patients, mean age 62+/- 8 years, 52% female and forced expiratory volume in 1 s (FEV1) predicted 30+/- 13%, admitted with an acute hypercapnic exacerbation of COPD and receiving a first-ever NIV treatment between 2000 and 2012. RESULTS: A total of 40% of the patients required hospital readmission due to respiratory reasons within 1 year. Persistent hypercapnia leading to the prescription of domiciliary NIV, older age and lower body mass index (BMI) were risk factors for readmission due to respiratory reasons. Survival rates were 79% and 63% at 1 and 2 years after discharge, respectively. A shorter time to readmission and recurrent hypercapnic failure, lower BMI and acidemia on the first admission, as well as hypercapnia at hospital discharge were correlated with a decreased long-term survival. CONCLUSION: Patients with COPD surviving their first episode of AHRF requiring NIV are at high risk for readmission and death. Severe respiratory acidosis, chronic respiratory failure and a lower BMI imply shorter long-term survival.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6209011/pdf/508_2018_Article_1364.pdf

Finch, D. K., V. R. Stolberg, et al. (2018). **"Lung Dendritic Cells Drive Natural Killer Cytotoxicity in Chronic Obstructive Pulmonary Disease via IL-15Ralpha."** Am J Respir Crit Care Med **198**(9): 1140-1150.

RATIONALE: Lung natural killer cells (NKs) kill a greater percentage of autologous lung parenchymal cells in chronic obstructive pulmonary disease (COPD) than in nonobstructed smokers. To become cytotoxic, NKs require priming, typically by dendritic cells (DCs), but whether priming occurs in the lungs in COPD is unknown. METHODS: We used lung tissue and in some cases peripheral blood from patients

undergoing clinically indicated resections to determine in vitro killing of CD326(+) lung epithelial cells by isolated lung CD56(+) NKs. We also measured the cytotoxicity of unprimed blood NKs after preincubation with lung DCs. To investigate mechanisms of DC-mediated priming, we used murine models of COPD induced by cigarette smoke (CS) exposure or by polymeric immunoglobulin receptor (pIgR) deficiency, and blocked IL-15Ralpha (IL-15 receptor alpha subunit) trans-presentation by genetic and antibody approaches. RESULTS: Human lung NKs killed isolated autologous lung epithelial cells; cytotoxicity was increased (P = 0.0001) in COPD, relative to smokers without obstruction. Similarly, increased lung NK cytotoxicity compared with control subjects was observed in CS-exposed mice and pIgR(-/-) mice. Blood NKs both from smokers without obstruction and subjects with COPD showed minimal epithelial cell killing, but in COPD, preincubation with lung DCs increased cytotoxicity. NKs were primed by CS-exposed murine DCs in vitro and in vivo. Inhibiting IL-15Ralpha trans-presentation eliminated NK priming both by murine CS-exposed DCs and by lung DCs from subjects with COPD. CONCLUSIONS: Heightened NK cytotoxicity against lung epithelial cells in COPD results primarily from lung DC-mediated priming via IL-15 trans-presentation on IL-15Ralpha. Future studies are required to test whether increased NK cytotoxicity contributes to COPD pathogenesis.

Fireman Klein, E., Y. Adir, et al. (2019). **"Ultrafine particles in airways: a novel marker of COPD exacerbation risk and inflammatory status."** Int J Chron Obstruct Pulmon Dis **14**: 557-564.

Purpose: Ultrafine particles (UFP) are toxic due to their small size and penetration into deeper lung compartments. We aimed to evaluate the exhaled breath condensate (EBC)-UFP content as a reflection of inflammation and oxidative stress status in COPD patients and as an exacerbation risk marker. Methods: EBC was collected by conventional methods. Particles were analyzed with NanoSight LM20. EBC carbonyl and 8-hydroxydeoxyguanosine (8-OHdG) levels were measured using ELISA kits. Study population (58 COPD patients and 40 healthy smoker and non-smoker controls) underwent spirometry, diffusion capacity, EBC testing, and blood sampling. Results: Absolute eosinophil count, C-reactive protein (CRP), and lactate dehydrogenase in serum were elevated in the COPD group compared with the controls (224 U/L, 5 mg/L, and 391 U/L vs 154 U/L, 3 mg/L, and 330 U/L, P=0.009, P=0.05, and P=0.004, respectively). COPD patients had lower UFP concentrations in EBC compared with controls (0.24 E8/mL vs 0.51 E8/mL, P</=0.001). A mirror image was detected in serum: COPD patients had higher UFP concentrations compared with controls (9.8 E8/mL vs 6.7 E8/mL, respectively, P=0.03). EBC carbonyl and 8-OHdG levels were higher among COPD patients compared with controls (5.1 per 1 microg/mL protein and 0.036 ng/mL vs 0.41 per 1 microg/mL protein and 0.003 ng/mL, P=0.001 and P</=0.001, respectively). EBC UFP concentrations were negatively correlated with pack years (R=-0.44, P </=0.001) and positively correlated with FEV1 and diffusing lung capacity for carbon monoxide (R=0.46, 0.23, P </=0.001 and P=0.04, respectively). Low EBC UFP concentrations (</=0.18 E8/mL) and CRP levels >/=5 mg/L were independent predictors of the frequent exacerbator phenotype (OR 3.6; 95% CI: 1.06-7.97; P=0.04 and OR 4.4; 95% CI: 1.24-10.2; P=0.02, respectively). Conclusion: UFP content in EBC reflects the inflammatory state of airways. Low UFP concentrations in EBC and high in serum of COPD patients support our hypothesis that increased epithelial permeability could be the mechanism behind those findings.

https://www.dovepress.com/getfile.php?fileID=48367

Gardner, L. D., D. C. Loffredo Ph, et al. (2018). **"Associations between history of chronic lung disease and non-small cell lung carcinoma in Maryland: variations by sex and race."** Ann Epidemiol **28**(8): 543-548.

PURPOSE: Lung cancer is a multifactorial malignancy for which some risk factors, such as chronic lung diseases, their interactions with smoking, and how they differ by race and sex, are not fully understood. We investigated the associations between chronic inflammatory lung disease and non-small cell lung carcinoma (NSCLC) and how sex and race may affect such associations. METHODS: Using logistic regression, we analyzed 1660 lung cancer cases and 1959 population controls and estimated adjusted

odds ratios (AORs) and 95% confidence intervals (CIs). RESULTS: Chronic lung disease was significantly associated with higher odds of having NSCLC in never (AOR = 1.99; 95% CI = 1.19-3.34), former (AOR = 1.68; 95% CI = 1.29-2.20), and current smokers (AOR = 2.40; 95% CI = 1.62-3.57), after adjustment for relevant covariates. For each 5-year increment in chronic lung disease duration, the risk of lung cancer increased only among females (AOR = 1.07; 95% CI = 1.02-1.13). Females, but not males, with asthma were at risk for NSCLC (AOR = 2.08; 95% CI = 1.40-3.10). CONCLUSIONS: This study provides support for chronic lung inflammation as a potential contributing factor to lung cancer risk and possible sex difference in the inflammatory events underlying disease mechanisms.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6333311/pdf/nihms-1000577.pdf

Ghebre, M. A., P. H. Pang, et al. (2018). **"Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles."** J Allergy Clin Immunol **141**(6): 2027-2036.e12.

BACKGROUND: Exacerbations of asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous. OBJECTIVE: We sought to investigate the sputum cellular, mediator, and microbiome profiles of both asthma and COPD exacerbations. METHODS: Patients with severe asthma or moderate-to-severe COPD were recruited prospectively to a single center. Sputum mediators were available in 32 asthmatic patients and 73 patients with COPD assessed at exacerbation. Biologic clusters were determined by using factor and cluster analyses on a panel of sputum mediators. Patterns of clinical parameters, sputum mediators, and microbiome communities were assessed across the identified clusters. RESULTS: The asthmatic patients and patients with COPD had different clinical characteristics and inflammatory profiles but similar microbial ecology. Three exacerbation biologic clusters were identified. Cluster 1 was COPD predominant, with 27 patients with COPD and 7 asthmatic patients exhibiting increased blood and sputum neutrophil counts, proinflammatory mediators (IL-1beta, IL-6, IL-6 receptor, TNF-alpha, TNF receptors 1 and 2, and vascular endothelial growth factor), and proportions of the bacterial phylum Proteobacteria. Cluster 2 had 10 asthmatic patients and 17 patients with COPD with increased blood and sputum eosinophil counts, type 2 mediators (IL-5, IL-13, CCL13, CCL17, and CCL26), and proportions of the bacterial phylum Bacteroidetes. Cluster 3 had 15 asthmatic patients and 29 patients with COPD with increased type 1 mediators (CXCL10, CXCL11, and IFN-gamma) and proportions of the phyla Actinobacteria and Firmicutes. CONCLUSIONS: A biologic clustering approach revealed 3 subgroups of asthma and COPD exacerbations, each with different percentages of patients with overlapping asthma and COPD. The sputum mediator and microbiome profiles were distinct between clusters.

http://spiral.imperial.ac.uk/bitstream/10044/1/59280/9/1-s2.0-S0091674918306250-main.pdf

Golpe, R., M. Suarez-Valor, et al. (2018). **"Risk Stratification in Chronic Obstructive Pulmonary Disease. Can the Spanish Guidelines be Improved?"** Arch Bronconeumol **54**(10): 533-535.

https://www.sciencedirect.com/science/article/pii/S0300289618300504?via%3Dihub

Gompelmann, D., V. Gerovasili, et al. (2018). **"Endoscopic Valve Removal >180 Days since Implantation in Patients with Severe Emphysema."** Respiration **96**(4): 348-354.

BACKGROUND: Valve implantation provides a reversible effective therapy in a selected group of emphysema patients. Knowing predictors for successful therapy, the rate of treatment failure has decreased. Some patients, however, do not benefit, so that the valves may have to be removed. OBJECTIVES: To assess implant-related events, complications during valve removal, and clinical outcome after endoscopic procedure. METHODS: The data of 76 consecutive emphysema patients who underwent valve removal > 6 months since implantation were collected. RESULTS: Seventy-six patients (mean age 62 years, 54%

male) underwent removal of all valves after a mean time of 624 days (193-3,043 days) since implantation. Granulation tissue was observed in 39.5% (30/76) and significant secretion in 34.2% (26/76). In 5.3% (4/76), valve removal was complicated requiring another bronchoscopy in 2 of them. In 5.3% (4/76) of the patients, one valve could not be removed and remained in situ. Bleeding requiring intervention occurred in 3.9% (3/76) during valve removal. Following bronchoscopy, there was a need for antibiotics in 34.2% (26/76), glucocorticosteroids in 1.3% (1/76), and both in 6.6% (5/76) due to productive cough or chronic obstructive pulmonary disease (COPD) exacerbation. Due to respiratory failure, invasive ventilation or noninvasive ventilation was necessary in 2.6% (2/76) and 6.6% (5/76), respectively, following procedure. No statistical significant change in lung function was observed following valve removal. CONCLUSIONS: Valve removal after > 6 months since implantation is feasible and associated with an acceptable safety profile. However, close monitoring of these patients with limited pulmonary reserve is recommended with particular attention to COPD exacerbations and respiratory failure.

https://www.karger.com/Article/Abstract/489887

Graumam, R. Q., M. M. Pinheiro, et al. (2018). **"Increased rate of osteoporosis, low lean mass, and fragility fractures in COPD patients: association with disease severity."** Osteoporos Int **29**(6): 1457-1468.

A very high rate of osteoporosis, fractures, and low lean mass was observed in patients with chronic obstructive pulmonary disease (COPD). Disease severity was associated with bone and muscle adverse outcomes, while age >/= 63.5 years old, low lean mass, higher iPTH, and a T-score below - 2.5 were all associated with higher risk of fracture. INTRODUCTION: Osteoporosis is frequently neglected in patients with COPD. We aimed at evaluating the rate of osteoporosis, fractures, and low lean mass in patients with COPD. METHODS: Ninety-nine patients with COPD (53 women, 64.5 +/- 9.6 years old, and 46 men, 65.9 +/- 8.0 years old) underwent bone densitometry (DXA) with body composition analyses. Healthy individuals (N = 57) not exposed to tobacco matched by sex, age, and body mass index (BMI) were used as controls. Spirometry, routine laboratory workout, and conventional thoracolumbar radiography surveying for vertebral deformities were performed in all patients. RESULTS: Osteoporosis was found in 40.4% of the COPD patients against only 13.0% of the healthy controls (p = 0.001). Vertebral fractures were seen in 24.4% of the men and 22.0% of the women with COPD. Disease severity (GOLD 3 and 4) was significantly associated with higher risk of vitamin D deficiency (p = 0.032), lower BMD (both men and women at all sites), higher frequency of osteoporosis (in women at all sites), lower skeletal mass index, and higher rate of low lean mass (in both men and women) than healthy controls and COPD patients with milder disease (GOLD 1 and 2). Age was a main predictor of vertebral fractures (OR = 1.164 (1.078-9.297); p < 0.001), while high plasma iPTH (OR = 1.045 (1.005-1.088); p = 0.029) and low ALM (OR = 0.99965 (0.99933-0.99997); p = 0.031) were predictors of non-vertebral fractures. CONCLUSION: Highly prevalent in COPD, osteoporosis and low lean mass were associated with FEV1% < 50%. Age, low lean mass, high iPTH, and low bone mass were all significantly associated with fractures in COPD patients.

https://link.springer.com/article/10.1007%2Fs00198-018-4483-z

Gulati, S., J. M. Wells, et al. (2019). **"Fibroblast Growth Factor 23 is Associated with a Frequent Exacerbator Phenotype in COPD: A Cross-Sectional Pilot Study."** Int J Mol Sci **20**(9)Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory airway disease punctuated by exacerbations (AECOPD). Subjects with frequent AECOPD, defined by having at least two exacerbations per year, experience accelerated loss of lung function, deterioration in quality of life and increase in mortality. Fibroblast growth factor (FGF)23, a hormone associated with systemic inflammation and altered metabolism is elevated in COPD. However, associations between FGF23 and AECOPD are unknown. In this cross-sectional study, individuals with COPD were enrolled between June 2016 and December 2016. Plasma samples were analyzed for intact FGF23 levels. Logistic regression analyses were used to measure associations between clinical variables, FGF23, and the frequent exacerbator phenotype. Our results showed that FGF23 levels were higher in frequent exacerbators as compared to patients without

frequent exacerbations. FGF23 was also independently associated with frequent exacerbations (OR 1.02; 95%CI 1.004-1.04; p = 0.017), after adjusting for age, lung function, smoking, and oxygen use. In summary, FGF23 was associated with the frequent exacerbator phenotype and correlated with number of exacerbations recorded retrospectively and prospectively. Further studies are needed to explore the role of FGF 23 as a possible biomarker for AECOPD to better understand the pathobiology of COPD and to help develop therapeutic targets.

https://res.mdpi.com/d_attachment/ijms/ijms-20-02292/article_deploy/ijms-20-02292.pdf

Gulsen, A. (2019). **"Effects of Bronchoscopic Lung Volume Reduction Coil Treatment on Arterial Blood Gases."** J Bronchology Interv Pulmonol **26**(2): 90-95.

BACKGROUND: Bronchoscopic lung volume reduction (BLVR) coil treatment is an increasingly used treatment modality for selected severe emphysema patients in recent years. Emphysema causes dynamic hyperinflation, loss of elastic recoil, air trapping, and decreased exercise capacity in advanced stages. This process progresses over time, leading to hypoxic and hypercapnic respiratory failure. The goal of this study is to elucidate the effects of BLVR coil treatment on arterial blood gas parameters in severe emphysema patients with respiratory failure. METHODS: This is a retrospective study performed at a single pneumology center in Turkey. In total, this study included 39 patients diagnosed with severe emphysema who underwent bilateral BLVR coil treatment according to the general inclusion and exclusion criteria in the literature. The patients baseline and 12-month data were collected from medical records. RESULTS: Twelve months after BLVR coil treatment, significant improvements were observed in patients' pulmonary function tests, an increase in partial pressure of oxygen in arterial blood (PaO2) from 58.05+/-9.36 to 73.82+/-13.3 (P<0.000) and decrease in partial pressure of carbon dioxide in arterial blood (PaCO2) of hypercapnic patients (from 51.60+/-4.1 to 46.55+/-6.6 mm Hg; P=0.001). CONCLUSION: BLVR coil treatment is reliable and effective in emphysema patients who have hypoxic or mild hypercapnic respiratory failure. Besides improving lung function, BLVR coil treatment can significantly increase PaO2 and decrease PaCO2 in the medium term.

Habiel, D. M., A. Camelo, et al. (2017). **"Divergent roles for Clusterin in Lung Injury and Repair."** Sci Rep **7**(1): 15444.

Lung fibrosis is an unabated wound healing response characterized by the loss and aberrant function of lung epithelial cells. Herein, we report that extracellular Clusterin promoted epithelial cell apoptosis whereas intracellular Clusterin maintained epithelium viability during lung repair. Unlike normal and COPD lungs, IPF lungs were characterized by significantly increased extracellular Clusterin whereas the inverse was evident for intracellular Clusterin. In vitro and in vivo studies demonstrated that extracellular Clusterin promoted epithelial cell apoptosis while intercellular Clusterin modulated the expression of the DNA repair proteins, MSH2, MSH6, OGG1 and BRCA1. The fibrotic response in Clusterin deficient (CLU-/-) mice persisted after bleomycin and it was associated with increased DNA damage, reduced DNA repair responses, and elevated cellular senescence. Remarkably, this pattern mirrored that observed in IPF lung tissues. Together, our results show that cellular localization of Clusterin leads to divergent effects on epithelial cell regeneration and lung repair during fibrosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5684342/pdf/41598_2017_Article_15670.pdf

Hamesch, K., M. Mandorfer, et al. (2019). **"Liver Fibrosis and Metabolic Alterations in Adults With alpha-1-antitrypsin Deficiency Caused by the Pi*ZZ Mutation."** Gastroenterology **157**(3): 705-719.e18.

BACKGROUND & AIMS: Alpha-1 antitrypsin deficiency (AATD) is among the most common genetic disorders. Severe AATD is caused by a homozygous mutation in the SERPINA1 gene that encodes the Glu342Lys substitution (called the Pi*Z mutation, Pi*ZZ genotype). Pi*ZZ carriers may develop lung and liver diseases. Mutation-associated lung disorders have been well studied, but less is known about the effects in liver. We assessed the liver disease burden and associated features in adults with this form of AATD. METHODS: We collected data from 554 Pi*ZZ adults (403 in an exploratory cohort, 151 in a confirmatory cohort), in 9 European countries, with AATD who were homozygous for the Pi*Z mutation, and 234 adults without the Pi*Z mutation (controls), all without pre-existing liver disease. We collected data on demographic parameters, comorbidities, lung- and liver-related health, and blood samples for laboratory analysis. Liver fibrosis was assessed non-invasively via the serum tests Aspartate Aminotransferase to Platelet Ratio Index and HepaScore and via transient elastography. Liver steatosis was determined via transient elastography-based controlled attenuation parameter. We performed histologic analyses of livers from transgenic mice that overexpress the AATD-associated Pi*Z variant. RESULTS: Serum levels of liver enzymes were significantly higher in Pi*ZZ carriers vs controls. Based on non-invasive tests for liver fibrosis, significant fibrosis was suspected in 20%-36% of Pi*ZZ carriers, whereas signs of advanced fibrosis were 9- to 20-fold more common in Pi*ZZ carriers compared to non-carriers. Male sex; age older than 50 years; increased levels of alanine aminotransferase, aspartate aminotransferase, or gamma-glutamyl transferase; and low numbers of platelets were associated with higher liver fibrosis burden. We did not find evidence for a relationship between lung function and liver fibrosis. Controlled attenuation parameter >/=280 dB/m, suggesting severe steatosis, was detected in 39% of Pi*ZZ carriers vs 31% of controls. Carriers of Pi*ZZ had lower serum concentrations of triglyceride and low- and very-low-density lipoprotein cholesterol than controls, suggesting impaired hepatic secretion of lipid. Livers from Pi*Z-overexpressing mice had steatosis and down-regulation of genes involved in lipid secretion. CONCLUSIONS: In studies of AATD adults with the Pi*ZZ mutation, and of Pi*Z-overexpressing mice, we found evidence of liver steatosis and impaired lipid secretion. We identified factors associated with significant liver fibrosis in patients, which could facilitate hepatologic assessment and counseling of individuals who carry the Pi*ZZ mutation. ClinicalTrials.gov Number NCT02929940.

https://www.gastrojournal.org/article/S0016-5085(19)40894-9/fulltext

Hara, J., K. Kasahara, et al. (2019). **"A Single Institution Retrospective Study of the Clinical Efficacy of Tiotropium Respimat in Never-Smoking Elderly Asthmatics with Irreversible Airflow Limitation."** Drug Res (Stuttg) **69**(4): 211-217.

OBJECTIVE: In Japan, most asthma deaths occur among the elderly. We should improve the control of asthma in elderly patients to reduce the number of deaths due to asthma. This retrospective study aimed to evaluate the efficacy of tiotropium Respimat() (Tio-Res) in symptomatic, never-smoking, elderly asthmatics with irreversible airflow limitation despite the use of high-dose inhaled corticosteroids (ICS) plus long-acting beta2-adrenoceptor agonists (LABA). METHODS: The Asthma Control Test (ACT), pulmonary function tests, morning and evening peak flow (mPEF, ePEF, respectively, evaluated with an ASSESS((R)) peak flow meter), and respiratory impedance (assessed with MostGraph((R))) were measured before and after a minimum of one year of Tio-Res 5 microg/day administration. Sixteen symptomatic, never-smoking asthmatics, aged 75 or over with irreversible airflow limitation despite the use of high-dose ICS plus LABA, were analyzed. RESULTS: All patients were female (mean age, 81.6 years). Tio-Res led to statistically significant improvements in the total ACT score (19.9 to 23.6), FVC and FEV1 (1.97 to 2.14 L and 1.13 to 1.23 L, respectively), and mPEF and ePEF (229.9 to 253.8 L/min and 259.8 to 277.4 L/min, respectively). Tio-Res also resulted in statistically significant improvements in respiratory resistance at 5 Hz (R5), respiratory resistance at 20 Hz (R20), R5-R20, low-frequency reactant indices at 5 Hz (X5), resonant frequency (Fres) and low-frequency reactance area (ALX). CONCLUSIONS: Our retrospective study suggests that Tio-Res improves symptoms, pulmonary function, and respiratory impedance in symptomatic asthmatics aged 75 or over with irreversible airflow limitation despite the use of high-dose ICS plus LABA.

https://www.thieme-connect.com/products/ejournals/pdf/10.1055/a-0665-4379.pdf

Hayden, L. P., M. E. Hardin, et al. (2018). **"Asthma Is a Risk Factor for Respiratory Exacerbations Without Increased Rate of Lung Function Decline: Five-Year Follow-up in Adult Smokers From the COPDGene Study."** Chest **153**(2): 368-377.

BACKGROUND: Previous investigations in adult smokers from the COPDGene Study have shown that early-life respiratory disease is associated with reduced lung function, COPD, and airway thickening. Using 5-year follow-up data, we assessed disease progression in subjects who had experienced early-life respiratory disease. We hypothesized that there are alternative pathways to reaching reduced FEV1 and that subjects who had childhood pneumonia, childhood asthma, or asthma-COPD overlap (ACO) would have less lung function decline than subjects without these conditions. METHODS: Subjects returning for 5-year follow-up were assessed. Childhood pneumonia was defined by self-reported pneumonia at < 16 years. Childhood asthma was defined as self-reported asthma diagnosed by a health professional at < 16 years. ACO was defined as subjects with COPD who self-reported asthma diagnosed by a health-professional at </= 40 years. Smokers with and those without these early-life respiratory diseases were compared on measures of disease progression. RESULTS: Follow-up data from 4,915 subjects were examined, including 407 subjects who had childhood pneumonia, 323 subjects who had childhood asthma, and 242 subjects with ACO. History of childhood asthma or ACO was associated with an increased exacerbation frequency (childhood asthma, P < .001; ACO, P = .006) and odds of severe exacerbations (childhood asthma, OR, 1.41; ACO, OR, 1.42). History of childhood pneumonia was associated with increased exacerbations in subjects with COPD (absolute difference [beta], 0.17; P = .04). None of these early-life respiratory diseases were associated with an increased rate of lung function decline or progression on CT scans. CONCLUSIONS: Subjects who had early-life asthma are at increased risk of developing COPD and of having more active disease with more frequent and severe respiratory exacerbations without an increased rate of lung function decline over a 5-year period. TRIAL REGISTRY: ClinicalTrials.gov; No. NCT00608764; https://clinicaltrials.gov.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5815872/pdf/main.pdf

Hodgson, L. E., J. Congleton, et al. (2018). **"NEWS 2 - too little evidence to implement?"** Clin Med (Lond) **18**(5): 371-373.

The Royal College of Physicians (RCP) recently published the National Early Warning Score 2 (NEWS2), aiming to improve safety for patients with hypercapnic respiratory failure by suggesting a separate oxygen saturation (SpO2) parameter scoring system for such patients. A previously published study of patients (n=2,361 admissions) with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) demonstrated alternative scoring systems at admission did not outperform the original NEWS. Applying NEWS2 SpO2 parameters to this previously described cohort would have resulted in 44% (n=27/62) of patients who scored >/=7 points on the original NEWS and subsequently died being placed in a lower call-out threshold. NEWS2 loses the benefits of a unified, standardised scoring system and we suggest prospective research in this area before applying this adjustment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6334094/pdf/clinmed-18-5-371.pdf

Hurst, J. R. and D. D. Sin (2018). **"Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Disease. A View from the SUMMIT."** Am J Respir Crit Care Med **198**(1): 2-4.

Inoue, S. and H. Ikeda (2019). **"Differences in plasma amino acid levels in patients with and without bacterial infection during the early stage of acute exacerbation of COPD."** Int J Chron Obstruct Pulmon Dis **14**: 575-583.

Purpose: No consensus has been reached regarding appropriate nutritional intervention and rehabilitation during early acute exacerbation of COPD (AECOPD). Given the individual differences in symptoms of AECOPD, patients should be classified by their pathology. For example, it is known that there are differences in the inflammatory response between AECOPD with and without bacterial infection. However, there have been few reports on AECOPD from a nutritional perspective. The aim of this study was to investigate amino acid levels in patients with AECOPD. Patients and methods: Blood was collected from patients who were hospitalized with AECOPD and from patients with COPD that was in a stable state. We divided the patients with AECOPD into those without bacterial infection (group A) and those with bacterial infection (group B). The patients with COPD that was stable served as controls (group C). The plasma levels of 9 essential amino acids, 13 nonessential amino acids, and total amino acids were compared between the three groups. Results: In the early stages of AECOPD, differences in plasma levels of only three amino acids (glycine, phenylalanine, and arginine) were observed between groups C and A. Differences in total amino acids and 13 amino acids were observed between groups C and B. Group B had lower levels of total amino acids and of seven amino acids (asparagine, citrulline, glutamine, histidine, methionine, serine, and threonine) compared with the other study groups. Conclusion: The findings of this study show that amino acid levels in plasma differ in patients with AECOPD depending on whether or not bacterial infection is present. Our results suggest that specific amino acids (ie, asparagine, citrulline, glutamine, histidine, serine, and threonine) have potential utility as diagnostic markers to distinguish between bacterial and nonbacterial AECOPD.

https://www.dovepress.com/getfile.php?fileID=48355

Irie, H., S. Chubachi, et al. (2018). **"Impact of cataract on health-related quality of life in a longitudinal Japanese chronic obstructive pulmonary cohort."** Chron Respir Dis **15**(4): 329-338.

Cigarette smoking increases the risk of developing both cataract and chronic obstructive pulmonary disease (COPD). The prevalence of cataract and the clinical characteristics of COPD patients with cataract were retrospectively investigated in a 2-year observational COPD cohort. We analyzed 395 patients with complete data on ophthalmologic evaluation (319 subjects with COPD and 76 subjects at risk of COPD). There was no difference in the prevalence of cataract between COPD patients and those at risk (47.0% vs. 42.1%, p = 0.44). Age >/= 75 years, low body mass index, and hypertension were independently associated with cataract as a comorbidity in COPD. The incidence of exacerbation within 2 years was significantly higher in COPD patients with cataract than those without cataract (36.6% vs. 18.3%, p = 0.0019). COPD patients with cataract exhibited significantly higher COPD assessment test score compared to those without cataract (13.7 +/- 8.9 vs. 11.5 +/- 7.2, p = 0.0240). Overall St George's Respiratory Questionnaire score and each component were significantly worse in COPD patients with cataract compared to those without cataract. COPD patients with cataract exhibited poor health-related quality of life and frequent exacerbations. The association between cataract and exacerbations of COPD deserves further attention.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6234576/pdf/10.1177_1479972317745735.pdf

Islam, S., N. K. Sarkar, et al. (2019). **"Association of Serum Vitamin D (25OHD) Level with Acute Exacerbation of Chronic Obstructive Pulmonary Disease."** Mymensingh Med J **28**(2): 441-448.

Acute exacerbations of COPD is characterized by a change in the patients baseline dyspnoea, cough and/or sputum that is beyond normal day to day differences and guides to a change in standard medications in a patient with COPD. Vitamin D influences the innate & adaptive immune system, and exerts pleiotropic antimicrobial and anti-inflammatory responses. Vitamin D deficiency is frequent among COPD patients but its contributory role in disease exacerbations is widely debated. This study was aimed to assess relationship between reduced serum vitamin D (25-OHD) level with COPD severity and acute

exacerbation. This observational cross-sectional study was carried out in the department of Respiratory Medicine, NIDCH, Mohakhali, Dhaka, Bangladesh from October 2016 to September 2017. Consecutive 80 hospital admitted patients with acute exacerbation of chronic obstructive pulmonary disease diagnosed on the basis of clinical history & pulmonary function tests and 78 age & sex matched controls were investigated for serum vitamin D (25-OHD) level. Among the COPD patients, 37% had Vitamin D deficiency (<20ng/ml) and 28.75% had Vitamin D insufficiency (20-29ng/ml). Mean vitamin D (25-OHD) level of COPD patients (25.82+/-10.62ngm/ml) was found to be significantly lower than healthy controls (32.57+/-11.32ngm/ml). Vitamin D deficiency was found, by Pearson correlation test, to be significantly associated with severity of COPD. Multivariate analysis showed that age (in years), FEV1 (percent predicted), frequent exacerbators (>/=2 in the last year), and smoking (>40 pack year) were significantly associated with Vitamin D deficiency. Acute exacerbation of chronic obstructive pulmonary disease patients was found to have vitamin D deficiency and vitamin D deficiency was significantly associated with severity of COPD. Vitamin D deficiency was also associated with frequent disease exacerbation.

Jenkins, A. R., N. S. Holden, et al. (2018). **"Pulmonary Rehabilitation, Exercise, and Exacerbations of COPD: Known Clinical Efficacy and the Unknown Mechanisms."** Chest **153**(5): 1281-1282.

https://journal.chestnet.org/article/S0012-3692(18)30343-X/pdf

Kalhan, R., M. T. Dransfield, et al. (2018). **"Respiratory Symptoms in Young Adults and Future Lung Disease. The CARDIA Lung Study."** Am J Respir Crit Care Med **197**(12): 1616-1624.

RATIONALE: There are limited data on factors in young adulthood that predict future lung disease. OBJECTIVES: To determine the relationship between respiratory symptoms, loss of lung health, and incident respiratory disease in a population-based study of young adults. METHODS: We examined prospective data from 2,749 participants in the CARDIA (Coronary Artery Risk Development in Young Adults) study who completed respiratory symptom questionnaires at baseline and 2 years later and repeated spirometry measurements over 30 years. MEASUREMENTS AND MAIN RESULTS: Cough or phlegm, episodes of bronchitis, wheeze, shortness of breath, and chest illnesses at both baseline and Year 2 were the main predictor variables in models assessing decline in FEV1 and FVC from Year 5 to Year 30, incident obstructive and restrictive lung physiology, and visual emphysema on thoracic computed tomography scan. After adjustment for covariates, including body mass index, asthma, and smoking, report of any symptom was associated with -2.71 ml/yr excess decline in FEV1 ($P < 0.001$) and -2.18 in FVC ($P < 0.001$) as well as greater odds of incident (prebronchodilator) obstructive (odds ratio [OR], 1.63; 95% confidence interval [CI], 1.24-2.14) and restrictive (OR, 1.40; 95% CI, 1.09-1.80) physiology. Cough-related symptoms (OR, 1.56; 95% CI, 1.13-2.16) were associated with greater odds of future emphysema. CONCLUSIONS: Persistent respiratory symptoms in young adults are associated with accelerated decline in lung function, incident obstructive and restrictive physiology, and greater odds of future radiographic emphysema.

Kalil-Filho, F. A., A. C. L. Campos, et al. (2019). **"PHYSIOTHERAPEUTIC APPROACHES AND THE EFFECTS ON INSPIRATORY MUSCLE FORCE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN THE PRE-OPERATIVE PREPARATION FOR ABDOMINAL SURGICAL PROCEDURES."** Arq Bras Cir Dig **32**(2): e1439.

BACKGROUND: Abdominal disorders can alter respiratory function and increase the morbidity and mortality of patients with chronic obstructive pulmonary disease. AIM: To improve the physiotherapeutic and

muscular capacity in chronic obstructive pulmonary muscular inspiration in the preoperative preparation in abdominal surgeries. METHOD: Retrospective and documentary study using SINPE (c) , clinical database software of patients with chronic obstructive pulmonary disease and candidates to abdominal operation. The sample consisted of 100 men aged 55-70 years, all with chronic obstructive pulmonary disease who underwent preoperative physiotherapeutic treatment. They were divided into two groups of 50 individuals (group A and group B). In group A the patients were treated with modern mobility techniques for bronchial clearance and the strengthening of the respiratory muscles was performed with IMT (R) Threshold. In group B the treatment performed for bronchial obstruction was with classic maneuvers and for the strengthening of the respiratory muscles for flow incentive was used Respiron (R) . RESULTS: Both groups obtained improvement in the values of the PiMax after the different treatments. Group A obtained greater change in the intervals and a more significant increase of the values of the PiMax in relation to the average pre and post-treatment. However, when analyzing the variance and the standard deviation of the samples, group B presented the best results showing more homogeneity. CONCLUSIONS: The modern and traditional bronchial clearance techniques associated with inspiratory muscle training were equally effective in gaining inspiratory muscle strength with increased Pmax. In this way, the two can be used in the preoperative preparation of patients with chronic obstructive pulmonary disease and referred to abdominal operations.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6713053/pdf/0102-6720-abcd-32-02-e1439.pdf

Kichler, C. M., F. A. Cothran, et al. (2018). **"Effect of a Palliative Screening Tool on Referrals: An Approach to Increase Access to Palliative Care Services."** J Hosp Palliat Nurs **20**(6): 548-553.

The aim of this study was to develop and trial a screening tool to increase palliative care referrals for hospitalized patients with chronic obstructive pulmonary disease (COPD) at a community hospital. Baseline data were collected retrospectively to determine the palliative care referral rate of patients with COPD at a high risk for readmission using the LACE index. A palliative care referral tool was developed to screen the patients who were at a high risk for readmission for palliative care referral. A 3-month pilot project prospectively evaluated the palliative care referral rate after educating staff on the use of the screening tool and implementing its use. During the baseline study, 2 palliative care referrals were placed out of 19 patients who were deemed appropriate by the screening tool (10.5%). During the pilot project, 16 palliative care referrals were placed out of 45 patients who were deemed appropriate by the screening tool (35.6%). Emergency room visits and readmissions were not significantly different between those with palliative referrals and those without. Barriers to palliative care referral were explored. The improvement in palliative care referrals, which occurred after the introduction of the consensus-driven screening process for patients with COPD, suggests the possibility of improved patient care using this model.

Kirby, M. and D. D. Sin (2018). **"Imaging End Points in COPD Clinical Trials: Are We There Yet?"** Chest **154**(1): 3-5.

https://journal.chestnet.org/article/S0012-3692(18)30259-9/pdf

Lazar, Z., A. Kelemen, et al. (2018). **"Central and peripheral airway nitric oxide in patients with stable and exacerbated chronic obstructive pulmonary disease."** J Breath Res **12**(3): 036017.

Nitrative stress pathways are involved in airway inflammation characterizing chronic obstructive pulmonary disease (COPD). Extended nitric oxide (NO) analysis allows the partitioned measurement of nitrative stress in the conducting bronchi and peripheral airways/alveolar spaces. However, pulmonary NO production at these two sites has not been systemically studied in stable and exacerbated COPD.

Twenty-eight patients with stable COPD, 34 patients during an exacerbation, and 15 smoking controls were recruited. Exhaled NO was measured at constant flow rates of 50 ml s(-1) (for FENO50) and 100-150-200-250 ml s(-1) (for the extended NO analysis). Clinical variables, including lung function, white blood cell count, C-reactive protein concentration, blood gas values and symptom score (COPD assessment test) were collected. The measurements were repeated in 26 patients with an exacerbation during convalescence. The exhaled NO parameters were analysed with non-parametric tests. The alveolar NO (CANO) was higher in stable COPD (median (interquartile range), 4.24 (2.35-6.09) ppb, $p < 0.01$) and in patients with an exacerbation (3.83 (2.31-6.62) ppb, $p < 0.05$) than in the controls (2.05 (1.77-2.80) ppb), but no difference was found between the stable and exacerbated disease ($p > 0.05$). The CANO correlated with the blood eosinophil percentage in all COPD patients ($r = 0.29$, $p = 0.02$). The total flux of bronchial NO (JawNO) increased in an exacerbation (exacerbated: 1.01 (0.45-2.44) nl s(-1) versus stable: 0.47 (0.16-0.81) nl s(-1), $p < 0.01$; exacerbated versus control: 0.38 (0.27-0.80) nl s(-1), $p < 0.05$), and it was reduced in convalescence after therapy (0.50 (0.31-0.96) nl s(-1), $p = 0.01$). Neither CANO and JawNO or their change were related to the clinical variables or the length of hospital stay in COPD. JawNO correlated with FENO50 during exacerbation ($r = 0.80$, $p < 0.001$). Extended NO analysis is a feasible method to monitor nitrative stress at different anatomical sites within the airways in stable and exacerbated COPD patients. Our results suggest that nitrative stress is constantly elevated in the small airways in COPD and increases in the conducting airways during an exacerbation.

https://iopscience.iop.org/article/10.1088/1752-7163/aac10a

Lee, K. C., Y. T. Wu, et al. (2019). **"Chronic obstructive pulmonary disease combined with vertebral compression fracture increases the risk of temporomandibular disorder: A population-based cohort study."** Medicine (Baltimore) **98**(37): e17162.

Vertebral compression fracture (VCF) is a common comorbidity of chronic obstructive pulmonary disease (COPD), and the coexistence of COPD and temporomandibular disorder (TMD) has been clinically noted. The present study aimed to investigate whether VCF increases the risk of TMD in patients with COPD.With a follow-up period of 15 years, this retrospective, population-based longitudinal cohort study enrolled sex- and age-matched COPD patients with and without VCF (1:3) who were identified from Taiwan's National Health Insurance Research Database from 2000 to 2015. Multivariate Cox regression analysis was performed to determine the risk of TMD in COPD patients with and without VCF. The cumulative risk of TMD between groups was estimated using Kaplan-Meier analysis.The risk factors for TMD in patients with COPD were VCF, osteoporosis, and winter season. The COPD with VCF group was more likely to develop TMD (adjusted hazard ratio = 3.011, $P < .001$) than the COPD without VCF group after adjustment for sex, age, variables, and comorbidities. In the subgroup analysis, the COPD with VCF group had a higher risk of TMD than the COPD without VCF group in almost all stratifications.COPD patients with VCF are at a higher risk of developing TMD. Clinicians taking care of patients with COPD should be aware of the occurrence of TMD as a comorbidity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6750274/pdf/medi-98-e17162.pdf

Lee, M. K., C. J. Xu, et al. (2019). **"Genome-wide DNA methylation and long-term ambient air pollution exposure in Korean adults."** Clin Epigenetics **11**(1): 37.

BACKGROUND: Ambient air pollution is associated with numerous adverse health outcomes, but the underlying mechanisms are not well understood; epigenetic effects including altered DNA methylation could play a role. To evaluate associations of long-term air pollution exposure with DNA methylation in blood, we conducted an epigenome-wide association study in a Korean chronic obstructive pulmonary disease cohort (N = 100 including 60 cases) using Illumina's Infinium HumanMethylation450K Beadchip. Annual average concentrations of particulate matter </= 10 mum in diameter (PM10) and nitrogen dioxide (NO_2) were estimated at participants' residential addresses using exposure prediction models. We used robust linear regression to identify differentially methylated probes (DMPs) and two different approaches, DMRcate and comb-p, to identify differentially methylated regions (DMRs). RESULTS: After

multiple testing correction (false discovery rate < 0.05), there were 12 DMPs and 27 DMRs associated with PM10 and 45 DMPs and 57 DMRs related to NO2. DMP cg06992688 (OTUB2) and several DMRs were associated with both exposures. Eleven DMPs in relation to NO2 confirmed previous findings in Europeans; the remainder were novel. Methylation levels of 39 DMPs were associated with expression levels of nearby genes in a separate dataset of 3075 individuals. Enriched networks were related to outcomes associated with air pollution including cardiovascular and respiratory diseases as well as inflammatory and immune responses. CONCLUSIONS: This study provides evidence that long-term ambient air pollution exposure impacts DNA methylation. The differential methylation signals can serve as potential air pollution biomarkers. These results may help better understand the influences of ambient air pollution on human health.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6396524/pdf/13148_2019_Article_635.pdf

Lee, S. M., J. G. Lee, et al. (2019). **"CT Image Conversion among Different Reconstruction Kernels without a Sinogram by Using a Convolutional Neural Network."** Korean J Radiol **20**(2): 295-303.

OBJECTIVE: The aim of our study was to develop and validate a convolutional neural network (CNN) architecture to convert CT images reconstructed with one kernel to images with different reconstruction kernels without using a sinogram. MATERIALS AND METHODS: This retrospective study was approved by the Institutional Review Board. Ten chest CT scans were performed and reconstructed with the B10f, B30f, B50f, and B70f kernels. The dataset was divided into six, two, and two examinations for training, validation, and testing, respectively. We constructed a CNN architecture consisting of six convolutional layers, each with a 3 x 3 kernel with 64 filter banks. Quantitative performance was evaluated using root mean square error (RMSE) values. To validate clinical use, image conversion was conducted on 30 additional chest CT scans reconstructed with the B30f and B50f kernels. The influence of image conversion on emphysema quantification was assessed with Bland-Altman plots. RESULTS: Our scheme rapidly generated conversion results at the rate of 0.065 s/slice. Substantial reduction in RMSE was observed in the converted images in comparison with the original images with different kernels (mean reduction, 65.7%; range, 29.5-82.2%). The mean emphysema indices for B30f, B50f, converted B30f, and converted B50f were 5.4 +/- 7.2%, 15.3 +/- 7.2%, 5.9 +/- 7.3%, and 16.8 +/- 7.5%, respectively. The 95% limits of agreement between B30f and other kernels (B50f and converted B30f) ranged from -14.1% to -2.6% (mean, -8.3%) and -2.3% to 0.7% (mean, -0.8%), respectively. CONCLUSION: CNN-based CT kernel conversion shows adequate performance with high accuracy and speed, indicating its potential clinical use.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6342751/pdf/kjr-20-295.pdf

Lococo, F., L. Boracchia, et al. (2018). **"Cervical subcutaneous emphysema and pneumomediastinum as an unusual complication of idiopathic pulmonary fibrosis."** ANZ J Surg **88**(10): E747-e748.

https://onlinelibrary.wiley.com/doi/abs/10.1111/ans.13723

Louvaris, Z., I. Vogiatzis, et al. (2018). **"Improvement in respiratory muscle O2 delivery is associated with less dyspnoea during exercise in COPD."** Clin Respir J **12**(3): 1308-1310.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12663

Marchand, E., J. P. d'Odemont, et al. (2019). **"A Patient with GOLD Stage 3 COPD << cured >> by One-Way Endobronchial Valves."** Medicina (Kaunas) **55**(3)Lung hyperinflation is a main determinant of dyspnoea in patients with chronic obstructive pulmonary disease (COPD). Surgical or bronchoscopic lung volume reduction are the most efficient therapeutic approaches for reducing hyperinflation in selected patients with emphysema. We here report the case of a 69-year old woman with COPD (GOLD stage 3-D) referred for lung volume reduction. She complained of persistent disabling dyspnoea despite appropriate therapy. Chest imaging showed marked emphysema heterogeneity as well as severe hyperinflation of the right lower lobe. She was deemed to be a good candidate for bronchoscopic treatment with one-way endobronchial valves. In the absence of interlobar collateral ventilation, 2 endobronchial valves were placed in the right lower lobe under general anaesthesia. The improvement observed 1 and 3 months after the procedure was such that the patient no longer met the pulmonary function criteria for COPD. The benefit persisted after 3 years.

https://res.mdpi.com/d_attachment/medicina/medicina-55-00065/article_deploy/medicina-55-00065-v2.pdf

Martin-Ontiyuelo, C., A. Rodo-Pin, et al. (2019). **"Is iron deficiency modulating physical activity in COPD?"** Int J Chron Obstruct Pulmon Dis **14**: 211-214.

There is evidence that iron plays a key role in the adequate functioning of skeletal muscle. While it has been demonstrated that nonanemic iron deficiency (NAID) affects exercise tolerance and response to exercise training in patients with COPD, the impact on daily physical activities (DPAs) remains unknown. Eighteen COPD patients with NAID (ferritin <100 ng/mL or ferritin 100-299 ng/mL with a transferrin saturation <20%) and 18 COPD patients without this abnormality, matched for age, gender, and the degree of airflow limitation (control group), were enrolled to the study. The primary outcome was the level of DPA assessed by accelerometers. Patients were (mean [SD]) 66 (7) years and were mostly male (70%) and former smokers (52%). Their forced expiratory volume at 1 second was 41 (16)% predicted, carbon monoxide diffusing capacity was 47 (14)% predicted and oxygen arterial pressure reached 70 (11) mmHg. DPA and the number of steps per day were lower in NAID COPD patients compared with controls (physical activity level 1.39 vs 1.59, $P<0.05$; and 4,402 vs 6,975 steps/day, $P<0.05$, respectively). The percentage of patients with increased time spent sitting per day (>6 hours) was higher in patients with NAID compared with controls (73% vs 37%, $P<0.05$). In addition, the percentage of patients doing moderate to vigorous physical activity per day (>3 metabolic equivalents of task, at least 30 minutes) was lower in this group (66% vs 100%, $P<0.05$). The presence of iron deficiency was associated with reduced DPA in COPD patients. Further studies are needed to evaluate iron reposition and their impact on the level of physical activity in these patients.

https://www.dovepress.com/getfile.php?fileID=47456

Mason, M., J. Hernandez-Sanchez, et al. (2018). **"Usefulness of the STOP-Bang Questionnaire in a Cardiac Surgical Population."** J Cardiothorac Vasc Anesth **32**(6): 2694-2699.

OBJECTIVE: The aim of this study was to assess the predictive accuracy of the STOP-Bang questionnaire in relation to obstructive sleep apnea (OSA) detected by nocturnal oximetry, as well as postoperative outcomes, in a population undergoing cardiac surgery. DESIGN: A prospective observational cohort study. SETTING: The specialist cardiothoracic center at the Royal Papworth Hospital, Cambridge University Health Partners, United Kingdom. PARTICIPANTS: All adult patients, undergoing elective coronary artery bypass grafting with or without cardiac valve surgery between March 2013 and July 2014 were included. The authors excluded patients participating in other interventional studies, those who had a tracheostomy before surgery, and those who required emergency surgery or were due to be admitted on the day of surgery. INTERVENTIONS: None. MEASUREMENTS AND RESULTS: Cardiac surgical patients were screened for the risk of OSA with the use of STOP-Bang questionnaire. The presence of OSA prior to surgery was assessed with overnight oximetry. The predictive performance of the STOP-Bang questionnaire was assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC)-receiver operating characteristic curve (ROC). Multiple-

logistic regression models were used to assess for associations between the STOP-Bang scores and postoperative outcomes. The STOP-Bang questionnaire discriminated poorly between mild OSA (AUC-ROC 0.57 [95% confidence interval (CI) 0.47-0.67]) and moderate/severe OSA (AUC-ROC 0.82 (95% CI 0.69-0.95)]. Accuracy was increased by modifying the cut-off value to 6 or greater, with sensitivity and specificity of 75% and 77%, respectively. A STOP-Bang score indicating the possibility of OSA was not significantly associated with prolonged intensive care unit lengths of stay (hazard ratio [HR] 1.1; 95% CI 0.99-1.19; p = 0.08) or postoperative complications (odds ratio [OR] 1.0; 95% CI 0.59-1.72; p = 0.98). CONCLUSIONS: In the study population, a STOP-Bang questionnaire score of 3 or greater had limited predictive value for identifying cardiac surgical patients at high risk of OSA. STOP-Bang scores were not significantly associated with worse postoperative outcomes. A STOP-Bang score of 6 or greater could help identify patients in need of a sleep study to confirm the presence of OSA as such patients may be at increased risk of postoperative complications.

https://www.jcvaonline.com/article/S1053-0770(18)30282-9/fulltext

Mejza, F., P. Nastalek, et al. (2018). **"Coexistence of Chronic Bronchitis in Chronic Obstructive Lung Disease."** Adv Exp Med Biol **1114**: 1-9.

The incidence of chronic obstructive pulmonary disease (COPD) is on the rise worldwide. Chronic bronchitis is a frequent accompaniment of COPD, which increases the burden of COPD in affected individuals. The aim of this study was to characterize the phenotype of chronic bronchitis in COPD patients. The study was based on the survey data retrospectively retrieved from the Action Health-Lung Cancer Prophylaxis and Health Care Improvement screening program that concerned all the inhabitants, aged over 40, of the Proszowice administrative region situated in the Lesser Poland Voivodeship in southern Poland. Participants with the symptoms suggestive of a lung disease were subject to further evaluation. The findings were that 546 (13.3%) out of the 4105 individuals displayed spirometry features of COPD. Symptoms of chronic bronchitis were present in 92 (16.8%) out of the COPD afflicted persons. Chronic bronchitis was commoner in current smokers and its incidence increased with increasing severity of airway obstruction. In multivariate analysis, chronic bronchitis was independently related to lower FEV1, FVC, FEV1/FVC, and to dyspnea. In regression model, factors related to increased risk of chronic bronchitis were current smoking, asthma, and lower lung function. We conclude that COPD with coexisting chronic bronchitis is linked to severer dyspnea and worse lung function. Current smoking, asthma, and lower lung function are related to increased risk of chronic bronchitis accompanying COPD.

https://link.springer.com/chapter/10.1007%2F5584_2018_200

Meteran, H., S. F. Thomsen, et al. (2018). **"Self-reported intake of fruit and vegetables and risk of chronic obstructive pulmonary disease: A nation-wide twin study."** Respir Med **144**: 16-21.

BACKGROUND: Although smoking is the major risk factor for chronic obstructive pulmonary disease (COPD) many patients with obstructive lung function suggesting COPD are never-smokers. Therefore, other lifestyle factors have been suggested as risk factors. AIMS: i) To examine the association between self-reported intake of fruit and vegetables and risk of COPD and ii) to examine whether the association between these traits are due to underlying genetic factors. METHODS: 12,449 twins, aged 40-80, from the Danish Twin Registry were recruited. The participants completed a questionnaire on medical history and lifestyle factors and participated in clinical examination. COPD was defined according to ATS/ERS recommendations. Multivariate logistic regressions were used to estimate the risk of COPD in individuals with a low intake of fruit and vegetables. Co-twin control analyses were performed to examine whether the association between fruit and vegetables and COPD is explained by genetic factors. Self-reported physician-diagnosed asthmatic individuals were excluded. RESULTS: Of the 11,458 individuals were included in the analyses, 48% of the participants were males. Mean age was 58.9 (years)+/-SD 9.6, mean BMI (kg/m(2))26.6+/-SD 4.4. A multivariate logistic regression, including sex, age and BMI showed that both smoking, no and heavy drinking and physical inactivity were independent predictors of COPD. There was a significant frequency-pendent association between intake of fruit and vegetables and

increased risk of COPD. Conditional logistic regression analyses showed that the association might be controlled by genetic factors. CONCLUSIONS: This study shows that low intake of fruit and vegetables is associated with an increased risk of COPD and the association might be under influence of genetic factors.

https://www.resmedjournal.com/article/S0954-6111(18)30295-6/fulltext

Moretz, C., S. Annavarapu, et al. (2019). **"Spirometry evaluation to assess performance of a claims-based predictive model identifying patients with undiagnosed COPD."** Int J Chron Obstruct Pulmon Dis **14**: 439-446.

Background: A claims-based model to predict patients likely to have undiagnosed COPD was developed by Moretz et al in 2015. This study aims to assess the performance of the aforementioned model using prospectively collected spirometry data. Methods: A study population aged 40-89 years enrolled in a Medicare Advantage plan with prescription drug coverage or commercial health plan and without a claim for COPD diagnosis was identified from April 1, 2012 to March 31, 2016 in the Humana claims database. This population was stratified into subjects likely or unlikely to have undiagnosed COPD using the claims-based predictive model. Subjects were randomly selected for spirometry evaluation of FEV1 and FVC. The predictive model was validated using airflow limitation ratio (FEV1/FVC <0.70). Results: A total of 218 subjects classified by the predictive model as likely and 331 not likely to have undiagnosed COPD completed spirometry evaluation. Those predicted to have undiagnosed COPD had a higher mean age (70.2 vs 67.9 years, P=0.0012) and a lower mean FEV1/FVC ratio (0.724 vs 0.753, P=0.0002) compared to those predicted not to have undiagnosed COPD. Performance metrics for the predictive model were: area under the curve =0.61, sensitivity =52.5%, specificity =64.6%, positive predictive value =33.5%, and negative predictive value =80.1%. Conclusion: The claims-based predictive model identifies those not at risk of having COPD eight out of ten times, and those who are likely to have COPD one out of three times.

https://www.dovepress.com/getfile.php?fileID=48074

Morrow, J. D., R. P. Chase, et al. (2019). **"RNA-sequencing across three matched tissues reveals shared and tissue-specific gene expression and pathway signatures of COPD."** Respir Res **20**(1): 65.

BACKGROUND: Multiple gene expression studies have been performed separately in peripheral blood, lung, and airway tissues to study COPD. We performed RNA-sequencing gene expression profiling of large-airway epithelium, alveolar macrophage and peripheral blood samples from the same subset of COPD cases and controls from the COPDGene study who underwent bronchoscopy at a single center. Using statistical and gene set enrichment approaches, we sought to improve the understanding of COPD by studying gene sets and pathways across these tissues, beyond the individual genomic determinants. METHODS: We performed differential expression analysis using RNA-seq data obtained from 63 samples from 21 COPD cases and controls (includes four non-smokers) via the R package DESeq2. We tested associations between gene expression and variables related to lung function, smoking history, and CT scan measures of emphysema and airway disease. We examined the correlation of differential gene expression across the tissues and phenotypes, hypothesizing that this would reveal preserved and private gene expression signatures. We performed gene set enrichment analyses using curated databases and findings from prior COPD studies to provide biological and disease relevance. RESULTS: The known smoking-related genes CYP1B1 and AHRR were among the top differential expression results for smoking status in the large-airway epithelium data. We observed a significant overlap of genes primarily across large-airway and macrophage results for smoking and airway disease phenotypes. We did not observe specific genes differentially expressed in all three tissues for any of the phenotypes. However, we did observe hemostasis and immune signaling pathways in the overlaps across all three tissues for emphysema, and amyloid and telomere-related pathways for smoking. In peripheral blood, the emphysema results were enriched for B cell related genes previously identified in lung tissue studies. CONCLUSIONS: Our integrative analyses across COPD-relevant tissues and prior studies revealed shared

and tissue-specific disease biology. These replicated and novel findings in the airway and peripheral blood have highlighted candidate genes and pathways for COPD pathogenesis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6446359/pdf/12931_2019_Article_1032.pdf

Mostafavi, B., E. Piitulainen, et al. (2019). **"Survival in the Swedish cohort with alpha-1-antitrypsin deficiency, up to the age of 43-45 years."** Int J Chron Obstruct Pulmon Dis **14**: 525-530.

Background: Alpha-1-antitrypsin deficiency (AATD) is a hereditary disorder. AATD is a known risk factor for the development of emphysema and liver disease. A cohort of severe (PiZZ) and moderate (PiSZ) AAT-deficient newborn infants was identified by the Swedish national neonatal AAT screening in 1972-1974 and has been followed up since birth. Our aim was to study survival in this cohort up to 43-45 years of age in comparison with the general Swedish population. Methods: Data from 127 PiZZ, 2 PiZnull, 54 PiSZ, and 1 PiSnull subjects, who were identified by the neonatal screening in 1972-1974, were included in the study. To compare death rates in the PiZZ and PiSZ individuals with the general Swedish population, a standardized mortality ratio (SMR) was calculated as the ratio of observed to expected deaths. Results: Seven PiZZ subjects died during the follow-up, to be compared with an expected 3.66 deaths for the general population, giving an SMR of 1.91 (95% CI 0.77-3.94). Four PiSZ subjects died compared to an expected 1.53 deaths, giving an SMR of 2.61 (95% CI 0.71-6.71). The cumulative probability of survival up to the age of 45 years was 94% (95% CI 90%-98%) for the study population. Six deaths occurred before the age of 8 years. Conclusion: Up to 43-45 years of age, there was no difference in survival between PiZZ and PiSZ individuals in comparison with the Swedish general population. The majority of deaths occurred during childhood.

https://www.dovepress.com/getfile.php?fileID=48350

Oliveira, A., A. Machado, et al. (2018). **"Minimal Important and Detectable Differences of Respiratory Measures in Outpatients with AECOPD(dagger)."** Copd **15**(5): 479-488.

Interpreting clinical changes during acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is challenging due to the absence of established minimal detectable (MDD) and important (MID) differences for most respiratory measures. This study established MDD and MID for respiratory measures in outpatients with AECOPD following pharmacological treatment. COPD assessment test (CAT), modified Borg scale (MBS), modified British Medical Research Council (mMRC) questionnaire, peripheral oxygen saturation (SpO2), computerised respiratory sounds and forced expiratory volume in one second (FEV1) were collected within 24-48 hour of an AECOPD and after 45 days of pharmacological treatment. MID and MDD were calculated using anchor- (receiver operating characteristic and linear regression analysis) and distribution-based methods (effect size, SEM, 0.5*SD and MDC95) and pooled using Meta XL. Forty-four outpatients with AECOPD (31male symbol; 68.2 +/- 9.1 years; FEV1 51.1 +/- 20.3%predicted) participated. Significant correlations with CAT were found for the MBS (r = 0.34), mMRC (r = 0.39) and FEV1 (r = 0.33), resulting in MIDs of 0.8, 0.5-0.6 and 0.03L, respectively. MDD of 0.5-1.4 (MBS), 0.4-1.2 (mMRC), 0.10-0.28L (FEV1), 3.6-10.1% (FEV1%predicted), 0.9-2.4% (SpO2), 0.7-1.9 (number of inspiratory crackles), 1.1-4.5 (number of expiratory crackles), 7.1-25.8% (inspiratory wheeze rate) and 11.8-63.0% (expiratory wheeze rate) were found. Pooled data of MID/MDD showed that improvements of 0.9 for the MBS, 0.6 for the mMRC, 0.15L for the FEV1, 7.6% for the FEV1%predicted, 1.5% for the SpO2, 1.1 for the inspiratory and 2.4 for the number of expiratory number of crackles, 14.1% for the inspiratory and 32.5% for the expiratory wheeze rate are meaningful following an AECOPD managed with pharmacological treatment on an outpatient basis.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1537366

Oliveira, A. and A. Marques (2018). **"Understanding symptoms variability in outpatients with AECOPD."** Pulmonology **24**(6): 357-360.

https://pdf.sciencedirectassets.com/318509/1-s2.0-S2531043718X00075/1-s2.0-S2531043718301557/main.pdf?X-Amz-Security-Token=AgoJb3JpZ2luX2VjEDIaCXVzLWVhc3QtMSJHMEUCIQCXRfXQMfXvNluImuiN07DHJHSLjLuSlVz8FiQqUTemXgIgEqRj2S6zmm2UFMnfiX6veT1aU%2FtKbwXNFiprc7WmWp4q2gMIOxACGgwwNTkwMDM1NDY4NjUiDDcGRrS3s%2F1rJ7yj3Sq3A8Ip3aZVOZpBUwnGUNcWADiHzZ09dSDELp177SPxykA1aqvL%2B2wagzUW1GZuHOILN0vz2IuuffCC2FAIdDc6wu2jVAnNDbUm6KSdSnbBCHsEJsDcp%2B5VRgFC6Y9Hva4YE%2BALREVpWk4VyEZLolBn465YMk63bQoz3asOrKWBwXfyN37FGA9ScqXyhWNE4z6gAZEMvcsEZMVqzgNadrNioAqNuDrWsRh8z2RaH2eKV%2FA5whRbeFnv%2FnkJXzSy4tfvn3vDUrZFtRVDUTK3kEjmv2%2BTyFYEYP%2FpEiLp%2B%2BHpmPa%2FqG0xnXbgZRjRsUHbUBPr0kLZplD23SI%2B4UY6xeWtcr8UJ0%2FdFOfMuRETPOeh9fRrS7XAQatzvXPVFyVlCkCQNS3v0EjcQQc97J0%2FmS2nf1z3zxcAXhfirQFL9OLSc1oRB5LGbjd7UpHxOy7sNrJWexAFb1fs%2B7JOOVJJE3pWU69N2KwP6sz7Hs3uP95bKfzYVHeF0%2Fzde6lHoGETKcR%2FKOlOuD3mg9cJyNZtVcXyweOk4nLO4%2B38wXWjuoAgJuj02%2BEzMyhJRnCOAoFIhB2dc6XuVc3boGUwhq7J7QU6tAHZFmW0yt2aQ4nR8r0z9JYZhtCOiOfgP6piZsQsMOvTFQD5LTXHxUTWH1Q77R8LxMO7uY%2BGOP%2BDHkmsVk2ESdnyzzMgU6WBUNOsXKoRFodTfA3X%2FREwC5w9bwsFnklWNKZmJf%2FxXVq5KEBpph%2B%2F2pwfmcc9xtqDxKd%2B46WZ2oIE9Ky%2FPVnm4D%2BV8w3gSmxiBG3mZSsnGymrbTFmph4znBtx0pJ1Qk51Bmn5LfZy7xCkr0n3XoY%3D&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Date=20191025T023228Z&X-Amz-SignedHeaders=host&X-Amz-Expires=300&X-Amz-Credential=ASIAQ3PHCVTYSK7JNREG%2F20191025%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Signature=0124d541eb58f9d97ea8865d15a9ff304e5d2a928f537f4ae4444db6c8f5b987&hash=f6a2bf5faceb31ef70574902b6eba66c528e9c2969d1bda191016cec1e2f2e95&host=68042c943591013ac2b2430a89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S2531043718301557&tid=spdf-71ebf580-fe94-4a05-b772-947ab60c67ea&sid=c45dcb8c9db9d74b333b0a27cc54ef11c900gxrqa&type=client

Orme, M. W., M. C. Steiner, et al. (2019). **"24-hour accelerometry in COPD: Exploring physical activity, sedentary behavior, sleep and clinical characteristics."** Int J Chron Obstruct Pulmon Dis **14**: 419-430.

Background: The constructs and interdependency of physical behaviors are not well described and the complexity of physical activity (PA) data analysis remains unexplored in COPD. This study examined the interrelationships of 24-hour physical behaviors and investigated their associations with participant characteristics for individuals with mild-moderate airflow obstruction and healthy control subjects. Patients and methods: Vigorous PA (VPA), moderate-to-vigorous PA (MVPA), light PA (LPA), stationary time (ST), average movement intensity (vector magnitude counts per minute), and sleep duration for 109 individuals with COPD and 135 healthy controls were obtained by wrist-worn accelerometry. Principal components analysis (PCA) examined interrelationships of physical behaviors to identify distinct behavioral constructs. Using the PCA component loadings, linear regressions examined associations with participant (+, positive correlation; -, negative correlation), and were compared between COPD and healthy control groups. Results: For both groups PCA revealed ST, LPA, and average movement intensity as distinct behavioral constructs to MVPA and VPA, labeled "low-intensity movement" and "high-intensity movement," respectively. Sleep was also found to be its own distinct behavioral construct. Results from linear regressions supported the identification of distinct behavioral constructs from PCA. In COPD, low-intensity movement was associated with limitations with mobility (-), daily activities (-), health status (+), and body mass index (BMI) (-) independent of high-intensity movement and sleep. High-intensity movement was associated with age (-) and self-care limitations (-) independent of low-intensity movement and sleep. Sleep was associated with gender (0= female, 1= male; [-]), lung function (-), and percentage body fat (+) independent of low-intensity and high-intensity movement. Conclusion: Distinct behavioral constructs comprising the 24-hour day were identified as "low-intensity movement," "high-intensity movement," and "sleep" with each construct independently associated with different participant characteristics. Future research should determine whether modifying these behaviors improves health outcomes in COPD.

https://www.dovepress.com/getfile.php?fileID=48100

Paplinska-Goryca, M., K. Goryca, et al. (2018). **"Genetic characterization of macrophages from induced sputum of patients with asthma and chronic obstructive pulmonary disease."** Pol Arch Intern Med **128**(9): 559-562.

Pedersen, F., U. M. Zissler, et al. (2019). **"Rating sputum cell quality in clinical trials for asthma and COPD treatment."** Int J Chron Obstruct Pulmon Dis **14**: 195-198.

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Quint, J. K. (2018). **"Response."** Chest **153**(5): 1282-1283.

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Ramos, K. J., M. O. Harhay, et al. (2019). **"Which Shall I Choose? Lung Transplantation Listing Preference for Individuals with Interstitial Lung Disease and Chronic Obstructive Pulmonary Disease."** Ann Am Thorac Soc **16**(2): 193-195.

Raymakers, A. J. N., M. Sadatsafavi, et al. (2018). **"Response."** Chest **153**(2): 578-579.

https://journal.chestnet.org/article/S0012-3692(17)33238-5/pdf

Reijnders, T., M. Schuler, et al. (2018). **"The Impact of Loneliness on Outcomes of Pulmonary Rehabilitation in Patients with COPD."** Copd **15**(5): 446-453.

Psychological factors such as negative affect have been demonstrated to impact course and treatment of chronic obstructive pulmonary disease (COPD). However, little is known about the respective impact of social factors. In several other chronic diseases, loneliness has been shown to predict morbidity, but little is known about its impact on COPD. Therefore, this study examined the associations between loneliness and outcome measures of a pulmonary rehabilitation program (PR). Before and after a 3-week inpatient PR program, patients with COPD (N = 104) underwent a 6-min walking test to measure functional exercise capacity. Loneliness was assessed with the Loneliness Scale. The Medical Outcomes Study 36-item short form, 9-item Patient Health Questionnaire, and 7-item General Anxiety Disorder questionnaire were administered as measures of health-related quality of life (HQoL), depression, and anxiety, respectively. Multiple regression analyses showed that at the start of PR, more loneliness was associated with worse levels of functional exercise capacity, HQoL, depression, and anxiety, but with greater improvements in functional exercise capacity and HQoL over the course of PR, even after controlling for age, sex, lung function, and smoking status. Patients with stronger decreases in loneliness from start to end of PR showed stronger improvements in functional exercise capacity and HQoL over the course of

PR. The present study shows that subjective loneliness is associated with relevant treatment outcomes in patients with COPD undergoing pulmonary rehabilitation. Therefore, loneliness should be addressed in patients with COPD as it could play a significant role in their disease progression.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1471128

Rezaei, S. S., C. Rinner, et al. (2018). **"Use of beta-blocker is associated with lower mortality in patients with coronary artery disease with or without COPD."** Clin Respir J **12**(12): 2627-2634.

INTRODUCTION: Beta-blockers are indicated for secondary prevention of coronary artery disease (CAD). However, in patients with co-morbidity of chronic obstructive pulmonary disease (COPD) an underuse of beta-blocker has been reported. MATERIALS AND METHODS: Prescription and demographic data and information on hospital discharge diagnoses from 13 Austrian health insurance funds for the years 2006-2007 were analyzed. The primary end point was all-cause mortality of patients with CAD with or without COPD and its association with use of beta-blockers. RESULTS: In 2006 and 2007, 65717 patients (37% female, 63% male) were discharged with a diagnosis of CAD. Among these patients, 46% had a co-diagnosis of COPD, 24% had diabetes, and 75% received beta-blockers. Use of beta-blockers was comparable in CAD patients with COPD and without COPD with 77% and 74%, respectively. Thousand eight hundred seventy-two (8.1%) and 1473 (5.6%) patients with and without COPD, who used beta-blockers died within months in 2006 and 2007. Thousand five hundred fifty-three (22.0%) and 1862 (22.2%) of patients with and without COPD and without beta-blockers died during the corresponding time period. DISCUSSION: Use of beta-blockers was similar in patients with CAD with or without co-diagnosis of COPD. However, mortality of beta-blocker users was markedly lower than that of nonusers in patients with CAD with or without COPD.

https://onlinelibrary.wiley.com/doi/full/10.1111/crj.12968

Ruppert, A. M., J. Perrin, et al. (2018). **"Effect of cannabis and tobacco on emphysema in patients with spontaneous pneumothorax."** Diagn Interv Imaging **99**(7-8): 465-471.

PURPOSE: To compare imaging findings on thoracic computed tomography (CT) examination in patients with primary spontaneous pneumothorax (SP), depending on their tobacco and/or cannabis consumption. MATERIALS AND METHODS: A total of 83 patients who had thoracic CT for primary SP were prospectively included. There were 65 men and 18 women with a median age of 33 years (IQR: 27; 44 years). The patients were further categorized into three groups according to their smoking habits. Thirteen patients were non-smokers, 38 were tobacco only smokers and 32 were tobacco and cannabis smokers. CT examinations were retrospectively reviewed for the presence of blebs, centrilobular and paraseptal emphysema and lung nodules in each group for comparison. RESULTS: Emphysema was detected in 43/85 patients (51.8%), including 1/13 patients (7.7%) in the non-smoking group, 19/38 patients (50%) in the tobacco only group and 23/32 patients (71.9%) in the tobacco and cannabis smokers, with no difference between tobacco only and tobacco and cannabis smokers. No differences in type and location of emphysema was found between tobacco only and tobacco and cannabis smokers. Tobacco and cannabis smokers with emphysema were significantly younger than tobacco only smokers with emphysema (35 vs. 46 years, respectively) (P=0.009). CONCLUSION: The prevalence of emphysema visible on CT is not different between tobacco and tobacco/cannabis smokers, however, it occurs at a younger age in tobacco and cannabis smokers. This result suggests that cannabis, when added to tobacco, may lead to emphysema at a younger age.

https://pdf.sciencedirectassets.com/280852/1-s2.0-S2211568418X00072/1-s2.0-S2211568418300391/main.pdf?X-Amz-Security-Token=AgoJb3JpZ2luX2VjEDIaCXVzLWVhc3QtMSJIMEYCIQCMQv1DlUSoatIe3kZ2qqqjtd1NtUA7HykSx9r025LOpwIhAIh787U%2FJ1Qja2YIho%2BwcelTwNWzOYzGrm%2B9owQ1X2qpKvwDCDsQAhoMMDU5MDAzNTQ2ODY1IgwgNOTh%2BvMPiQOss2Mq2QNPtPiShsI7kBuIQyIi64IqN7812VDwLrm9VAINEh4BjE072hm%2BFAu1YgE8ry1uVprdpX%2FO8Ov9TGYS1a%2BAmguepHFLU8DR94jdDRKrU3JZ%2B6CHt97QjuRCDe

qU4Q80ZbQOTnVV%2F0sotnJpg%2BqmTlLOrHgL4X6hUVp5gPKXKltLwWlMqAGqpTZEVvIwCiag%2BJoa0%2FT4EPijh1CqFEmSTOarWhNN4qXnBzTDXEhExGUYWfPHU8En48AFT%2Bqj%2F2wyMwNnygi4Vy5sTYIv6W6uUHCn1wf02w8MlEpIdvJ%2FkiO7PDzCIsbDPgkkF8J49wqMJ%2Fmu5tTo29ZAD1KxfAvFN%2Fz4VLV5nvzjZHRt%2Fz6wLW2%2FBUgig2Roezi5xwOmEuRafJo6TEg284gYkH%2BlzD7z7s96tXG7PjinQ637ORrPci4xPm%2FoXyCqh9nxK9upUnYeKHZm5f2CWi9cTWOzFHQzG0YOLNkOhPIKjS5UvjCiR4Feop%2F5wFNZ8ol99bwJ%2FC8j9BSW6rKweUmkYAxozD3nTbRusMWJBP99KAwkjJc0eiQgLux%2Fm0rPTGK6nBSvOOorNXONfFiD6Z30fMZeIm25%2F51k9YqGOZMakQFOH8vR6qtkBRtkVbM46nCrqDD3ocntBTqzAfGlnH8iB9DNlHsV%2FmpXGLtF%2FSUy1tbks2sbaM88L%2BsXBr9uUFwC9PhO%2FjYzaNPUlseXWGRxxOmKhzbGr8KKWpt5SaEghP4KUhxQdq9hCUAzBkIHxZs%2FubYsJ2YK6IAKCN6QVmP9Pz1OBy77H7Ga%2F%2BtTAtQzC2Kf5wWeX4TXDLbu1QaIblGz8q6gyVglnVqTS%2FjI8Yvi1Wut6yYC6pV5NAjKTxO68UwFg2viNJb06ZICIIBh&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Date=20191025T023217Z&X-Amz-SignedHeaders=host&X-Amz-Expires=300&X-Amz-Credential=ASIAQ3PHCVTYVB5YLIO2%2F20191025%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Signature=58d42871d923f96ac6319377137a9d4591ed37f9dc0de0ef4d932f02a3dd41e0&hash=ce7794317fc435a72303f0373e22c030181831ee05d2b2776eae760fdf3e8bd1&host=68042c943591013ac2b2430a89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S2211568418300391&tid=spdf-5b661f1b-2360-4bd7-b35c-7a6380deffd7&sid=c45dcb8c9db9d74b333b0a27cc54ef11c900gxrqa&type=client

Saad Junior, R., J. M. A. Lopez, et al. (2019). **"Pneumostomy: an operative proposal for the treatment of severe diffuse pulmonary emphysema."** Rev Col Bras Cir **46**(3): e20192231.

OBJECTIVE: to evaluate a new operative technique for the treatment of advanced pulmonary emphysema. METHODS: we conducted a prospective analysis of nine patients with severe pulmonary emphysema submitted to pneumostomy. The procedure was performed under local anesthesia, in the anterior thoracic wall, hemiclavicular line, in the second intercostal space, through an anterior thoracotomy of 5cm for access to the upper lobe, whose anterior segment was pinched and fixed to the parietal pleura. We carried out the pneumostomy with electrocautery and blunt insertion of an intrapulmonary drain. To assess the procedure, we performed pulmonary function tests, imaging tests, six-minute walk test, and applied quality of life questionnaires, all measured preoperatively and 30 days after the procedure. RESULTS: no deaths occurred related to the procedure. Imaging studies showed a decrease in lung volume. The pulmonary function showed a significant reduction in the residual volume. The six-minute walk test showed an increase in the distance covered in the postoperative period. There was significant improvement of the quality of life as demonstrated through questionnaires Medical Outcomes Study 36 Item Short-Form Health Survey (SF-36), Saint-George Respiratory Questionnaire (SGRQ), Medical Research Council scale (MRC), and Eastern Cooperative Oncology Group Performance status (ECOG). CONCLUSION: the proposed technique is feasible, safe, easy to perform and to maintain.

Sakhamuri, S. and V. K. Chattu (2018). **"Statins in COPD: Selection Modalities and Mortalities."** Chest **153**(2): 578.

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Sam, A. and M. Kraft (2018). **"Asthma/COPD Overlap: A Gene by Environment Interaction?"** Chest **154**(6): 1270-1271.

https://journal.chestnet.org/article/S0012-3692(18)32578-9/pdf

Schneider, L. P., K. C. Furlanetto, et al. (2018). **"Sedentary Behaviour and Physical Inactivity in Patients with Chronic Obstructive Pulmonary Disease: Two Sides of the Same Coin?"** Copd **15**(5): 432-438.

Despite the growing interest in sedentarism, there is no available information on the profile of patients with COPD according to sedentary behaviour (SB) and with a detailed analysis of minute-by-minute bouts. Hence, the aims of this study were to quantify the time spent in SB, light activities and moderate-to-vigorous physical activities (MVPA) and to verify the relationship of MVPA and SB in individuals with COPD, as well as to identify the profile of those physically (in)active and (non)-sedentary. A cross-sectional study in which physical activity in daily life was objectively assessed through the use of SenseWear Pro 2 Armband (BodyMedia) during 2 consecutive weekdays, 12 h/day. Analysis was performed minute-by-minute for each day of each patient. MVPA comprised time spent >3 metabolic equivalents (MET), whereas light activities corresponded to time spent between 1.5 and 3 MET and SB to time spent <1.5 MET. A total of 137 subjects with COPD (66 +/- 8years; FEV1 46 [31-57] %pred; BMI 26 [22-30] kg/m(2)) were analysed. Time spent in MVPA and SB presented strong negative correlation (r = -0.72, P < 0.001). Minute-by-minute analysis showed that patients with COPD spend most of their time in SB. SB accounted for 40% of all bouts >1 minute, whereas only 14% these bouts concern MVPA. Patients combining two positive characteristics (physically active and non-sedentary) have better clinical profile than others. In conclusion, SB is negatively correlated with MVPA in patients with COPD. Furthermore, patients classified as physically active (i.e., those who reach MVPA recommendations) in combination with a non-sedentary lifestyle present markedly better clinical conditions.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1548587

Shafuddin, E., C. L. Chang, et al. (2018). **"Comparing severity scores in exacerbations of chronic obstructive pulmonary disease."** Clin Respir J **12**(12): 2668-2675.

INTRODUCTION: Prognostic scores help identify patients at a high risk of mortality in exacerbations of chronic obstructive pulmonary disease (COPD). The Dyspnoea, Eosinopaenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) score has been reported to perform better than other severity scores in predicting mortality from exacerbations of COPD in studies including patients with pneumonia. OBJECTIVE: To compare the performance of DECAF with other prognostic scores: CURB-65, CRB-65 and BAP-65, in predicting 30-day mortality in patients hospitalised with exacerbations of COPD without pneumonia. METHODS: Data from hospital admission of 423 patients from two cohorts of patients with exacerbations of COPD without consolidation on chest radiographs were used to compile the CURB-65, CRB-65, BAP-65 and DECAF scores. The performance of each prognostic score in predicting 30-day mortality was studied using receiver operating curve analysis. RESULTS: Thirty-one patients (7%) died within 30 days of hospital admission. One hundred patients (24%) did not have DECAF scores because of the incomplete laboratory data, while all 423 patients had the other scores available for analysis. All scores predicted mortality with similar areas under the receiver operating characteristic curve (CURB-65 = 0.69, CRB-65 = 0.64, BAP-65 = 0.64, DECAF = 0.65, P = 0.186). CONCLUSION: In patients hospitalised with exacerbations of COPD without pneumonia, simple clinical scores that rely on fewer laboratory measures perform at least as well as DECAF in predicting early mortality.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12973

Sheikh, M. A. (2018). **"Retrospectively reported childhood adversity is associated with asthma and chronic bronchitis, independent of mental health."** J Psychosom Res **114**: 50-57.

Several researchers have raised the concern that the cross-sectional association of retrospectively reported childhood adversity with self-reported onset of asthma and chronic bronchitis in adulthood may be confounded, as well as mediated by an individual's mental health. The aim of this study was to assess the effect of retrospectively reported childhood adversity on self-reported onset of asthma and chronic bronchitis in adulthood, independent of potential confounding and mediating variables (including

respondent's mental health). We used data collected in 2007-2008 within the framework of the Tromso Study (N=12,981), a representative study of adult men and women in Norway. The associations of childhood adversity with asthma and chronic bronchitis were assessed with Poisson regression models. Relative risks (RR) and 95% confidence intervals (CI) were estimated with bias-corrected bootstrapping. Childhood adversity was associated with a 9% increased risk of asthma (RR=1.09, 95% CI: 1.02, 1.16) and a 14% increased risk chronic bronchitis (RR=1.14, 95% CI: 1.03, 1.26) in adulthood, independent of age, sex, parental history of psychiatric problems/asthma/dementia, education, smoking, social support, and respondent's mental health. Controlling for indicators of respondent's mental health reduced the strength of associations of childhood adversity with asthma and chronic bronchitis; however, the associations were still present in the same direction (p<.05). These findings suggest that the association of retrospectively reported childhood adversity with asthma and chronic bronchitis is independent of respondent's mental health. We recommend controlling for indicators of the respondent's mental health to assess an unbiased association of retrospectively measured childhood adversity with self-reported asthma and chronic bronchitis.

https://www.sciencedirect.com/science/article/abs/pii/S0022399918307013?via%3Dihub

Shvaiko, L. I., K. D. Bazyka, et al. (2018). **"capital ES, CyrillicHRONIC OBSTRUCTIVE PULMONARY DISEASE IN THE CLEAN-UP WORKERS OF CHORNOBYL NPP ACCIDENT IN A REMOTE POST6ACCIDENT PERIOD (CLINICAL STUDY)."** Probl Radiac Med Radiobiol **23**: 490-498.

OBJECTIVE: to study the clinical differences in the course of chronic obstructive pulmonary disease in the clean-upworkers (CW) of Chornobyl nuclear power plant (ChNPP) in the remote post-accident period (30 years after the effectof radiation exposure). MATERIAL AND METHODS: 120 CW of ChNPP were examined (47 patients with chronic obstructive pulmonary disease(COPD) and 73 patients without bronchopulmonary disease) and 50 patients in the control group (20 patients with COPDand 30 without bronchopulmonary disease). Individually documented radiation exposure doses of CW were (25.2 +/- 13.7cSv, (M +/- SD)). The study program included clinical examination, functional pulmonary tests, and statistical analysis. RESULTS: The negative correlation dependence (r = -0,358, p < 0,05) between the 6-minute walk rate and the age ofCOPD patients was established. Negative correlation was observed between the distance at 6-minute walk test, andforced exhalation volume for 1 sec. (FEV1) (l) (r = 0.743; p < 0.05); forced vital capacity (FVC) (l) (r = 0.692;p < 0.05), the ratio of FEV1/FEV6 (r = 0.697; p < 0.05), forced exhalation volume for 6 sec (FEV6) (l) (r = 0.727; p < 0.05),Diffusion Lung Capacity (mmol/min/kPa) (r = 0.754, p <0, 05). A positive correlation was found between the dose ofradiation exposure and the index of intra-thoracic pressure (ITGV) in the CW (r = 0.1494, p <0.05), and the values ofFEV1 and forced expiration flow (FEF75), regardless of the presence of COPD. In the subgroup of patients with COPDCW there was a significantly higher proportion of patients with cardiovascular and cerebrovascular pathology, whichcorresponded with the higher level of cholesterol compared with the control group ((5.52 +/- 1.34) mmol/l and(4.46 +/- 1.74) mmol/l, respectively, p < 0.05). CONCLUSIONS: In the CW at the ChNPP, compared with the group of nosological control, there were significantly lowerindicators of the shortness of breath degree and the frequency of exacerbations per year, more pronounced distur-bance of exercise tolerance, higher comorbidity. Dependence of development of COPD on radiation dose and age atthis stage of research was not estimated.

Simpson, A. J. and S. J. Fowler (2018). **"Reclassification of Bronchodilator Reversibility in the U-BIOPRED Adult Asthma Cohort Using z Scores."** Chest **153**(4): 1070-1072.

https://journal.chestnet.org/article/S0012-3692(18)30255-1/pdf

Singh Patidar, B., A. Meena, et al. (2018). **"Adenosine Metabolism in COPD: A Study on Adenosine Levels, 5'-Nucleotidase, Adenosine Deaminase and Its Isoenzymes Activity in Serum, Lymphocytes and Erythrocytes."** Copd **15**(6): 559-571.

Adenosine is a signaling molecule which is produced in high concentrations during airway inflammation. Airway inflammation is a characteristic feature of COPD. Therefore, the current study was designed to evaluate the changes in adenosine metabolism in COPD and correlate these changes with severity of the disease. The study was conducted on 50 healthy controls (25 healthy non-smokers and 25 healthy smokers) and 46 COPD patients (21 moderate, 15 severe and 10 very severe). The patients were sub-divided into moderate, severe and very severe categories as per the GOLD spirometric classification. Blood was collected from each subject and serum, lymphocytes and erythrocytes were separated. The adenosine levels and activities of 5'-nucleotidase, adenosine deaminase and its isoenzymes were assessed in serum, lymphocytes and erythrocytes. The data were analyzed statistically. A p value < 0.05 was considered as significant. In healthy smokers and COPD patients the adenosine levels increased. In COPD patients 5'-nucleotidase activity increased significantly in serum, lymphocytes and erythrocytes. The activities of ADA and isoenzymes decreased significantly in serum of healthy smokers and COPD patients, in lymphocytes and erythrocytes of very severe COPD patients and of ADA and ADA2 in lymphocytes and erythrocytes of moderate and severe COPD patients. The FEV1 (% of predicted) showed a significant negative correlation with adenosine levels and 5'-nucleotidase activity in serum, lymphocytes and erythrocytes and significant positive correlation with ADA and isoenzymes activity in serum and lymphocytes of COPD patients. We conclude that the adenosine metabolism changes in COPD. The adenosine levels and 5'-nucleotidase activity increase, and ADA activity decreases with severity of the disease.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1537365

Soltani, A., M. Q. Mahmood, et al. (2019). **"Cancer-protective effects of inhaled corticosteroids in COPD are likely related to modification of epithelial activation."** Eur Respir J **54**(3)
https://erj.ersjournals.com/content/54/3/1901088

Spila-Alegiani, S., F. Trotta, et al. (2018). **"Comparative Effectiveness of Two Tiotropium Formulations: A Retrospective Cohort Study."** Copd **15**(5): 418-423.

The effectiveness of the tiotropium Respimat((R)) formulation in routine clinical practice is still an open issue due to concern about the generalizability of the Tiotropium Safety and Performance in Respimat((R)) (TIOSPIR) trial findings. Our aim was to compare the incidence of acute respiratory events between new users of tiotropium Respimat((R)) and HandiHaler((R)). The study population comprised patients aged >/=45 years resident in two Italian regions who received a first tiotropium prescription (HandiHaler((R)) or Respimat((R))) between 1 July 2011 and 30 November 2013. The cohort was identified within the database of drug prescriptions reimbursed by the Italian National Health Service. Clinical outcomes were obtained from hospital records. The primary outcome was the first hospitalization for respiratory events, including chronic obstructive pulmonary disease (COPD) exacerbation, respiratory failure, hypoxemia/hyperventilation and pneumonia, during the exposure period. The hazard ratios were estimated for the propensity score matched groups with Cox regression. After matching, 31,334 patients with incident tiotropium prescriptions were included. Similar incidence rates of the primary outcome between the Respimat((R)) and HandiHaler((R)) users were identified (adjusted hazard ratio 0.95, 95% CI 0.84-1.07). No differences emerged in the subgroup analyses conducted according to the baseline characteristics of the tiotropium users. This study confirms the findings observed in the TIOSPIR trial in a more heterogeneous population that included patient subgroups with severe respiratory disease and unstable COPD.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1554032

Stanbrook, M. B. (2018). **"In COPD, new use of long-acting bronchodilators was linked to CV events at </= 30 days, but not > 30 days."** Ann Intern Med **168**(8): Jc47.

https://annals.org/aim/article-abstract/2678487/copd-new-use-long-acting-bronchodilators-linked-cv-events-30?doi=10.7326%2fACPJC-2018-168-8-047

Stanford, R. H., A. Nag, et al. (2018). **"Claims-based risk model for first severe COPD exacerbation."** Am J Manag Care **24**(2): e45-e53.

OBJECTIVES: To develop and validate a predictive model for first severe chronic obstructive pulmonary disease (COPD) exacerbation using health insurance claims data and to validate the risk measure of controller medication to total COPD treatment (controller and rescue) ratio (CTR). STUDY DESIGN: A predictive model was developed and validated in 2 managed care databases: Truven Health MarketScan database and Reliant Medical Group database. This secondary analysis assessed risk factors, including CTR, during the baseline period (Year 1) to predict risk of severe exacerbation in the at-risk period (Year 2). METHODS: Patients with COPD who were 40 years or older and who had at least 1 COPD medication dispensed during the year following COPD diagnosis were included. Subjects with severe exacerbations in the baseline year were excluded. Risk factors in the baseline period were included as potential predictors in multivariate analysis. Performance was evaluated using C-statistics. RESULTS: The analysis included 223,824 patients. The greatest risk factors for first severe exacerbation were advanced age, chronic oxygen therapy usage, COPD diagnosis type, dispensing of 4 or more canisters of rescue medication, and having 2 or more moderate exacerbations. A CTR of 0.3 or greater was associated with a 14% lower risk of severe exacerbation. The model performed well with C-statistics, ranging from 0.711 to 0.714. CONCLUSIONS: This claims-based risk model can predict the likelihood of first severe COPD exacerbation. The CTR could also potentially be used to target populations at greatest risk for severe exacerbations. This could be relevant for providers and payers in approaches to prevent severe exacerbations and reduce costs.

Sujatha-Bhaskar, S., R. F. Alizadeh, et al. (2018). **"Respiratory complications after colonic procedures in chronic obstructive pulmonary disease: does laparoscopy offer a benefit?"** Surg Endosc **32**(3): 1280-1285.

BACKGROUND: Patients with severe chronic obstructive pulmonary disease (COPD) are at a higher risk for postoperative respiratory complications. Despite the benefits of a minimally invasive approach, laparoscopic pneumoperitoneum can substantially reduce functional residual capacity and raise alveolar dead space, potentially increasing the risk of respiratory failure which may be poorly tolerated by COPD patients. This raises controversy as to whether open techniques should be preferentially employed in this population. METHODS: The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database from 2011 to 2014 was used to examine the clinical data from patients with COPD who electively underwent laparoscopic and open colectomy. Patients defined as having COPD demonstrated either functional disability, chronic use of bronchodilators, prior COPD-related hospitalization, or reduced forced expiratory reserve volumes on lung testing (FEV1 <75%). Demographic data and preoperative characteristics were compared. Linear and logistic regressions were utilized to perform multivariate analysis and determine risk-adjusted outcomes. RESULTS: Of the 4397 patients with COPD, 53.8% underwent laparoscopic colectomy (LC) while 46.2% underwent open colectomy (OC). The LC and OC groups were similar with respect to demographic data and preoperative comorbidities. Equivalent frequencies of exertional dyspnea (LC 35.4 vs OC 37.7%, P = 0.11) were noted. After multivariate risk adjustment, OC demonstrated an increased rate of overall respiratory complications including pneumonia, reintubation, and prolonged ventilator dependency when compared to LC (OR 1.60, 95% CI 1.30-1.98, P < 0.01). OC was associated with longer length of stay (10

+/- 8 vs. 6.7 +/- 7 days, P < 0.01) and higher readmission (OR 1.36, 95% CI 1.09-1.68, P < 0.01) compared to LC. CONCLUSION: Despite the potential risks of laparoscopic pneumoperitoneum in the susceptible COPD population, a minimally invasive approach was associated with lower risk of postoperative respiratory complications, shorter length of stay, and decrease in postoperative morbidity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6281393/pdf/nihms-996195.pdf

Synn, A. and M. B. Rice (2018). **"Is Bucolic Life Bad for Chronic Obstructive Pulmonary Disease?"** Ann Am Thorac Soc **15**(7): 799-800.

Szpak, R., G. C. Strapasson, et al. (2020). **"Legal demands of the tiotropium bromide for treatment of chronic obstructive pulmonary disease and their financial impact for the State of Parana, Brazil."** Einstein (Sao Paulo) **18**: eGS4442.

OBJECTIVE: To analyze the legal demands of tiotropium bromide to treat chronic obstructive pulmonary disease. METHODS: We included secondary data from the pharmaceutical care management systems made available by the Parana State Drug Center. RESULTS: Public interest civil action and ordinary procedures, among others, were the most common used by the patients to obtain the medicine. Two Health Centers in Parana (Londrina and Umuarama) concentrated more than 50% of the actions. The most common specialty of physicians who prescribed (33.8%) was pulmonology. There is a small financial impact of tiotropium bromide on general costs with medicines of the Parana State Drug Center. However, a significant individual financial impact was observed because one unit of the medicine represents 38% of the Brazilian minimum wage. CONCLUSION: Our study highlights the need of incorporating this medicine in the class of long-acting anticholinergic bronchodilator in the Brazilian public health system.

https://journal.einstein.br/wp-content/uploads/articles_xml/2317-6385-eins-18-eGS4442/2317-6385-eins-18-eGS4442.pdf

Tan, G. P., N. McArdle, et al. (2018). **"Patterns of use, survival and prognostic factors in patients receiving home mechanical ventilation in Western Australia: A single centre historical cohort study."** Chron Respir Dis **15**(4): 356-364.

Home mechanical ventilation (HMV) is used in a wide range of disorders associated with chronic hypoventilation. We describe the patterns of use, survival and predictors of death in Western Australia. We identified 240 consecutive patients (60% male; mean age 58 years and body mass index 31 kg m(-2)) referred for HMV between 2005 and 2010. The patients were grouped into four categories: motor neurone disorders (MND; 39%), pulmonary disease (PULM; 25%, mainly chronic obstructive pulmonary disease), non-MND neuromuscular and chest wall disorders (NMCW; 21%) and the obesity hypoventilation syndrome (OHS; 15%). On average, the patients had moderate ventilatory impairment (forced vital capacity: 51%predicted), sleep apnoea (apnoea-hypopnea index: 25 events h(-1)), sleep-related hypoventilation (transcutaneous carbon dioxide rise of 20 mmHg) and daytime hypercarbia (PCO2: 54 mmHg). Median durations of survival from HMV initiation were 1.0, 4.2, 9.9 and >11.5 years for MND, PULM, NMCW and OHS, respectively. Independent predictors of death varied between primary indications for HMV; the predictors included (a) age in all groups except for MND (hazard ratios (HRs) 1.03-1.10); (b) cardiovascular disease (HR: 2.35, 95% confidence interval (CI): 1.08-5.10) in MND; (c) obesity (HR: 0.28, 95% CI: 0.13-0.62) and oxygen therapy (HR: 0.33, 95% CI: 0.14-0.79) in PULM; and (d) forced expiratory volume in 1 s (%predicted; HR: 0.93, 95% CI: 0.88-1.00) in OHS.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6234575/pdf/10.1177_1479972318755723.pdf

Tang, S. and F. Gong (2019). **"Cdc42 participates in the occurrence of chronic obstructive pulmonary disease by regulating migration of inflammatory cells."** Minerva Med **110**(5): 477-480.

Thiruvenkatarajan, V., T. Maycock, et al. (2018). **"Anaesthetic management for endobronchial valve insertion: lessons learned from a single centre retrospective series and a literature review."** BMC Anesthesiol **18**(1): 206.

BACKGROUND: Endoscopic lung volume reduction using one or more endobronchial valves is a treatment option for a select group of patients with severe emphysema. Patients presenting for this procedure pose various challenges to the anaesthetist; in addition to their lung condition, they are often elderly with multiple comorbidities. The procedure is usually performed outside the operating room. Monitored anaesthesia care with intravenous sedation, and general anaesthesia with an endotracheal tube have both been described for these procedures, aiming for adequate ventilation and haemodynamic stability. METHODS: We present our experience on 20 of these procedures in relation to the anaesthetic techniques employed and discuss the perioperative challenges involved in managing these cases. RESULTS: Twenty one planned endobronchial valve insertion procedures were identified on 18 patients. There were ten cases of monitored anaesthesia care with sedation and 10 cases which used general anaesthesia with an endotracheal tube. Two have been excluded; one had features of anaphylaxis and the procedure was abandoned, and the other required conversion from monitored anaesthesia care to general anaesthesia with endotracheal tube. CONCLUSIONS: Both monitored anaesthesia care with sedation and general anaesthesia with endotracheal tube were well tolerated during endobronchial valve insertion procedures. General anaesthesia with endotracheal tube may offer better interventional conditions, patient comfort and reduced anaesthetic time.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6309056/pdf/12871_2018_Article_670.pdf

Topic, A., V. Milovanovic, et al. (2018). **"Oxidized Alpha-1-Antitrypsin as a Potential Biomarker Associated with Onset and Severity of Chronic Obstructive Pulmonary Disease in Adult Population."** Copd **15**(5): 472-478.

Oxidative stress could reduce inhibitor activity of the alpha-1-antitrypsin (A1AT). Oxidative-modified A1AT (oxidized alpha-1-antitrypsin, OxyA1AT) significantly loses ability to protect the lungs from neutrophil elastase. We aimed to investigate OxyA1AT as a potential biomarker associated with onset and severity of chronic obstructive pulmonary disease (COPD) in adult population. The study included 65 patients with COPD (33 smokers and 32 no-smokers) and 46 healthy participants (17 smokers and 29 no-smokers). Determination of OxyA1AT in serum was based on the difference between the inhibitory activities of normal and oxidized A1AT against trypsin and elastase. The level of OxyA1AT was significantly increased in the group of COPD smokers compared to healthy no-smokers ($p = 0.030$) and COPD no-smokers ($p = 0.009$). The highest level of OxyA1AT was found in group of smokers with severe and very severe COPD in comparison to the following: no-smokers with the same stage of disease ($p = 0.038$), smokers with moderate COPD ($p = 0.022$), and the healthy control group, regardless of the smoking status (control no-smokers $p = 0.001$ and control smokers $p = 0.034$). In conclusion, serum level of OxyA1AT would be potentially good biomarker for the assessment of harmful effect of smoking to the onset and severity of COPD. Also, clinical significance of OxyA1AT as prognostic biomarker could be useful in assessing the effectiveness of antioxidant therapy for COPD and emphysema. Suitable and inexpensive laboratory method for determination of OxyA1AT is additional benefit for the introduction of OxyA1AT into routine clinical practice for diagnosis and monitoring of COPD.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1541448

Toren, K., M. Andersson, et al. (2018). **"Airflow limitation classified with the fixed ratio or the lower limit of normal and cause-specific mortality - A prospective study."** Respir Med **144**: 36-41.

BACKGROUND: There is controversy as to whether airflow limitation should be defined as forced expiratory volume in 1s (FEV1)/vital capacity (VC)<0.7 or as FEV1/VC< the lower limit of normal (LLN). The aim was to examine whether different definitions of airflow limitation differ in predicting mortality. METHODS: Longitudinal prospective study of a national cohort of Swedish workers (199,408 men; 7988 women), aged 20-64 years with spirometry without bronchodilation at baseline followed from 1979 until death, or censorship at 2010. Airflow limitation (AL) by Global Obstructive Lung Disease criteria, ALGOLD, was defined as FEV1/VC<0.7; ALLLN as FEV1/VC<LLN. All all-cause, COPD and cardiovascular disease mortality was analyzed among men and women in relation to ALGOLD and ALLLN, adjusted for age and smoking. RESULTS: Among men, all-cause mortality risks were similar by airflow limitation criteria: ALGOLD RR=1.32, 95% CI 1.26-1.38; ALLLN, RR=1.37, 95% CI 1.31-1.44. The risk estimates were also similar by airflow limitation definition for cardiovascular mortality and for COPD mortality. Among women, all-cause mortality was also similar by airflow limitation criteria, but significantly higher as compared to men: ALGOLD RR=2.10, 95% CI 1.66-2.66; ALLLN, RR=2.09, 95% CI 1.66-2.62. Also cardiovascular and COPD mortality by airflow limitation criteria was significantly higher among women as compared to men. CONCLUSIONS: Defined either as FEV1/VC<0.7 or as FEV1/VC<LLN, airflow limitation predicted excess mortality risk of similar magnitude. Mortality in relation to airflow limitation was higher among women compared to men.

https://www.resmedjournal.com/article/S0954-6111(18)30306-8/fulltext

Uysal, P., G. Simsek, et al. (2019). **"Evaluation of plasma antimicrobial peptide LL-37 and nuclear factor-kappaB levels in stable chronic obstructive pulmonary disease."** Int J Chron Obstruct Pulmon Dis **14**: 321-330.

Background: Antimicrobial peptides are effectors of host defence against infection and inflammation and can encourage wound repair. Objectives: The objectives of this study were to investigate the plasma antimicrobial peptide LL-37 and nuclear factor-kappaB (NF-kappaB) levels in patients with stable COPD compared with a control group and to highlight their importance in immune inflammation. Methods: One hundred and thirty-eight stable COPD patients and 33 control subjects were enrolled in the study. The COPD patients were classified into four groups based on FEV1 (groups I-IV) and also divided into "low-risk and high-risk" groups (groups A-B [low risk], C-D [high risk]). Results: Plasma LL-37 levels were significantly lower while plasma NF-kappaB levels of the COPD patients were significantly higher than those of the control subjects (P<0.001, both). LL-37 levels were significantly lower in group IV than in groups I, II, and III (P<0.01, all). NF-kappaB levels were significantly higher in groups III and IV than in groups I and II (P<0.05, both). There was a positive correlation between FEV1 and FEV1/FVC in all COPD patients (r=0.742, P<0.001) and in group D (r=0.741, P<0.001). Furthermore, there was an inverse correlation between LL-37 and NF-kappaB in both the groups C (r=-0.566, P<0.001) and D (r=-0.694, P<0.001) and group C+D combined (r=-0.593, P<0.001). Furthermore, in group C, LL-37 and FEV1 were positively correlated (r=0.633, P<0.001). Conclusion: Our study indicated that plasma LL-37 and NF-kappaB may play an important role in chronic immune inflammation. Decreased LL-37 levels may be particularly high risk for patients in stage IV disease. The role of LL-37 as a target for treatment of the immune system and COPD must be widely evaluated.

https://www.dovepress.com/getfile.php?fileID=47746

Vestbo, J. (2018). **"Childhood Asthma, Lung Function Trajectories, and Chronic Obstructive Pulmonary Disease: An Additional Step Forward."** Ann Am Thorac Soc **15**(9): 1030-1031.

Vianello, A., M. Caminati, et al. (2018). **"Spontaneous pneumomediastinum complicating severe acute asthma exacerbation in adult patients."** J Asthma **55**(9): 1028-1034.

Objectives: The real incidence of pneumomediastinum (PNM) in adult patients with severe acute asthma exacerbation continues to be unknown. The current study aims to investigate the occurrence of PNM in an adult population of patients presenting a severe asthma attack and to evaluate the risk factors associated to its development. Methods: The 45 consecutive subjects who were admitted to our Division between January 1, 2015 and December 31, 2016 for severe acute asthma exacerbation underwent a diagnostic protocol including a standard chest X-ray and continuous monitoring of arterial oxygen saturation (SaO2) during the first 24 hours following admission. The patients showing persistence or deterioration of oxyhemoglobin desaturation were prescribed a chest Computed Tomographic (CT) scan. Results: Five out of the 45 patients (11.1%) with severe acute asthma exacerbation were diagnosed with PNM, in one case on the basis of an X-ray image and in four on the basis of a chest CT scan. Data analysis showed that the PNM patients were younger [21 (17-21) vs 49.5 (20-73) yrs; p < 0.001] and more likely to show sensitization to Alternaria (2/5 vs 0/40; p = 0.0101) with respect to their non-PNM counterparts. The duration of hospital stay was similar in the two groups [8 (4-12) vs 7 (3-15) days; p = 0.6939]. Conclusions: PNM is a common clinical entity in young adults with severe acute asthma exacerbation, particularly in those with unsatisfactory response to initial medical therapy. Although generally benign, patients with suspected PNM should be closely monitored because of the risk of developing severe hypoxemia.

https://www.tandfonline.com/doi/full/10.1080/02770903.2017.1388392

Viceconte, M., I. S. Rocco, et al. (2018). **"Chronic obstructive pulmonary disease severity influences outcomes after off-pump coronary artery bypass."** J Thorac Cardiovasc Surg **156**(4): 1554-1561.

OBJECTIVE: To analyze the impact and severity of chronic obstructive pulmonary disease (COPD) on pulmonary function and postoperative clinical outcome based on the Global Initiative for Obstructive Lung Disease criteria in patients undergoing off-pump coronary artery bypass grafting (CABG). METHODS: Patients were allocated into 3 groups according to presence and severity of COPD: no or mild COPD (n = 144); moderate COPD (n = 77); and severe COPD (n = 30). Spirometry values were obtained preoperatively and on postoperative days (PODs) 2 and 5. The incidences of pneumonia and reintubation, time of mechanical ventilation, and length of postoperative hospital stay were recorded. RESULTS: Significant impairment in pulmonary function was observed in all groups on PODs 2 and 5 (P < .001). However, postoperative pulmonary dysfunction was significantly higher in the moderate and severe COPD groups compared with the no or mild COPD group (P < .05). On multivariable analysis, severe COPD was associated with an elevated risk for composite outcomes (odds ratio, 1.37; 95% confidence interval, 1.20-1.57; P < .001). A preoperative forced expiratory volume in 1 second (FEV1) <50% of the predicted value was associated with poor outcome. A significant negative correlation was found between FEV1 at POD 5 and postoperative length of stay (r = -0.5; P < .001). CONCLUSIONS: More severe COPD was associated with greater impairment in pulmonary function and worse clinical outcomes after off-pump CABG surgery. A preoperative FEV1 <50% of predicted value appears to be an important predictor of postoperative complications.

https://www.jtcvs.org/article/S0022-5223(18)31231-5/fulltext

Vitacca, M., S. Marino, et al. (2018). **"Bacterial Colonization in COPD Patients Admitted to a Rehabilitation Respiratory Unit and Impact on Length of Stay: A Real-Life Study."** Copd **15**(6): 581-587.

Bacterial colonization is a well-known phenomenon in acute care, but scant information is available regarding the rehabilitation setting. We retrospectively analyzed, in COPD patients admitted to a Respiratory Rehabilitative unit in 2010, the number of cultures requested, of positive cultures, and of cultures showing multiple drug resistant (MDR) organisms. We also compared hospital admissions (HA) with versus without positive cultures and with versus without MDR and investigated which baseline variables may predict length of stay (LOS) > 30 days. Of 286 COPD admissions (involving 269 patients, age 71 +/- 11 years, males 66%), culture samples were requested in 62 (22%). The rate of colonization and of MDR organisms was 61 and 39%, respectively. Patients with a positive culture had a worse clinical condition and disability, and were more frequently tracheostomized, on invasive mechanical ventilation (MV) and admitted from/discharged to acute care. Patients with MDR cultures showed a lower exercise tolerance. Factors predicting LOS > 30 days were the presence of comorbidities, invasive MV, age > 65 years, and lower functional status, but not a positive culture or MDR presence. To our knowledge, this is the first real-life Italian study investigating the epidemiology of colonization and the association between colonization and LOS in a respiratory rehabilitation setting. Further investigation is necessary to clarify the relationship between colonization burden and patients' baseline clinical status and outcomes.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1572731

Wan, E. S., S. Fortis, et al. (2018). **"Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study."** Am J Respir Crit Care Med **198**(11): 1397-1405.

RATIONALE: Increasing awareness of the prevalence and significance of Preserved Ratio Impaired Spirometry (PRISm), alternatively known as restrictive or Global Initiative for Chronic Obstructive Lung Disease (GOLD)-unclassified spirometry, has expanded the body of knowledge on cross-sectional risk factors. However, longitudinal studies of PRISm remain limited. OBJECTIVES: To examine longitudinal patterns of change in lung function, radiographic characteristics, and mortality of current and former smokers with PRISm. METHODS: Current and former smokers, aged 45 to 80 years, were enrolled in COPDGene (phase 1, 2008-2011) and returned for a 5-year follow-up (phase 2, 2012-2016). Subjects completed questionnaires, spirometry, chest computed tomography scans, and 6-minute-walk tests at both study visits. Baseline characteristics, longitudinal change in lung function, and mortality were assessed by post-bronchodilator lung function categories: PRISm (FEV1/FVC < 0.7 and FEV1 < 80%), GOLD0 (FEV1/FVC > 0.7 and FEV1 > 80%), and GOLD1-4 (FEV1/FVC < 0.7). MEASUREMENTS AND MAIN RESULTS: Although the prevalence of PRISm was consistent (12.4-12.5%) at phases 1 and 2, subjects with PRISm exhibited substantial rates of transition to and from other lung function categories. Among subjects with PRISm at phase 1, 22.2% transitioned to GOLD0 and 25.1% progressed to GOLD1-4 at phase 2. Subjects with PRISm at both phase 1 and phase 2 had reduced rates of FEV1 decline (-27.3 +/- 42.1 vs. -33.0 +/- 41.7 ml/yr) and comparable proportions of normal computed tomography scans (51% vs. 52.7%) relative to subjects with stable GOLD0 spirometry. In contrast, incident PRISm exhibited accelerated rates of lung function decline. Subjects with PRISm at phase 1 had higher mortality rates relative to GOLD0 and lower rates relative to the GOLD1-4 group. CONCLUSIONS: PRISm is highly prevalent, is associated with increased mortality, and represents a transitional state for significant subgroups of subjects. Additional studies to characterize longitudinal progression in PRISm are warranted.

Wang, M., C. P. Aaron, et al. (2019). **"Association Between Long-term Exposure to Ambient Air Pollution and Change in Quantitatively Assessed Emphysema and Lung Function."** Jama **322**(6): 546-556.

Importance: While air pollutants at historical levels have been associated with cardiovascular and respiratory diseases, it is not known whether exposure to contemporary air pollutant concentrations is associated with progression of emphysema. Objective: To assess the longitudinal association of ambient ozone (O3), fine particulate matter (PM2.5), oxides of nitrogen (NOx), and black carbon exposure with change

in percent emphysema assessed via computed tomographic (CT) imaging and lung function. Design, Setting, and Participants: This cohort study included participants from the Multi-Ethnic Study of Atherosclerosis (MESA) Air and Lung Studies conducted in 6 metropolitan regions of the United States, which included 6814 adults aged 45 to 84 years recruited between July 2000 and August 2002, and an additional 257 participants recruited from February 2005 to May 2007, with follow-up through November 2018. Exposures: Residence-specific air pollutant concentrations (O3, PM2.5, NOx, and black carbon) were estimated by validated spatiotemporal models incorporating cohort-specific monitoring, determined from 1999 through the end of follow-up. Main Outcomes and Measures: Percent emphysema, defined as the percent of lung pixels less than -950 Hounsfield units, was assessed up to 5 times per participant via cardiac CT scan (2000-2007) and equivalent regions on lung CT scans (2010-2018). Spirometry was performed up to 3 times per participant (2004-2018). Results: Among 7071 study participants (mean [range] age at recruitment, 60 [45-84] years; 3330 [47.1%] were men), 5780 were assigned outdoor residential air pollution concentrations in the year of their baseline examination and during the follow-up period and had at least 1 follow-up CT scan, and 2772 had at least 1 follow-up spirometric assessment, over a median of 10 years. Median percent emphysema was 3% at baseline and increased a mean of 0.58 percentage points per 10 years. Mean ambient concentrations of PM2.5 and NOx, but not O3, decreased substantially during follow-up. Ambient concentrations of O3, PM2.5, NOx, and black carbon at study baseline were significantly associated with greater increases in percent emphysema per 10 years (O3: 0.13 per 3 parts per billion [95% CI, 0.03-0.24]; PM2.5: 0.11 per 2 mug/m3 [95% CI, 0.03-0.19]; NOx: 0.06 per 10 parts per billion [95% CI, 0.01-0.12]; black carbon: 0.10 per 0.2 mug/m3 [95% CI, 0.01-0.18]). Ambient O3 and NOx concentrations, but not PM2.5 concentrations, during follow-up were also significantly associated with greater increases in percent emphysema. Ambient O3 concentrations, but not other pollutants, at baseline and during follow-up were significantly associated with a greater decline in forced expiratory volume in 1 second per 10 years (baseline: 13.41 mL per 3 parts per billion [95% CI, 0.7-26.1]; follow-up: 18.15 mL per 3 parts per billion [95% CI, 1.59-34.71]). Conclusions and Relevance: In this cohort study conducted between 2000 and 2018 in 6 US metropolitan regions, long-term exposure to ambient air pollutants was significantly associated with increasing emphysema assessed quantitatively using CT imaging and lung function.

https://jamanetwork.com/journals/jama/article-abstract/2747669

Welling, J. B. A., J. E. Hartman, et al. (2018). **"Chartis Measurement of Collateral Ventilation: Conscious Sedation versus General Anesthesia - A Retrospective Comparison."** Respiration **96**(5): 480-487.

BACKGROUND: Absence of interlobar collateral ventilation using the Chartis measurement is the key predictor for successful endobronchial valve treatment in severe emphysema. Chartis was originally validated in spontaneous breathing patients under conscious sedation (CS); however, this can be challenging due to cough, mucus secretion, mucosal swelling, and bronchoconstriction. Performing Chartis under general anesthesia (GA) avoids these problems and may result in an easier procedure with a higher success rate. However, using Chartis under GA with positive pressure ventilation has not been validated. OBJECTIVES: In this study we investigated the impact of anesthesia technique, CS versus GA, on the feasibility and outcomes of Chartis measurement. METHODS: We retrospectively analyzed all Chartis measurements performed at our hospital from October 2010 until December 2017. RESULTS: We analyzed 250 emphysema patients (median forced expiratory volume in 1 s 26%, range 12-52% predicted). In 121 patients (48%) the measurement was performed using CS, in 124 (50%) using GA, and in 5 (2%) both anesthesia techniques were used. In total, 746 Chartis readings were analyzed (432 CS, 277 GA, and 37 combination). Testing under CS took significantly longer than GA (median 19 min [range 5-65] vs. 11 min [3-35], $p < 0.001$) and required more measurements (3 [1-13] vs. 2 [1-6], $p < 0.001$). There was no significant difference in target lobe volume reduction after treatment (-1,123 mL [-3,604 to 332] in CS vs. -1,251 mL [-3,333 to -1] in GA, $p = 0.35$). CONCLUSIONS: In conclusion, Chartis measurement under CS took significantly longer and required more measurements than under GA, without a difference in treatment outcome. We recommend a prospective trial comparing both techniques within the same patients to validate this approach.

https://www.karger.com/Article/Pdf/490733

Xin, H., H. Li, et al. (2019). **"Disrupted resting-state spontaneous neural activity in stable COPD."** Int J Chron Obstruct Pulmon Dis **14**: 499-508.

Introduction and aim: Abnormal brain structure and function in COPD has been reported on MRI. However, the deficit in local synchronization of spontaneous activity in patients with stable COPD remains unknown. The main aim of the present study was to explore spontaneous brain activity in patients with COPD compared with normal controls using the regional homogeneity (ReHo) method based on resting-state functional MRI. Methods: Nineteen patients with stable COPD and 20 well-matched (including age, sex, and number of years of education) normal controls who were recruited for the present study underwent resting-state functional MRI examinations and a series of neuropsychological and clinical assessments. The ReHo method was used to assess the strength of local brain signal synchrony. The mean ReHo values in brain areas with abnormal ReHo were evaluated with a receiver operating characteristic curve. The relationships between the brain regions with altered ReHo values and the clinical and neuropsychological parameters in COPD patients were assessed using Pearson's correlation. Results: Patients with COPD showed significantly lower ReHo values in the left occipital lobe and the right lingual, bilateral precuneus, and right precentral gyrus. The result of receiver operating characteristic curve analysis showed that the altered average ReHo values have high efficacy for distinguishing function. The mean lower ReHo values in the precuneus gyrus showed a significant positive correlation with FEV1%, FEV1/FVC, and orientation function but a significant negative correlation with arterial partial pressure of carbon dioxide. Conclusion: The COPD patients demonstrated abnormal synchrony of regional spontaneous activity, and the regions with abnormal activity were all correlated with visual processing pathways, which might provide us with a new perspective to further understand the underlying pathophysiology of cognitive impairment in patients with COPD.

https://www.dovepress.com/getfile.php?fileID=48301

Xu, Y., T. Yamashiro, et al. (2019). **"Strain measurement on four-dimensional dynamic-ventilation CT: quantitative analysis of abnormal respiratory deformation of the lung in COPD."** Int J Chron Obstruct Pulmon Dis **14**: 65-72.

Purpose: Strain measurement is frequently used to assess myocardial motion in cardiac imaging. This study aimed to apply strain measurement to pulmonary motion observed by four-dimensional dynamic-ventilation computed tomography (CT) and to clarify motion abnormality in COPD. Materials and methods: Thirty-two smokers, including ten with COPD, underwent dynamic-ventilation CT during spontaneous breathing. CT data were continuously reconstructed every 0.5 seconds. In the series of images obtained by dynamic-ventilation CT, five expiratory frames were identified starting from the peak inspiratory frame (first expiratory frame) and ending with the fifth expiratory frame. Strain measurement of the scanned lung was performed using research software that was originally developed for cardiac strain measurement and modified for assessing deformation of the lung. The measured strain values were divided by the change in mean lung density to adjust for the degree of expiration. Spearman's rank correlation analysis was used to evaluate associations between the adjusted strain measurements and various spirometric values. Results: The adjusted strain measurement was negatively correlated with FEV1/FVC (rho=-0.52, P<0.01), maximum mid-expiratory flow (rho=-0.59, P<0.001), and peak expiratory flow (rho=-0.48, P<0.01), suggesting that abnormal deformation of lung motion is related to various patterns of expiratory airflow limitation. Conclusion: Abnormal deformation of lung motion exists in COPD patients and can be quantitatively assessed by strain measurement using dynamic-ventilation CT. This technique can be expanded to dynamic-ventilation CT in patients with various lung and airway diseases that cause abnormal pulmonary motion.

https://www.dovepress.com/getfile.php?fileID=47039

Zeng, Y. Y., W. P. Hu, et al. (2019). **"Altered serum levels of type I collagen turnover indicators accompanied by IL-6 and IL-8 release in stable COPD."** Int J Chron Obstruct Pulmon Dis **14**: 163-168.

Background: COPD, characterized by chronic inflammation and airway remodeling, has significant pathological alterations in composition and deposition of the extracellular matrix. The expression of procollagen 1 C-terminal peptide (PICP) and collagen type 1 C-terminal telopeptide (ICTP), two major by-products in the synthesis and degradation of collagen, was shown to be positively correlated with inflammatory mediator levels in previous studies. Purpose: In this study, we investigated whether the serum concentrations of PICP and ICTP were associated with the inflammation level for patients with stable COPD. Patients and methods: We collected serum samples from 25 control subjects and 20 patients with stable COPD from December 2011 to October 2012 in Shanghai Zhongshan Hospital and Shanghai Dahua Hospital. We determined concentrations of PICP, ICTP, C-reactive protein (CRP), IL-6, IL-8, and tumor necrosis factor (TNF)-alpha by using enzyme-linked immunosorbent assay methods. Results: Demographic characteristics were comparable between the two groups. In patients with stable COPD, serum levels of CRP, IL-6, IL-8, and TNF-alpha were all elevated compared to control subjects, but only changes of IL-6 achieved statistical significance. Serum concentration of PICP was significantly elevated in patients with COPD, and level of ICTP was slightly decreased. Moreover, serum concentrations of PICP were positively correlated with the levels of both IL-6 and IL-8. Conclusion: The increased levels of serum PICP in COPD might indicate the condition of airway remodeling, and IL-6 and/or IL-8 might play an important role in stimulating collagen synthesis.

https://www.dovepress.com/getfile.php?fileID=47330

Zewari, S., L. Hadi, et al. (2018). **"Obesity in COPD: Comorbidities with Practical Consequences?"** Copd **15**(5): 464-471.

COPD and obesity often coexist and there is a complex interaction between them. Our aim was to evaluate the prevalence of obesity in a secondary care COPD population. Furthermore, the presence of comorbidities in obese (COPDOB) and non-obese COPD (COPDNO) individuals was studied. In 1654 COPD patients (aged >/=18 years) who visited a pulmonologist between January 2015 and December 2015, patient characteristics, pulmonary function tests and comorbidities were obtained from the medical records. Subjects were categorized according their BMI as underweight (<18.5 kg/m(2)), normal weight (18.5-24.9 kg/m(2)), overweight (25.0-29.9 kg/m(2)) or obese (BMI >/=30.0 kg/m(2)). The Charlson comorbidity index and COTE index were used to quantify comorbidities. The prevalence of obesity was 21.8% in our COPD population. Obesity was significantly less common in GOLD stage IV (10.1%) compared to GOLD I (20.5%), II (27.8%) and III (18.9%). COPDOB had different comorbidities compared with COPDNO. Hypertension, diabetes mellitus, atrial fibrillation and congestive heart failure were significantly more prevalent in COPDOB compared with COPDNO. Osteoporosis and lung cancer were significantly more common in COPDNO compared with COPDOB. Obesity is common in patients with COPD and is most prevalent in COPD GOLD I-II and least prevalent in COPD GOLD IV. Obese COPD patients have different comorbidities than non-obese COPD patients. Cardiovascular and metabolic comorbidities, especially hypertension and diabetes mellitus, are highly prevalent in obese COPD patients. Active screening for these conditions should be a priority for physicians treating obese COPD patients.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1509951

Zhou, L., L. Guan, et al. (2017). **"High-pressure versus low-pressure home non-invasive positive pressure ventilation with built-in software in patients with stable hypercapnic COPD: a pilot study."** Sci Rep **7**(1): 16728.

High-pressure non-invasive positive pressure ventilation (NPPV) is a new strategy targeted at maximally reducing arterial carbon dioxide. However, high inspiratory positive airway pressure (IPAP) might cause respiratory adverse events likely to diminish the benefit of NPPV. In the setting of ventilatory support, monitoring NPPV efficacy and resolving problems promptly are critical. This study assessed the treatment effect of high and low-pressure NPPV in chronic hypercapnic COPD using home ventilator with built-in software.

In this pilot study, we investigated 34 patients using NPPV for 3 months. 13 patients used high-pressure ventilation and 21 patients used low-pressure ventilation. The primary outcome was daytime partial pressure of arterial blood carbon dioxide (PaCO2). There were no between-group differences in daytime PaCO2 and FEV1, but a trend favouring high-pressure NPPV was observed. Significant between-group differences were found in the transition dyspnoea index (TDI) (high-pressure, 1.69 +/- 1.75, versus low-pressure, -0.04 +/- 2.71, p = 0.044). No differences were found in usage time, leakage, health-related quality of life, spirometry, or 6-minute walk test. High-pressure NPPV with built-in software monitoring in patients with chronic hypercapnic COPD is associated with improvement in TDI scores and a positive trend in favour of high-pressure NPPV for improving PaCO2 is observed.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5711850/pdf/41598_2017_Article_17142.pdf

Zielinski, M., M. Gasior, et al. (2018). **"Influence of Gaseous Pollutants on COPD Exacerbations in Patients with Cardiovascular Comorbidities."** Adv Exp Med Biol **1114**: 11-17.

Exacerbations of chronic obstructive pulmonary disease (COPD) are a serious public health issue. Ambient pollution and meteorological factors are considered among precipitating factors. There are few data concerning the impact of ambient pollutants other than particulates on COPD exacerbations. Among gaseous pollutants four main groups of substances are primarily monitored: nitrogen oxides (NOx), sulphur dioxide (SO2), carbon monoxide (CO), and ozone (O3). In this study, 12,889 hospitalizations in the years 2006-2014 due to exacerbations of COPD in patients having a co-existing cardiovascular pathology were retrospectively analyzed. Cardiovascular disease was ruled out as the underlying reason of hospitalization. Data concerning the then accompanying gaseous pollutants and weather conditions were collected. The findings were that the impact of SO2 content was significantly associated with the relative risk (RR) of COPD exacerbation when the exposure took place at least 30 days or longer before hospital admission (RR 1.04-1.05; $p < 0.05$). In contrast, risk of COPD exacerbation rose when a shortening of the time lag between exposure to NOx and hospital admission was considered (RR 1.02-1.04; $p < 0.05$). O3 exposure was associated with a lower risk irrespective of the length of exposure/exacerbation lag (RR 0.77-0.90; $p < 0.05$). There were insignificant associations observed for CO. In conclusion, the study demonstrates a salient influence of a co-existing cardiovascular malady on the appearance of COPD-related respiratory exacerbations when the pollutant SO2 and NOx contents rose. In contrast, higher O3 content was associated with a lower risk of COPD exacerbation.

https://link.springer.com/chapter/10.1007%2F5584_2018_206

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]

Alma, H., C. de Jong, et al. (2019). **"Baseline health status and setting impacted minimal clinically important differences in COPD: an exploratory study."** J Clin Epidemiol **116**: 49-61.

OBJECTIVES: Minimal clinically important differences (MCIDs) are used as fixed numbers in the interpretation of clinical trials. Little is known about its dynamics. This study aims to explore the impact of baseline score, study setting, and patient characteristics on health status MCIDs in chronic obstructive pulmonary disease (COPD). STUDY DESIGN AND SETTING: Baseline and follow-up data on the COPD Assessment Test (CAT), Clinical COPD Questionnaire (CCQ), and St. George's Respiratory Questionnaire (SGRQ) were retrospectively analyzed from pulmonary rehabilitation (PR) and routine clinical practice (RCP). Anchor- and distribution-based MCID estimates were calculated and tested between settings, gender, age, Global initiative for Obstructive Lung Disease (GOLD) classification, comorbidities, and baseline health status. RESULTS: In total, 658 patients were included with 2,299 change score measurements. MCID estimates for improvement and deterioration ranged for all subgroups 0.50-6.30 (CAT), 0.10-0.84 (CCQ), and 0.33-12.86 (SGRQ). Larger MCID estimates for improvement and smaller ones for deterioration were noted in patients with worse baseline health status, females, elderly, GOLD I/II patients, and patients with less comorbidities. Estimates from PR were larger. CONCLUSION: Baseline health status and setting affected MCID estimates of COPD health status questionnaires. Patterns were observed for gender, age, spirometry classification, and comorbidity levels. These outcomes would advocate the need for tailored MCIDs.

https://www.jclinepi.com/article/S0895-4356(18)30992-2/pdf

Alter, P., B. A. Mayerhofer, et al. (2019). **"Prevalence of cardiac comorbidities, and their underdetection and contribution to exertional symptoms in COPD: results from the COSYCONET cohort."** Int J Chron Obstruct Pulmon Dis **14**: 2163-2172.

Background: A substantial prevalence of cardiovascular disease is known for COPD, but detection of its presence, relationship to functional findings and contribution to symptoms remains challenging. The present analysis focusses on the cardiovascular contribution to COPD symptoms and their relationship to the patients' diagnostic status, medication and echocardiographic findings. Methods: Patients from the COPD cohort COSYCONET with data on lung function, including FEV1, residual volume/total lung capacity (RV/TLC) ratio, diffusing capacity TLCO, and echocardiographic data on left ventricular ejection fraction (LVEF) and end-diastolic diameter (LVEDD), medical history, medication, modified British Medical Research Council dyspnea scale (mMRC) and Saint Georges Respiratory Questionnaire (SGRQ) were analyzed. Results: A total of 1591 patients (GOLD 0-4: n=230/126/614/498/123) fulfilled the inclusion criteria. Ischemic heart disease, myocardial infarction or heart failure were reported in 289 patients (18.2%); 860 patients (54%) received at least one cardiovascular medication, with more than one in many patients. LVEF<50% or LVEDD>56 mm was found in 204 patients (12.8%), of whom 74 (36.3%) had neither a cardiovascular history nor medication. Among 948 patients (59.6%) without isolated hypertension, there were 21/55 (38.2%) patients with LVEF<50% and 47/88 (53.4%) with LVEDD>56 mm, who lacked both a cardiac diagnosis and medication. LVEDD and LVEF were linked to medical history; LVEDD was dependent on RV/TLC and LVEF on FEV1. Exertional COPD symptoms were best described by mMRC and the SGRQ activity score. Beyond lung function, an independent link from LVEDD on symptoms was revealed. Conclusion: A remarkable proportion of patients with suspicious echocardiographic findings were undiagnosed and untreated, implying an increased risk for an unfavorable prognosis. Cardiac size and function were dependent on lung function and only partially linked to cardiovascular history. Although the contribution of LV size to COPD symptoms was small compared to lung function, it was detectable irrespective of all other influencing factors. However, only the mMRC and SGRQ activity component were found to be suitable for this purpose.

https://www.dovepress.com/getfile.php?fileID=52891

Angeli, F., G. Reboldi, et al. (2019). **"Detrimental Impact of Chronic Obstructive Pulmonary Disease in Atrial Fibrillation: New Insights from Umbria Atrial Fibrillation Registry."** Medicina (Kaunas) **55**(7)Background and objectives: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Among extra-pulmonary manifestations of COPD, atrial fibrillation (AF) is commonly observed in clinical practice. The coexistence of COPD and AF significantly affects the risk of cardiovascular morbidity and mortality. Nonetheless, the mechanisms explaining the increased risk of vascular events and death associated to the presence of COPD in AF are complex and not completely understood. We analyzed data from an Italian network database to identify markers and mediators of increased vascular risk among subjects with AF and COPD. Materials and Methods: Cross-sectional analysis of the Umbria Atrial Fibrillation (Umbria-FA) Registry, a multicenter, observational, prospective on-going registry of patients with non-valvular AF. Of the 2205 patients actually recruited, 2159 had complete clinical data and were included in the analysis. Results: the proportion of patients with COPD was 15.6%. COPD patients had a larger proportion of permanent AF when compared to the control group (49.1% vs. 34.6%, $p < 0.0001$) and were more likely to be obese and current smokers. Other cardiovascular risk factors including chronic kidney disease (CKD), peripheral artery disease and subclinical atherosclerosis were more prevalent in COPD patients (all $p < 0.0001$). COPD was also significantly associated with higher prevalence of previous vascular events and a history of anemia (all $p < 0.0001$). The thromboembolic and bleeding risk, as reflected by the CHA2DS2VASc and HAS-BLED scores, were higher in patients with COPD. Patients with COPD were also more likely to have left ventricular (LV) hypertrophy at standard ECG than individuals forming the cohort without COPD ($p = 0.018$). Conclusions: AF patients with COPD have a higher risk of vascular complications than AF patients without this lung disease. Our analysis identified markers and mediators of increased risk that can be easily measured in clinical practice, including LV hypertrophy, CKD, anemia, and atherosclerosis of large arteries.

https://res.mdpi.com/d_attachment/medicina/medicina-55-00358/article_deploy/medicina-55-00358-v2.pdf

Antonelli Incalzi, R., G. W. Canonica, et al. (2019). **"The COPD multi-dimensional phenotype: A new classification from the STORICO Italian observational study."** PLoS One **14**(9): e0221889.

BACKGROUND: This paper is aimed to (i) develop an innovative classification of COPD, multi-dimensional phenotype, based on a multidimensional assessment; (ii) describe the identified multi-dimensional phenotypes. METHODS: An exploratory factor analysis to identify the main classificatory variables and, then, a cluster analysis based on these variables were run to classify the COPD-diagnosed 514 patients enrolled in the STORICO (trial registration number: NCT03105999) study into multi-dimensional phenotypes. RESULTS: The circadian rhythm of symptoms and health-related quality of life, but neither comorbidity nor respiratory function, qualified as primary classificatory variables. Five multidimensional phenotypes were identified: the MILD COPD characterized by no night-time symptoms and the best health status in terms of quality of life, quality of sleep, level of depression and anxiety, the MILD EMPHYSEMATOUS with prevalent dyspnea in the early-morning and day-time, the SEVERE BRONCHITIC with nocturnal and diurnal cough and phlegm, the SEVERE EMPHYSEMATOUS with nocturnal and diurnal dyspnea and the SEVERE MIXED COPD distinguished by higher frequency of symptoms during 24h and worst quality of life, of sleep and highest levels of depression and anxiety. CONCLUSIONS: Our results showed that properly collected respiratory symptoms play a primary classificatory role of COPD patients. The longitudinal observation will disclose the discriminative and prognostic potential of the proposed multidimensional phenotype. TRIAL REGISTRATION: Trial registration number: NCT03105999, date of registration: 10th April 2017.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6743765/pdf/pone.0221889.pdf

Arjomandi, M., S. Zeng, et al. (2019). **"Radiographic Lung Volumes Predict Progression to COPD in Smokers with Preserved Spirometry in SPIROMICS."** Eur Respir JThe characteristics that predict progression to overt COPD in smokers without spirometric airflow obstruction are not clearly defined.We conducted a post-hoc analysis of 849 current and former smokers (>/=20 pack-years) with preserved spirometry from the SPIROMICS cohort who had baseline computed tomography (CT) scans of lungs and serial spirometry. We examined whether CT-derived lung volumes representing air trapping could predict adverse respiratory outcomes and more rapid decline in spirometry to overt COPD using mixed effect linear modelling.Among these subjects with normal forced expiratory volume in 1 s to forced vital capacity ratio (FEV1/FVC), CT-measured residual volume to total lung capacity ratio (RVCT/TLCCT) varied widely, from 21% to 59%. Over 2.5+/-0.7 years of follow-up, subjects with higher RVCT/TLCCT had a greater differential rate of decline in FEV1/FVC; those in the upper RVCT/TLCCT tertile had a 0.66% [95%CI=0.06%-1.27%] faster rate of decline per year compared to those in the lower tertile (p=0.015) regardless of demographics, baseline spirometry, respiratory symptoms score, smoking status (former versus current), or smoking burden (pack-years). Accordingly, subjects with higher RVCT/TLCCT were more likely to develop spirometric COPD (odds ratio=5.7 [95%CI=2.4-13.2] in upper versus lower RVCT/TLCCTtertile; p<0.001). Other CT indices of air trapping showed similar patterns of association with lung function decline; however, when all CT indices of air trapping, emphysema, and airway disease were included in the same model, only RVCT/TLCCT retained its significance.Increased air trapping based on radiographic lung volumes predicts accelerated spirometry decline and progression to COPD in smokers without obstruction.

https://erj.ersjournals.com/content/early/2019/07/17/13993003.02214-2018

Avdeev, S., Z. Aisanov, et al. (2019). **"Withdrawal of inhaled corticosteroids in COPD patients: rationale and algorithms."** Int J Chron Obstruct Pulmon Dis **14**: 1267-1280.

Observational studies indicate that overutilization of inhaled corticosteroids (ICS) is common in patients with chronic obstructive pulmonary disease (COPD). Overprescription and the high risk of serious ICS-related adverse events make withdrawal of this treatment necessary in patients for whom the treatment-related risks outweigh the expected benefits. Elaboration of an optimal, universal, user-friendly algorithm for withdrawal of ICS therapy has been identified as an important clinical need. This article reviews the available evidence on the efficacy, risks, and indications of ICS in COPD, as well as the benefits of ICS treatment withdrawal in patients for whom its use is not recommended by current guidelines. After discussing proposed approaches to ICS withdrawal published by professional associations and individual authors, we present a new algorithm developed by consensus of an international group of experts in the field of COPD. This relatively simple algorithm is based on consideration and integrated assessment of the most relevant factors (markers) influencing decision-making, such a history of exacerbations, peripheral blood eosinophil count, presence of infection, and risk of community-acquired pneumonia.

https://www.dovepress.com/getfile.php?fileID=50449

Baillargeon, J., G. Singh, et al. (2019). **"Association of Opioid and Benzodiazepine Use with Adverse Respiratory Events in Older Adults with Chronic Obstructive Pulmonary Disease."** Ann Am Thorac Soc **16**(10): 1245-1251.

Rationale: Older adults with chronic obstructive pulmonary disease (COPD) are at substantially increased risk for medication-related adverse events. Two frequently prescribed classes of drugs that pose a particular risk to this patient group are opioids and benzodiazepines. Research on this topic has yielded conflicting findings.Objectives: The purpose of this study was to examine, among older adults with COPD, whether: 1) independent or concurrent use of opioid and benzodiazepine medications was associated with hospitalizations for respiratory events, and 2) this association was exacerbated by the presence of

obstructive sleep apnea (OSA).Methods: We conducted a case-control study of Medicare beneficiaries aged >/=66 years, who were diagnosed with COPD in 2013, using the 5% national Medicare database. Cases (n = 3,232) were defined as patients hospitalized for a primary COPD-related respiratory diagnosis in 2014 and were matched with up to two control subjects (n = 6,247) on index date, age, sex, socioeconomic status, comorbidity, presence of OSA, COPD medication, and COPD complexity.Results: In comparison to the referent (no opioid or benzodiazepine use), opioid use alone (adjusted odds ratio [aOR], 1.73; 95% confidence interval [CI], 1.52-1.97), benzodiazepine use alone (aOR, 1.42; 95% CI, 1.21-1.66), and concurrent opioid/ benzodiazepine use (aOR, 2.32; 95% CI, 1.94-2.77) in the 30 days before the event/index date were all associated with an increased risk of hospitalization for a respiratory condition. Risk of hospitalization was higher with concurrent opioid and benzodiazepine use when compared with use of either medication alone. There was no statistically significant interaction between OSA and either of the drugs, alone or in combination. However, the adverse respiratory effects of concurrent opioid and benzodiazepine use were increased in patients with a high degree of COPD complexity. All of the above findings persisted using exposure windows that extended to 60 and 90 days before the event/index date.Conclusions: Among older adults with COPD, use of opioid and benzodiazepine medications alone or in combination were associated with increased adverse respiratory events. The adverse effects of these medications were not exacerbated in patients with COPD-OSA overlap syndrome. However, the adverse impact of dual opioid and benzodiazepine was greater in patients with high-complexity COPD.

Bak, S. H., S. O. Kwon, et al. (2019). **"Computed tomography-derived area and density of pectoralis muscle associated disease severity and longitudinal changes in chronic obstructive pulmonary disease: a case control study."** Respir Res **20**(1): 226.

BACKGROUND: Muscle wasting is associated with prognosis in patients with chronic obstructive pulmonary disease (COPD). The cross-sectional area of skeletal muscles on computed tomography (CT) could serve as a method to evaluate body composition. The present study aimed to determine the ability of CT-derived pectoralis muscle area (PMA) and pectoralis muscle density (PMD) to determine the severity of COPD and change in longitudinal pulmonary function in patients with COPD. METHODS: A total of 293 participants were enrolled in this study, a whom 222 had undergone at least two spirometry measurements within 3 years after baseline data acquisition. PMA and PMD were measured from a single axial slice of chest CT above the aortic arch at baseline. The emphysema index and bronchial wall thickness were quantitatively assessed in all scans. The generalized linear model was used to determine the correlation between PMA and PMD measurements and pulmonary function. RESULTS: PMA and PMD were significantly associated with baseline lung function and the severity of emphysema ($P < 0.05$). Patients with the lowest PMA and PMD exhibited significantly more severe airflow obstruction (beta = - 0.06; 95% confidence interval: - 0.09 to - 0.03]. PMA was statistically associated with COPD assessment test (CAT) score ($P = 0.033$). However, PMD did not exhibit statistically significant correlation with either CAT scores or modified Medical Research Council scores ($P > 0.05$). Furthermore, neither PMA nor PMD were associated with changes in forced expiratory volume in 1 s over a 3-year periods. CONCLUSIONS: CT-derived features of the pectoralis muscle may be helpful in predicting disease severity in patients with COPD, but are not necessarily associated with longitudinal changes in lung function.

https://respiratory-research.biomedcentral.com/track/pdf/10.1186/s12931-019-1191-y

Blakemore, A., C. Dickens, et al. (2019). **"Depression predicts emergency care use in people with chronic obstructive pulmonary disease: a large cohort study in primary care."** Int J Chron Obstruct Pulmon Dis **14**: 1343-1353.

Background: Depression is common in people with chronic obstructive pulmonary disease (COPD) and has been associated with a variety of poor outcomes. A large proportion of health care costs in the UK are spent on emergency care. This study examined the prospective relationship between depression and use of

emergency care in patients with COPD managed in primary care. Methods: This was a twelve-month, prospective longitudinal study of 355 patients with COPD in six primary care practices in the UK. Baseline measures included demographic characteristics, depression and anxiety, severity of COPD, presence or absence of other chronic diseases, and prior use of emergency care. Outcome measures were (a) number of emergency department (ED) visits; or (b) an emergency hospital admission in the follow-up year. Results: Older age, number of comorbid physical health conditions, severity of COPD, prior use of emergency care, and depression were all independently associated with both ED attendance and an emergency hospital admission in the follow-up year. Subthreshold depression (HADS depression score 4-7) was associated with a 2.8 times increased odds of emergency hospital admission, and HADS depression >8 was associated with 4.8 times increased odds. Conclusion: Depression is a predictor of emergency care in COPD, independent of severity of disease or physical comorbidity. Even mild (subthreshold) symptoms of depression more than double the risk of using emergency care, suggesting there is a strong case to develop and deploy integrated preventive strategies in primary care that can promote mental health in people with COPD.

https://www.dovepress.com/getfile.php?fileID=50796

Boer, L., E. Bischoff, et al. (2019). **"A Smart Mobile Health Tool Versus a Paper Action Plan to Support Self-Management of Chronic Obstructive Pulmonary Disease Exacerbations: Randomized Controlled Trial."** JMIR Mhealth Uhealth **7**(10): e14408.

BACKGROUND: Many patients with chronic obstructive pulmonary disease (COPD) suffer from exacerbations, a worsening of their respiratory symptoms that warrants medical treatment. Exacerbations are often poorly recognized or managed by patients, leading to increased disease burden and health care costs. OBJECTIVE: This study aimed to examine the effects of a smart mobile health (mHealth) tool that supports COPD patients in the self-management of exacerbations by providing predictions of early exacerbation onset and timely treatment advice without the interference of health care professionals. METHODS: In a multicenter, 2-arm randomized controlled trial with 12-months follow-up, patients with COPD used the smart mHealth tool (intervention group) or a paper action plan (control group) when they experienced worsening of respiratory symptoms. For our primary outcome exacerbation-free time, expressed as weeks without exacerbation, we used an automated telephone questionnaire system to measure weekly respiratory symptoms and treatment actions. Secondary outcomes were health status, self-efficacy, self-management behavior, health care utilization, and usability. For our analyses, we used negative binomial regression, multilevel logistic regression, and generalized estimating equation regression models. RESULTS: Of the 87 patients with COPD recruited from primary and secondary care centers, 43 were randomized to the intervention group. We found no statistically significant differences between the intervention group and the control group in exacerbation-free weeks (mean 30.6, SD 13.3 vs mean 28.0, SD 14.8 weeks, respectively; rate ratio 1.21; 95% CI 0.77-1.91) or in health status, self-efficacy, self-management behavior, and health care utilization. Patients using the mHealth tool valued it as a more supportive tool than patients using the paper action plan. Patients considered the usability of the mHealth tool as good. CONCLUSIONS: This study did not show beneficial effects of a smart mHealth tool on exacerbation-free time, health status, self-efficacy, self-management behavior, and health care utilization in patients with COPD compared with the use of a paper action plan. Participants were positive about the supportive function and the usability of the mHealth tool. mHealth may be a valuable alternative for COPD patients who prefer a digital tool instead of a paper action plan. TRIAL REGISTRATION: ClinicalTrials.gov NCT02553096; https://clinicaltrials.gov/ct2/show/NCT02553096.

Bordon, J., M. Slomka, et al. (2019). **"Hospitalization due to community-acquired pneumonia in patients with chronic obstructive pulmonary disease: incidence, epidemiology and outcomes."** Clin Microbiol InfectOBJECTIVES: Community-acquired pneumonia (CAP) is an important complication in patients with chronic obstructive pulmonary disease (COPD). This study aimed to define incidence, and outcomes of

COPD patients hospitalized with pneumonia in the city of Louisville, and to estimate the burden of disease in the US population. METHODS: This was a secondary analysis of a prospective population-based cohort study of residents in Louisville, Kentucky, 40 years old and older, from 1 June 2014 to 31 May 2016. All adults hospitalized with CAP were enrolled. The annual incidence of pneumonia in COPD patients in Louisville was calculated and the total number of adults with COPD hospitalized in the United States was estimated. Clinical outcomes included time to clinical stability (TCS), length of hospital stay (LOS) and mortality. RESULTS: From a Louisville population of 18 246 patients with COPD, 3419 pneumonia hospitalizations were documented during the 2-year study. The annual incidence was 9369 patients with pneumonia per 100 000 COPD population, corresponding to an estimated 506 953 adults with COPD hospitalized due to pneumonia in the United States. The incidence of CAP in patients without COPD was 509 (95% CI 485-533) per 100 000. COPD patients had a median (interquartile range) TCS and LOS of 2 (1-4) and 5 (3-9) days respectively. The mortality of COPD patients during hospitalization, at 30 days, 6 months and 1 year was 193 of 3419 (5.6%), 400 of 3374 (11.9%), 816 of 3363 (24.3%) and 1104 of 3349 (33.0%), respectively. CONCLUSIONS: There was an annual incidence of 9369 cases of hospitalized CAP per 100 000 COPD patients in the city of Louisville. This was an approximately 18-fold greater incidence of CAP in COPD patients than in those without COPD.

https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(19)30371-4/fulltext

Boutou, A. K., Y. Raste, et al. (2019). **"Progression of physical inactivity in COPD patients: the effect of time and climate conditions - a multicenter prospective cohort study."** Int J Chron Obstruct Pulmon Dis **14**: 1979-1992.

Purpose: Longitudinal data on the effect of time and environmental conditions on physical activity (PA) among COPD patients are currently scarce, but this is an important factor in the design of trials to test interventions that might impact on it. Thus, we aimed to assess the effect of time and climate conditions (temperature, day length and rainfall) on progression of PA in a cohort of COPD patients. Patients and methods: This is a prospective, multicenter, cohort study undertaken as part of the EU/IMI PROactive project, in which we assessed 236 COPD patients simultaneously wearing two activity monitors (Dynaport MiniMod and Actigraph GT3X). A multivariable generalized linear model analysis was conducted to describe the effect of the explanatory variables on PA measures, over three time points (baseline, 6 and 12 months). Results: At 12 months (n=157; FEV1% predicted=57.7+/-21.9) there was a significant reduction in all PA measures (Actigraph step count (4284+/-3533 vs 3533+/-293)), Actigraph moderate- to vigorous-intensity PA ratio (8.8 (18.8) vs 6.1 (15.7)), Actigraph vector magnitude units (374,902.4 (265,269) vs 336,240 (214,432)), MiniMod walking time (59.1 (34.9) vs 56.9 (38.7) mins) and MiniMod PA intensity (0.183 (0) vs 0.181 (0)). Time had a significant, negative effect on most PA measures in multivariable analysis, after correcting for climate factors, study center, age, FEV1% predicted, 6MWD and other disease severity measures. Rainfall was the only climate factor with a negative effect on most PA parameters. Conclusion: COPD patients demonstrate a significant decrease in PA over 1 year follow-up, which is further affected by hours of rainfall, but not by other climate considerations.

https://www.dovepress.com/getfile.php?fileID=52473

Bui, K. L., N. Maia, et al. (2019). **"Reliability of quadriceps muscle power and explosive force, and relationship to physical function in people with chronic obstructive pulmonary disease: an observational prospective multicenter study."** Physiother Theory Pract: 1-9.

Background: Muscle power declines with age and is a stronger determinant of physical function than strength. Muscle power using computerized dynamometry has not been investigated in COPD. Objectives: To determine: 1) test-retest reliability of quadriceps power using a standardized protocol with computerized dynamometry; and 2) associations between quadriceps strength and power, and functional capacity. Design/Setting: Prospective observational study in four Canadian research labs. Participants: People with mild to very severe COPD. Methods: Tests were conducted on two days. Quadriceps muscle maximal

strength was evaluated during a static maneuver using maximal voluntary isometric contractions (MVIC). Rate of torque development (RTD) during MVIC was used to assess explosive force. Muscle power was measured using a dynamic, isotonic protocol from which peak and average power and peak velocity were derived. Functional capacity was assessed with the Short Physical Performance Battery (SPPB). Reliability was assessed using intraclass correlation coefficients (ICC), standard error of measurements (SEM), and Bland Altman plots. Spearman and Pearson correlation coefficients were used for associations. Results: 65 patients (age 69 +/- 8 years; FEV1 48 +/- 21% of predicted) were included. ICC was 0.77 for RTD and 0.87-0.98 for isotonic power measures (95%CI 0.63-0.99, p < .001); SEM < 10% for average/peak power and peak velocity, and > 30% for RTD. SPPB had moderate correlation with average power, but not with MVIC or RTD. Conclusion: The standardized isotonic protocol with computerized dynamometry was reliable in assessing quadriceps power in COPD. Our data highlights that average power correlates best with functional capacity, indicating higher relevance than static measures when investigating determinants of function.

https://www.tandfonline.com/doi/full/10.1080/09593985.2019.1669233

Burge, A. T., A. E. Holland, et al. (2019). **"Home-based pulmonary rehabilitation for COPD using minimal resources: An economic analysis."** RespirologyBACKGROUND AND OBJECTIVE: This study aimed to compare the cost-effectiveness and cost-utility of home and centre-based pulmonary rehabilitation for adults with stable chronic obstructive pulmonary disease (COPD). METHODS: Prospective economic analyses were undertaken from a health system perspective alongside a randomized controlled equivalence trial in which participants referred to pulmonary rehabilitation undertook a standard 8-week outpatient centre-based or a new home-based programme. Participants underwent clinical assessment prior to programme commencement, immediately following completion and 12 months following programme completion. They provided data for utility (quality-adjusted life years (QALY) determined using SF6D (utility scores for health states) calculated from 36-Item Short Form Health Survey version 2) and effectiveness (change in distance walked on 6-min walk test (Delta6MWD) following pulmonary rehabilitation). Individual-level cost data for the 12 months following programme completion was sourced from healthcare administration and government databases. RESULTS: Between-group mean difference point estimates for cost (-$4497 (95% CI: -$12 250 to $3257), utility (0.025 (-0.038 to 0.086) QALY) and effectiveness (14 m (-11 to 39) Delta6MWD) favoured the home-based group. Cost-utility analyses demonstrated 63% of estimates falling in the dominant southeast quadrant and the probability that the new home-based model was cost-effective at a $0 threshold for willingness to pay was 78%. Results were robust to a range of sensitivity analyses. Programme completion was associated with significantly lower healthcare costs in the following 12 months. CONCLUSION: Home-based pulmonary rehabilitation provides a cost-effective alternative model for people with COPD who cannot access traditional centre-based programmes.

https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13667

Canas-Arboleda, A., C. Hernandez-Florez, et al. (2019). **"Colonization by Pneumocystis jirovecii in patients with chronic obstructive pulmonary disease: association with exacerbations and lung function status."** Braz J Infect DisExposure to Pneumocystis jirovecii (P. jirovecii) can lead to a wide variety of presenting features ranging from colonization in immunocompetent patients with lung disease, to invasive infections in immunocompromised hosts. Colonization by this fungus in patients with chronic obstructive pulmonary disease (COPD) could be associated with higher rates of exacerbations and impaired lung function in these patients. Our objective was to determine whether colonization by P. jirovecii in patients with COPD is associated with increased exacerbations and deterioration of lung function. This was a prospective cohort study on patients with COPD. All participants meeting selection criteria underwent clinical and microbiological assessments and were then classified as colonized vs. non-colonized patients. Chi-squared tests were performed and multivariate logistic models were fitted in order to obtain risk ratios (RR) with 95% confidence intervals (CI). We documented a frequency of

colonization by P. jirovecii of 32.3%. Most patients were categorized as having GOLD B and D COPD. The history of significant exacerbations in the last year, health status impairment (COPD Assesment Tool >/=10), airflow limitation (percent of post-bronchodilator FEV1), and BODEx score (>/=5) were similar between groups. After a 52-week follow-up period, the rate of adjusted significant exacerbations did not differ between groups. However, a decrease in FEVI was found in both groups.

https://pdf.sciencedirectassets.com/280278/AIP/1-s2.0-S141386701930426X/main.pdf?X-Amz-Security-Token=AgoJb3JpZ2luX2VjEDIaCXVzLWVhc3QtMSJIMEYCIQCMQv1DlUSoatIe3kZ2qqqjtd1NtUA7HykSx9r025LOpwIhAIh787U%2FJ1Qja2YIho%2BwcelTwNWzOYzGrm%2B9owQ1X2qpKvwDCDsQAhoMMDU5MDAzNTQ2ODY1IgwgNOTh%2BvMPiQOss2Mq2QNPtPiShsI7kBuIQyIi64IqN7812VDwLrm9VAINEh4BjE072hm%2BFAu1YgE8ry1uVprdpX%2FO8Ov9TGYS1a%2BAmguepHFLU8DR94jdDRKrU3JZ%2B6CHt97QjuRCDeqU4Q80ZbQOTnVV%2F0sotnJpg%2BqmTlLOrHgL4X6hUVp5gPKXKltLwWlMqAGqpTZEVvIwCiag%2BJoa0%2FT4EPijh1CqFEmSTOarWhNN4qXnBzTDXEhExGUYWfPHU8En48AFT%2Bqj%2F2wyMwNnygi4Vy5sTYIv6W6uUHCn1wf02w8MIEpIdvJ%2FkiO7PDzCIsbDPgkkF8J49wqMJ%2Fmu5tTo29ZAD1KxfAvFN%2Fz4VLV5nvzjZHRt%2Fz6wLW2%2FBUgig2Roezi5xwOmEuRafJo6TEg284gYkH%2BlzD7z7s96tXG7PjinQ637ORrPci4xPm%2FoXyCqh9nxK9upUnYeKHZm5f2CWi9cTWOzFHQzG0YOLNkOhPIKjS5UvjCiR4Feop%2F5wFNZ8ol99bwJ%2FC8j9BSW6rKweUmkYAxozD3nTbRusMWJBP99KAwkjJc0eiQgLux%2Fm0rPTGK6nBSvOOorNXONfFiD6Z30fMZeIm25%2F51k9YqGOZMakQFOH8vR6qtkBRtkVbM46nCrqDD3ocntBTqzAfGlnH8iB9DNlHsV%2FmpXGLtF%2FSUy1tbks2sbaM88L%2BsXBr9uUFwC9PhO%2FjYzaNPUlseXWGRxxOmKhzbGr8KKWpt5SaEghP4KUhxQdq9hCUAzBkIHxZs%2FubYsJ2YK6IAKCN6QVmP9Pz1OBy77H7Ga%2F%2BtTAtQzC2Kf5wWeX4TXDLbu1QaIblGz8q6gyVglnVqTS%2FjI8Yvi1Wut6yYC6pV5NAjKTxO68UwFg2viNJb06ZICIIBh&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Date=20191025T024003Z&X-Amz-SignedHeaders=host&X-Amz-Expires=300&X-Amz-Credential=ASIAQ3PHCVTYVB5YLIO2%2F20191025%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Signature=0a40bd26bb1fab4c913859c6b79513a5910c395a17429b3da3f4017237f64e0c&hash=674f5d830817ec88da4068c018ccfbb1e3cf5af9e3102159d80c7a88d3db59c5&host=68042c943591013ac2b2430a89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S141386701930426X&tid=spdf-7f4e9736-756c-4f37-b360-bbebb2afd65a&sid=c45dcb8c9db9d74b333b0a27cc54ef11c900gxrqa&type=client

Candemir, I., P. Ergun, et al. (2019). **"Use of i-BODE index to determine efficacy of pulmonary rehabilitation in COPD patients."** Tuberk Toraks **67**(2): 116-123.

Introduction: Pulmonary rehabilitation (PR) is well-proven approach on improving dyspnea, exercise intolerance which are two components of BODE index. But, PR is known to have minimal effect on pulmonary function which is another component of BODE index. There are few studies evaluating PR efficacy by using i-BODE index. Our aim was to evaluate efficacy of PR in patients with chronic obstructive pulmonary disease (COPD) with i-BODE index and to investigate changes in i-BODE index according to GOLD 2011 combined assessment. Materials and Methods: A total of 228 stable COPD patients who completed a comprehensive 8 week duration PR program were enrolled into this retrospective study. Result: The patients were with mean age of 63.3 +/- 8.6 years and mean FEV1% was 38.6 +/- 16.2%. According to combined assessment of COPD, 23 patients were group A, 30 patients were B, 31 patients were C and 144 patients were D. Baseline i-BODE scores correlated with body compositions, pulmonary function, dyspnea, exercise capacity, psychological status, quality of life, and age. i-BODE index score decreased from 4.7 +/- 2.2 to 3.5 +/- 1.8 after PR ($p<0.001$), improved by 26%. Significant improvements were found in dyspnea, quality of life and i-BODE index in more symptomatic patients (group B and D). Conclusions: This study highlights that changes in i-BODE scores after PR significantly correlated with improvements in dyspnea, exercise capacity and quality of life. i-BODE score could be a better predictor of efficacy of PR than some individual variables such as BMI or FEV1. Significant improvements in dyspnea sensation, quality of life and i-BODE index could be seen symptomatic patients in after PR.

Candemir, I., P. Ergun, et al. (2019). **"Comparison of unsupervised home-based pulmonary rehabilitation versus supervised hospital outpatient pulmonary rehabilitation in patients with chronic obstructive pulmonary disease."** Expert Rev Respir Med: 1-9.

Background: Pulmonary rehabilitation (PR) is an effective treatment in patients with chronic obstructive pulmonary disease (COPD) but still underutilized. The aim of this study was to compare unsupervised home PR with supervised outpatient PR in terms of various clinical variables in COPD patients. Methods: We conducted retrospective study consisting of 247 patients with COPD who were categorized into three group. 127 patients underwent unsupervised home PR, of whom 60 (47%) completed program (finishers), 67(53%) were lost to follow-up (non-finishers), 120 completed supervised outpatient PR. We compared baseline, post-treatment changes in demographic, clinical variables. Results: Sex, age were statistically similar between groups. Finishers of home PR had higher exercise capacity ($p = 0.003$), quality of life ($p = 0.045$), FEV1 ($p = 0.001$), lower pack-year smoking ($p < 0.001$) than outpatient PR.After home PR, exercise capacity ($p < 0.05$), quality of life ($p < 0.001$), dyspnea($p < 0.05$), anxiety ($p < 0.001$), depression ($p < 0.001$) were improved except endurance shutte test. Improvements in exercise capacity ($p < 0.05$), quality of life ($p < 0.001$), dyspnea ($p = 0.023$), anxiety ($p < 0.001$), depression ($p = 0.001$) scores were different between completed PR programs, in favor of supervised outpatient PR. Non-finishers of home PR had more pack-year smoking than finishers of home PR ($p = 0.039$); other baseline parameters were similar. Conclusion: Unsupervised home PR was effective in terms of improving exercise capacity, quality of life, dyspnea, psychological status, but less than supervised outpatient programs.

https://www.tandfonline.com/doi/full/10.1080/17476348.2019.1675516

Champtiaux, N., V. Cottin, et al. (2019). **"Combined pulmonary fibrosis and emphysema in systemic sclerosis: A syndrome associated with heavy morbidity and mortality."** Semin Arthritis Rheum **49**(1): 98-104.

BACKGROUND: 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.

https://www.sciencedirect.com/science/article/abs/pii/S0049017217305115?via%3Dihub

Chen, W., D. D. Sin, et al. (2019). **"An Individualized Prediction Model for Long-term Lung Function Trajectory and Risk of COPD in the General Population."** ChestBACKGROUND: Prediction of future lung function will enable the identification of individuals at high risk of developing COPD, but the trajectory of lung function decline varies greatly among individuals. This study involved the development and validation of an individualized prediction model of lung function trajectory and risk of airflow limitation in the general population. METHODS: Data were obtained from the Framingham Offspring Cohort, which included 4,167 participants >/= 20 years of age and who had >/= 2 valid spirometry assessments. The primary outcome was prebronchodilator FEV1; the secondary outcome was the risk of

airflow limitation (defined as FEV1/FVC less than the lower limit of normal). Mixed effects regression models were developed for individualized prediction, and a machine learning algorithm was used to determine essential predictors. The model was validated in two large, independent multicenter cohorts (N = 2,075 and 12,913, respectively). RESULTS: With 20 common predictors, the model explained 79% of the variation in FEV1 decline in the derivation cohort. In two validation datasets, the model had low error in predicting FEV1 decline (root mean square error range, 0.18-0.22 L) and high discriminative power in predicting risk of airflow limitation (C-statistic range, 0.86-0.87). This model was implemented in a freely accessible website-based application, which allows prediction based on flexible sets of predictors (http://resp.core.ubc.ca/ipress/FraminghamFEV1). CONCLUSIONS: The individualized predictor is an accurate tool to predict long-term lung function trajectories and risk of airflow limitation in the general population. This model enables identifying individuals at higher risk of COPD, who can then be targeted for preventive therapies.

https://journal.chestnet.org/article/S0012-3692(19)33868-1/fulltext

Cho, J., C. H. Lee, et al. (2019). **"Outcome of Regular Inhaled Treatment in GOLD A Chronic Obstructive Pulmonary Disease Patients."** Respiration **98**(4): 312-320.

BACKGROUND: The 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends regular bronchodilator therapy in all group A patients with chronic obstructive pulmonary disease (COPD). OBJECTIVE: The aim of this study was to evaluate whether regular inhaled treatment in group A patients with COPD improves their health outcomes, including exacerbations and symptoms. METHODS: We recruited patients from 2 Korean prospective cohorts. Eligible COPD patients had a modified Medical Research Council (mMRC) dyspnea score of <2, a St. George's Respiratory Questionnaire for COPD (SGRQ-C) total score of <25, and had no more than 1 exacerbation and no hospitalizations during the previous year. Incidence rates of exacerbations and changes in symptom scores were analyzed. RESULTS: After propensity score matching, there were 107 patient pairs, with and without regular inhaled treatment, who were followed up for mean times of 2.6 and 3.1 years, respectively. The incidence rates of exacerbations in those with and without regular treatment were not significantly different (incidence rate ratio 1.24 [95% CI 0.68 to 2.25]). Significant differences in favor of regular treatment were observed at 6 and 12 months for the SGRQ-C total scores (mean between-group difference -4.7 [95% CI -7.9 to -1.6] and -4.8 [95% CI -7.9 to -1.7], respectively). Regular treatment with a long-acting bronchodilator was also associated with significantly better scores on the SGRQ-C (mean between-group difference -5.0 [95% CI -8.6 to -1.4]) compared to no regular treatment at 12 months of follow-up. CONCLUSIONS: Regular inhaled treatment in group A patients with COPD was associated with a symptomatic benefit but not with a reduction of exacerbation rates.

https://www.karger.com/Article/Abstract/495756

Ciftci, F., E. Sen, et al. (2019). **"Does exercise capacity, dyspnea level, or quality of life actually predict mortality in patients with COPD? 8-year follow-up."** Tuberk Toraks **67**(2): 83-91.

Introduction: The goals of chronic obstructive pulmonary disease (COPD) treatment are to relieve dyspnea, increase exercise capacity, and improve quality of life. The relation of exercise capacity, dyspnea level, and quality of life with long-term mortality is unclear. Aim of the study was to assess the effect of exercise capacity, dyspnea level and quality of life on long-term mortality risk in patients with COPD. Materials and Methods: Dyspnea level was assessed using the modified Medical Research Council (mMRC), Borg and Baseline Dyspnea Index (BDI) and Body Obstruction Dyspnea Exercise (BODE), health-related quality of life with St. George's Respiratory Questionnaire, and exercise capacity with the 6-minute walking test (6MWT) and cardiopulmonary exercise test. At the end of 8-year follow-up period, the relation between these tests and mortality was examined. Result: A total of 42 patients with stable COPD were included in the study. Sixteen patients died during the approximately 8-year follow-up period. Univariate analysis revealed that VO2 peak [HR: 1.845; CI: (1.336-2.55); p<0.001], BODE index [HR: 0.787; CI: (0.703-0.880); p<0.001], and SGRQ [HR: 1.073; CI: (1.028-1.119); p= 0.001] were significantly

correlated to mortality risk. Multivariate Cox regression analysis revealed VO2 peak [HR: 1.031; CI: (0.683-1.120); p= 0.01] as the single significant predictor of mortality. VO2 peak less than 22.5 had a sensitivity of 82%, specificity of 80%, and area under the curve of 0.142 [95% CI: (0.027-0.257); p< 0.001] for mortality risk with ROC analysis. Conclusions: Cardiopulmonary disturbances during maximal exercise may be an important indicator of mortality risk.

Colak, Y., S. Afzal, et al. (2019). **"Prognosis of COPD depends on severity of exacerbation history: A population-based analysis."** Respir Med **155**: 141-147.

BACKGROUND: Differences in previous exacerbation history may influence prognosis of chronic obstructive pulmonary disease (COPD). We hypothesized that prognosis differs between individuals with a history of only medically treated exacerbations (moderate exacerbations) and those with a history of hospitalised exacerbations (severe exacerbations). METHODS: We included 98614 adults from the Copenhagen General Population Study and assessed risk of moderate and severe exacerbations, pneumonia hospitalisation, and respiratory and all-cause mortality from 2003 until 2013 according to exacerbation history. RESULTS: Among 6545 individuals with COPD, 6290 had no exacerbations in the preceding year, 109 had one moderate exacerbation, 108 had two or more moderate exacerbations, and 38 had one or more severe exacerbations. During 9.4 years of follow-up, we observed 926 moderate and 244 severe exacerbations, 477 pneumonias, and 707 deaths, including 69 from respiratory disease. Compared to individuals without previous exacerbations, lung function and symptom adjusted hazard ratios (HRs) for future moderate exacerbation were 4.68 (95% confidence interval:3.31-6.62) for individuals with one previous moderate exacerbation, 21 (13-33) for individuals with two or more previous moderate exacerbations, and 5.30 (3.44-8.15) for individuals with one or more previous severe exacerbations. Corresponding HRs were 1.62(0.78-3.34), 1.29(0.57-2.89), and 5.43 (2.56-12) for severe exacerbation, 1.86(1.06-3.27), 1.74(1.01-2.99), and 4.85 (2.94-8.02) for pneumonia, 0.53(0.10-2.99), 1.65(0.53-5.17), and 2.98 (1.14-7.83) for respiratory mortality, and 1.34(0.79-2.29), 1.57(1.00-2.47), and 1.49 (0.85-2.62) for all-cause mortality, respectively. CONCLUSION: Individuals with COPD and a history of hospitalised exacerbations carried the poorest prognosis compared to those with a history of only medically treated exacerbations, suggesting difference in risk profile.

https://www.resmedjournal.com/article/S0954-6111(19)30245-8/fulltext

Comes, J., G. Prieur, et al. (2019). **"Changes in Cycle-Ergometer Performance during Pulmonary Rehabilitation Predict COPD Exacerbation."** Copd **16**(3-4): 261-265.

Early diagnosis of COPD exacerbations is vital. Exacerbations are characterised by an increase in dyspnoea that could be affect physical capacity. Changes in the physical capacity of patients with COPD during pulmonary rehabilitation could provide a predictive indication regarding the occurrence of exacerbation. This was a retrospective study of forty for patients with COPD who participated in a pulmonary rehabilitation programme between January 2015 and October 2018. Patients to have experienced at least one exacerbation during their pulmonary rehabilitation programme are included. The performance variable and dyspnoea on the cycle ergometer and the treadmill were collected during the five sessions prior to the exacerbation and the three sessions following the exacerbation. Seventy exacerbations were analysed. We found a significant decrease in the performance on the cycle ergometer during the last session before exacerbation compared with previous sessions (mean difference: 74.5% (95%CI 12.6-136.5); p < 0.01). The optimal threshold value was a 17% decrease in performance compared to the previous training session. Sensitivity was 0.46 (95%CI 0.34-0.59), specificity was 0.83 (95%CI 0.72-0.91) and the area under the curve was 0.65 (95%CI 0.56-0.74) (p < 0.01). The analysis of performance data from cycle ergometer is a potentially useful method to predict the occurrence of exacerbation.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1645106

Cortegiani, A., F. Longhini, et al. (2019). **"High-flow nasal therapy versus noninvasive ventilation in COPD patients with mild-to-moderate hypercapnic acute respiratory failure: study protocol for a noninferiority randomized clinical trial."** Trials **20**(1): 450.
BACKGROUND: Noninvasive ventilation (NIV) is indicated to treat respiratory acidosis due to exacerbation of chronic obstructive pulmonary disease (COPD). Recent nonrandomized studies also demonstrated some physiological effects of high-flow nasal therapy (HFNT) in COPD patients. We designed a prospective, unblinded, multicenter, randomized controlled trial to assess the noninferiority of HFNT compared to NIV with respect to the reduction of arterial partial pressure of carbon dioxide (PaCO2) in patients with hypercapnic acute respiratory failure with mild-to-moderate respiratory acidosis. METHODS: We will enroll adult patients with acute hypercapnic respiratory failure, as defined by arterial pH between 7.25 and 7.35 and PaCO2 >/= 55 mmHg. Patients will be randomly assigned 1:1 to receive NIV or HFNT. NIV will be applied through a mask with a dedicated ventilator in pressure support mode. Positive end-expiratory pressure will be set at 3-5 cmH2O with inspiratory support to obtain a tidal volume between 6 and 8 ml/kg of ideal body weight. HFNT will be initially set at a temperature of 37 degrees C and a flow of 60 L/min. At 2 and 6 h we will assess arterial blood gases, vital parameters, respiratory rate, treatment intolerance and failure, need for endotracheal intubation, time spent under mechanical ventilation (both invasive and NIV), intensive care unit and hospital length of stay, and hospital mortality. Based on an alpha error of 5% and a beta error of 80%, with a standard deviation for PaCO2 equal to 15 mmHg and a noninferiority limit of 10 mmHg, we computed a sample size of 56 patients. Considering potential drop-outs and nonparametric analysis, the final computed sample size was 80 patients (40 per group). DISCUSSION: HFNT is more comfortable than NIV in COPD patients recovering from an episode of exacerbation. If HFNT would not be inferior to NIV, HFNT could be considered as an alternative to NIV to treat COPD patients with mild-to-moderate respiratory acidosis. TRIAL REGISTRATION: ClinicalTrials.gov, NCT03370666 . Registered on December 12, 2017.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6647141/pdf/13063_2019_Article_3514.pdf

Criner, G. J., B. R. Celli, et al. (2019). **"Predicting response to benralizumab in chronic obstructive pulmonary disease: analyses of GALATHEA and TERRANOVA studies."** Lancet Respir MedBACKGROUND: Benralizumab did not significantly reduce exacerbations compared with placebo in the phase 3 GALATHEA and TERRANOVA trials of benralizumab for patients with chronic obstructive pulmonary disease (COPD). We aimed to identify clinical and physiological characteristics of patients with COPD that could help to identify people who are likely to have the greatest treatment effect with benralizumab. METHODS: We analysed individual study and pooled results from GALATHEA and TERRANOVA. At study enrolment, patients from GALATHEA and TERRANOVA were aged 40-85 years, had moderate to very severe airflow limitation, had elevated blood eosinophil counts, and at least two exacerbations or one severe exacerbation in the previous year despite dual inhaled therapy (inhaled corticosteroids plus long-acting beta2-agonists or long-acting beta2-agonists plus long-acting muscarinic antagonists) or triple inhaled therapy (inhaled corticosteroids plus long-acting beta2-agonists plus long-acting muscarinic antagonists). We analysed data for 3910 patients who received benralizumab (30 mg or 100 mg subcutaneously every 8 weeks; first three doses every 4 weeks) or placebo with dual or triple therapy to identify factors consistently associated with annual exacerbation rate reduction. We evaluated the annual exacerbation rate for benralizumab versus placebo as the primary endpoint. GALATHEA and TERRANOVA are registered with ClinicalTrials.gov, NCT02138916 and NCT02155660, respectively. FINDINGS: For 2665 patients with elevated blood eosinophil counts, treatment effect with benralizumab every 8 weeks at 100 mg, but not at 30 mg, occurred for patients with a history of more frequent exacerbations, poorer baseline lung function, or greater baseline lung function improvement with short-acting bronchodilators. Patients with baseline blood eosinophil counts of 220 cells per muL or greater with: three or more exacerbations in the previous year receiving benralizumab every 8 weeks versus placebo, had rate ratios (RRs) of 0.69 (95% CI 0.56-0.83) for 100 mg and 0.86 (0.71-1.04) for 30 mg; postbronchodilator FEV1 of less than 40% had RRs of 0.76 (0.64-0.91) for 100 mg and 0.90 (0.76-1.06) for 30 mg; and postbronchodilator response of at least 15% had RRs of 0.67

(0.54-0.83) for 100 mg and 0.87 (0.71-1.07) for 30 mg. When combined factors were examined, patients with elevated baseline blood eosinophil counts, with three or more exacerbations in the previous year, and who were receiving triple therapy were identified as likely to benefit from benralizumab 100 mg every 8 weeks versus placebo (RR 0.70 [95% CI 0.56-0.88]). Benralizumab 30 mg every 8 weeks did not benefit patients meeting these criteria compared with placebo (RR 0.99 [95% CI 0.79-1.23]). INTERPRETATION: Elevated blood eosinophil counts combined with clinical characteristics identified a subpopulation of patients with COPD who had reductions in exacerbations with benralizumab treatment. These hypothesis-generating analyses identified the potential efficacy of benralizumab 100 mg for this subpopulation. These findings require prospective evaluation in clinical trials. FUNDING: AstraZeneca.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30338-8/fulltext

De la Rosa Carrillo, D., C. Olveira, et al. (2019). **"COPD Assessment Test in Bronchiectasis: Minimum Clinically Important Difference and Psychometric Validation: A Prospective Study."** Chest BACKGROUND: Health-related quality of life (QoL) is one of the most important end points in bronchiectasis (BE). However, the majority of health-related QoL questionnaires are time-consuming or not validated in BE. The COPD Assessment Test (CAT) is an easy-to-use questionnaire. The objective of this study was to perform a complete validation of the CAT in BE. METHODS: This was an observational, multicenter, prospective study in patients with BE. Psychometric properties of the CAT were measured: internal consistency (Cronbach alpha), repeatability (test-retest; intraclass correlation coefficient), discriminant validity (correlation with severity scores), convergent validity (correlation with some validated QoL questionnaire and other clinical variables of interest), longitudinal validity (measuring before and after each exacerbation during follow-up to determine the sensitivity to change and responsiveness), predictive validity to future exacerbations, and finally minimum clinically important difference. RESULTS: Ninety-six patients were included and followed up for 1 year. Their mean age was 62.2 (15.6) years (79.2% women). The CAT showed excellent internal consistency (alpha, 0.95) and repeatability (intraclass correlation coefficient, 0.95). The validity of the CAT was excellent in all the measures (almost all with a Pearson coefficient > 0.40) except for the correlations with severity scores (Pearson coefficient between 0.22 and 0.26). Sensitivity to change before and after exacerbations was set at between 5.4 and 5.8 points. A CAT value >/= 10 points showed prognostic value for patients with more than one exacerbation, and finally the minimum clinically important difference was set at 3 points. CONCLUSIONS: The CAT presented excellent psychometric properties and is a questionnaire that is easy to use and interpret in patients with BE.

https://journal.chestnet.org/article/S0012-3692(19)33460-9/fulltext

De Matteis, S., D. Jarvis, et al. (2019). **"The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort."** Eur Respir J **54**(1)Occupational exposures are important, preventable causes of chronic obstructive pulmonary disease (COPD). Identification of COPD high-risk jobs is key to focus preventive strategies, but a definitive job-list is unavailable.We addressed this issue by evaluating the association of lifetime job-histories and lung function data in the population-based UK Biobank cohort, whose unprecedented sample size allowed analyses restricted to never-smokers to rule out the most important confounder, tobacco smoking. COPD was spirometrically defined as forced expiratory volume in 1 s/forced vital capacity ratio below the lower limit of normal. Lifetime job-histories were collected via OSCAR (Occupations Self-Coding Automatic Recording), a new validated online tool that automatically codes jobs into the UK Standard Occupational Classification v.2000. Prevalence ratios for COPD by employment duration in each job compared to lifetime office workers were estimated using robust Poisson regression adjusted for age, sex, centre and smoking. Only associations confirmed among never-smokers and never-asthmatics were considered reliable.From the 116 375 participants with complete job-histories, 94 551 had acceptable/repeatable spirometry data and smoking information and were included in the analysis. Six occupations showed an increased COPD risk among never-smokers and never-asthmatics; most of these also with positive exposure-response trends.

Interesting new findings included sculptors, gardeners and warehouse workers.COPD patients, especially never-smokers, should be asked about their job-history for better disease management. Focussed preventive strategies in COPD high-risk jobs are warranted.

https://erj.ersjournals.com/content/54/1/1900186

Ding, Y., Q. Li, et al. (2019). **"CYP2B6 genetic polymorphisms influence chronic obstructive pulmonary disease susceptibility in the Hainan population."** Int J Chron Obstruct Pulmon Dis **14**: 2103-2115.

Introduction: Chronic obstructive pulmonary disease (COPD) is a lung disease closely related to exposure to exogenous substances. CYP2B6 can activate many exogenous substances, which in turn affect lung cells. The aim of this study was to assess the association of single-nucleotide polymorphisms (SNPs) in CYP2B6 with COPD risk in a Chinese Han population. Materials and methods: Genotypes of the five candidate SNPs in CYP2B6 were identified among 318 cases and 508 healthy controls with an Agena MassARRAY method. The association between CYP2B6 polymorphisms and COPD risk was evaluated using genetic models and haplotype analyses. Results: In allele model, we observed that rs4803420 G and rs1038376 A were related to COPD risk. And rs4803420 G/T and G/T-T/T were related to a decreased COPD risk compared to GG genotype in the co-dominant and dominant models, respectively. When comparing with the AA genotype, rs1038376 A/T and A/T-T/T were associated with an increased COPD risk in the co-dominant and dominant models, respectively. Further gender stratification co-dominant and dominant models analysis showed that genotype G/T and G/T-T/T of rs4803420, and genotype A/T and A/T-T/T of rs1038376 were significantly associated with COPD risk compared to the wide type in males and females, while allele C of rs12979270 was only associated with COPD risk in females. Smoking status stratification analysis showed that rs12979270 C was significantly associated with an increased COPD risk under the allele model compared with allele A in the smoking subgroup. Haplotype analysis showed that haplotype GTA and TAA were related to COPD risk. Conclusion: Our data is the first to demonstrate that CYP2B6 polymorphisms may exert effects on COPD susceptibility in the Chinese Han population.

https://www.dovepress.com/getfile.php?fileID=52568

Diver, S., M. Richardson, et al. (2019). **"Sputum microbiomic clustering in asthma and COPD reveals a Haemophilus-predominant subgroup."** AllergyBACKGROUND: Airway ecology is altered in asthma and chronic obstructive pulmonary disease (COPD). Anti-microbial interventions might have benefit in subgroups of airway disease. Differences in sputum microbial profiles at acute exacerbation of airways disease are reflected by the gammaProteobacteria:Firmicutes (gammaP:F) ratio. We hypothesized that sputum microbiomic clusters exist in stable airways disease, which can be differentiated by the sputum gammaP:F ratio. METHODS: Sputum samples were collected from 63 subjects with severe asthma and 78 subjects with moderate-to-severe COPD in a prospective single centre trial. Microbial profiles were obtained through 16S rRNA gene sequencing. Topological data analysis was used to visualize the data set and cluster analysis performed at genus level. Clinical characteristics and sputum inflammatory mediators were compared across the clusters. RESULTS: Two ecological clusters were identified across the combined airways disease population. The smaller cluster was predominantly COPD and was characterized by dominance of Haemophilus at genus level (n = 20), high gammaP:F ratio, increased H influenzae, low diversity measures and increased pro-inflammatory mediators when compared to the larger Haemophilus-low cluster (n = 121), in which Streptococcus demonstrated the highest relative abundance at the genus level. Similar clusters were identified within disease groups individually and the gammaP:F ratio consistently differentiated between clusters. CONCLUSION: Cluster analysis by airway ecology of asthma and COPD in stable state identified two subgroups differentiated according to dominance of Haemophilus. The gammaP:F ratio was able to distinguish the Haemophilus-high versus Haemophilus-low subgroups, whether the Haemophilus-high group might benefit from treatment strategies to modulate the airway ecology warrants further investigation.

https://onlinelibrary.wiley.com/doi/full/10.1111/all.14058

Dransfield, M. T., H. Voelker, et al. (2019). **"Metoprolol for the Prevention of Acute Exacerbations of COPD."** N Engl J MedBACKGROUND: Observational studies suggest that beta-blockers may reduce the risk of exacerbations and death in patients with moderate or severe chronic obstructive pulmonary disease (COPD), but these findings have not been confirmed in randomized trials. METHODS: In this prospective, randomized trial, we assigned patients between the ages of 40 and 85 years who had COPD to receive either a beta-blocker (extended-release metoprolol) or placebo. All the patients had a clinical history of COPD, along with moderate airflow limitation and an increased risk of exacerbations, as evidenced by a history of exacerbations during the previous year or the prescribed use of supplemental oxygen. We excluded patients who were already taking a beta-blocker or who had an established indication for the use of such drugs. The primary end point was the time until the first exacerbation of COPD during the treatment period, which ranged from 336 to 350 days, depending on the adjusted dose of metoprolol. RESULTS: A total of 532 patients underwent randomization. The mean (+/-SD) age of the patients was 65.0+/-7.8 years; the mean forced expiratory volume in 1 second (FEV1) was 41.1+/-16.3% of the predicted value. The trial was stopped early because of futility with respect to the primary end point and safety concerns. There was no significant between-group difference in the median time until the first exacerbation, which was 202 days in the metoprolol group and 222 days in the placebo group (hazard ratio for metoprolol vs. placebo, 1.05; 95% confidence interval [CI], 0.84 to 1.32; P = 0.66). Metoprolol was associated with a higher risk of exacerbation leading to hospitalization (hazard ratio, 1.91; 95% CI, 1.29 to 2.83). The frequency of side effects that were possibly related to metoprolol was similar in the two groups, as was the overall rate of nonrespiratory serious adverse events. During the treatment period, there were 11 deaths in the metoprolol group and 5 in the placebo group. CONCLUSIONS: Among patients with moderate or severe COPD who did not have an established indication for beta-blocker use, the time until the first COPD exacerbation was similar in the metoprolol group and the placebo group. Hospitalization for exacerbation was more common among the patients treated with metoprolol. (Funded by the Department of Defense; BLOCK COPD ClinicalTrials.gov number, NCT02587351.).

https://www.nejm.org/doi/10.1056/NEJMoa1908142

Dumas, O., R. Varraso, et al. (2019). **"Association of Occupational Exposure to Disinfectants With Incidence of Chronic Obstructive Pulmonary Disease Among US Female Nurses."** JAMA Netw Open **2**(10): e1913563.

Importance: Exposure to disinfectants in health care workers has been associated with respiratory health outcomes, including asthma. Despite the biological plausibility of an association between disinfectants (irritant chemicals) and risk of chronic obstructive pulmonary disease (COPD), available data are sparse. Objective: To investigate the association between exposure to disinfectants and COPD incidence in a large cohort of US female nurses. Design, Setting, and Participants: The Nurses' Health Study II is a US prospective cohort study of 116429 female registered nurses from 14 US states who were enrolled in 1989 and followed up through questionnaires every 2 years since. The present study included women who were still in a nursing job and had no history of COPD in 2009, and used data from the 2009 through 2015 questionnaires. Clean and complete data used for this analysis were available in July 2018, and analyses were conducted from September 2018 through August 2019. Exposures: Occupational exposure to disinfectants, evaluated by questionnaire and a job-task-exposure matrix (JTEM). Main Outcomes and Measures: Incident physician-diagnosed COPD evaluated by questionnaire. Results: Among the 73 262 women included in the analyses, mean (SD) age at baseline was 54.7 (4.6) years and 70 311 (96.0%) were white, 1235 (1.7%) black, and 1716 (2.3%) other; and 1345 (1.8%) Hispanic, and 71 917 (98.2%) non-Hispanic. Based on 368145 person-years of follow-up, 582 nurses reported incident physician-diagnosed COPD. Weekly use of disinfectants to clean surfaces only (16 786 [22.9%] of participants exposed) and to clean medical instruments (13 899 [19.0%] exposed) was associated with COPD incidence, with adjusted hazard ratios of 1.38 (95% CI, 1.13-1.68) for cleaning surfaces only and

1.31 (95% CI, 1.07-1.61) for cleaning medical instruments after adjustment for age, smoking (pack-years), race, ethnicity, and body mass index. High-level exposure, evaluated by the JTEM, to several specific disinfectants (ie, glutaraldehyde, bleach, hydrogen peroxide, alcohol, and quaternary ammonium compounds) was significantly associated with COPD incidence, with adjusted hazard ratios ranging from 1.25 (95% CI, 1.04-1.51) to 1.36 (95% CI, 1.13-1.64). Associations were not modified by smoking or asthma status (P for interaction > .15). Conclusions and Relevance: These longitudinal results suggest that regular use of chemical disinfectants among nurses may be a risk factor for developing COPD. If future studies confirm these results, exposure-reduction strategies that are compatible with infection control in health care settings should be developed.

https://jamanetwork.com/journals/jamanetworkopen/articlepdf/2753247/dumas_2019_oi_190517.pdf

Echevarria, C., J. Steer, et al. (2019). **"Comparison of early warning scores in patients with COPD exacerbation: DECAF and NEWS score."** Thorax **74**(10): 941-946.

BACKGROUND: The National Early Warning Score 2 (NEWS2) includes two oxygen saturation scales; the second adjusts target saturations to 88%-92% for those with hypercapnic respiratory failure. Using this second scale in all patients with COPD exacerbation ('NEWS2All COPD') would simplify practice, but the impact on alert frequency and prognostic performance is unknown. Admission NEWS2 score has not been compared with DECAF (dyspnoea, eosinopenia, consolidation, acidaemia, atrial fibrillation) for inpatient mortality prediction. METHODS: NEWS, NEWS2 and NEWS2All COPD and DECAF were calculated at admission in 2645 patients with COPD exacerbation attending consecutively to one of six UK hospitals, all of whom met spirometry criteria for COPD. Alert frequency and appropriateness were assessed for all NEWS iterations. Prognostic performance was compared using the area under the receiver operating characteristic (AUROC) curve. Missing data were imputed using multiple imputation. FINDINGS: Compared with NEWS, NEWS2 reclassified 3.1% patients as not requiring review by a senior clinician (score>/=5). NEWS2All COPD reduced alerts by 12.6%, or 16.1% if scoring for injudicious use of oxygen was exempted. Mortality was low in reclassified patients, with no patients dying the same day as being identified as low risk. NEWS2All COPD was a better prognostic score than NEWS (AUROC 0.72 vs 0.65, p<0.001), with similar performance to NEWS2 (AUROC 0.72 vs 0.70, p=0.090). DECAF was superior to all scores (validation cohort AUROC 0.82) and offered a more clinically useful range of risk stratification (DECAF=1.2%-25.5%; NEWS2=3.5%-15.4%). CONCLUSION: NEWS2All COPD safely reduces the alert frequency compared with NEWS2. DECAF offers superior prognostic performance to guide clinical decision-making on admission, but does not replace repeated measures of NEWS2 during hospitalisation to detect the deteriorating patient.

https://thorax.bmj.com/content/thoraxjnl/74/10/941.full.pdf

Elbehairy, A. F., C. D. O'Donnell, et al. (2019). **"Low resting diffusion capacity, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease."** J Appl Physiol (1985) **127**(4): 1107-1116.

The mechanisms linking reduced diffusing capacity of the lung for carbon monoxide (DlCO) to dyspnea and exercise intolerance across the chronic obstructive pulmonary disease (COPD) continuum are poorly understood. COPD progression generally involves both DlCO decline and worsening respiratory mechanics, and their relative contribution to dyspnea has not been determined. In a retrospective analysis of 300 COPD patients who completed symptom-limited incremental cardiopulmonary exercise tests, we tested the association between peak oxygen-uptake (Vo2), DlCO, and other resting physiological measures. Then, we stratified the sample into tertiles of forced expiratory volume in 1 s (FEV1) and inspiratory capacity (IC) and compared dyspnea ratings, pulmonary gas exchange, and respiratory mechanics during exercise in groups with normal and low DlCO [i.e., <lower limit of normal (LLN)] using Global Lung Function Initiative reference values. DlCO was associated with peak Vo2 (P = 0.006), peak work-rate (P = 0.005), and dyspnea/Vo2 slope (P < 0.001) after adjustment for other independent variables (airway obstruction and hyperinflation). Within FEV1 and IC tertiles, peak Vo2 and work rate were lower (P < 0.05) in low versus normal DlCO groups. Across all tertiles, low DlCO groups

had higher dyspnea ratings, greater ventilatory inefficiency and arterial oxygen desaturation, and showed greater mechanical volume constraints at a lower ventilation during exercise than the normal DlCO group (all P < 0.05). After accounting for baseline resting respiratory mechanical abnormalities, DlCO<LLN was consistently associated with greater dyspnea and poorer exercise performance compared with preserved DlCO. The higher dyspnea ratings and earlier exercise termination in low DlCO groups were linked to significantly greater pulmonary gas exchange abnormalities, higher ventilatory demand, and associated accelerated dynamic mechanical constraints.NEW & NOTEWORTHY Our study demonstrated that chronic obstructive pulmonary disease patients with diffusing capacity of the lung for carbon monoxide (DlCO) less than the lower limit of normal had greater pulmonary gas exchange abnormalities, which resulted in higher ventilatory demand and greater dynamic mechanical constraints at lower ventilation during exercise. This, in turn, led to greater exertional dyspnea and exercise intolerance compared with patients with normal DlCO.

https://www.physiology.org/doi/abs/10.1152/japplphysiol.00341.2019

El-Gazzar, A. G., M. H. Kamel, et al. (2019). **"Prognostic value of platelet and neutrophil to lymphocyte ratio in COPD patients."** Expert Rev Respir Med: 1-6.

Background: Chronic obstructive pulmonary disease (COPD) is the third driving reason for death around the world and a real number of patients suffers from disease exacerbation. Platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) are novel biomarkers in acute exacerbation of COPD (AECOPD) and related to expanded 90-day mortality in patients with COPD. Objectives: This work aimed to assess NLR and PLR in COPD patients. Methods: This case-control study was carried out on 100 COPD patients and 60 healthy subjects. Complete blood count (CBC) with differential was made during and after exacerbation to define NLR and PLR. Results: The cases and controls groups were matched as regards age, sex, and body mass index (BMI) (P-values: 0.3, 0.2, and 0.06 respectively). NLR and PLR were increased significantly in COPD patients (2.24 +/- 0.56 and 157.1 +/- 28.36) compared to control group (1.31 +/- 0.23 and 102.82 +/- 3.99) (P-value < 0.0001). During exacerbation NLR and PLR were elevated significantly compared to stable condition (P-value < 0.0001). NLR and PLR show a significant positive correlation with smoking index, COPD stage, and dyspnea severity. Conclusion: NLR and PLR increased in stable COPD patients and further increased during exacerbation that can predict in hospital mortality.

https://www.tandfonline.com/doi/full/10.1080/17476348.2019.1675517

Feldhaus, F. W., D. C. Theilig, et al. (2019). **"Quantitative CT analysis in patients with pulmonary emphysema: is lung function influenced by concomitant unspecific pulmonary fibrosis?"** Int J Chron Obstruct Pulmon Dis **14**: 1583-1593.

Purpose: Quantitative analysis of CT scans has proven to be a reproducible technique, which might help to understand the pathophysiology of chronic obstructive pulmonary disease (COPD) and combined pulmonary fibrosis and emphysema. The aim of this retrospective study was to find out if the lung function of patients with COPD with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages III or IV and pulmonary emphysema is measurably influenced by high attenuation areas as a correlate of concomitant unspecific fibrotic changes of lung parenchyma. Patients and methods: Eighty-eight patients with COPD GOLD stage III or IV underwent CT and pulmonary function tests. Quantitative CT analysis was performed to determine low attenuation volume (LAV) and high attenuation volume (HAV), which are considered to be equivalents of fibrotic (HAV) and emphysematous (LAV) changes of lung parenchyma. Both parameters were determined for the whole lung, as well as peripheral and central lung areas only. Multivariate regression analysis was used to correlate HAV with different parameters of lung function. Results: Unlike LAV, HAV did not show significant correlation with parameters of lung function. Even in patients with a relatively high HAV of more than 10%, in contrast to HAV (p=0.786) only LAV showed a significantly negative correlation with forced expiratory volume in 1 second (r=-0.309, R(2)=0.096, p=0.003). A severe decrease of DLCO% was associated with both larger HAV (p=0.045) and larger LAV (p=0.001). Residual volume and FVC were not influenced by LAV or HAV.

Conclusion: In patients with COPD GOLD stage III-IV, emphysematous changes of lung parenchyma seem to have such a strong influence on lung function, which is a possible effect of concomitant unspecific fibrosis is overwhelmed.

https://www.dovepress.com/getfile.php?fileID=51291

Fischer, A., I. Johansson, et al. (2019). **"Adherence to a Mediterranean-like Diet as a Protective Factor Against COPD: A Nested Case-Control Study."** Copd **16**(3-4): 272-277.

A diet rich in nutrients has been suggested to have protective effects against the development of chronic obstructive pulmonary disease (COPD). Since the traditional Mediterranean diet is high in nutrients, including antioxidants, vitamins, and minerals, it is of interest to study as a protective factor against COPD. Our aim was therefore to study its associations with development of COPD using population-based prospective data from the Vasterbotten Intervention Programme (VIP) cohort. Data on diet from 370 individuals, who later visited the Department of Medicine at the University Hospital, Umea, Sweden, with a diagnosis of COPD, were compared to 1432 controls. Adherence to a Mediterranean diet was assessed by a modified version of the Mediterranean diet score (MDS). Cases were diagnosed with COPD 11.1 years (mean) (standard deviation [SD] 4.5 years) after first stating their dietary habits in the VIP at a mean age of 55.5 years (SD 6.6 years). Higher MDS was associated with a higher level of education and not living alone. After adjustment for co-habiting and education level, individuals with an intermediate MDS and those with the highest MDS had a lower odds of developing COPD (odds ratio [OR] 0.73, 95% confidence interval [CI] 0.56-0.95; OR 0.56, 95% CI 0.37-0.86, respectively). These results remained also after adjustment for smoking intensity, i.e., numbers of cigarettes smoked per day (OR 0.73, 95% CI 0.53-0.99; OR 0.59, 95% CI 0.35-0.97), respectively). To conclude, adherence to a Mediterranean-like diet seems to be inversely associated with the development of COPD.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2019.1634039?needAccess=true

Freedman, N. (2019). **"Reducing COPD Readmissions: Strategies for the Pulmonologist to Improve Outcomes."** Chest **156**(4): 802-807.

Hospitalizations for patients with acute exacerbations of COPD are associated with several adverse patient outcomes as well as with significant health-care costs. Despite many interventions targeted at reducing readmissions following an initial hospitalization, there are few strategies that have been consistently associated with reductions in this outcome. Despite the lack of consensus as to the best strategies to deploy to reduce readmissions related to acute exacerbations of COPD, efforts must continue to focus on determining the best approaches for this population. These tactics will need to be cost-effective for payers while not being cost-prohibitive for providers. In addition, these interventions will need to be relatively easy to institute while not being overbearing for patients or providers. Larger systems with their greater financial resources will likely find success with technology and data-driven comprehensive programs; independent hospitals and practices are more likely to succeed with less resource-intensive interventions such as early postdischarge follow-up, coaching, action plans, self-management education, and pulmonary rehabilitation. Choosing the right interventions that will utilize financial and human resources in a cost-effective manner, while tailoring the approaches to meet the needs of a specific patient group, will be of key importance.

https://journal.chestnet.org/article/S0012-3692(19)31233-4/fulltext

Gagne, M., S. Lauzier, et al. (2019). **"COPD-Specific Self-Management Support Provided by Trained Educators in Everyday Practice is Associated with Improved Quality of Life, Health-Directed Behaviors, and Skill and Technique Acquisition: A Convergent Embedded Mixed-Methods Study."**

PatientBACKGROUND: There is a necessity to better document the effect of continuing education activities targeted at respiratory educators providing self-management support for patients with chronic obstructive pulmonary disease (COPD). We therefore sought to describe real-life COPD-specific self-management support delivered by respiratory educators who participated in a lecture-based continuing education activity and assess the outcomes of patients with COPD. METHODS: We conducted a convergent embedded mixed-methods study. Respiratory educators attended a 7-h, lecture-based continuing education activity on self-management support held in Quebec, Canada. Four months after the continuing education activity, in their professional practice, trained educators provided self-management support to patients with COPD. One month later, to describe the components of self-management support provided, individual telephone interviews were conducted with educators. Interviews were transcribed verbatim and were qualitatively analyzed. Before self-management support and 6 months afterwards, we assessed the following clinical outcomes of patients with COPD: (1) quality of life (St. George's Respiratory Questionnaire for COPD patients, Impact domain; score 0-100; minimal clinically important difference = - 4; telephone administered); (2a) whether patients had one or more unscheduled doctor visit, (2b) one or more emergency room visit, and (2c) one or more hospitalization in the 6 preceding months (Survey on Living with Chronic Diseases in Canada; telephone administered); and (3a) health-directed behaviors and (3b) skill and technique acquisition (Health Education Impact Questionnaire; score 1-4; self-administered at home). We used mixed models to estimate mean differences and prevalence ratios, with associated 95% confidence intervals. RESULTS: Trained respiratory educators (nurse: n = 1; respiratory therapist: n = 3; >/= 15 years of experience of care with patients with chronic disease) invited 75 patients with COPD to participate in the study. Fifty-four individuals with COPD (age, mean +/- standard deviation: 68 +/- 8 years; men: n = 31) were enrolled and received self-management support. Qualitative analyses revealed that self-management support consisted of one to two visits that included: (1) provision of information on COPD; (2) training in inhalation technique; and (3) smoking cessation advice. No educator reported implementing two or more follow-up visits because of a lack of time and human resources in their work setting. Among patients with COPD, improvements in quality of life were clinically important (adjusted mean difference = - 12.75; 95% confidence interval - 18.79 to - 6.71; p = 0.0001). Health-resource utilization was not different over time (all p values > 0.05). Improvements in health-directed behaviors and skill and technique acquisition were statistically significant (health-directed behaviors: adjusted mean difference = 0.50; 95% confidence interval 0.23-0.77; p = 0.0005; skill and technique acquisition: adjusted mean difference = 0.12; 95% confidence interval 0.01-0.23; p = 0.0293). CONCLUSIONS: Following a 7-h, lecture-based continuing education activity on COPD-specific self-management support, respiratory educators with significant experience of care provided self-management support that included provision of information, inhalation technique training, and smoking cessation advice. This resulted in enhanced patient quality of life, health-directed behaviors, and skill and technique acquisition. To decrease health resource utilization, the training could employ active learning methods. More time and resources could also be devoted to implementing regular follow-up visits. CLINICAL TRIALS REGISTRATION NO: NCT02870998.

https://link.springer.com/article/10.1007%2Fs40271-019-00386-7

Gay, E., S. Desai, et al. (2019). **"A Multidisciplinary Intervention to Improve Care for High-Risk COPD Patients."** Am J Med Qual: 1062860619865329.

Chronic obstructive pulmonary disease (COPD) exacerbations contribute to both costs and patient morbidity. The authors designed a quality project to improve care for high-risk COPD patients admitted with an exacerbation. An electronic medical record report was used to target admitted high-risk COPD patients for an intervention that included pulmonary and respiratory therapy consults, post-discharge phone calls from a patient navigator, referrals to palliative services when appropriate, and bedside delivery of medications. The control population was a similar group of patients at a community partner hospital who received usual care. In all, 157 unique patients were enrolled over 16 months; referrals to palliative care services increased and rates of outpatient follow-up improved. There was no difference in readmissions or emergency department visits between the 2 groups. Better coordination of outpatient care and attention to psychosocial burdens were identified as possible targets for future interventions.

https://journals.sagepub.com/doi/10.1177/1062860619865329

George, L., A. R. Taylor, et al. (2019). **"Blood eosinophil count and airway epithelial transcriptome relationships in COPD versus asthma."** AllergyBACKGROUND: Whether the clinical or pathophysiologic significance of the "treatable trait" high blood eosinophil count in COPD is the same as for asthma remains controversial. We sought to determine the relationship between the blood eosinophil count, clinical characteristics and gene expression from bronchial brushings in COPD and asthma. METHODS: Subjects were recruited into a COPD (emphysema versus airway disease [EvA]) or asthma cohort (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes, U-BIOPRED). We determined gene expression using RNAseq in EvA (n = 283) and Affymetrix microarrays in U-BIOPRED (n = 85). We ran linear regression analysis of the bronchial brushings transcriptional signal versus blood eosinophil counts as well as differential expression using a blood eosinophil > 200 cells/muL as a cut-off. The false discovery rate was controlled at 1% (with continuous values) and 5% (with dichotomized values). RESULTS: There were no differences in age, gender, lung function, exercise capacity and quantitative computed tomography between eosinophilic versus noneosinophilic COPD cases. Total serum IgE was increased in eosinophilic asthma and COPD. In EvA, there were 12 genes with a statistically significant positive association with the linear blood eosinophil count, whereas in U-BIOPRED, 1197 genes showed significant associations (266 positive and 931 negative). The transcriptome showed little overlap between genes and pathways associated with blood eosinophil counts in asthma versus COPD. Only CST1 was common to eosinophilic asthma and COPD and was replicated in independent cohorts. CONCLUSION: Despite shared "treatable traits" between asthma and COPD, the molecular mechanisms underlying these clinical entities are predominately different.

https://onlinelibrary.wiley.com/doi/full/10.1111/all.14016

Gompelmann, D., T. Heinhold, et al. (2019). **"Long-term follow up after endoscopic valve therapy in patients with severe emphysema."** Ther Adv Respir Dis **13**: 1753466619866101.

BACKGROUND AND OBJECTIVE: Endoscopic valve therapy is a treatment modality in patients with advanced emphysema and absent interlobar collateral ventilation (CV). So far, long-term outcome following valve implantation has been insufficiently evaluated. The aim of this study was to investigate the real-world efficacy of this interventional therapy over 3 years. METHODS: From 2006 to 2013, 256 patients with severe emphysema in whom absent CV was confirmed underwent valve therapy. The 3-year effectiveness was evaluated by pulmonary function testing (VC, FEV1, RV, TLC), 6-minute-walk test (6-MWT) and dyspnea questionnaire (mMRC). Long-term outcome was also assessed according to the radiological outcome following valve placement. RESULTS: Of 256 patients treated with valves, 220, 200, 187, 100 and 66 patients completed the 3-month, 6-month, 1-year, 2-year and 3-year follow-up (FU) visit, respectively. All lung function parameters, 6-MWT and mMRC were significantly improved at 3- and 6-month FU. At 1-year FU, patients still experienced a significant improvement of all outcome parameters expect VC (L) and TLC (%). At 2 years, RV (L and %) and TLC (L and %) remained significantly improved compared to baseline. Three years after valve therapy, sustained significant improvement in mMRC was observed and the proportion of patients achieving a minimal clinically important difference from baseline in RV and 6-MWT was still 71% and 46%, respectively. Overall, patients with complete lobar atelectasis exhibited superior treatment outcome with 3-year responder rates to FEV1, RV and 6-MWT of 10%, 79% and 53%, respectively. CONCLUSIONS: Patients treated by valves experienced clinical improvement over 1 year following valve therapy. Afterwards, clinical benefit gradually declines more likely due to COPD progression.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6681249/pdf/10.1177_1753466619866101.pdf

Gonzalez, J., C. I. Henschke, et al. (2019). **"Emphysema phenotypes and lung cancer risk."** PLoS One **14**(7): e0219187.

BACKGROUND: To assess the relationship between lung cancer and emphysema subtypes. OBJECTIVE: Airflow obstruction and emphysema predispose to lung cancer. Little is known, however, about the lung cancer risk associated with different emphysema phenotypes. We assessed the risk of lung cancer based on the presence, type and severity of emphysema, using visual assessment. METHODS: Seventy-two consecutive lung cancer cases were selected from a prospective cohort of 3,477 participants enrolled in the Clinica Universidad de Navarra's lung cancer screening program. Each case was matched to three control subjects using age, sex, smoking history and body mass index as key variables. Visual assessment of emphysema and spirometry were performed. Logistic regression and interaction model analysis were used in order to investigate associations between lung cancer and emphysema subtypes. RESULTS: Airflow obstruction and visual emphysema were significantly associated with lung cancer (OR = 2.8, 95%CI: 1.6 to 5.2; OR = 5.9, 95%CI: 2.9 to 12.2; respectively). Emphysema severity and centrilobular subtype were associated with greater risk when adjusted for confounders (OR = 12.6, 95%CI: 1.6 to 99.9; OR = 34.3, 95%CI: 25.5 to 99.3, respectively). The risk of lung cancer decreases with the added presence of paraseptal emphysema (OR = 4.0, 95%CI: 3.6 to 34.9), losing this increased risk of lung cancer when it occurs alone (OR = 0.7, 95%CI: 0.5 to 2.6). CONCLUSIONS: Visual scoring of emphysema predicts lung cancer risk. The centrilobular phenotype is associated with the greatest risk.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6657833/pdf/pone.0219187.pdf

Gonzalez-Barcala, F. J., M. E. San-Jose, et al. (2019). **"Blood eosinophils could be useful as a biomarker in chronic obstructive pulmonary disease exacerbations."** Int J Clin Pract: e13423.

Introduction The aim of analysing the usefulness of the blood eosinophil count (BEC) as a prognostic marker in exacerbations of patients with Chronic Obstructive Pulmonary Disease (COPD), evaluating its relationship with hospital mortality, the length of stay and the early and late re-admissions. Materials and Methods We have carried out a retrospective study including all patients who required hospital admission from 1 January 2008 to 31 December 2009, with a diagnosis on hospital discharge of COPD exacerbation. These patients were classified using three cut-off points of BEC: less than 200 vs >/= 200/microL, less than 300 vs >/= 300/microL and less than 400 vs >/= 400/microL. Results There were a total of 1626 hospital admissions during the study period with the diagnosis of exacerbation of COPD. In this study we have included 358 patients. The probability of any late re-admission increased with a BEC >/= 300/microL (odds ratio: 1.684) and for those with a BEC >/= 400/microL (odds ratio: 2.068). The BEC does not appear to be related to hospital mortality or the probability of early re-admission after an exacerbation of COPD. Conclusions In our study an elevated BEC is associated with a higher incidence of late hospital readmissions in COPD exacerbations.

https://onlinelibrary.wiley.com/doi/full/10.1111/ijcp.13423

Grotheer, M., J. Hirschberger, et al. (2019). **"Comparison of signalment, clinical, laboratory and radiographic parameters in cats with feline asthma and chronic bronchitis."** J Feline Med Surg: 1098612x19872428.

OBJECTIVES: Feline asthma (FA) and feline chronic bronchitis (CB) are common respiratory conditions in cats, frequently referred to as 'feline lower airway disease'. However, the aetiologies of both inflammatory airway diseases are probably different. Little is known about the differences in signalment, clinical signs, laboratory abnormalities and radiographic features between cats with these two airway diseases. The aim of the study was to investigate whether certain parameters can help in differentiating between both diseases, as distinguished by airway cytology. METHODS: Seventy-three cats with FA and 24 cats with CB were included in the retrospective study. Inclusion criteria were compatible clinical signs and a cytological evaluation of bronchoalveolar lavage fluid indicating either FA (eosinophilic inflammation) or CB (neutrophilic inflammation) without cytological or microbiological evidence of bacterial infection. Parameters of signalment, physical examination, haematology and thoracic radiographs of both disease

groups were compared statistically (P <0.05). RESULTS: The median age of cats with FA was 6 years, and was 7.5 years in cats with CB (P = 0.640). The most commonly reported clinical signs in both groups were a cough (95% FA/96% CB; P = 1.000), pathological pulmonary auscultatory sounds (82% FA/79% CB; P = 0.766) and dyspnoea (73% FA/79% CB; P = 0.601). Abnormal radiographic lung patterns were detected in 94% of cats with FA and 91% with CB (P = 0.629), respectively. Blood eosinophilia was significantly more common in cats with FA (40%) compared with CB (27%) (P = 0.026). CONCLUSIONS AND RELEVANCE: The study indicates that a differentiation of FA and CB by means of signalment, a single clinical sign, and haematological and radiographic findings is not possible.

https://journals.sagepub.com/doi/10.1177/1098612X19872428

Gu, A., S. Wu, et al. (2019). **"Impact of Chronic Obstructive Pulmonary Disease on Postoperative Complications Following Simultaneous Bilateral Total Knee Arthroplasty."** J Knee SurgFor patients who qualify, simultaneous bilateral total knee arthroplasty (TKA) is a viable option for the treatment of bilateral symptoms. However, the incidence of chronic obstructive pulmonary disease (COPD) has been steadily rising over the past few decades and may impact those who qualify as candidates for bilateral TKA. As such, the aim of this study was to determine the impact of COPD on postoperative outcomes in patients who receive simultaneous bilateral TKA. A retrospective cohort study was conducted utilizing data provided through the American College of Surgeons National Surgical Quality Improvement Program. All patients who had undergone simultaneous bilateral TKA between 2007 and 2016 were identified and further stratified into groups based upon the COPD status. Incidence of adverse events after TKA in the acute postoperative period was evaluated with univariate and multivariate analyses. COPD was found to be an independent risk factor for the development of major (odds ratio [OR]: 2.5; p = 0.015), renal (OR: 5.1; p = 0.02), and thromboembolic complications (OR: 2.5; p = 0.027). In addition, patients with COPD were at increased risk for having an extended hospital length of stay (LOS; p < 0.001) and development of urinary tract infections (p < 0.001). Patients with COPD are at higher risk for development of overall major complications, as well as renal and thromboembolic complications after simultaneous bilateral TKA. Interestingly, patients were not at increased risk for the development of pulmonary or wound complications. When considering a staged versus simultaneous bilateral TKA, surgeons should be aware of the impact COPD status has on the postoperative complication rate.

https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-0039-1695766

Gu, J., J. Xu, et al. (2019). **"Exophiala Dermatitis & Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)."** QjmExophiala dermatitidis, a rare fungus which usually causes cutaneous or subcutaneous disease, rarely causes pulmonary infection. A 76-year-old man was admitted to our hospital with complaints of exacerbating cough and purulent sputum for one day. Repeated sputum culture revealed no other infectious agent except Exophiala dermatitidis. His illness was improved by administrations of voriconazole for 22 days. The patient has been in good health and there has been no worsening of symptom during the 4-month follow-up period. Our case illustrated the role of Exophiala dermatitidis responsible for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Although the optimal treatment remains unknown, the prognosis may be favorable when the infections were limited to the lung and treated with appropriate antifungal drugs.

https://watermark.silverchair.com/hcz190.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAocwggKDBgkqhkiG9w0BBwagggJ0MIICcAIBADCCAmkGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMkTcNs1IZB30khlW_AgEQgIICOuK0VMGeeaPwDhj5nbRBpviMKDl0vKjI1333_9g9Q6DeZ1NRhP7QAAt9NJBMeHBijsDs09USirJK_Mk_0g-r9YqpgHBMNN-2DAb2gP8eW5r9-w6w85x5X3yMkNVw2fDY7Vh6e4gf2yRqFsHqo7fz-wY9gNhGvtK759ch2jYChebDE0ed977tBfblmkqfqZRo0CvyVEnzMllkDq0ddBa14rEBfeskdYAOa6WrE_JOhDqmV95rYRG2Jkwi_tsFN-7-3OpZI0Ia4FBstGlZVw0Zp02IaZKT80VJDoQoPpxqhM-LrGdgrYonvgDSkQtPY2-Jfc7W9AFMMrD5ReFvyqxS7Bo_hhbp0Ek2iCf4pQAr3ZGL0Hgx8w1Mnz0yOYq4mNVqJgNXH-

IWRtfRSbA1kflZ18z72Mw4HCMbon1GdUZ_tEmE0Cka-8AYdRFIsyXdYhqy_ogQupCc5492clVN-7Q-XV92wQ35eIM9fQV2RP9wIGX7aKuuKZSVxkwBjM7FinGFFsxeSL9XROqcd1z0WWROg6op_4pzSIf1QPDZtqS0fahb9lVg8PL2oPNIBakAlzk4iiA9bzzT0iyp1vgI1D3Qvcb9_Ka_fn6jqWcsS-6GNYrrXQyHP5h-o14-0VWtdcVVeS0wzbLLEFE5020UYgMh4Zd1f1CzAE0dlwbOGv3yJF_wx1S7DHTAk8lRq8CucQwE7GO0oI-r6zZM6JmXY4TBY2OC5V5iwC4NVTN3JvqbecqXFxaddKwFklOgzg

Hassen, M. F., N. Tilouche, et al. (2019). **"Incidence and Impact of Pulmonary Embolism During Severe COPD Exacerbation."** Respir CareBACKGROUND: Patients with COPD are at a high risk for pulmonary embolism (PE) because of systemic inflammation and co-existing comorbidities. We aimed to determine the incidence, risk factors, and impact of PE during COPD exacerbation requiring mechanical ventilation. METHODS: This prospective cohort study was conducted between March 2013 and May 2017. Subjects with severe COPD exacerbation requiring mechanical ventilation were included. A lower-limb ultrasonography or a multidetector helical computed tomography scan (MDCT) was performed according to Wells score. Subjects with ultrasonographic signs of phlebitis underwent MDCT to confirm PE. RESULTS: During the study period, 131 COPD subjects were admitted to the ICU for severe COPD exacerbation. The incidence of PE was 13.7%. Factors independently associated with PE were increased sputum volume (odds ratio [OR] = 0.106, 95% CI 0.029-0.385, P = .001), recent immobilization >/= 7 d (OR = 5.024, 95% CI 1.470-17.170, P = .01), age >/= 70 y (OR = 5.483, 95% CI 1.269-23.688, P = .02), and invasive mechanical ventilation at ICU admission (OR = 3.615, 95% CI 1.005-13.007, P = .049). ICU mortality was higher in the PE group (44% vs 11%). Predictive factors of mortality were PE (OR = 7.135, 95% CI 2.042-24.931, P = .002), SAPS II score at admission OR = 1.040, 95% CI 1.005-1.077, P = .02), and duration of mechanical ventilation (OR = 1.098, 95% CI 1.044-1.154, P < .001). CONCLUSIONS: PE was found to be a common etiology of severe exacerbation of COPD, leading to high mortality. Age, invasive mechanical ventilation, and immobilization were risk factors for PE.

http://rc.rcjournal.com/content/early/2019/08/06/respcare.06661

Hayes Watson, C., H. Nuss, et al. (2019). **"Health beliefs associated with poor disease self-management in smokers with asthma and/or COPD: a pilot study."** J Asthma **56**(9): 1008-1015.

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, G. X., N. Li, et al. (2019). **"Benefits of different intensities of pulmonary rehabilitation for patients with moderate-to-severe COPD according to the GOLD stage: a prospective, multicenter, single-blinded, randomized, controlled trial."** Int J Chron Obstruct Pulmon Dis **14**: 2291-2304.

Purpose: Pulmonary rehabilitation (PR) is essential to manage patients with COPD. The aim of this study was to investigate the appropriate intensity of PR exercise training for patients with moderate-to-severe COPD. Patients and methods: A prospective multicenter randomized controlled trial was conducted from January 2014 to October 2018. The subjects were randomly assigned to three groups with different intensities of PR, according to their maximum oxygen uptake percentage determined by cardiopulmonary exercise testing. After 20 weeks of exercise training, the effects of low-, moderate-, and high-intensity exercise interventions on patients were compared to determine the most appropriate PR prescription. Results: For patients with moderate COPD, all the measured parameters were significantly improved in the moderate- and high-intensity PR groups (P<0.01), while there was no significant difference in the frequency of acute exacerbations and the mMRC questionnaire after 20 weeks of PR exercise in the low-intensity PR group. For patients with severe COPD, all variables were also improved in the high-intensity PR group (P<0.05), while the mean differences of pre- and post-PR were lower than those in patients with moderate COPD. Moreover, the Hamilton Anxiety Scale and body mass index showed no significant difference in low-intensity PR group (P>0.05). Conclusion: High-intensity PR exercise is helpful for patients with moderate to severe COPD. Moderate COPD patients need to receive intensive PR training; the improvement degrees from PR intervention were higher than those of the severe COPD patients. For patients with severe COPD, high-intensity PR exercise may be more beneficial if patients can tolerate it.

https://www.dovepress.com/getfile.php?fileID=53184

Hendryx, M., J. Luo, et al. (2019). **"Air pollution exposures from multiple point sources and risk of incident chronic obstructive pulmonary disease (COPD) and asthma."** Environ Res **179**(Pt A): 108783.

BACKGROUND: Exposure to environmental air pollutants exacerbates respiratory illness, but prospective studies of disease incidence are uncommon. Further, attempts to estimate effects from multiple point sources have rarely been undertaken. The current study examined risk of incident chronic obstructive pulmonary disease (COPD) and asthma in association with emissions of multiple air pollutants from point pollution sources in Australia. METHODS: We analyzed prospective cohort data from the Australian Longitudinal Study on Women's Health. Women from three age-cohorts (N=35,755) were followed for up to 21 years for incident COPD and asthma. Exposures were measured from the National Pollutant Inventory and included carbon monoxide, nitrogen oxides, sulfur dioxide, and particulate matter (PM2.5 and PM10). We identified inverse-distance weighted emissions in kilograms that women experienced over time from point sources within 10km of their residences. Cox proportional hazards regression models examined risk of self-reported doctor-diagnosed COPD and asthma in association with pollutant exposures and covariates. RESULTS: New COPD cases numbered 3616 (11.5%) and new asthma cases numbered 2725 (9.4%). Participants were exposed to an average of 47-59 sites with air pollution emissions within 10km of their residences. Fossil fuel electricity generation and mining made the largest contributions to air pollution but hundreds of other types of emissions also occurred. Controlling for covariates, all five air pollutants modeled individually were significantly associated with risk of COPD. Modeled jointly, only sulfur dioxide (SO2) remained significantly associated with COPD (HR=1.038, 95% CI=1.010-1.067), although the five pollutants were highly correlated (r=0.89). None of the pollutants were significantly associated with adult onset asthma. Cohort-specific analyses indicated that COPD risk was significantly associated with SO2 exposure for younger (HR=1.021, CI=1.001-1.047), middle-age (HR=1.019, CI=1.004-1.034) and older cohorts (HR=1.025, CI=1.004-1.047). CONCLUSIONS: Multiple exposure sources and pollutants contributed to COPD risk, including electricity generation and mining but extending to many industrial processes. The results highlight the importance of policy efforts and technological improvements to reduce harmful air pollution emissions across the industrial landscape.

https://www.sciencedirect.com/science/article/pii/S0013935119305808?via%3Dihub

Heraganahally, S. S., S. L. Wasgewatta, et al. (2019). **"Chronic Obstructive Pulmonary Disease In Aboriginal Patients Of The Northern Territory Of Australia: A Landscape Perspective."** Int J Chron Obstruct Pulmon Dis **14**: 2205-2217.

Background: The Aboriginal population of Australia has a higher burden of chronic health conditions than non-Aboriginal Australians. However, there is a paucity of data on clinical and demographic characteristics of chronic obstructive pulmonary disease (COPD) in this population. Method: In this retrospective study we evaluated the clinical, demographic and environmental influences in adult Aboriginal patients with COPD living in the regional and remote communities of the Northern Territory of Australia. Results: There were 380 patients (49%) with a diagnosis of COPD of the 767 patients referred to specialist respiratory outreach clinics. The mean age was 57 years (56% were female) and mean+/-SD BMI was 24.30+/-7.01 kg/m(2). Smoking history was noted in 93% of the study cohort. The most common respiratory symptom was shortness of breath in 62%, and inhaled medications (salbutamol, tiotropium, salmeterol/fluticasone) were used by 79%, 44% and 58% of patients, respectively. Spirometry showed obstructive impairment (FEV1/FVC <0.7) in 79% (0.56+/-0.17), with mean FEV1 42% of predicted, and a bronchodilator response was present in 28.6%. Comorbid bronchiectasis was diagnosed in 49.8% along with COPD. The relationship between COPD and community demography showed a higher proportion of smokers and those with underlying bronchiectasis to have lower FEV1/FVC ratios. Communities with a higher proportion of asthma were younger and had higher smoking rates. Mortality increased with increasing number of exacerbations and hospital admissions. Conclusion: The Aboriginal population with COPD has a higher prevalence of smoking, moderate to severe airflow obstruction on spirometry and frequently co-diagnosed bronchiectasis with increased severity of ventilatory impairment.

https://www.dovepress.com/getfile.php?fileID=53011

Hirai, K., T. Shirai, et al. (2019). **"Comparison of the association between circulating vitamin D3 levels and clinical outcomes in patients with asthma and chronic obstructive pulmonary disease: a prospective observational study."** Biol Pharm BullVitamin D has an immune-modulating effect, related to the pathophysiology of asthma and chronic obstructive pulmonary disease (COPD). However, few studies have focused on the difference between patients with asthma and COPD in the association of circulating vitamin D levels with clinical outcomes. We sought to investigate the associations of circulating vitamin D levels with health-related quality of life (HR-QOL), severity, and exacerbations. Subjects included 152 asthma patients and 50 COPD patients. We measured plasma concentrations of 25-hydroxyvitamin D3 [25(OH)D3]. HR-QOL was assessed using the EuroQoL 5-Dimension (EQ-5D) and the 12-item Short Form Health Survey (SF-12) scales. Exacerbations were recorded during a one-year follow-up. Associations between plasma 25 (OH)D3 concentrations and outcome variables were evaluated using linear regression. Plasma concentrations of 25(OH)D3 were positively associated with the EQ-5D index value and the SF-12 physical component score in patients with asthma; however, such associations were not observed in patients with COPD. A significant association between severity and plasma concentrations of 25(OH)D3 was found only in patients with COPD. The hazard ratios (95% confidence interval) of plasma 25(OH)D3 concentrations (per 1 ng/mL decrease) for time to first exacerbation was 1.38 (1.10-1.75; p = 0.006) and 0.95 (0.87-1.03; p = 0.179) in patients with COPD and asthma, respectively. Lower concentrations of plasma 25(OH)D3 contributed to lower HR-QOL in patients with asthma, and were associated with severity and risk of future exacerbations in patients with COPD.

https://www.jstage.jst.go.jp/article/bpb/advpub/0/advpub_b19-00385/_pdf

Hoesterey, D., N. Das, et al. (2019). **"Spirometric indices of early airflow impairment in individuals at risk of developing COPD: Spirometry beyond FEV1/FVC."** Respir Med **156**: 58-68.

Spirometry is the current gold standard for diagnosing and monitoring the progression of Chronic Obstructive Pulmonary Disease (COPD). However, many current and former smokers who do not meet established spirometric criteria for the diagnosis of this disease have symptoms and clinical courses similar to those with diagnosed COPD. Large longitudinal observational studies following individuals at risk of developing COPD offer us additional insight into spirometric patterns of disease development and progression. Analysis of forced expiratory maneuver changes over time may allow us to better understand early changes predictive of progressive disease. This review discusses the theoretical ability of spirometry to capture fine pathophysiologic changes in early airway disease, highlights the shortcomings of current diagnostic criteria, and reviews existing evidence for spirometric measures which may be used to better detect early airflow impairment.

https://www.resmedjournal.com/article/S0954-6111(19)30260-4/fulltext

Hori, R., R. Ishida, et al. (2019). **"Effects of noninvasive ventilation on the coordination between breathing and swallowing in patients with chronic obstructive pulmonary disease."** Int J Chron Obstruct Pulmon Dis **14**: 1485-1494.

Purpose: As shown in our previous study, inspiration after swallowing (SW-I) increases during the bi-level positive airway pressure ventilation (BiPAP) in healthy subjects because swallowing-associated non-inspiratory flow (SNIF) triggers inspiratory support, while SW-I during continuous positive pressure ventilation (CPAP) is rare. In the present study, we evaluated the coordination between breathing and swallowing during spontaneous breathing, BiPAP, and CPAP in patients with chronic obstructive pulmonary disease (COPD). Patients and methods: This study is a prospective intervention study at the Hoshigaoka Medical Center (November 01, 2015-April 30, 2018). We simultaneously recorded the respiratory flow, laryngeal motion, and swallowing sounds during saliva swallowing in patients with COPD. We estimated the respiratory phase after swallowing, frequency of SNIF, the duration of the respiratory pause during swallowing, and timing of swallowing in the respiratory cycle and compared these parameters among control, CPAP, and BiPAP conditions. Results: The expiration after swallowing (SW-E) frequency was associated with the occurrence of SNIF ($p<0.01$), pause duration </=0.8 s ($p<0.01$), and timing of swallowing at the intermediate respiratory phase (50-80% of the respiratory cycle from the onset of inspiration) ($p<0.01$). In particular, the occurrence of SNIF most substantially affected the SW-E frequency. The SW-I frequencies under the control, CPAP, and BiPAP conditions were 35.0%, 3.0%, and 37.7%, respectively. The pause durations were shorter during CPAP and BiPAP than under the control condition ($p<0.01$). During CPAP, the occurrence rates of SW-E. Residual denotes the percentage difference between observed and expected values (residual =10.8: $p<0.01$) and SNIF (residual =9.1: $p<0.01$) were significantly increased, and timing of swallowing shifted toward the intermediate respiratory phase (residual=3.5: $p<0.01$). Conclusion: CPAP decreases the SW-I frequency, increases the SNIF occurrence, and normalizes the timing of swallowing, all of which suggest that CPAP alleviates the risk of aspiration in patients with COPD.

https://www.dovepress.com/getfile.php?fileID=51045

Hosseini, H. M., D. R. Pai, et al. (2019). **"COPD: Does Inpatient Education Impact Hospital Costs and Length of Stay?"** Hosp Top **97**(4): 165-175.

Background: Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in the United States and costs approximately $50 billion in annual healthcare costs. Certain interventions such as COPD inpatient education programs have demonstrated effectiveness in reducing healthcare utilization and reducing healthcare associated costs. Purpose: To assess the effectiveness of chronic obstructive pulmonary disease (COPD) inpatient education using existing respiratory therapy staff in an academic health system. Methodology/Approach: This retrospective observational study employed a matched case-control design. Inpatients admitted with a COPD related condition in this study received self-management interventions from Registered Respiratory Therapists (RTs). The sample includes retrospective administrative and medical record data on 84 inpatients with a diagnosis of COPD

admitted in 2016 through 2017. Patients received self-management interventions at the bedside by trained RTs while admitted to acute care areas, progressive care units and intermediate care units. Effectiveness of inpatient education was compared before and after the interventions. Hospitalization costs and length of stay (LOS) are the primary outcome measures. Results: Statistical analyses revealed that inpatient COPD education appears to reduce hospital length of stay and associated costs. Post hoc regression analyses revealed that age, gender, marital status, and number of visits were significantly associated with LOS; whereas, smoking, LOS, and number of visits were significantly associated with hospitalization costs. Practice Implications: COPD patient education may be an effective strategy at reducing hospital costs and healthcare utilization overall. Empowering patients to take responsibility for their own health outcomes by improving self-efficacy has proven to demonstrate value.

https://www.tandfonline.com/doi/full/10.1080/00185868.2019.1677540

Huang, W. C., C. C. Huang, et al. (2019). **"The association between airflow limitation and blood eosinophil levels with treatment outcomes in patients with chronic obstructive pulmonary disease and prolonged mechanical ventilation."** Sci Rep **9**(1): 13420.

The clinical implications of airflow limitation severity and blood eosinophil level in patients with chronic obstructive pulmonary disease (COPD) and prolonged mechanical ventilation (PMV) are unknown. Thus, this study aimed to identify whether or not these two indicators were significantly associated with short-term in-respiratory care center (RCC) treatment outcomes in this population. Of all participants (n = 181) in this retrospective cross-sectional study, 41.4%, 40.9%, 8.3%, and 52.5% had prolonged RCC admission (RCC length of stay >21 days), failed weaning, death, and any adverse outcomes of interest, respectively. Compared to participants without any adverse outcomes of interest, moderate (the Global Initiative for Chronic Obstructive Lung Disease (GOLD) II) and/or severe (GOLD III) airflow limitation were significantly associated with short-term in-RCC adverse outcomes in terms of failed weaning (for III versus I, OR = 15.06, p = 0.003) and having any adverse outcomes of interest (for II versus I, OR = 17.66, p = 0.002; for III versus I, OR = 37.07, p = 0.000) though the severity of airflow limitation did not have associations with prolonged RCC admission and death after adjustment. Meanwhile, blood eosinophilia defined by various cut-off values was not associated with any adverse outcomes. The findings have significant clinical implications and are useful in the management of patients with COPD and PMV.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6748958/pdf/41598_2019_Article_49918.pdf

Hudson, M., S. Dell'Aniello, et al. (2019). **"Comparative safety of biologic versus conventional synthetic DMARDs in rheumatoid arthritis with COPD: a real-world population study."** Rheumatology (Oxford)OBJECTIVES: Abatacept, a biologic DMARD, was associated with respiratory adverse events in a small subgroup of RA patients with chronic obstructive pulmonary disease (COPD) in a trial. Whether this potential risk is specific to abatacept or extends to all biologics and targeted synthetic DMARDs (tsDMARDs) is unclear. We assessed the risk of adverse respiratory events associated with biologic and tsDMARDs compared with conventional synthetic DMARDs (csDMARDs) among RA patients with concomitant COPD in a large, real-world cohort. METHODS: We used a prevalent new-user design to study RA patients with COPD in the US-based MarketScan databases. New users of biologic DMARDs and/or tsDMARDs were matched on time-conditional propensity scores to new users of csDMARDs. Adverse respiratory events were estimated using Cox models comparing current use of biologic/tsDMARDs with csDMARDs. RESULTS: The cohort included 7424 patients initiating biologic/tsDMARDs and 7424 matched patients initiating csDMARDs. The adjusted hazard ratio of hospitalized COPD exacerbation comparing biologic/tsDMARD vs csDMARD was 0.76 (95% CI: 0.55, 1.06), while it was 1.02 (95% CI: 0.82, 1.27) for bronchitis, 1.21 (95% CI: 0.92, 1.58) for hospitalized pneumonia or influenza and 0.99 (95% CI: 0.87, 1.12) for outpatient pneumonia or influenza. The hazard ratio of the combined end point of COPD exacerbation, bronchitis and hospitalized pneumonia or influenza was 1.04 (95% CI: 0.89, 1.21). CONCLUSION: In this large, real-world comparative safety study,

biologic and tsDMARDs, including abatacept, were not associated with an increased risk of adverse respiratory events when compared with csDMARDs in patients with RA and COPD.

https://academic.oup.com/rheumatology/advance-article-abstract/doi/10.1093/rheumatology/kez359/5559568?redirectedFrom=fulltext

Hurst, J. R., V. McMillan, et al. (2019). **"The National COPD Audit - what you need to know."** Clin Med (Lond)The secondary care work stream of the National COPD Audit Programme aims to improve care and outcomes for patients with exacerbation of chronic obstructive pulmonary disease (COPD) wherever and whenever they are admitted to hospital. To achieve this, prospective audit is combined with real-time feedback of data to individual units, together with support for quality improvement and high-level change levers. COPD exacerbations comprise a large proportion of the acute take. Only by working collaboratively across emergency, acute and general medicine, respiratory, geriatric and other teams can individual trusts deliver optimal care. This review provides background to the national COPD audit programme, relevant to all those caring for people with COPD exacerbations in secondary care.

Hwang, H. J., S. M. Lee, et al. (2019). **"Assessment Of Changes In Regional Xenon-Ventilation, Perfusion, And Ventilation-Perfusion Mismatch Using Dual-Energy Computed Tomography After Pharmacological Treatment In Patients With Chronic Obstructive Pulmonary Disease: Visual And Quantitative Analysis."** Int J Chron Obstruct Pulmon Dis **14**: 2195-2203.

Purpose: To assess changes in regional ventilation (V), perfusion (Q), and V-Q mismatch in patients with chronic obstructive pulmonary disease (COPD) after pharmacologic treatment using combined xenon-enhanced V and iodine-enhanced Q dual-energy CT (DECT). Patients and methods: Combined V and Q DECT were performed at baseline and after three-month pharmacologic treatment in 52 COPD patients. Anatomically co-registered virtual non-contrast images, V, Q, and V/Qratio maps were obtained. V/Q pattern was visually determined to be matched, mismatched, or reversed-mismatched and compared with the regional parenchymal disease patterns of each segment. DECT parameters for V, Q, and V-Q imbalance were quantified. Results: The parenchymal patterns on CT were not changed at follow-up. The segments with matched V/Q pattern were increased (80.2% to 83.6%) as the segments with reversed-mismatched V/Q pattern were decreased with improving ventilation (17.6% to 13.8%) after treatment. Changes of V/Q patterns were mostly observed in segments with bronchial wall thickening. Compared with patients without bronchial wall thickening, the quantified DECT parameters of V-Q imbalance were significantly improved in patients with bronchial wall thickening ($p < 0.05$). Changes in forced expiratory volume in one second after treatment were correlated with changes in the quantified DECT parameters ($r = 0.327$-0.342 or $r = -0.406$ and -0.303; $p < 0.05$). Conclusion: DECT analysis showed that the V-Q imbalance was improved after the pharmacological treatment in COPD patients, although the parenchymal disease patterns remained unchanged. This improvement of V-Q imbalance may occur mostly in the areas with bronchial wall thickening.

https://www.dovepress.com/getfile.php?fileID=52980

Hyun, D. G., Y. M. Oh, et al. (2019). **"Clinical Phenotypes, Comorbidities, and Exacerbations according to Serum 25-OH Vitamin D and Plasma Fibrinogen Levels in Chronic Obstructive Pulmonary Disease."** J Korean Med Sci **34**(29): e195.

BACKGROUND: Although vitamin D deficiency is prevalent in patients with chronic obstructive pulmonary disease (COPD), the influence of vitamin D deficiency on COPD has not been fully established. Moreover, the inflammation process is associated with vitamin D deficiency in the general population. Therefore, this

study aimed to determine whether clinical phenotypes, comorbidities, and exacerbation rates are affected by the level of plasma fibrinogen, well studied by an inflammatory marker in COPD patients, and 25-hydroxy (25-OH) vitamin D. METHODS: This retrospective study analyzed patients with COPD whose inflammatory marker levels, especially plasma fibrinogen and 25-OH vitamin D levels, had been examined. A correlation analysis was conducted for inflammatory markers and 25-OH vitamin D. Clinical characteristics, comorbidities and exacerbation rates were compared among four groups based on plasma fibrinogen concentrations (threshold, 350 mg/dL) and 25-OH vitamin D levels (threshold, 20 ng/mL). RESULTS: Among 611 patients with COPD, 236 were included in the study. The levels of inflammatory markers had no statistical correlation with the serum 25-OH vitamin D levels. The four groups showed no statistically significant differences in age, sex, smoking history, inhaler use, and severity of comorbidities. Patients with high plasma fibrinogen concentrations and low 25-OH vitamin D levels had lower lung function, higher severity index, and higher annual rate of severe exacerbations 12 months before (0.23/year) and after (0.41/year) the measurement of 25-OH vitamin D levels than did the other patients. CONCLUSION: Our findings suggested an interaction between vitamin D deficiency and COPD. The measurement of plasma fibrinogen concentrations could help identify a severe phenotypic group among patients with vitamin D deficiency.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6660320/pdf/jkms-34-e195.pdf

Ingebrigtsen, T. S., J. Vestbo, et al. (2019). **"beta2-Adrenergic genotypes and risk of severe exacerbations in COPD: a prospective cohort study."** Thorax **74**(10): 934-940.

BACKGROUND: Individual susceptibility to exacerbations in chronic obstructive pulmonary disease (COPD) is likely influenced by genetic factors; however, most such variance is unexplained. We hypothesised that beta2-adrenergic receptor genotypes, Gly16Arg (rs1042713, c.46G>A) and Gln27Glu (rs1042714, c.79C>G) influence risk of severe exacerbations in COPD. METHODS: Among 96 762 individuals in the Copenhagen General Population Study, we identified 5262 with COPD (forced expiratory volume in one second divided by forced vital capacity, FEV1/FVC, below 0.7, FEV1 less than 80% of predicted value, age above 40 years and no asthma) who had genotyping performed. Severe exacerbations were defined as acute admissions due to COPD during 5 years of follow-up (mean 3.4 years). 923 individuals with COPD diagnosed similarly in the Copenhagen City Heart Study (CCHS) were used for replication analyses. RESULTS: We recorded 461 severe exacerbations in 5262 subjects. The HRs for severe exacerbations were 1.62 (95% CI 1.30 to 2.03, p=0.00002) for 16Gly/Arg heterozygotes and 1.41 (1.04 to 1.91, p=0.03) for 16Arg homozygotes, compared with 16Gly homozygotes. HRs were 1.35 (1.03 to 1.76, p=0.03) for 27Gln/Glu heterozygotes and 1.49 (1.12 to 1.98, p=0.006) for 27Gln homozygotes, compared with 27Glu homozygotes. Similar trends were observed in the CCHS. Among 27Gln homozygotes only, HRs were 5.20 (1.81 to 14.9, p=0.002) for 16Gly/Arg heterozygotes and 4.03 (1.40 to 11.6, p=0.01) for 16Arg homozygotes, compared with 16Gly homozygotes. CONCLUSION: Common beta2-adrenergic receptor genotypes influence risk of severe exacerbations in COPD, potentially mainly by genetic influence of the 16Arg allele in rs1042713.

https://thorax.bmj.com/content/74/10/934.long

Jaoude, P. and A. A. El-Solh (2019). **"Predictive factors for COPD exacerbations and mortality in patients with overlap syndrome."** Clin Respir J **13**(10): 643-651.

INTRODUCTION: Patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA)-overlap syndrome-have a substantially greater risk of morbidity and mortality, compared to those with either COPD or OSA alone. OBJECTIVES: The aim of this retrospective study was to identify clinical modifiable factors associated with COPD exacerbations and all-cause mortality in patients with overlap syndrome. METHODS: The electronic records of patients with simultaneous COPD and OSA who had a documented acute exacerbation of COPD during a 42-month period were evaluated for reviewed. A control group of overlap syndrome patients without exacerbations was matched 1:1 for age and body mass index. Vital status and cause of death were assessed through the population death registry.

RESULTS: Out of 225 eligible cases, 92 patients had at least one episode of COPD exacerbation. There was no significant association between severity of airflow limitation and apnoea hypopnea index (P = .31). After adjusting for confounding variables, patients who had at least one COPD exacerbation were more likely to be active smokers (P = .01), have poorer lung function (P = .001) and less likely to adhere to continuous positive airway pressure (CPAP) use (P = .03). All-cause mortality was also correlated with low forced expiratory volume in 1 second (P = .006), CPAP use (P = .007), and burden of comorbidities (P < .001). CONCLUSION: Lung function and CPAP use were independent predictors of COPD exacerbations and all-cause mortality in a cohort of patients with overlap syndrome. These factors should be taken into account when considering the management and prognosis of these patients.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13079

Josephs, L., D. Culliford, et al. (2019). **"COPD overdiagnosis in primary care: a UK observational study of consistency of airflow obstruction."** NPJ Prim Care Respir Med **29**(1): 33.

Chronic obstructive pulmonary disease (COPD) is heterogeneous, but persistent airflow obstruction (AFO) is fundamental to diagnosis. We studied AFO consistency from initial diagnosis and explored factors associated with absent or inconsistent AFO. This was a retrospective observational study using patient-anonymised routine individual data in Care and Health Information Analytics (CHIA) database. Identifying a prevalent COPD cohort based on diagnostic codes in primary care records, we used serial ratios of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC%) from time of initial COPD diagnosis to assign patients to one of three AFO categories, according to whether all (persistent), some (variable) or none (absent) were <70%. We described respiratory prescriptions over 3 years (2011-2013) and used multivariable logistic regression to estimate odds of absent or variable AFO and potential predictors. We identified 14,378 patients with diagnosed COPD (mean +/- SD age 68.8 +/- 10.7 years), median (IQR) COPD duration of 60 (25,103) months. FEV1/FVC% was recorded in 12,491 (86.9%) patients: median (IQR) 5 (3, 7) measurements. Six thousand five hundred and fifty (52.4%) had persistent AFO, 4507 (36.1%) variable AFO and 1434 (11.5%) absent AFO. Being female, never smoking, having higher BMI or more comorbidities significantly predicted absent and variable AFO. Despite absent AFO, 57% received long-acting bronchodilators and 60% inhaled corticosteroids (50% and 49%, respectively, in those without asthma). In all, 13.1% of patients diagnosed with COPD had unrecorded FEV1/FVC%; 11.5% had absent AFO on repeated measurements, yet many received inhalers likely to be ineffective. Such prescribing is not evidence based and the true cause of symptoms may have been missed.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6695394/pdf/41533_2019_Article_145.pdf

Katsimigas, A., O. D. Tupper, et al. (2019). **"Opportunistic screening for COPD in primary care: a pooled analysis of 6,710 symptomatic smokers and ex-smokers."** Int J Chron Obstruct Pulmon Dis **14**: 1633-1638.

Objective: To investigate the prevalence and predictors of COPD in a large cohort of symptomatic smokers and ex-smokers in a primary care setting. Methods: General practitioners (n=390) consecutively recruited individuals >/=35 years, with current or previous tobacco exposure, at least one respiratory symptom, and no previous diagnosis of obstructive airways disease; and obtained data on tobacco exposure, body mass index (BMI), and dyspnea (Medical Research Council dyspnea scale). All individuals with airflow obstruction, ie, FEV1/FVC <0.70 at initial lung function test, had diagnostic spirometry, including bronchodilator reversibility test. COPD was defined as respiratory symptom(s), tobacco exposure, and nonreversible airflow limitation. Results: Of the 6,710 at-risk individuals screened with spirometry (52% male sex, mean age 58 years [SD 10.9]), 1,185 were diagnosed with COPD (17.7%). Apart from age and pack-years, multivariate logistics regression analysis, adjusted for FEV1, revealed that BMI <25 kg/m(2) (OR 4.2, 95% CI 3.0-5.9, p<0.001), BMI 35+ kg/m(2) (OR 1.6, 95% CI 1.2-2.3), self-reported dyspnea (OR 1.2, 95% CI 1.1-14, p=0.04), wheeze (OR 1.3, 95% CI 1.1-1.6, p=0.001), phlegm (OR 1.4, 95% CI 1.1-1.6, p<0.001), and MRC >/=3 (OR 1.6, 95% CI 1.2-2.0, p=0.001) were associated with a significantly higher likelihood of being diagnosed with COPD. No association was found between sex, cough, and recurrent

respiratory tract infections and a diagnosis of COPD. Conclusion: The prevalence of COPD is high among smokers and ex-smokers with one or more respiratory symptoms seen in primary care, and the presence of wheeze, phlegm and dyspnea, together with both low BMI and obesity identify a subgroup with an even higher likelihood of COPD.

https://www.dovepress.com/getfile.php?fileID=51384

Keller, A., N. Ludwig, et al. (2019). **"Low miR-150-5p and miR-320b Expression Predicts Reduced Survival of COPD Patients."** Cells **8**(10)Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of death, reducing life expectancy on average between 5 and 7 years. The survival time after diagnosis, however, varies considerably as a result of the heterogeneity of COPD. Therefore, markers that predict individual survival of COPD patients are of great value. We analyzed baseline molecular profiles and collected 54 months of follow-up data of the cohort study "COPD and SYstemic consequences-COmorbidities NETwork" (COSYCONET). Genome-wide microRNA signatures from whole blood collected at time of the inclusion in the study were generated for 533 COPD patients including patients that deceased during the 54-month follow-up period (n = 53) and patients that survived this period (n = 480). We identified two blood-born microRNAs (miR-150-5p and miR-320b) that were highly predictive for survival of COPD patients. The expression change was then confirmed by RT-qPCR in 245 individuals. Ninety percent of patients with highest expression of miR-150-5p survived the 54-month period in contrast to only 50% of patients with lowest expression intensity. Moreover, the abundance of the oncogenic miR-150-5p in blood of COPD patients was predictive for the development of cancer. Thus, molecular profiles measured at the time of a COPD diagnosis have a high predictive power for the survival of patients.

https://res.mdpi.com/d_attachment/cells/cells-08-01162/article_deploy/cells-08-01162.pdf

Kendzerska, T., S. D. Aaron, et al. (2019). **"Effectiveness and Safety of Inhaled Corticosteroids in Older Individuals with Chronic Obstructive Pulmonary Disease and/or Asthma. A Population Study."** Ann Am Thorac Soc **16**(10): 1252-1262.

Rationale: Inhaled corticosteroids (ICS) are established medications for the management of both asthma and chronic obstructive pulmonary disease (COPD), two common chronic airway diseases. However, there is still uncertainty with respect to their use in some cases, specifically in older adults with asthma, people with concurrent asthma and COPD, and some people with COPD (given the association of ICS with pneumonia).Objectives: To compare the effectiveness and safety of ICS in older adults with asthma, COPD, or features of both in a real-word setting.Methods: In this retrospective longitudinal population cohort study, individuals 66 years of age or older in Ontario, Canada, who met a validated case definition of physician-diagnosed COPD and/or asthma between 2003 and 2014 were followed until March 2015 through provincial health administrative data. Overlap in COPD and asthma diagnoses was permitted and stratified for in subgroup analyses. The exposure was new receipt of ICS. The primary effectiveness and safety outcomes were hospitalizations for obstructive lung disease (OLD) and hospitalizations for pneumonia, respectively. Propensity scores were used to adjust for confounders.Results: The study included 87,690 individuals with asthma (27% with concurrent COPD) and 150,593 individuals with COPD (25% with concurrent asthma). In terms of effectiveness, controlling for confounders, ICS was associated with fewer hospitalizations for OLD (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.79-0.88) in subjects with asthma alone, with concurrent COPD attenuating the benefit. A similar association was seen in subjects with COPD and concurrent asthma (HR, 0.88; 95% CI, 0.84-0.92), but not in those with COPD alone, where ICS receipt had little impact on hospitalizations. In terms of safety, ICS receipt was associated with a marginally increased risk of pneumonia hospitalizations in people with COPD and no asthma (HR, 1.03; 95% CI, 1.00-1.06), but not in the other groups.Conclusions: ICS was associated with fewer hospitalizations for OLD in older adults with asthma and concurrent asthma and COPD, but had little impact on OLD and pneumonia hospitalizations in those with COPD alone.

Kendzerska, T., J. W. Nickerson, et al. (2019). **"End-of-life care in individuals with respiratory diseases: a population study comparing the dying experience between those with chronic obstructive pulmonary disease and lung cancer."** Int J Chron Obstruct Pulmon Dis **14**: 1691-1701.

Purpose: Among individuals with COPD and/or lung cancer, to describe end-of-life health service utilization, costs, and place of death; to identify predictors of home palliative care use, and to assess benefits associated with palliative care use. Patients and methods: We conducted a retrospective population-based study using provincial linked health administrative data (Ontario, Canada) between 2010 and 2015. We examined health care use in the last 90 days of life in adults 35 years and older with physician-diagnosed COPD and/or lung cancer identified using a validated algorithm and the Ontario Cancer Registry, respectively. Four mutually exclusive groups were considered: (i) COPD only, (ii) lung cancer only, (iii) COPD and lung cancer, and (iv) neither COPD nor lung cancer. Multivariable generalized linear models were employed. Results: Of 445,488 eligible deaths, 34% had COPD only, 4% had lung cancer only, 5% had both and 57% had neither. Individuals with COPD only received less palliative care (20% vs 57%) than those with lung cancer only. After adjustment, people with lung cancer only were far more likely to receive palliative care (OR=4.22, 4.08-4.37) compared to those with neither diagnosis, while individuals with COPD only were less likely to receive palliative care (OR=0.82, 0.81-0.84). Home palliative care use was associated with reduced death and fewer days in acute care, and less cost, regardless of the diagnosis. Conclusion: Although individuals with lung cancer were much more likely to receive palliative care than those with COPD, both populations were underserviced. Results suggest greater involvement of palliative care may improve the dying experience of these populations and reduce costs.

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Kim, K. Y., M. Miravitlles, et al. (2019). **"Comparison of clinical baseline characteristics between Asian and Western COPD patients in a prospective, international, multicenter study."** Int J Chron Obstruct Pulmon Dis **14**: 1595-1601.

We aimed to compare clinical characteristics between Asian and Western chronic obstructive pulmonary disease (COPD) patients. This was a sub-analysis of an international, multicenter, prospective cohort study. Asian patients were enrolled in Singapore and South Korea. Western patients were enrolled in Spain, Poland, Ireland, the United Kingdom, and Malta. A total of 349 patients were analyzed. Among them, 110 (32%) patients were Asian and 239 (68%) Western. Male sex was more predominant in Asian than in Western (95% versus 63%, respectively; P<0.01). Body mass index was significantly lower in Asian (23.5 versus 27.1; P<0.01). The proportion of patients with a history of exacerbation was lower in Asian (12% versus 64%; P<0.01). Although patients were enrolled by same inclusion criteria, there were several differences between Asian and Western COPD patients. Our study has shown unbiased real-world differences between Asian and Western COPD patients. Since prospective follow-up study is currently ongoing, the result of this study can be fundamental base of future analysis.

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Kim, M., O. Doganay, et al. (2019). **"CT-based Airway Flow Model to Assess Ventilation in Chronic Obstructive Pulmonary Disease: A Pilot Study."** Radiology: 190395.

Background The lack of functional information in thoracic CT remains a limitation of its use in the clinical management of chronic obstructive pulmonary disease (COPD). Purpose To compare the distribution of pulmonary ventilation assessed by a CT-based full-scale airway network (FAN) flow model with hyperpolarized xenon 129 ((129)Xe) MRI (hereafter, (129)Xe MRI) and technetium 99m-

diethylenetriaminepentaacetic acid aerosol SPECT ventilation imaging (hereafter, V-SPECT) in participants with COPD. Materials and Methods In this prospective study performed between May and August 2017, pulmonary ventilation in participants with COPD was computed by using the FAN flow model. The modeled pulmonary ventilation was compared with functional imaging data from breath-hold time-series (129)Xe MRI and V-SPECT. FAN-derived ventilation images on the coronal plane and volumes of interest were compared with functional lung images. Percentage lobar ventilation estimated by the FAN model was compared with that measured at (129)Xe MRI and V-SPECT. The statistical significance of ventilation distribution between FAN and functional images was demonstrated with the Spearman correlation coefficient and chi(2) distance. Results For this study, nine participants (seven men [mean age, 65 years +/- 5 {standard deviation}] and two women [mean age, 63 years +/- 7]) with COPD that was Global Initiative for Chronic Obstructive Lung Disease stage II-IV were enrolled. FAN-modeled ventilation profile showed strong positive correlation with images from (129)Xe MRI (rho = 0.67; P < .001) and V-SPECT (rho = 0.65; P < .001). The chi(2) distances of the ventilation histograms in the volumes of interest between the FAN and (129)Xe MRI and FAN and V-SPECT were 0.16 +/- 0.08 and 0.28 +/- 0.14, respectively. The ratios of lobar ventilations in the models were linearly correlated to images from (129)Xe MRI (rho = 0.67; P < .001) and V-SPECT (rho = 0.59; P < .001). Conclusion A CT-based full-scale airway network flow model provided regional pulmonary ventilation information for chronic obstructive pulmonary disease and correlates with hyperpolarized xenon 129 MRI and technetium 99m-diethylenetriaminepentaacetic acid aerosol SPECT ventilation imaging. (c) RSNA, 2019 Online supplemental material is available for this article. See also the editorial by Schiebler and Parraga in this issue.

Kim, M. A., M. K. Suh, et al. (2019). **"Impact of symptom variability on clinical outcomes in COPD: analysis of a longitudinal cohort."** Int J Chron Obstruct Pulmon Dis **14**: 2135-2144.

Purpose: We compared clinical characteristics of COPD patients according to symptom variability and evaluated the effect of symptom variability during the first year of enrollment on clinical outcomes of COPD. Methods: We analyzed COPD patients' data from the Korean Obstructive Lung Disease (KOLD) cohort. Symptom variability was defined based on the value of standard deviation (SD) of mMRC scores obtained every 3 months during the follow-up period of the first year. Patients were divided into 2 groups: the consistent (SD of mMRC scores =0) and variable (SD of mMRC scores >0) groups. Clinical characteristics and outcomes were compared in terms of symptom variability. Results: A total of 407 patients were included in the analysis. Patient age was 67.2 years and 97.8% of the subjects were male. Initial mMRC was 1.5 and the SD of mMRC scores during the first year was 0.5. There were 137 subjects (33.7%) in the consistent group and 270 (66.3%) in the variable group. The variable group showed a lower FEV1 (P=0.019) and a higher mMRC score (P=0.001). The annual incidence of acute exacerbation of COPD (AE-COPD) tended to be higher in the variable group (P=0.078) and that of severe AE-COPD was higher in the variable group than in the consistent group (P=0.002). The variable group showed a higher proportion of annual exacerbators (P=0.001) and frequent exacerbators (P=0.017). In multivariate logistic regression analysis, the variable group was significantly associated with annual exacerbators (OR =1.963, P=0.011) and frequent exacerbators (OR =2.090, P=0.055). Conclusion: COPD patients with symptom variability may have higher exacerbation risk as well as lower lung function and more severe respiratory symptoms.

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Kim, W., M. H. Cho, et al. (2019). **"DSP variants may be associated with longitudinal change in quantitative emphysema."** Respir Res **20**(1): 160.

BACKGROUND: Emphysema, characterized by lung destruction, is a key component of Chronic Obstructive Pulmonary Disease (COPD) and is associated with increased morbidity and mortality. Genome-wide association studies (GWAS) have identified multiple genetic factors associated with cross-sectional

measures of quantitative emphysema, but the genetic determinants of longitudinal change in quantitative measures of emphysema remain largely unknown. Our study aims to identify genetic variants associated with longitudinal change in quantitative emphysema measured by computed tomography (CT) imaging. METHODS: We included current and ex-smokers from two longitudinal cohorts: COPDGene, a study of Non-Hispanic Whites (NHW) and African Americans (AA), and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). We calculated annual change in two quantitative measures of emphysema based on chest CT imaging: percent low attenuation area (</= - 950HU) (%LAA-950) and adjusted lung density (ALD). We conducted GWAS, separately in 3030 NHW and 1158 AA from COPDGene and 1397 Whites from ECLIPSE. We further explored effects of 360 previously reported variants and a lung function based polygenic risk score on annual change in quantitative emphysema. RESULTS: In the genome-wide association analysis, no variants achieved genome-wide significance (P < 5e-08). However, in the candidate region analysis, rs2076295 in the DSP gene, previously associated with COPD, lung function and idiopathic pulmonary fibrosis, was associated with change in %LAA-950 (beta (SE) = 0.09 (0.02), P = 3.79e-05) and in ALD (beta (SE) = - 0.06 (0.02), P = 2.88e-03). A lung function based polygenic risk score was associated with annual change in %LAA-950 (P = 4.03e-02) and with baseline measures of quantitative emphysema (P < 1e-03) and showed a trend toward association with annual change in ALD (P = 7.31e-02). CONCLUSIONS: DSP variants may be associated with longitudinal change in quantitative emphysema. Additional investigation of the DSP gene are likely to provide further insights into the disease progression in emphysema and COPD. TRIAL REGISTRATION: Clinicaltrials.gov Identifier: NCT00608764 , NCT00292552 .

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6642569/pdf/12931_2019_Article_1097.pdf

Kocak, A. O., Z. Cakir, et al. (2019). **"Comparison of two scores of short term serious outcome in COPD patients."** Am J Emerg Med: 158376.

INTRODUCTION: Chronic Obstructive Pulmonary Disease (COPD) related visits to the emergency department have increased substantially during the past decade. An important challenge facing emergency physicians when treating COPD patients is deciding on disposition. The aim of this study was to evaluate Integrated Pulmonary Index scoring to guide the disposition decisions of emergency physicians by comparing its compatibility with Ottawa COPD Risk Score. METHODS: This is a prospective methodological study, in which we compared the accuracies of the Integrated Pulmonary Index and Ottawa COPD Risk Score in predicting of the short-term serious outcomes in patients admitted to the emergency department with COPD exacerbation. Patients who admitted to our emergency department between 01.01.2019-31.03.2019 were evaluated. THE RESULTS: Among the 208 patients, there were 154 (74.0%) short-term serious outcomes. The AUCs were 0.915 and 0.943 for Integrated Pulmonary Index and Ottawa COPD Risk Score, respectively. The difference between AUCs for two scores was not statistically significant. The best cut-off point for Integrated Pulmonary Index and Ottawa COPD Risk Score were </=3 and >4, respectively. For these best cut-off points, the sensitivity and specificity of Integrated Pulmonary Index were 92.9 and 87.1, respectively. The sensitivity and specificity of Ottawa COPD Risk Score were 99.3 and 85.2, respectively. Besides, the accuracy of Integrated Pulmonary Index was 91.3, and the accuracy of Ottawa COPD Risk Score was 95.7. CONCLUSIONS: Integrated Pulmonary Index was a potential candidate for evaluating respiratory status and prediction of short-term severe events in patients with acute COPD exacerbation in emergency departments.

https://www.ajemjournal.com/article/S0735-6757(19)30506-6/fulltext

Lanclus, M., J. Clukers, et al. (2019). **"Machine Learning Algorithms Utilizing Functional Respiratory Imaging May Predict COPD Exacerbations."** Acad Radiol **26**(9): 1191-1199.

RATIONALE 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

Le, L. A. K., A. Johannessen, et al. (2019). **"Prevalence and prognostic ability of the GOLD 2017 classification compared to the GOLD 2011 classification in a Norwegian COPD cohort."** Int J Chron Obstruct Pulmon Dis **14**: 1639-1655.

Rationale: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 is based on an ABCD assessment tool of symptoms and exacerbation history and grade 1-4 of airflow limitation severity, facilitating classification either into 4 groups (ABCD) or 16 groups (1A-4D). We aimed to compare the GOLD 2011, GOLD 2017 ABCD, and GOLD 2017 1A-4D classifications in terms of their distribution and prediction of mortality and hospitalizations. Methods: In the GenKOLS study, 912 COPD patients with FEV1 less than 80% of the predicted answered questionnaires and performed lung function testing in 2003-2005. The patients were recruited from a hospital patient registry (n=662) and from the general population (n=250), followed up until 2011 with respect to all-cause and respiratory mortality, and all-cause and respiratory hospitalizations. We performed logistic regression and receiver operating curve (ROC) analyses for the different classifications with estimations of area under the curve (AUC) for comparisons. Results: Mean age at baseline was 60 years (SD 11), 55% were male. Mean duration of follow-up was 91 months. By GOLD 2011, 21% were classified as group A, 29% group B, 6% group C, and 43% as group D, corresponding percentages for GOLD 2017 were: 25%, 52%, 3%, and 20%. The GOLD 2011 classification had higher AUC values than the GOLD 2017 group ABCD classification for respiratory mortality and hospitalization, but after inclusion of airflow limitation severity in GOLD 2017 groups 2A-4D, AUC values were significantly higher with GOLD 2017. Conclusion: In a clinically relevant sample of COPD patients, the GOLD 2017 classification doubles the prevalence of group B and halves the prevalence of groups C and D as compared to the GOLD 2011 classification. The prediction of respiratory mortality and respiratory hospitalization was better for GOLD 2017 2A-4D taking airflow limitation severity into account, as compared to GOLD 2017 ABCD and GOLD 2011.

https://www.dovepress.com/getfile.php?fileID=51432

Lee, D., R. Lee, et al. (2019). **"Hemiarthroplasty versus total hip arthroplasty for femoral neck fractures in patients with chronic obstructive pulmonary disease."** Eur J Trauma Emerg SurgPURPOSE: This study sought to delineate whether total hip arthroplasty (THA) or hip hemiarthroplasty (HHA) had more complication rates following the treatment of femoral neck fractures (FNF) in chronic obstructive pulmonary disease (COPD) patients. MATERIALS AND METHODS: The ACS-NSQIP database was queried for all patients with a history of COPD who had undergone THA and HHA with FNFs, isolated by CPT codes and ICD-9/ICD-10 codes. Propensity score matching without replacement in a 1:1 manner was done to control for patient demographics/preoperative comorbidities. Multivariate logistic regression models were utilized to assess the independent effect of HHA in comparison to THA. RESULTS: The propensity-matched (PM) HHA cohort was significantly older (76.14 years vs. 73.33 years, $p = 0.001$) and

had significantly higher rates of pneumonia (p = 0.017), extended length of stay (LOS) (p = 0.017), and mortality (p = 0.002), but lower rates of blood transfusions (p = 0.016) and reoperation (p = 0.020). HHA was independently associated with an increased risk of pneumonia (p = 0.043), extended LOS (p = 0.050), and death (p = 0.044) but a decreased risk for blood transfusions (p = 0.008) and reoperation (p = 0.028) when compared to THA. DISCUSSION: Patients with more comorbidities are more likely to receive HHA than THA, which may explain some of the increased complications and mortality associated with HHA for FNFs compared to THA. Patients undergoing THA were at increased risk for blood transfusion and reoperation. THA does not appear to result in increased morbidity in this population compared to HHA. While THA should be considered in these patients given improved functional outcomes, further prospective studies are needed to establish superiority. LEVEL OF EVIDENCE: III.

https://link.springer.com/article/10.1007%2Fs00068-019-01234-x

Lee, K. M., G. Lee, et al. (2019). **"Clinical outcomes of radial probe endobronchial ultrasound using a guide sheath for diagnosis of peripheral lung lesions in patients with pulmonary emphysema."** Respir Res **20**(1): 177.

BACKGROUND: Generally, structural destruction of lung parenchyma, such as pulmonary emphysema, is considered to be related to the low diagnostic yields and high complication rates of lung biopsies of peripheral lung lesions. Currently, little is known about the clinical outcomes of using endobronchial ultrasound with a guide sheath (EBUS-GS) to diagnose peripheral lesions in patients with emphysema. METHODS: This retrospective study was performed to identify the clinical outcomes of EBUS-GS in patients with pulmonary emphysema. This study included 393 consecutive patients who received EBUS-GS between February 2017 and April 2018. The patients were classified according to the severity of their emphysema, and factors possibly contributing to a successful EBUS-GS procedure were evaluated. RESULTS: The overall diagnostic yield of EBUS-GS in patients with no or mild emphysema was significantly higher than in those with moderate or severe pulmonary emphysema (78% vs. 61%, P = 0.007). There were no procedure-related complications. The presence of a bronchus sign on CT (P < 0.001) and a "within the lesion" status on EBUS (P = 0.009) were independently associated with a successful EBUS-GS procedure. Although the diagnostic yield of EBUS-GS in patients with moderate-to-severe emphysema was relatively low, a bronchus sign and "within the lesion" status on EBUS were contributing factors for a successful EBUS-GS. CONCLUSIONS: EBUS-GS is a safe procedure with an acceptable diagnostic yield, even when performed in patients with pulmonary emphysema. The presence of a bronchus sign and "within the lesion" status on EBUS were predictors of a successful procedure.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6683511/pdf/12931_2019_Article_1149.pdf

Lee, S. H., K. U. Kim, et al. (2019). **"Sleep disturbance in patients with mild-moderate chronic obstructive pulmonary disease."** Clin Respir JINTRODUCTION: Although sleep problems have an important impact on daily life and health outcome measures in patients with chronic obstructive pulmonary disease (COPD), patterns of sleep disturbance in patients with mild-moderate COPD remain unknown. OBJECTIVE: The aim of this study was to investigate patterns of sleep disturbance and factors associated with sleep impairment in patients with mild-moderate COPD. METHODS: This prospective cross-sectional study enrolled 148 male patients with COPD. At enrolment, all patients completed a disease-specific sleep measure, the COPD and Asthma Sleep Impact Scale (CASIS) to assess sleep impairment. Health-related quality of life (HRQL) was measured using the St. George's Respiratory Questionnaire (SGRQ) and the 36-item Short-Form health survey (SF-36). Anxiety and depression status were assessed using the Hospital Anxiety and Depression Scale (HADS). Self-efficacy was measured by the COPD Self-Efficacy Scale (CSES). RESULTS: The mean age of the subjects was 67 years [standard deviation (SD) = 8.11]. The proportion of patients who indicated that they had a bad night's sleep was 33.1%. Univariated analysis showed that CASIS score was significantly correlated with the modified Medical Research Council (mMRC) dyspnea scale, SGRQ, SF-36 Physical Component Summary, SF-36 Mental Component Summary, HADS-anxiety, HADS-depression and CSES scores (all P < 0.05). In a multivariate analysis,

SGRQ and CSES were independently associated with CASIS score. CONCLUSION: Poorer HRQL and lower self-efficacy are significantly associated with sleep disturbance and perhaps may be improved by better sleep quality. Future research is required to enhance sleep quality in patients with mild-moderate COPD.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13085

Lehr, C. J., M. Skeans, et al. (2019). **"Effect of Including Important Clinical Variables on Accuracy of the Lung Allocation Score for Cystic Fibrosis and Chronic Obstructive Pulmonary Disease."** Am J Respir Crit Care Med **200**(8): 1013-1021.

Rationale: Clinical variables associated with shortened survival in patients with advanced-stage cystic fibrosis (CF) are not included in the lung allocation score (LAS).Objectives: To identify variables associated with wait-list and post-transplant mortality for CF lung transplant candidates using a novel database and to analyze the impact of including new CF-specific variables in the LAS system.Methods: A deterministic matching algorithm identified patients from the Scientific Registry of Transplant Recipients and the Cystic Fibrosis Foundation Patient Registry. LAS wait-list and post-transplant survival models were recalculated using CF-specific variables. This multicenter, retrospective, population-based study of all lung transplant wait-list candidates aged 12 years or older from January 1, 2011, to December 31, 2014, included 9,043 patients on the lung transplant waiting list and 6,110 lung transplant recipients between 2011 and 2014, comprising 1,020 and 677 with CF, respectively.Measurements and Main Results: Measured outcomes were changes in LAS and lung allocation rank. For CF candidates, any Burkholderia sp. (hazard ratio [HR], 2.8; 95% confidence interval [CI], 1.2-6.6), 29-42 days hospitalized (HR 2.8; CI 1.3-5.9), massive hemoptysis (HR 2.1; CI 1.1-3.9), and relative drop in FEV1 >/=30% over 12 months (HR 1.7; CI 1.0-2.8) increased wait-list mortality risk; pulmonary exacerbation time 15-28 days (1.8; 1.1-2.9) increased post-transplant mortality risk. A relative drop in FEV1 >/=10% in chronic obstructive pulmonary disease (COPD) candidates was associated with increased wait-list mortality risk (HR 2.6; CI 1.2-5.4). Variability in LAS score and rank increased in patients with CF. Priority for transplant increased for COPD candidates. Access did not change for other diagnosis groups.Conclusions: Adding CF-specific variables improved discrimination among wait-listed CF candidates and benefited COPD candidates.

Li, L., S. Y. Li, et al. (2019). **"SERPINE2 rs16865421 polymorphism is associated with a lower risk of chronic obstructive pulmonary disease in the Uygur population: A case-control study."** J Gene Med **21**(9): e3106.

BACKGROUND: The present study aimed to investigate the relationship between seven polymorphisms of the serine protease inhibitor-2 (SERPINE2) gene and the risk of chronic obstructive pulmonary disease (COPD) in the Uygur population via a case-control study. METHODS: In total, 440 Uygur patients with COPD were included in the patient group and 384 healthy individuals were recruited in the matched control group. Data on demographic variables, smoking status, occupational dust exposure history and living conditions were collected. Polymorphism analysis was performed for seven loci of the SERPINE2 gene by mass spectrometry. RESULTS: The genotype distribution of rs16865421 showed a significant difference between the patient and control groups ($p < 0.05$). Participants carrying the rs16865421-AG heterozygous mutant genotype had a lower risk of COPD compared to those with the rs16865421-A allele (odds ratio = 0.68, 95% confidence interval = 0.47-0.98, $p = 0.041$). However, no such association was found for rs1438831, rs6734100, rs6748795, rs7583463, rs840088 and rs975278. No significant interaction was observed between the genotypes and risk factors. CONCLUSIONS: Polymorphisms of rs16865421-AG carried by the Uygur population may be protective against COPD.

https://onlinelibrary.wiley.com/doi/abs/10.1002/jgm.3106

Li, Z., X. Mao, et al. (2019). **"Functional variations of the TLR4 gene in association with chronic obstructive pulmonary disease and pulmonary tuberculosis."** BMC Pulm Med **19**(1): 184.

OBJECTIVE: Chronic obstructive pulmonary disease (COPD) and pulmonary tuberculosis (PTB) share a number of common risk factors, including innate immunity-related genetic factors. In the present study, we compared the role of genetic variations of the TLR4 gene in susceptibility to COPD and PTB and illuminated the underlying molecular mechanism of functional single-nucleotide polymorphisms (SNPs). METHODS: A population-based case control study was performed in a Chinese Han population and included 152 COPD cases, 1601 PTB cases and 1727 controls. Five SNPs in the TLR4 gene (rs10759932, rs2737190, rs7873784, rs11536889, and rs10983755) were genotyped using TaqMan allelic discrimination technology. We estimated the effects of SNPs using the odds ratio (OR) together with 95% confidence interval (CI). Dual-luciferase reporter vectors expressing different genotypes of SNPs were constructed and transfected into the human HEK 293 T cell line to explore their effects on potential transcription activity. RESULTS: After Bonferroni correction, the genetic polymorphisms of all five SNPs remained significantly associated with COPD, while rs10759932 and rs2737190 were also associated with PTB. Compared with rs10759932-TT, individuals carrying TC (OR: 0.42, 95% CI: 0.28-0.64) or CC (OR: 0.24, 95% CI: 0.09-0.63) had a significantly reduced risk of COPD. However, individuals carrying TC (OR: 1.28, 95% CI: 1.11-1.49) or CC (OR: 1.26, 95% CI: 0.98-1.62) had an increased risk of PTB. The OR (95% CI) for allele rs10759932-C was 0.45 (0.32-0.62) for COPD and 1.18 (1.07-1.32) for PTB. For rs2737190, heterozygous AG was related to a decreased risk of COPD (OR: 0.32, 95% CI: 0.21-0.49) and an increased risk of PTB (OR: 1.30, 95% CI: 1.11-1.52). The dual-luciferase reporter assay showed decreased transcription activity caused by rs10759932-C and rs2737190-G. CONCLUSION: Genetic polymorphisms of rs10759932 and rs2737190 in TLR4 are significantly related to both COPD and PTB but with inverse effects. The altered transcription activity caused by mutations in these two loci may partly explain the observed relationship.

https://bmcpulmmed.biomedcentral.com/track/pdf/10.1186/s12890-019-0939-y

Li, Z., Y. Xia, et al. (2019). **"The importance of CT quantitative evaluation of emphysema in lung cancer screening cohort with negative findings by visual evaluation."** Clin Respir JINTRODUCTION: One-stop quantitative evaluation of emphysema and lung nodule in lung cancer screening is very important for patient. OBJECTIVE: To evaluate the quantitative emphysema in the large-sample low-dose CT lung cancer screening cohort with negative CT findings by subjective visual assessment. METHODS: One thousand, two hundred and thirty-one participants with negative visual evaluation were included in this retrospective study. The lungs were automatically segmented and the following were calculated: total lung volume (TLV), total emphysema volume (TEV), emphysema index (EI), 15th percentile lung density and mean lung density. EI >/=6% was defined as emphysema. The quantitative parameters were compared between different genders and ages. The quantitative parameters and risk factors were compared between emphysema and non-emphysema groups. RESULTS: The proportion of smokers, TLV, TEV and EI of men were greater than that of women ($P < 0.001$). No correlation was found between age and volumes; the TEV and EI of people older than 60 years were greater than those younger than 60 years ($P < 0.05$) by age categorisation. One hundred and two participants showed emphysema, accounting for 8.29%. The incidence of emphysema in men was greater than that in women in total ($P < 0.05$). All the CT quantitative parameters were significantly different between emphysema and non-emphysema groups. The ratio of male, secondhand smoke exposure and chronic bronchitis history was greater in emphysema than that in the non-emphysema group ($P < 0.05$). CONCLUSION: CT quantitative emphysema evaluation is recommended in people older than 60 years, especially in males, providing more precise information, aiding the early diagnosis of emphysema and informing early intervention.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13084

Liang, Z., F. Long, et al. (2019). **"Identification of clinically relevant subgroups of COPD based on airway and circulating autoantibody profiles."** Mol Med Rep **20**(3): 2882-2892.

Autoimmunity may serve a role in the pathological features of a subgroup of patients with chronic obstructive pulmonary disease (COPD); however, in immunological subgroups of COPD patients, the interrelationships between airway and circulating autoantibody responses, and clinical parameters, remain unclear. The present study was undertaken to evaluate these interrelationships in various immunological subgroups of COPD patients. Sputum supernatant and serum obtained from 102 patients with stable COPD were assayed for the presence of immunoglobulin G antibodies against ten autoantigens via Luminex multiplex technology. Hierarchical clustering based on principal components was performed on autoantibody profiles to classify patients into clusters. Networkbased and module analyses were conducted to explore interrelationships among autoantibodies and clinical variables in each cluster. Topological characteristics were compared between clusters. Unsupervised clustering identified four clusters: No significant differences in the majority of clinical characteristics were observed among clusters. In cluster 1, retrospective exacerbation was only positively associated with COPD assessment test score. Lung functions (predicted % of forced expiratory volume in 1 sec and maximal midexpiratory flow) were negatively associated with exacerbation risk only in cluster 2. Sputum autoantibodies (against U1 small nuclear ribonucleoprotein, proteinase3 and Ro/Sjogren syndrome type A antigen) were negatively associated with exacerbation risks in cluster 2, but positively associated in cluster 3. The four networks also exhibited distinct topological properties. In COPD, autoantibody responses were heterogeneous and differentially associated with exacerbation risk in certain subgroups; their dual character should be considered in future research.

https://www.spandidos-publications.com/mmr/20/3/2882

Lim, J. U., C. K. Park, et al. (2019). **"The Difficulty Of Improving Quality Of Life In COPD Patients With Depression And Associated Factors."** Int J Chron Obstruct Pulmon Dis **14**: 2331-2341.

Objectives: Depression is a major comorbidity that affects clinical outcomes in patients with chronic obstructive pulmonary disease (COPD). COPD patients with depression are hospitalized more frequently, and show more acute exacerbations, decreased physical and social activities, and higher mortality compared to their non-depressed counterparts. In the present study, we investigated the clinical impact of depressive symptoms and associated clinical factors in Korean patients with COPD by evaluating multicenter cohort data. Materials and methods: Patients with COPD enrolled in the Korean COPD Subtype Study, a multicenter observational study, from December 2011 to October 2014 were selected for evaluation. The initial evaluation of all patients included pulmonary function tests, 6 min walk distance (6MWD), the COPD Assessment Test (CAT), and the COPD-specific version of the St. George's Respiratory Questionnaire (SGRQ-C). Significant depression was defined as a Beck Depression Inventory-II (BDI-II) score >/=17. Results: Among the 270 study patients, 19.6% had significant depression. The depressed group showed a higher proportion of females (41.4%), lower body mass index (BMI), and lower education level compared to the non-depressed group ($p = 0.002$, $p = 0.008$, and $p = 0.019$, respectively). The depressed group had significantly higher CAT and SGRQ-C scores, as well as a lower 6MWD, compared to the non-depressed group based on 6 month-interval serial measurements over 3 years. The total SGRQ-C score and the symptoms, activity, and impact domain scores were significant predictors of depression (area under curves [AUCs] of 0.699 [0.613-0.786], 0.670 [0.581-0.758], 0.680 [0.589-0.770], and 0.689 [0.603-0.776], respectively). From CAT score domains, sleep and energy scores were significant predictors of depression (AUCs of 0.619 [0.522-0.715] and 0.595 [0.504-0.685], respectively). SGRQ-C score, low BMI, and decreased 6MWD were significantly associated with depression in a multivariable analysis. Conclusion: A considerable proportion of patients with COPD had depression, and a high SGRQ-C score, low BMI, and low 6MWD were significantly associated with depression. As improving quality of life in this subgroup is difficult, physicians should be more active in screening patients with significant depression.

https://www.dovepress.com/getfile.php?fileID=53220

Lim, S. Y., D. Zhao, et al. (2019). **"Risk of chronic obstructive pulmonary disease in healthy individuals with high C-reactive protein levels by smoking status: a population-based cohort study in Korea."** Int J Chron Obstruct Pulmon Dis **14**: 2037-2046.

Purpose: Chronic obstructive pulmonary disease (COPD) is associated with systemic inflammation. We investigated whether elevated baseline serum C-reactive protein (CRP) levels in healthy individuals are associated with the risk of incident COPD by smoking status. Patients and methods: This was a cohort study of 63,260 adult men and women who were older than 40 years, free of COPD at baseline, and underwent health screening from 2002 to 2016 with at least one follow-up visit through December 2016. We investigated the association between baseline high-sensitivity CRP (hsCRP) levels and incident COPD by smoking status, using flexible parametric proportional hazards models and pooled logistic regression analyses. Results: The multivariable-adjusted hazard ratio (95% confidence interval) comparing participants in the 90th to those in the 10th percentile of hsCRP was 1.19 (1.08, 1.31). The corresponding hazard ratio in never, former, and current smokers were 1.07 (0.89, 1.29), 1.22 (1.05, 1.42), and 1.22 (1.05, 1.41), respectively. The association between hsCRP levels and incident COPD had a similar dose-response pattern in former and current smokers, but not in never smokers. Conclusion: Higher baseline hsCRP is associated with an increased risk to develop COPD in ever smokers but not in never smokers.

https://www.dovepress.com/getfile.php?fileID=52510

Lopez Caro, J. C., M. Santibanez, et al. (2019). **"Sputum Microbiome Dynamics in Chronic Obstructive Pulmonary Disease Patients during an Exacerbation Event and Post-Stabilization."** Respiration: 1-8.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) affects up to 65 million people worldwide, and COPD exacerbation causes tissue damage and subsequent loss of lung function. It is a multifactorial event in which respiratory infections are involved, but little is known about its dynamics. OBJECTIVES: The objective of our study was to determine the microbiome composition during an exacerbation event and post-stabilization. METHODS: We conducted an observational analytical study of a cohort of 55 COPD patients in which 2 sputum samples (the first taken during an exacerbation event and the second during clinical post-stabilization) were submitted to 16s RNA ribosomal analysis by Illumina Miseq Next Generation Sequencing (NGS). The presence of respiratory viruses was also determined. RESULTS: Our study found a stable microbiome composition in the post-stabilization sputum samples of COPD patients, and 4 additional microbiomes in samples taken during the exacerbation, 3 of which showed a marked dysbiosis by Haemophilus, Pseudomonas, and Serratia. The fourth exacerbation microbiome had a very similar composition to post-stabilization samples, but some pathogens such as Moraxella and respiratory viruses were also found. CONCLUSIONS: Our study reveals the main protagonists involved in lung microbiome dynamics during an exacerbation event and post-stabilization in COPD patients by NGS analysis.

https://www.karger.com/Article/Abstract/501988

Lorentzou, C., G. Kouvarakis, et al. (2019). **"Extreme desert dust storms and COPD morbidity on the island of Crete."** Int J Chron Obstruct Pulmon Dis **14**: 1763-1768.

Introduction and objectives: Short-term extreme increases in desert-derived particulate-matter with aerodynamic diameter below 10 mum (PM10) may affect emergency department (ED) visits due to COPD exacerbations. Research question: Our aim was to identify the effect of extreme increases in desert-derived PM10 on ED visits for dyspnea and COPD exacerbations and on the related hospital admissions. Methods: We performed a retrospective analysis of dyspnea-related ED visits and hospital admissions in Heraklion, Crete, during four consecutive storms of desert-derived PM10 that happened during March 2018. We collected data from over 17,000 ED visits and recorded patients with atopic symptoms, COPD exacerbations, and dyspnea, as well as admissions to the departments of pulmonary medicine, internal medicine, and cardiology. PM10 data were collected from a monitoring station in the same geographic area. Results: Four desert dust storms were recorded during the study period with 238, 203, 1138, and

310 mug/m(3) average-daily PM10 and 652, 308, 4262, and 778 mug/m(3) hourly mean day-peak PM10, respectively. There was no clinically important increase in total ED visits, total admissions or admissions to the departments of cardiology, pulmonary medicine, or internal medicine, during PM10 peaks. However, during the desert dust storm with daily-average PM10 above 500 mug/m(3), there was a striking increase in dyspnea-related ED visits (including COPD exacerbations, 3.6-fold increase), while there was no clinically important increase in non-asthma allergy-related ED visits. Conclusion: Extreme desert dust storm episodes may cause meaningful increases in ED visits for dyspnea and COPD exacerbations/admissions.

https://www.dovepress.com/getfile.php?fileID=51799

Manfredi, S., M. Fabbi, et al. (2019). **"Ultrasonographic differentiation between portal venous and parenchymal gas may be important for the prognosis of canine and feline hepatic emphysema: 37 cases."** Vet Radiol UltrasoundThe aim of this retrospective, cross-sectional, study was to evaluate clinical findings and outcomes for different ultrasonographic patterns of hepatic emphysema in dogs and cats. Dogs and cats with an ultrasonographic diagnosis of hepatic emphysema and a known outcome, from January 2010 to January 2018, were enrolled. The following data were recorded from medical and ultrasonographic records: ultrasonographic patterns of hepatic emphysema (parenchymal, portal venous, biliary), clinical signs, laboratory findings, and outcomes (favorable, poor). A total of 33 dogs and four cats met the inclusion criteria. Among these, 23 cases were classified as hepatic portal venous gas, 10 as parenchymal emphysema, and four as biliary emphysema. Clinical diagnosis categories were as follows: infection/sepsis (9), gastro-intestinal disease (9), iatrogenic (9), trauma (5), and liver neoplasia (5). An increase in serum liver enzymes was significantly associated with parenchymal emphysema (P = .03). Other clinical and laboratory findings were not associated with the type of hepatic emphysema. Hepatic portal venous gas was mostly transient in patients with ultrasonographic follow-up. The overall mortality was 40.5%. A significant difference was found between mortality by portal venous gas (21.7%) and mortality by parenchymal emphysema (90%) (P = .003). In conclusion, the ultrasonographic differentiation of hepatic emphysema between hepatic portal venous gas and parenchymal emphysema may be important for the prognosis of hepatic emphysema. The presence of parenchymal emphysema may be a poor prognostic indicator, while hepatic portal venous gas may be more benign. However, ultrasound findings should be carefully evaluated in the context of clinical findings.

https://onlinelibrary.wiley.com/doi/abs/10.1111/vru.12797

Marchioro, J., M. R. Gazzotti, et al. (2019). **"Anthropometric status of individuals with COPD in the city of Sao Paulo, Brazil, over time - analysis of a population-based study."** J Bras Pneumol **45**(6): e20170157.
OBJECTIVE: To evaluate the anthropometric data obtained for residents of the city of Sao Paulo, Brazil, in a study of Latin America conducted in two phases (baseline, in 2003, and follow-up, in 2012). METHODS: This was an analysis of data obtained for Sao Paulo residents in a two-phase population-based study evaluating the prevalence of COPD and its relationship with certain risk factors among individuals >/= 40 years of age. The anthropometric data included values for weight, height, body mass index (BMI), and waist circumference. In the follow-up phase of that study, the same variables were evaluated in the same population sample as that of the baseline phase. RESULTS: Of the 1,000 Sao Paulo residents enrolled in the baseline phase of that study, 587 participated in the follow-up phase, and 80 (13.6%) of those 587 subjects had COPD. Comparing the baseline and follow-up phases, we found increases in all anthropometric measures in both groups (COPD and non-COPD), although the differences were significant only in the non-COPD group. The subjects with mild COPD showed increases in weight and BMI (Deltaweight = 1.6 +/- 5.7 and DeltaBMI = 0.7 +/- 2.2), whereas those with moderate or severe COPD showed reductions (Deltaweight = -1.7 +/- 8.1 and DeltaBMI = -0.4 +/- 3.0), as did those with severe or very severe COPD (Deltaweight = -0.5 +/- 5.4 and DeltaBMI = -0.8 +/- 3.3). CONCLUSIONS: Between the two phases of the study, the subjects with mild COPD showed increases in weight and BMI, whereas those with a more severe form of the disease showed reductions.

Marco, E., D. Sanchez-Rodriguez, et al. (2019). **"Malnutrition according to ESPEN consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease."** Clin Nutr **38**(5): 2180-2186.

BACKGROUND: 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

Menon, S., P. Nightingale, et al. (2019). **"Chronic Obstructive Pulmonary Disease and the Risk of Esophagitis, Barrett's Esophagus, and Esophageal Adenocarcinoma: A Primary Care Case-Control Study."** J Clin Gastroenterol **53**(10): e451-e455.

BACKGROUND: 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's 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's 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's esophagus, compared with 62 (34 EAC) and 329 Barrett's 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's 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's esophagus but not EAC.

https://www.ingentaconnect.com/content/wk/jcga/2019/00000053/00000010/art00008

Milner, S. C., J. Bourbeau, et al. (2019). **"Improving acceptance and uptake of pulmonary rehabilitation after acute exacerbation of COPD: Acceptability, feasibility, and safety of a PR "taster" session delivered before hospital discharge."** Chron Respir Dis **16**: 1479973119872517.

The objectives of this study were to (1) assess the acceptability, feasibility, and safety of delivering a pulmonary rehabilitation (PR) "taster" session to patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease; (2) evaluate the changes in patient knowledge and readiness to commence PR; and (3) make recommendations for future intervention iterations. Acceptability was measured by the proportion of patients that accepted to participate. Feasibility was measured by the proportion of eligible participants. Knowledge was evaluated using the modified versions of the Understanding COPD (UCOPD) and Bristol COPD Knowledge (BCKQ) questionnaires. Readiness to commence PR was measured by a modified version of the Readiness to Change Exercise Questionnaire. All measures were delivered pre- and post-intervention. Thirty-one of 34 eligible individuals were able to be approached. Prospective acceptability was low, with 24 individuals declining the intervention, 1 being discharged without making a decision, and only 6 participating. Positive median change was recorded in the modified UCOPD questionnaire (+8), but not the BCKQ (0). Three of the patients were already in the action phase pre-intervention, with all but one in that phase post-intervention. The delivery of a PR "taster" session was not prospectively acceptable to a large portion of patients and only feasible with modifications to the original protocol.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6737870/pdf/10.1177_1479973119872517.pdf

Mochizuki, F., H. Iijima, et al. (2019). **"The Concavity of the Maximal Expiratory Flow-Volume Curve Reflects the Extent of Emphysema in Obstructive Lung Diseases."** Sci Rep **9**(1): 13159.

A concave-shaped maximal expiratory flow-volume (MEFV) curve is a spirometric feature in chronic obstructive pulmonary disease (COPD). The MEFV curve is characterized by an increase in the Obstructive Index, which is defined as a ratio of forced vital capacity to the volume-difference between two points of half of the peak expiratory flow on the MEFV curve. We hypothesized that the Obstructive Index would reflect the severity of emphysema in patients with COPD and asthma-COPD overlap (ACO). Thus, the aim of this retrospective study was to evaluate whether the Obstructive Index on spirometry is associated with the extent of emphysema on computed tomography (CT) in patients with COPD, ACO, and asthma (N = 65, 15, and 53, respectively). The percentage of low-attenuation volume (LAV%) and wall area (WA%) were measured on CT. The Obstructive Index was higher in patients with COPD and ACO than in those with asthma. Spearman correlation showed that a greater Obstructive Index was associated with a higher LAV%, but not WA%. Multivariate analysis showed that Obstructive Index was associated with LAV% (standardized beta = 0.43, $P < 0.0001$) independent of other spirometric indices. The Obstructive Index is a useful spirometric index that reflects the extent of emphysema.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6739348/pdf/41598_2019_Article_49591.pdf

Molinos-Castro, S., P. M. Pesqueira-Fontan, et al. (2019). **"Clinical factors associated with pulmonary aspergillosis in patients with chronic obstructive pulmonary disease."** Enferm Infecc Microbiol ClinOBJECTIVE: To explore the clinical and epidemiological characteristics of chronic obstructive pulmonary disease (COPD) patients with Aspergillus spp. isolation from respiratory samples, and to identify which factors may help us to distinguish between colonisation and infection. METHODS: A retrospective cohort study was performed. All patients with COPD and respiratory isolation of Aspergillus spp. over a 12-year period were included. Patients were assigned to 2 categories: colonisation and pulmonary aspergillosis (PA), which includes the different clinical forms of aspergillosis. A binary logistic regression model was performed to identify the predictive factors of PA. RESULTS: A total of 123 patients were included in the study: 48 (39.0%) with colonisation and 75 (61.0%) with PA: 68 with probable invasive pulmonary aspergillosis and 7 with chronic pulmonary aspergillosis. Spirometric stages of the GOLD classification were not correlated with a higher risk of PA. Four independent

predictive factors of PA in COPD patients were identified: home oxygen therapy (OR: 4.39; 95% CI: 1.60-12.01; P=.004), bronchiectasis (OR: 3.61; 95% CI: 1.40-9.30; P=.008), hospital admission in the previous three months (OR: 3.12; 95% CI: 1.24-7.87; P=.016) and antifungal therapy against Candida spp. in the previous month (OR: 3.18; 95% CI: 1.16-8.73; P=.024). CONCLUSIONS: Continuous home oxygen therapy, bronchiectasis, hospital admission in the previous three months and administration of antifungal medication against Candida spp. in the previous month were associated with a higher risk of pulmonary aspergillosis in patients with COPD.

https://www.sciencedirect.com/science/article/pii/S0213005X19302034?via%3Dihub

Moon, S. W., M. S. Park, et al. (2019). **"Combined pulmonary fibrosis and emphysema and idiopathic pulmonary fibrosis in non-small cell lung cancer: impact on survival and acute exacerbation."** BMC Pulm Med **19**(1): 177.

BACKGROUND: In non-small cell lung cancer (NSCLC) patients, concomitant idiopathic pulmonary fibrosis (IPF) and emphysema (CPFE) are independently related to poor survival. CPFE is a condition with features of both pulmonary fibrosis and emphysema. Here, we evaluated the effect of CPFE and IPF alone on the outcomes of NSCLC patients. PATIENTS AND METHODS: We retrospectively evaluated 283 patients with CPFE or IPF who were diagnosed with NSCLC between November 2003 and February 2018 at two tertiary care hospitals in South Korea. Patients were classified into CPFE and IPF groups according to chest computed tomography findings. RESULTS: One-hundred-and-seven patients (37.8%; mean age: 70.1 years; men 97.2%) had CPFE. Compared with IPF patients, CPFE patients had a heavier smoking history; lower diffusing capacity of carbon monoxide (78.0% vs 64.8%, p < 0.001), and lower forced expiratory volume in 1 s. Of all patients with NSCLC, 71.7% overall died during the follow-up period; 71.6% died in the CPFE group and 72.0% in the IPF group. Multivariate logistic regression analysis showed that CPFE (odds ratio [OR]: 2.26, 95% confidence interval [CI]: 1.09-4.69; P = 0.029) was significantly correlated with acute exacerbations (AEs). In a Cox proportional hazards analysis, stage > III NSCLC, higher Eastern Cooperative Oncology Group performance status, and higher gender-age-physiology index score was related to higher mortality. However, CPFE was not related to a higher mortality rate in univariate (hazard ratio [HR]: 1.00; 95% CI: 0.75-1.32, P = 0.972) or multivariate analysis (HR: 0.89; 95% CI: 0.66-1.21, P = 0.466). CONCLUSIONS: AE risk, but not all-cause mortality, was higher in patients with CPFE and NSCLC than in those with IPF and NSCLC. Physicians should be aware of the exaggerated risk of AE in patients with concomitant CPFE and NSCLC.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6792261/pdf/12890_2019_Article_951.pdf

Morantes-Caballero, J. A. and H. A. Fajardo Rodriguez (2019). **"Effects of air pollution on acute exacerbation of chronic obstructive pulmonary disease: a descriptive retrospective study (pol-AECOPD)."** Int J Chron Obstruct Pulmon Dis **14**: 1549-1557.

Purpose: Acute exacerbation of COPD (AECOPD) is among the most frequent causes for hospital admission, causing morbidity and mortality. Infection is the most frequent cause, and studies on pollution have shown higher hospital admission and mortality with inconsistent results. The objective was to identify if there is a change in levels of particulate matter (PM) during the days leading up to the symptom onset. Patients and methods: A retrospective study was carried out on medical records of patients with AECOPD from a University Hospital. PM values of the consultation day, onset symptoms, and up to three previous days were recorded. Moreover, clinical presentation, laboratory findings, treatments, and hospital outcomes were recorded. Results: A total of 250 medical records were included, mean age of 77 years, hospital stay mean of 6.7 days, 26.8% with no previous exposure was identified, coexistence with asthma was 5%, Obstructive Sleep Apnea Syndrome 15%, Pulmonary Hypertension 34%, antibiotic use 62%, ICU admission of 14% with non-invasive mechanical ventilation of 68%, and in-patient mortality of 2.4%. PM 2.5 of 48 hrs before onset symptoms median was 20.1 mug/m(3) versus 15 and 16.5 for the day of symptoms and 3 days prior to onset symptoms (p<0.001). PM 10 of 46.65 mug/m(3), versus 39 and 35.6, respectively (p<0.001). Expectoration OR 4.74; Purulence OR 6.58; Pleuritic pain OR 3.62;

Antibiotic use OR 2.87, and corticoids use OR 2.62, all with p<0.05. Conclusions: Patients with AECOPD have a higher median of particulate matter 48 hrs prior to symptomatic onset, as well as greater use of antibiotics and corticosteroids.

https://www.dovepress.com/getfile.php?fileID=51138

Moretz, C., L. Sharpsten, et al. (2019). **"Real-world effectiveness of umeclidinium/vilanterol versus fluticasone propionate/salmeterol as initial maintenance therapy for chronic obstructive pulmonary disease (COPD): a retrospective cohort study."** Int J Chron Obstruct Pulmon Dis **14**: 1721-1737.

Background and objective: Retrospective claims data in patients with chronic obstructive pulmonary disease (COPD) initiating maintenance therapy with inhaled fixed-dose combinations of long-acting muscarinic antagonist/long-acting beta2-agonist (LAMA/LABA) versus inhaled corticosteroid (ICS)/LABA have not been reported. Methods: Retrospective observational study in a COPD-diagnosed population of commercial and Medicare Advantage with Part D (MAPD) enrollees aged >/=40 years from a US health insurer database. Patients initiated umeclidinium/vilanterol (UMEC/VI [62.5/25 microg]) or fluticasone propionate/salmeterol (FP/SAL [250/50 microg]) between April 1, 2014 and August 31, 2016 (index date) and had 12 months continuous enrollment pre- and post-index. Exclusion criteria included an asthma diagnosis in the pre-index period/index date; ICS-, LABA-, or LAMA-containing therapy during the pre-index period; or pharmacy fills for both UMEC/VI and FP/SAL, multiple-inhaler triple therapy, a non-index therapy, or COPD exacerbation on the index date. Adherence (proportion of days covered [PDC] >/=80%) was modeled using weighted logistic regression following inverse probability of treatment weighting (IPTW). Weighted Kaplan-Meier and Cox proportional hazards regression following IPTW were performed for incidence of COPD exacerbation and escalation to multiple-inhaler triple therapy. Results: The study population included 5306 patients (1386 initiating UMEC/VI and 3920 initiating FP/SAL). Adjusted odds of adherence were 2.00 times greater among UMEC/VI than FP/SAL initiators (95% confidence interval [CI]: 1.62 horizontal line 2.46; P<0.001). The adjusted hazard ratio (HR) for first exacerbation was 0.87 (95% CI: 0.74-1.01; P=0.067) among UMEC/VI versus FP/SAL initiators. UMEC/VI initiators had 35% lower adjusted risk of escalation to multiple-inhaler triple therapy (HR 0.65; 95% CI: 0.47-0.89; P=0.008) versus FP/SAL. On-treatment, UMEC/VI initiators had an adjusted 30% reduced risk of a first moderate/severe COPD exacerbation (HR 0.70; 95% CI: 0.54-0.90; P=0.006). Conclusion: Patients with COPD initiating UMEC/VI had higher adherence and longer time before escalation to multiple-inhaler triple therapy than FP/SAL initiators.

https://www.dovepress.com/getfile.php?fileID=51707

Mouronte-Roibas, C., V. Leiro-Fernandez, et al. (2019). **"Predictive value of a series of inflammatory markers in COPD for lung cancer diagnosis: a case-control study."** Respir Res **20**(1): 198.

BACKGROUND: There is a relationship between Chronic Obstructive Pulmonary Disease (COPD) and the development of lung cancer (LC). The aim of this study is to analyse several blood markers and compare their concentrations in patients with only COPD and LC + COPD. METHODS: Case-control study with cases presenting combined LC and COPD and two control groups (patients presenting only COPD and patients presenting only LC). We also included LC patients with descriptive purposes. In both groups, peripheral blood analyses of TNF-alpha, IL-6, IL-8, total leukocyte, lymphocyte and neutrophil counts, neutrophil-to-lymphocyte ratio, total platelet count, mean platelet volume, platelet-to-lymphocyte ratio, alpha 1-antitripsin (A1AT), IgE, C-reactive protein, fibrinogen, cholesterol and bilirubin were performed. We developed univariate and multivariate analyses of these markers, as well as a risk score variable, and we evaluated its performance through ROC curves. RESULTS: We included 280 patients, 109 cases (LC + COPD), 83 controls (COPD) and 88 LC without COPD. No differences were observed in the distribution by sex, age, BMI, smoking, occupational exposure, lung function, GOLD stage or comorbidity. Patients with LC + COPD had significantly higher levels of neutrophils [OR 1.00 (95%CI 1.00-1.00), p = 0.03] and A1AT [OR 1.02 (95%CI 1.01-1.03), p = 0.003] and lower cholesterol levels [OR 0.98 (95%CI 0.97-0.99), p = 0.009] than COPD controls. We developed a risk score variable combining neutrophils, A1AT and

cholesterol, achieving a sensitivity of 80%, a negative predictive value of 90.7% and an area under the curve of 0.78 (95%CI 0.71-0.86). CONCLUSIONS: COPD patients who also have LC have higher levels of neutrophils and A1AT and lower of cholesterol. These parameters could be potentially predicting biomarkers of LC in COPD patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6712782/pdf/12931_2019_Article_1155.pdf

Nakanishi, M., Y. Minakata, et al. (2019). **"Simple standard equation for daily step count in Japanese patients with chronic obstructive pulmonary disease."** Int J Chron Obstruct Pulmon Dis **14**: 1967-1977.

Purpose: The improvement of physical activity in patients with COPD is an important issue. However, no standard for the recommended number of steps for patients with COPD has been determined. We conducted a retrospective observational study to create a simple standard equation for the daily step count, which makes it easier to determine whether each subject is attaining his/her predicted value or not. Patients and methods: Stable outpatients diagnosed with COPD whose physical activities had been measured using a triaxial accelerometer for more than 2 weeks were recruited from 5 institutes in Japan. Factors associated with the step count were detected by multivariate regression analysis. After the data were transformed to a normalized distribution, a multivariate linear regression equation was created using stepwise regression. Results: One hundred sixty-two patients aged 72.3 (7.2) years and of FEV1 %pred 59.2 (22.8) % were recruited. Among the parameters, age, mMRC dyspnea scale and inspiratory capacity (IC) were detected by the stepwise method. The created standard equation was "Step count = (-0.079x[age]-1.595x[mMRC]+2.078x[IC]+18.149)(3)". The correlations between the calculated values and the measured values were observed, and fixed, and proportional biases between them were also observed. When patients with <6500 steps/day were selected, no systematic bias between them could be detected. Conclusion: A simple standard equation for Japanese patients with COPD was created using age, mMRC and IC, and could provide an individual-predicted value, especially for patients with <6500 steps/day.

https://www.dovepress.com/getfile.php?fileID=52432

Navaie, M., B. R. Celli, et al. (2019). **"Exacerbations, Health Resource Utilization, and Costs Among Medicare Beneficiaries with Chronic Obstructive Pulmonary Disease Treated with Nebulized Arformoterol Following a Respiratory Event."** Chronic Obstr Pulm Dis **6**(4)Background: Long-acting beta2-agonists (LABAs), with or without inhaled corticosteroids (ICSs), delivered by handheld inhalers or nebulizers are recommended as maintenance therapy in chronic obstructive pulmonary disease (COPD). This study evaluated exacerbations, health resource utilization (HRU), and costs among Medicare beneficiaries with COPD on handheld ICS+LABA who switched to nebulized arformoterol (ARF) or continued ICS+LABA following a respiratory event. Methods: Using Medicare claims, we identified beneficiaries with COPD (international classification of disease, 9th revision, clinical modification [ICD-9-CM] 490-492.xx, 494.xx, 496.xx) between 2010-2014 who had >/= 1 year of continuous enrollment in Parts A, B, and D; >/= 2 COPD-related outpatient visits >/= 30 days apart or >/= 1 hospitalization(s); ICS+LABA use 90-days before ARF initiation; and a respiratory event (COPD-related hospitalization or emergency department [ED] visit < 30 days before ARF initiation). Using propensity scores, 423 beneficiaries who switched to ARF were matched to 423 beneficiaries who continued on handheld ICS+LABA (controls). Difference-in-difference regression models examined outcomes at 180-days follow-up. Results: Beneficiaries who switched to ARF had 1.5 fewer exacerbations (p=0.015) but no difference in hospitalizations and ED visits compared to controls. Durable medical equipment (DME) costs were higher among ARF users than controls ($1590), yet total health care costs were similar due to cost offsets by ARF in pharmacy (-$794), inpatient (-$524), and outpatient care (-$65). ARF accounted for 55% ($886.63) of DME costs, with the remaining costs attributed to oxygen therapy ($428.10) and nebulized corticosteroids ($590.85). Conclusions: Switching from handheld ICS+LABA to nebulized ARF resulted in fewer COPD exacerbations among Medicare beneficiaries. Nebulized LABAs may improve outcomes in selected patients with COPD.

https://journal.copdfoundation.org/Portals/0/JCOPDF/Files/Volume6-Issue4/JCOPDF-2019-0127-Navaie.pdf

Nguyen, H. Q., M. L. Moy, et al. (2019). **"Effect of Physical Activity Coaching on Acute Care and Survival Among Patients With Chronic Obstructive Pulmonary Disease: A Pragmatic Randomized Clinical Trial."** JAMA Netw Open **2**(8): e199657.

Importance: While observational studies show that physical inactivity is associated with worse outcomes in chronic obstructive pulmonary disease (COPD), there are no population-based trials to date testing the effectiveness of physical activity (PA) interventions to reduce acute care use or improve survival. Objective: To evaluate the long-term effectiveness of a community-based PA coaching intervention in patients with COPD. Design, Setting, and Participants: Pragmatic randomized clinical trial with preconsent randomization to the 12-month Walk On! (WO) intervention or standard care (SC). Enrollment occurred from July 1, 2015, to July 31, 2017; follow-up ended in July 2018. The setting was Kaiser Permanente Southern California sites. Participants were patients 40 years or older who had any COPD-related acute care use in the previous 12 months; only patients assigned to WO were approached for consent to participate in intervention activities. Interventions: The WO intervention included collaborative monitoring of PA step counts, semiautomated step goal recommendations, individualized reinforcement, and peer/family support. Standard COPD care could include referrals to pulmonary rehabilitation. Main Outcomes and Measures: The primary outcome was a composite binary measure of all-cause hospitalizations, observation stays, emergency department visits, and death using adjusted logistic regression in the 12 months after randomization. Secondary outcomes included self-reported PA, COPD-related acute care use, symptoms, quality of life, and cardiometabolic markers. Results: All 2707 eligible patients (baseline mean [SD] age, 72 [10] years; 53.7% female; 74.3% of white race/ethnicity; and baseline mean [SD] percent forced expiratory volume in the first second of expiration predicted, 61.0 [22.5]) were randomly assigned to WO (n = 1358) or SC (n = 1349). The intent-to-treat analysis showed no differences between WO and SC on the primary all-cause composite outcome (odds ratio [OR], 1.09; 95% CI, 0.92-1.28; P = .33) or in the individual outcomes. Prespecified, as-treated analyses compared outcomes between all SC and 321 WO patients who participated in any intervention activities (23.6% [321 of 1358] uptake). The as-treated, propensity score-weighted model showed nonsignificant positive estimates in favor of WO participants compared with SC on all-cause hospitalizations (OR, 0.84; 95% CI, 0.65-1.10; P = .21) and death (OR, 0.62; 95% CI, 0.35-1.11; P = .11). More WO participants reported engaging in PA compared with SC (47.4% [152 of 321] vs 30.7% [414 of 1349]; P < .001) and had improvements in the Patient-Reported Outcomes Measurement Information System 10 physical health domain at 6 months. There were no group differences in other secondary outcomes. Conclusions and Relevance: Participation in a PA coaching program by patients with a history of COPD exacerbations was insufficient to effect improvements in acute care use or survival in the primary analysis. Trial Registration: ClinicalTrials.gov identifier: NCT02478359.

https://jamanetwork.com/journals/jamanetworkopen/articlepdf/2748055/nguyen_2019_oi_190379.pdf

Nicola, S., A. I. Raffaele, et al. (2019). **"Circadian rhythm of COPD symptoms in clinically based phenotypes. Results from the STORICO Italian observational study."** BMC Pulm Med **19**(1): 171.

BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) encompasses various phenotypes that severely limit the applicability of precision respiratory medicine. The present investigation is aimed to assess the circadian rhythm of symptoms in pre-defined clinical COPD phenotypes and its association with health-related quality of life (HR-QoL), the quality of sleep and the level of depression/anxiety in each clinical phenotype. METHODS: The STORICO (NCT03105999) Italian observational prospective cohort study enrolled COPD subjects. A clinical diagnosis of either chronic bronchitis (CB), emphysema (EM) or mixed COPD-asthma (MCA) phenotype was made by clinicians at enrollment. Baseline early-morning, day-time and nocturnal symptoms (gathered via the Night-time, Morning and Day-time Symptoms of COPD questionnaire), HR-QoL (via the St. George's Respiratory Questionnaire), anxiety and depression levels (via the Hospital Anxiety and Depression Scale), quality of sleep (via COPD and Asthma Sleep Impact

Scale), physical activity (via the International Physical Activity Questionnaire) as well as lung function were recorded. RESULTS: 606 COPD subjects (age 71.4 +/- 8.2 years, male 75.1%) were studied. 57.9, 35.5 5.3 and 1.3% of the sample belonged to the CB, EM, MCA and EM + CB phenotypes respectively. The vast majority of subjects reported early-morning and day-time symptoms (79.5 and 79.2% in the CB and 75.8 and 77.7% in the EM groups); the proportion suffering from night-time symptoms was higher in the CB than in the EM group (53.6% vs. 39.5%, p = 0.0016). In both CB and EM, indiscriminately, the presence of symptoms during the 24-h day was associated with poorer HR-QoL, worse quality of sleep and higher levels of anxiety/depression. CONCLUSIONS: The findings highlight the primary classificatory role of nocturnal symptoms in COPD. TRIAL REGISTRATION: Trial registration number: NCT03105999 , date of registration: 10th April 2017.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6734215/pdf/12890_2019_Article_935.pdf

Oelsner, E. C., V. E. Ortega, et al. (2019). **"A Genetic Risk Score Associated with Chronic Obstructive Pulmonary Disease Susceptibility and Lung Structure on Computed Tomography."** Am J Respir Crit Care Med **200**(6): 721-731.

Rationale: 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 MESA Lung (Multi-Ethnic Study of Atherosclerosis Lung Study), a U.S. general population-based cohort, and SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study). A weighted GRS was calculated from 83 SNPs that were 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 airway measures, attenuated associations between the GRS and FEV1/FVC by 100% and 60% in MESA and SPIROMICS, respectively. Lung structure ($P < 0.0001$), but not the GRS ($P > 0.10$), 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.

Ogan, N., P. A. Ozer, et al. (2019). **"Short-term variations of optic coherence tomography findings in mild and severe chronic obstructive pulmonary disease."** Eye (Lond)OBJECTIVE: To evaluate the short-term changes in subfoveal choroidal thickness (SFCT), ganglion cell complex (GCC) analysis, and retinal nerve fiber length (RNFL) of patients with chronic obstructive pulmonary disease (COPD) in a 3-month follow-up. MATERIALS AND METHODS: Forty-eight patients with COPD (96 eyes) and 40 control subjects (80 eyes) were enrolled in our study. COPD patients were grouped according to disease severity as Group 1 (mild-moderate) and Group 2 (advanced). GCC, RNFL, and SFCT analysis by Cirrus SD-OCT were obtained for all eyes, in two consecutive examinations with a 3-month interval. RESULTS: SFCT in Group 2 was lower than Group 1 and control group in the initial and 3rd month examination ($p < 0.001$, respectively). Inferior RNFL in Group 2 were lower than control group in the initial and 3rd month examination ($p = 0.002$, $p < 0.001$, respectively) Temporal RNFL were lower in Group 2 than Group 1 in 3rd month examination ($p = 0.009$). Average, superior, superotemporal, inferior, and inferonasal GCC analyses of the Group 2 were lower than control group both in the initial and 3rd month examination ($p = 0.001$, $p < 0.001$, respectively) SFCT, average, and superior GCC of Group 2 were significantly reduced during the 3-month follow-up ($p < 0.001$). CONCLUSION: Hypoxia is thought to be the underlying

mechanism in COPD, which may influence retinal and choroidal OCT parameters. Decrease in blood flow of optic nerve head, increased vascular resistance, and reduced blood flow in choroid may affect the visual ability in these patients, which should be kept in mind during their follow-up.

https://www.nature.com/articles/s41433-019-0613-x

Oh, E. G. and J. Y. Yoo (2019). **"Progression of erectile function in men with chronic obstructive pulmonary disease: a cohort study."** BMC Pulm Med **19**(1): 139.

BACKGROUND: Although sexual function is a quality of life aspect that is markedly affected in males with chronic obstructive pulmonary disease (COPD), this topic has not attracted much attention and research on this matter is lacking. In this study, we investigated longitudinal changes in the erectile function of men with COPD in order to identify latent groups and influencing factors. METHODS: A total of 185 men with COPD from the Korean Obstructive Lung Disease study, which was conducted from 2005 to 2013, were analyzed in this study. Data on their erectile function, based on the International Index of Erectile Function-5, were collected over a period of 4 years. Growth mixture modeling and logistic regression analysis were used to determine the factors predicting distinct erectile function changes over time. RESULTS: Overall, subjects' erectile function slightly improved in the first year and then gradually worsened over time. Using growth mixture modeling, we identified four distinct latent groups, which we labeled as follows: "consistently maintained normal erectile function" (9.7%), "rapidly worsened and then rapidly improved" (9.2%), "gradually improved in the early stage and then gradually worsened" (36.8%), and "consistently maintained poor erectile function" (44.3%). Progression of erectile function was significantly associated with age, economic status, and self-rated health status. CONCLUSIONS: This suggests that comprehensive patient care involving the management of COPD as well as erectile dysfunction in patients with chronic respiratory disease is important from a prophylactic perspective and should be developed in accordance with the characteristics of the disease process.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6718002/pdf/12890_2019_Article_902.pdf

Paone, G., L. Lanata, et al. (2019). **"A prospective study of the effects of carbocysteine lysine salt on frequency of exacerbations in COPD patients treated with or without inhaled steroids."** Eur Rev Med Pharmacol Sci **23**(15): 6727-6735.

OBJECTIVE: COPD is one of the major causes of morbidity and mortality worldwide and represents one of the most important issues for public health. Frequent exacerbations induce a faster decline in lung function and poorer quality of life, increase mortality, and have a socio-economic impact with a high burden in terms of resources and healthcare costs. The clinical trials evaluated the effect of mucolytics in COPD and showed that the long-term carbocysteine, associated with bronchodilators, anticholinergics, and steroids, reduces the frequency of exacerbations and improves the quality of life. PATIENTS AND METHODS: The aim of this prospective real-life study was to evaluate the long-term impact on exacerbations (at 1 year) in COPD patients treated with carbocysteine lysine salt (single dose of 2.7 g once a day) in addition to background therapy with or without inhaled steroids. RESULTS: In a total of 155 evaluable patients, our study showed that the addition of a single dose of carbocysteine lysine salt to background therapy determines a statistically significant reduction of the average number of exacerbations vs. the number observed in the previous year (from 1.97+/-0.10 to 1.03+/-0.11; $p<0.01$), irrespective of treatment with or without inhaled steroids. In particular, in patients with >/=2 exacerbations in the previous year, the addition of carbocysteine lysine salt resulted in a statistically significant reduction in the exacerbations rate from 69% to 33% and from 58% to 25%, respectively ($p<0.01$) in patients with or without inhaled steroids. CONCLUSIONS: In summary, our data highlighted the efficacy of long-term administration of a single daily dose of carbocysteine lysine salt (2.7 g/day) in reducing the number and rate of exacerbations in COPD patients, independently from the use of inhaled steroids.

Park, H. Y., D. Kang, et al. (2019). **"Impact of chronic obstructive pulmonary disease on mortality: A large national cohort study."** RespirologyBACKGROUND AND OBJECTIVE: The global burden of chronic obstructive pulmonary disease (COPD) is increasing and COPD patients are at higher risk for all-cause mortality. We aimed to evaluate the impact of COPD on specific-cause mortality using national data. METHODS: This was nationwide retrospective cohort study of 340, 767 adults aged 40-84 years who lacked COPD diagnosis at baseline between 1 January 2003 and 31 December 2013. Incident COPD was defined by reference to COPD claim codes and prescription of COPD medication at least twice annually. Cox proportional hazard ratio (HR) for each cause of death in the COPD group was compared to that of the non-COPD group, with other causes of death accounted as the competing risk. RESULTS: All-cause mortality was higher in the COPD (2,978 per 100, 000 person-years) than the non-COPD group (629 per 100, 000 person-years) and adjusted HR was 1.41 (95% CI = 1.32, 1.50). The association was particularly strong for chronic lower airway disease (adjusted sub-HR = 9.67; 95% CI = 7.21, 12.96) and lung cancer (adjusted sub-HR = 3.16; 95% CI = 2.68, 3.71), and the association was stronger in those aged <60 years. CONCLUSION: In this large national cohort, COPD patients were at a statistically significant higher risk for all-cause mortality than those without COPD. They were more likely to die from chronic lower airway disease, lung cancer and pneumonia than subjects without COPD. The impact of COPD on specific mortalities was stronger in younger subjects.

https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13678

Park, J., B. D. Hobbs, et al. (2019). **"Subtyping COPD by Using Visual and Quantitative CT Imaging Features."** ChestBACKGROUND: Multiple studies have identified COPD subtypes by using visual or quantitative evaluation of CT images. However, there has been no systematic assessment of a combined visual and quantitative CT imaging classification. We integrated visually defined patterns of emphysema with quantitative imaging features and spirometry data to produce a set of 10 nonoverlapping CT imaging subtypes, and we assessed differences between subtypes in demographic features, physiological characteristics, longitudinal disease progression, and mortality. METHODS: We evaluated 9,080 current and former smokers in the COPDGene study who had available volumetric inspiratory and expiratory CT images obtained using a standardized imaging protocol. We defined 10 discrete, nonoverlapping CT imaging subtypes: no CT imaging abnormality, paraseptal emphysema (PSE), bronchial disease, small airway disease, mild emphysema, upper lobe predominant centrilobular emphysema (CLE), lower lobe predominant CLE, diffuse CLE, visual without quantitative emphysema, and quantitative without visual emphysema. Baseline and 5-year longitudinal characteristics and mortality were compared across these CT imaging subtypes. RESULTS: The overall mortality differed significantly between groups ($P < .01$) and was highest in the 3 moderate to severe CLE groups. Subjects having quantitative but not visual emphysema and subjects with visual but not quantitative emphysema were unique groups with mild COPD, at risk for progression, and with likely different underlying mechanisms. Subjects with PSE and/or moderate to severe CLE had substantial progression of emphysema over 5 years compared with findings in subjects with no CT imaging abnormality ($P < .01$). CONCLUSIONS: The combination of visual and quantitative CT imaging features reflects different underlying pathological processes in the heterogeneous COPD syndrome and provides a useful approach to reclassify types of COPD. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00608764; URL: www.clinicaltrials.gov.

https://journal.chestnet.org/article/S0012-3692(19)31255-3/fulltext

Park, S. C., D. W. Kim, et al. (2019). **"Mortality of patients with chronic obstructive pulmonary disease: a nationwide populationbased cohort study."** Korean J Intern MedBackground/Aims: Chronic obstructive pulmonary disease (COPD) is a major cause of mortality in the world. There are no

population-based studies on longterm mortality in COPD patients in Korea. Methods: Using the large, population-based, National Health Insurance Service- National Sample Cohort (NHIS-NSC), we identified COPD patients using the International Classification of Disease-Tenth Revision (ICD-10) and prescription details in the NHIS-NSC during 2003 to 2013. We analyzed the survival curves of COPD patients by sex, age, and cause of death. Results: A total of 14,127 individuals older than 40 years were diagnosed with COPD. There were a total of 3,695 deaths (26.2%) in COPD patients during the study period. The 5-year mortality of COPD patients was 25.4% (29.9% in males and 19.1% in females). The mortality rate increased rapidly with age. The most common cause of death in COPD was chronic lower respiratory disease. Conclusions: This study described long-term mortality in COPD patients in Korea. Higher mortality was observed in males, and it was closely related to age.

http://kjim.org/upload/kjim-2017-428.pdf

Park, T. S., J. Kang, et al. (2019). **"Adherence to roflumilast under dose-escalation strategy in Korean patients with COPD."** Int J Chron Obstruct Pulmon Dis **14**: 871-879.

Background: Frequent development of adverse events and consequent low adherence are major barriers in the wide use of roflumilast. Asian patients may be more susceptible to adverse events due to low BMI. In this study, we aimed to determine if a dose-escalation strategy is useful to improve the drug adherence rate. Methods: This was a randomized, prospective, open-label, single-blind study to compare the adherence rate to roflumilast according to a dose-escalation or conventional dose strategy in patients with COPD in South Korea. Patients were randomized into two groups (1:1), either roflumilast 500 mug once daily for 12 weeks or roflumilast 250 mug once daily for 4 weeks, and then 500 mug for 12 weeks. The primary outcome was the percentage of patients prematurely discontinuing roflumilast due to adverse events. Results: A total of 55 patients were randomly assigned to either a conventional-dose group (n=28) or a dose-escalation group (n=27). Discontinuation rates of roflumilast due to adverse events were 46.4% for the conventional-dose group and 59.3% for the dose-escalation group. The median time to discontinuation was not different between groups (58 days for the conventional-dose group, 56 days for the dose-escalation group, p=0.629). In a multivariate analysis, older age was a significant risk factor for drug discontinuation. Conclusion: High discontinuation rates of roflumilast were observed in both groups regardless of the dose-escalation strategy. The frequent discontinuation suggests that the dose-escalation strategy may not be useful in Asian patients. Clinical trial: This study is registered at www.ClinicalTrials.gov with identifier number NCT02018432.

https://www.dovepress.com/getfile.php?fileID=49160

Parkin, L., J. Quon, et al. (2019). **"Underuse of beta-blockers by patients with COPD and co-morbid acute coronary syndrome: A nationwide follow-up study in New Zealand."** RespirologyBACKGROUND AND OBJECTIVE: Clinical guidelines recommend the use of beta-blockers and other cardiovascular prevention drugs in patients with acute coronary syndrome (ACS). Studies in several countries have found that beta-blockers are underused in patients with chronic obstructive pulmonary disease (COPD) and co-morbid heart disease, although most have only examined use in subgroups of patients. We undertook a nationwide follow-up study in New Zealand to describe the use of beta-blockers and other cardiovascular prevention drugs in patients with COPD and ACS. METHODS: National health and pharmaceutical dispensing data were used to derive the study cohort, identify patients who were admitted to hospital with ACS and/or heart failure before cohort entry and during follow-up, and ascertain drug use. RESULTS: The study cohort included 83 435 patients aged >/=45 years, with 290 400 person-years of follow-up. Among 2637 patients with >/=1 ACS admission during follow-up, only 56.6% received a beta-blocker in the 6 months following the first admission, while 87.7% and 81%, respectively, received aspirin and a statin. Patients with higher COPD severity were less likely to receive a beta-blocker than those with lower severity, as were those with no history of previous ACS and/or heart failure. CONCLUSION: Use of beta-blockers following an ACS admission was much lower than expected based on the findings of general audits of ACS management in New Zealand. Along with the higher

proportions using aspirin and statins, and the differences in beta-blocker dispensing by COPD severity, this suggests a particular reluctance to prescribe beta-blockers to patients with COPD.

https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13662

Perrotta, F., A. Cennamo, et al. (2019). **"Effects of a high-intensity pulmonary rehabilitation program on the minute ventilation/carbon dioxide output slope during exercise in a cohort of patients with COPD undergoing lung resection for non-small cell lung cancer."** J Bras Pneumol **45**(6): e20180132.

OBJECTIVE: Preoperative functional evaluation is central to optimizing the identification of patients with non-small cell lung cancer (NSCLC) who are candidates for surgery. The minute ventilation/carbon dioxide output (VE/VCO2) slope has proven to be a predictor of surgical complications and mortality. Pulmonary rehabilitation programs (PRPs) could influence short-term outcomes in patients with COPD undergoing lung resection. Our objective was to evaluate the effects of a PRP on the VE/VCO2 slope in a cohort of patients with COPD undergoing lung resection for NSCLC. METHODS: We retrospectively evaluated 25 consecutive patients with COPD participating in a three-week high-intensity PRP prior to undergoing lung surgery for NSCLC, between December of 2015 and January of 2017. Patients underwent complete functional assessment, including spirometry, DLCO measurement, and cardiopulmonary exercise testing. RESULTS: There were no significant differences between the mean pre- and post-PRP values (% of predicted) for FEV1 (61.5 +/- 22.0% vs. 62.0 +/- 21.1%) and DLCO (67.2 +/- 18.1% vs. 67.5 +/- 13.2%). Conversely, there were significant improvements in the mean peak oxygen uptake (from 14.7 +/- 2.5 to 18.2 +/- 2.7 mL/kg per min; $p < 0.001$) and VE/VCO2 slope (from 32.0 +/- 2.8 to 30.1 +/- 4.0; $p < 0.01$). CONCLUSIONS: Our results indicate that a high-intensity PRP can improve ventilatory efficiency in patients with COPD undergoing lung resection for NSCLC. Further comprehensive prospective studies are required to corroborate these preliminary results.

Pezzuto, A. and E. Carico (2019). **"Effectiveness of smoking cessation in smokers with COPD and nocturnal oxygen desaturation: functional analysis."** Clin Respir JINTRODUCTION: Chronic obstructive pulmonary disease (COPD) is the fourth cause of mortality and it's frequently associated with breathing sleep disorders (SBD) . OBJECTIVE: The aim of the study is to point out the benefit of smoking cessation over three months in terms of improvement of respiratory functional variables. METHODS: A retrospective analysis was performed evaluating the impact of smoking cessation on 145 patients with COPD and nocturnal oxygen desaturation. For this purpose for all patients overnight pulse oxymetry detection on room air , arterial blood sampling, plethysmography, exhaled test for carbon monoxide were performed at baseline and three months after the beginning. Smoking cessation was achieved by varenicline plus individual counseling . RESULTS: About 51% of patients quit smoking which was established by eCO measure (cutoff 5 ppm) . Patients who quit smoking displayed notably better results compared with patients who did not . The eCO significantly decreased by 16 ppm versus 4 ($p=0.01$), oxygen desaturation index (ODI) was reduced by 3 points versus 0.8 ($p=0.01$), forced expiratory in one second volume (FEV1) increased by 7% of predicted value versus 1% ($p=0.01$). The walking test (WT) was improved by 102 m versus 25 in sustainers ($p=0.01$). The CAT score was also improved by 10 versus 8 in sustainers ($p=0.01$) and PaO2 increased by 5 mmHg versus 0.5 ($p=0.04$). The percentage of SaO2<90% was improved by 6.7 versus 2.1 ($p=0.04$).The logistic regression analysis displayed the possible influence of CAT ($p=0.02$), mMRC ($p=0.05$) on ODI value. CONCLUSIONS: Smoking cessation notably improves pulmonary functional parameters in quitters reporting nocturnal oxygen desaturation.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13096

Pham, J., S. Pitney, et al. (2019). **"Poor initiation of smoking cessation therapies in hospitalised patients with COPD is associated with low levels of formal training amongst hospital doctors and under-utilisation of nursing-lead interventions."** Intern Med JBACKGROUND: Smoking cessation intervention is a key component in the management of chronic obstructive pulmonary disease (COPD). AIMS: The aim of this study was to evaluate the prescribing of smoking cessation therapies (SCT) amongst hospital clinicians and identify factors that may hinder delivery of effective interventions. METHODS: A retrospective analysis of medical records of patients admitted to the Royal Hobart Hospital with an acute exacerbation of COPD was performed. A survey of hospital clinicians was also performed to ascertain levels of training and confidence in prescribing SCT. RESULTS: Nearly all medical and non-medical hospital clinicians self-reported confidence in offering SCT (91.1% versus 82.5%, respectively. p=0.216). However, of the 122 eligible patients in our study population, the majority did not have any form of SCT initiated during their admission (n=68, 55.7%) and only 21 patients (17.2%) were referred to the nurse-lead smoking cessation service. Very few patients were initiated on efficacious regimes such as combination-NRT (n=8, 6.6%) or varenicline (n=2, 1.6%). Only a small proportion of hospital doctors reported confidence in prescribing varenicline and buproprion (17.2% and 6.9%, respectively). Furthermore, very few hospital doctors reported ever receiving formal training in SCT compared to non-medical hospital staff (42.2% versus 84.5%, p<0.001). CONCLUSION: Our study highlights the real-life challenges in tackling nicotine dependence in hospitals: under-utilisation of evidence-based pharmacotherapies, limited access to formal training for doctors and poor uptake of nurse-lead smoking cessation services. Granting limited prescribing rights for specialised nurses may help hospital clinicians to alleviate gaps in current clinical practice.

https://onlinelibrary.wiley.com/doi/abs/10.1111/imj.14645

Proboszcz, M., K. Mycroft, et al. (2019). **"Relationship between Blood and Induced Sputum Eosinophils, Bronchial Hyperresponsiveness and Reversibility of Airway Obstruction in Mild-to-Moderate Chronic Obstructive Pulmonary Disease."** Copd: 1-8.

Blood eosinophilia has been proposed as a surrogate marker for airway eosinophilia and as a predictor of treatment response in chronic obstructive pulmonary disease (COPD). The aim of the study was to assess the relationship between blood and sputum eosinophils and to investigate the association between blood and sputum eosinophil count and clinical features of mild-to-moderate COPD. We performed a retrospective analysis of blood and sputum eosinophil count, as well as demographic and lung function data in a cohort of 90 stable, steroid-naive (Global Initiative for Chronic Obstructive Lung Disease 1 or 2) COPD patients and 20 control subjects. Blood and sputum eosinophil count did not correlate both in patients with COPD (r = -0.04 p = 0.705) and in controls (r = 0.05, p = 0.838). Sputum eosinophilia (>/=3%) was present in 40% of COPD patients. The median blood eosinophil count in patients with COPD was 180 (interquartile range 90-270)/muL; patients with low blood eosinophils (<180/muL) did not differ from those with high blood eosinophils (>/=180/muL) in terms of forced expiratory volume in 1 second, bronchial reversibility or hyperresponsiveness. This was also the case when COPD patients with and without sputum eosinophilia were compared. At the same time, positive bronchial reversibility and positive bronchial hyperresponsiveness were observed in 2 (11%) COPD patients with high blood eosinophils and in 1 (5%) patient with sputum eosinophilia. There was a weak, albeit significant correlation (r = 0.22 p = 0.041) between blood eosinophil count and age in patients with COPD. Peripheral eosinophil count poorly reflects sputum eosinophils and lung function in stable steroid-naive mild-to-moderate COPD patients.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1675150

Radovanovic, D., M. Contoli, et al. (2019). **"Clinical and Functional Characteristics of COPD Patients Across GOLD Classifications: Results of a Multicenter Observational Study."** Copd **16**(3-4): 215-226.

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease. The severity grading systems proposed by the Global initiative for Chronic Obstructive Lung Disease (GOLD) have changed over time.

The aim of the study was to evaluate if the different GOLD classifications can capture the complexity of the disease by investigating the distribution of lung function and clinical parameters across the GOLD classification systems. This was an observational, retrospective, multicentre study. COPD patients were stratified according to the GOLD severity grading proposed in the 2007, and to the ABCD assessment tool present in the 2011, and 2017 versions of the initiative. Data from body plethysmography, DLCO, comorbidities, exacerbation history, pharmacological therapy and eosinophil counts were collected. A total of 1360 patients (73.4% males) were included in the analysis. Overall, 37% of the patients were severe-very severe according to GOLD 2007. Compared with GOLD 2011, applying the GOLD 2017 criteria, the proportion of the at risk categories (C and D) was reduced by approximately 23%. Impairment in inspiratory capacity, DLCO and the prevalence of emphysema paralleled the GOLD 2007 classification only. The proportion of patients with >/= 200 eosinophils/microL was higher in GOLD 2007 stages 3-4 compared with stages 1-2 (P = 0.008). Eosinophil levels were similar across risk classes in GOLD 2011 and 2017. Overall, 41.8% and 52.4% of the patients in the low risk groups according to GOLD 2011 and 2017 were exposed to inhaled corticosteroids. The GOLD 2011 and 2017 classifications, despite exploring symptoms and exacerbations, might miss other relevant patients' clinical characteristics such as lung function and phenotypes, which have a significant impact on outcomes and disease severity.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1659760

Ragland, M. F., C. J. Benway, et al. (2019). **"Genetic Advances in Chronic Obstructive Pulmonary Disease. Insights from COPDGene."** Am J Respir Crit Care Med **200**(6): 677-690.

Chronic 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. Over the past decade, the proliferation of genome-wide association studies, the accessibility of whole-genome sequencing, and the development of novel methods for analyzing genetic variation data have led to a substantial increase in the understanding of genetic variants that play a role in COPD susceptibility and COPD-related phenotypes. COPDGene (Genetic Epidemiology of COPD), 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-genome-wide association study analysis.

Redolfi, S., L. Grassion, et al. (2019). **"Abnormal Activity of Neck Inspiratory Muscle During Sleep as a Prognostic Indicator in COPD."** Am J Respir Crit Care MedRATIONALE: In patients with chronic obstructive pulmonary disease (COPD), increased activity of neck inspiratory muscles has been reported as a compensatory response to hyperinflation-related diaphragmatic dysfunction. The persistence of this activity during sleep could attenuate sleep-related hypoventilation, but also negatively impact sleep and clinical outcomes. OBJECTIVES: To assess the persistence of neck muscle activity during sleep in COPD patients recovering from severe exacerbations (i.e. requiring hospitalization), and its impact on sleep quality and recurrence of exacerbation. METHODS: Video-polysomnography with neck muscles electromyogram was performed in COPD patients recovering from severe exacerbation. The follow-up period lasted 6 months to record the next severe exacerbation. RESULTS: Twenty-six out of 29 patients included (median [25th-75th] age of 71 [64-72] years, 55% male, body mass index of 24 [21-29], % predicted forced expiratory volume in the first second of expiration of 37 [29-45], and BODE index 6 [5-7]), exhibited sleep-related neck muscles activity, which was intermittent (limited to N3 sleep) in 17 and

permanent throughout sleep in 9. Alpha-delta electroencephalographic activity during N3 sleep was observed in 87% of patients. Compared to patients with no or intermittent neck muscle activity, those with permanent neck muscle activity showed more disrupted sleep, had experienced more exacerbations in the previous year, and suffered their next severe exacerbation earlier. CONCLUSIONS: Sleep-related neck muscle activity during sleep is frequent in COPD patients recovering from severe exacerbation and seems to negatively affect sleep quality and prognosis, thus its identification might improve COPD management after severe exacerbation.

Roche, N., B. Aguilaniu, et al. (2019). **"Trends over time in COPD treatment choices by respiratory physicians: An analysis from the COLIBRI-COPD French cohort."** Respir Med **156**: 8-14.

INTRODUCTION: Over the last decade, new evidence and many guidelines have been published on COPD pharmacological treatments; prescriptions are often not in accordance with guidelines. MATERIALS AND METHODS: Trends in physician treatment choices from February 2012 to November 2018 (Feb.2012/Nov.2018) were analyzed using data from COPD patients (spirometry-confirmed diagnosis) included in the COLIBRI-COPD cohort. Inhaled drug treatments (short- or long-acting beta2-agonist [SABA or LABA], short- or long-acting anticholinergic [SAMA or LAMA], or corticosteroid [ICS]) were classified into 5 treatment categories: "No initial maintenance treatment (IMT)" (untreated, or only SAMA or SABA); "1 long-acting bronchodilator (LABD)" (LABA or LAMA); "2 LABDs" (LABA + LAMA); "1 LABD + ICS" (LABA or LAMA + ICS); "2 LABDs + ICS" (LABA + LAMA + ICS). For the purpose of the study, 4 periods were defined to achieve balanced samples (T1-T4). RESULTS: Data from 4537 patients were collected. Over time, 3 major changes were observed: (1) an increase in treatment category "No IMT", mostly for GOLD 1 or GOLD A categories (GOLD A: from 19.1% at T1 to 41.2% at T4); (2) an increase in treatment category "2 LABDs" for GOLD 2 to 4 and GOLD A to D categories (GOLD B: from 15.4% to 29.7%); (3) a decrease in ICS use ("1 LABD + ICS" or "2 LABDs + ICS"), mostly for GOLD 1 to 3 and GOLD A categories (GOLD A, 2 LABDs + ICS: from 35.3% to 11.1%). CONCLUSION: Changes over time in therapeutic profiles suggest that new evidence from scientific publications and recommendations may have had a rapid impact on clinical practice.

https://www.resmedjournal.com/article/S0954-6111(19)30247-1/fulltext

Rockenschaub, P., A. Jhass, et al. (2019). **"Opportunities to reduce antibiotic prescribing for patients with COPD in primary care: a cohort study using electronic health records from the Clinical Practice Research Datalink (CPRD)."** J Antimicrob ChemotherBACKGROUND: In primary care there is uncertainty about which patients with acute exacerbations of COPD (AECOPD) benefit from antibiotics. OBJECTIVES: To identify which types of COPD patients get the most antibiotics in primary care to support targeted antibiotic stewardship. METHODS: Observational study of COPD patients using a large English primary care database with 12 month follow-up. We estimated the incidence of and risk factors for antibiotic prescribing relative to the number of AECOPD during follow-up, considering COPD severity, smoking, obesity and comorbidity. RESULTS: From 157 practices, 19594 patients were diagnosed with COPD, representing 2.6% of patients and 11.5% of all prescribed antibiotics. Eight hundred and thirty-three (4.5%) patients with severe COPD and frequent AECOPD were prescribed six to nine prescriptions per year and accounted for 13.0% of antibiotics. Individuals with mild to moderate COPD and zero or one AECOPD received one to three prescriptions per year but accounted for 42.5% of all prescriptions. In addition to COPD severity, asthma, chronic heart disease, diabetes, heart failure and influenza vaccination were independently associated with increased antibiotic use. CONCLUSIONS: Patients with severe COPD have the highest rates of antibiotic prescribing but most antibiotics are prescribed for patients with mild to moderate COPD. Antibiotic stewardship should focus on the dual goals of safely reducing the volume of prescribing in patients with mild to moderate COPD, and optimizing prescribing in patients with severe disease who are at significant risk of drug resistance.

https://watermark.silverchair.com/dkz411.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAn8wggJ7BgkqhkiG9w0BBwagggJsMIICaAIBADCCAmEGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMhiRS7fHtGfXxVjDNAgEQgIICMsWNcFNplya4exZl09XF7OL_dXtIlMDHu29xfLSYpWm_i8TXlOt1XRu3Z_H2FYSNv9payamt6QG9Qa-i1dbfBIBhC5WvBEnOElcRiyHvg-gNHjEY6WmT_NTaN0gMR4yutfwoq3FRR_ChK1JT9h02D9Mf4VHwqvbQ25GvpoFXq8YqUxjiePYSP3b0OdJW5GND_J31om8IkGAAMkqPanpRmRCN2SRTO-WBv9sOtFSrpPbFEZnUuHtcgXya92OlA-M3iXKuljD5nSYP58nHgXxkqdTusiTB-cc2oHjqDY78nHKd1PBgkPaSOmWBMpap28dEoIYBhSbnB8R1klYtToeM6wcOPtxlQ67RPd4u4xr81VBdjxLxqnmSiBlleOwtxNqqaGGMZ6k9-4bCc1TEBdQI7kt0U4M2Cnfkm_d7Zj47G663zJlKrtuUwEsCjGVVg2LeVb3y09kuLiRgtxW4Oh6j7tM_08Y91tTQ7m8epqYWj2RzawpaIR36N_6muM_ZDGVYrTsxrdIyF80A53GZOCWiMYIDhHJTMjmNWAYI7I1cfgI84JG_WJxJmwJNs6Naz5IjDPmErNxjrRcLFPPI7DL7RsXbY7uJnTgip4Ni_sxD3IYJm97dQ-euVoXPTb-S35J5ay96F_Ymbx2h5yzv62ZzQUYEVZ2mg4Tk6EYIkcKyAZULkyHKpzj-UGbncs_a1j-wU6YV1GaIQ69rrn4wdZQ5VQM-X9QdEUGemlYFvLhALp7jeGk

Rodriguez-Aguilar, M., S. Ramirez-Garcia, et al. (2019). **"Ultrafast gas chromatography coupled to electronic nose to identify volatile biomarkers in exhaled breath from chronic obstructive pulmonary disease patients: A pilot study."** Biomed Chromatogr: e4684.

An analytical method to identify volatile organic compounds (VOCs) in the exhaled breath from patients with a diagnosis of chronic obstructive pulmonary disease (COPD) using a ultrafast gas chromatography system equipped with an electronic nose detector (FGC eNose) has been developed. A prospective study was performed in 23 COPD patients and 33 healthy volunteers; exhalation breathing tests were performed with Tedlar bags. Each sample was analyzed by FCG eNose and the identification of VOCs was based on the Kovats index. Raw data were reduced by principal component analysis (PCA) and canonical discriminant analysis [canonical analysis of principal coordinates (CAP)]. The FCG eNose technology was able to identify 17 VOCs that distinguish COPD patients from healthy volunteers. At all stages of PCA and CAP the discrimination between groups was obvious. Chemical prints were correctly classified up to 82.2%, and were matched with 78.9% of the VOCs detected in the exhaled breath samples. Receiver operating characteristic curve analysis indicated the sensitivity and specificity to be 96% and 91%, respectively. This pilot study demonstrates that FGC eNose is a useful tool to identify VOCs as biomarkers in exhaled breath from COPD patients. Further studies should be performed to enhance the clinical relevance of this quick and ease methodology for COPD diagnosis.

https://onlinelibrary.wiley.com/doi/abs/10.1002/bmc.4684

Savran, O., N. Godtfredsen, et al. (2019). **"COPD patients prescribed inhaled corticosteroid in general practice: Based on disease characteristics according to guidelines?"** Chron Respir Dis **16**: 1479973119867949.

In a primary care setting, our aim was to investigate characteristics of patients classified as having chronic obstructive pulmonary disease (COPD) and currently being prescribed inhaled corticosteroids (ICSs). The electronic patient record system in each participating general practice was searched for patients coded as COPD (ICPC, Second Edition code R95) and treated with ICS (ACT code R03AK and R03BA, that is, ICS in combination with a long-acting beta2-agonist) or ICS as monotherapy. Data, if available, on demographics, smoking habits, spirometry, COPD medication, symptom score, blood eosinophils, co-morbidity and exacerbation history were retrieved from the medical records for all identified cases. Of all patients registered in the 138 participating general practices, 12.560 (3%) were coded as COPD, of whom 32% were prescribed ICS. The final study sample comprised 2.289 COPD patients currently prescribed ICS (98% also prescribed long-acting beta2-agonist), with 24% being coded as both COPD and asthma. Post-bronchodilator spirometry was available in 79% (mean forced expiratory volume in 1 second 60% pred (standard deviation (SD) 23.3)), symptom severity score in 53% (mean Medical Research Council score 2.7 (SD 1.1)) and 56% of the COPD patients had had no exacerbation in the previous year (and 45% not within the 2 previous years). Blood eosinophils were measured in 67% of the patients. Information on severity of airflow limitation was missing in 15% of the patients, and the combined

information on symptom severity and exacerbation history was missing in in 46%. Most of the patients (74%) were managed only by their general practitioner. Although only one-third of the COPD patients were prescribed ICSs, our findings from this study of a large cohort of patients prescribed ICSs for COPD in general practice suggest that more detailed assessment of diagnosis and disease characteristics is likely to improve the risk-benefit ratio of maintenance therapy with ICSs in COPD patients managed in primary care.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6704538/pdf/10.1177_1479973119867949.pdf

Schofield, S. J., A. Woods, et al. (2019). **"COPD and Breathlessness in Older Workers Predict Economic Inactivity; A Prospective Cohort Study."** Am J Respir Crit Care MedRATIONALE: There is an aspiration to retain increasing numbers of older workers in employment and strategies to achieve this need to make provision for the increasing prevalence of chronic diseases with age. There is a consistent body of cross-sectional evidence that suggests that patients with chronic obstructive pulmonary disease are more likely to have adverse employment outcomes. OBJECTIVES: We report the findings of the first longitudinal study of this issue. METHODS: We recruited full-time employed men and women in their 50's and followed them for a period of 18 months; we examined, after adjustment for potential confounders, the associations between breathlessness and airway obstruction at baseline and loss of employment in the intervening period. MEASUREMENTS AND MAIN RESULTS: Among participants responding to the follow up questionnaire (1656/1773 (93%)), the majority (78.5%) continued in full-time employment, but 10.6% were in part-time employment and 10.9% were no longer in paid employment. The adjusted risk of loss of employment was significantly increased for those with moderate or severe chronic obstructive pulmonary disease (RR 2.89, 95% ci 1.80-4.65) or breathlessness (3.07, 2.16-4.37) at baseline. There was no evident modification by sex or by manual/non-manual work. CONCLUSIONS: Airway obstruction and breathlessness are independently associated with premature loss from the workforce in older workers; these observations provide strong support to the available cross-sectional evidence and suggest that interventions to help those with chronic obstructive pulmonary disease who wish to remain in work need to be tested.

Senthilselvan, A. and J. Beach (2019). **"Characteristics of asthma and COPD overlap syndrome (ACOS) in the Canadian population."** J Asthma **56**(11): 1129-1137.

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

Sessa, M., A. Mascolo, et al. (2019). **"Beta-blocker choice and exchangeability in patients with heart failure and chronic obstructive pulmonary disease: an Italian register-based cohort study."** Sci Rep **9**(1): 11465.

Clinical guidelines suggest that for patients with heart failure and concurrent chronic obstructive pulmonary disease (COPD), metoprolol/bisoprolol/nebivolol should be preferred over carvedilol. However, studies suggest a high proportion of carvedilol usage that remains unexplained. Therefore, we aimed to investigate the predictors of carvedilol choice in patients with heart failure and COPD that were naive to carvedilol or metoprolol/bisoprolol/nebivolol. Caserta Local Health Unit databases (Italy) were used as data sources. Age, sex, chronic/acute comorbidities, and co-medications were included in a logistic regression model to assess predictors of carvedilol choice. Chronic comorbidities include those defined in the Elixhauser comorbidity index and all hospitalizations within two years prior to the first beta-blocker prescription. Comedications include all redeemed prescriptions within one year prior to the beta-blocker prescription. Kernel density estimations were used to assess the overlap in propensity and preference scores distributions for receiving carvedilol and thereby potential beta-blocker exchangeability. Totally, 10091 patients composed the study population; 2011 were exposed to carvedilol. The overlapping of propensity scores distributions was 57%. Accordingly, the exchangeability was not reached. Atrioventricular block (Odds Ratio, OR 8.20; 95% Confidence Interval, 95% CI 1.30-51.80), cerebrovascular thrombosis (OR 7.06; 95% CI 1.14-43.68), chronic kidney disease (OR 4.32; 95% CI 1.16-16.02), and acute heart failure (OR 1.97; 95% CI 1.28-3.03) hospitalizations were statistically significantly associated with carvedilol choice. Analogously, human insulin (OR 3.00; 95% CI 1.24-7.24), fondaparinux (OR 2.47; 95% CI 1.17-5.21) or strontium ranelate (OR 2.03; 95% CI 1.06-3.90) redeemed prescriptions. In conclusion, this study suggests the absence of beta-blockers exchangeability and a preferential choice of carvedilol in patients with heart failure, COPD and concurrent chronic kidney disease, atrioventricular block, cerebrovascular thrombosis, acute heart failure or redeeming human insulin, fondaparinux or strontium ranelate prescriptions. Therefore, it suggests that choice of prescribing carvedilol over metoprolol/bisoprolol/nebivolol is driven by differences in comorbidities and co-treatments.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685956/pdf/41598_2019_Article_47967.pdf

Shah, N., A. Shafi, et al. (2019). **"Extensive Post-traumatic Surgical Emphysema Exacerbated by Cocaine Insufflation."** J Craniofac SurgSurgical emphysema (SE) is characterized by air in the soft tissues causing a crackling sensation on palpation. In oral and maxillofacial surgery, it might occur using conventional air-driven dental hand pieces, as a complication of trauma and with cocaine insufflation.The subcutaneous air may travel through tissue planes causing cervicofacial emphysema, pneumothorax, and pneumomediastinum. It may carry bacteria and potentially lead to cellulitis or necrotizing fasciitis.The SE is usually a self-limiting entity requiring analgesia, close observation of the airway, occasionally prophylactic antibiotics, and rarely steroids. Although, the consensus on antibiotic and corticosteroid therapy is unclear.Here presented an unusual and extensive presentation of surgical emphysema. A 29 years old male presented with emphysema following a left orbital-zygomatic complex fracture and following intranasal cocaine insufflation. It extended from the temple to the parotid region, down into the neck and into the mediastinum. No surgical intervention was required. The patient was discharged after 24 hours of observation with a week-long course of co-amoxiclav antibiotics and no corticosteroids administration.Typical instructions following facial bone fractures are to avoid nose blowing because of the risk of SE, however, avoidance of drug habits is rarely considered. This case report highlights the importance of tailored advice to this particular patient cohort.

Sicras Mainar, A., A. Huerta, et al. (2019). **"Economic impact of delaying initiation with multiple-inhaler maintenance triple therapy in Spanish patients with chronic obstructive pulmonary disease."** Int J Chron Obstruct Pulmon Dis **14**: 2121-2129.

Purpose: Guidelines recommend the use of triple therapy with an inhaled corticosteroid (ICS), a long-acting beta2 agonist (LABA) and a long-acting muscarinic antagonist (LAMA) to reduce the risk of future exacerbations in symptomatic COPD patients with a history of exacerbations. This study aimed to estimate COPD-related healthcare resource use and costs, and subsequent exacerbation rates, for patients initiating multiple-inhaler triple therapy (MITT) early (</=30 days) versus late (31-180 days) following an exacerbation, in a real-world clinical setting. Patients and methods: This was an observational, longitudinal, retrospective study using electronic medical records from the Spanish database of the Red de Investigacion en Servicios Sanitarios Foundation. Patients >/=40 years old with a confirmed COPD diagnosis who were newly prescribed MITT up to 180 days after an exacerbation between January 2013 and December 2015 were included. Patients were followed from the date of MITT initiation for up to 12 months to assess COPD-related health care resource use (routine and emergency visits, hospitalizations, pharmacologic treatment), exacerbation rate, and costs (euro2017); these endpoints were compared between early versus late groups. Results: The study included 1280 patients who met selection criteria: mean age 73 years, 78% male, and 41% had severe/very severe lung function impairment. The proportion of patients initiating MITT early versus late was 61.6% versus 38.4%, respectively. There were no statistically significant differences in baseline characteristics between groups. During follow-up, health care resource consumption was lower in the early versus late group, especially primary care and ED visits, leading to lower total costs (euro1861 versus euro1935; P<0.05). In the follow-up period, 28.0% of the patients in the early group experienced >/=1 exacerbation versus 36.4% in the late group (P=0.002), with an exacerbation rate of 0.5 versus 0.6 per person per year (P=0.022), respectively. Conclusion: Initiating MITT early (</=30 days after an exacerbation) may reduce health care costs and exacerbation rate compared with late MITT initiation.

https://www.dovepress.com/getfile.php?fileID=52716

Singh, B., N. Ghosh, et al. (2019). **"Effect of doxycyline in chronic obstructive pulmonary disease - An exploratory study."** Pulm Pharmacol Ther **58**: 101831.

PURPOSE: Various mechanisms, including oxidative stress, inflammation, and protease-antiprotease imbalance are proposed for the progressive decline in lung function in chronic obstructive pulmonary disease (COPD). Doxycycline, a broad spectrum tetracycline antibiotic, is reported to have non-antimicrobial matrix metalloproteinases (MMP) inhibitory action in various inflammatory conditions. The effect of doxycycline in COPD is hereby assessed in the present randomized prospective study. PATIENTS AND METHODS: The first group of COPD patients (n = 30; mild (n = 3), moderate (n = 6), severe (n = 7), very severe (n = 14) as per GOLD II & III criteria was prescribed the standard therapy, a combination of (i) short acting anti-muscarinic agent (SAMA) + short acting beta2 agonist (SABA) inhaled and (ii) corticosteroid inhaled (ICS) + long acting beta2 agonist (LABA) (iii) ICS + LABA + LAMA. Whereas doxycycline (100 mg), was used daily once or twice as per Body Mass Index (BMI), as an add-on to existing standard therapy for the second group of patients (n = 30; mild (n = 2), moderate (n = 7), severe (n = 8), very severe (n = 13). All recruited patients were followed-up after 3 months of treatment. Lung function index FEV1(%) predicted, FEV1/FVC (%), quality of life status including COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ) were assessed. Routine blood cell count also was performed. RESULTS: Biochemical analysis included estimation of oxidative stress markers, inflammatory cytokines and proteases in plasma of both the groups. Reduction in oxidative stress is evidenced by a significant decrease in Lipid hydro peroxides (LPO), total oxidative stress (TOS) and increase in glutathione peroxidase (GSH-PX), reduced glutathione (GSH) and total anti-oxidant capacity (TAO) nitrite and nitrate (NOx) along with peroxynitrate following 3 months of add-on doxycycline treatment. Reduced levels of cytokines such as interleukin IL-6, TNF-alpha, IL-8 were also observed. Multivariate analysis identified TNF-alpha major effective discriminant among pre and post doxycycline treated COPD patients. The expression of TNF-alpha was inversely correlated with FEV1/FVC (%) changes. The levels of MMP-2 and MMP-9/tissue inhibitors of metalloproteinases (TIMP)-1 ratio (MMP-9/ TIMP-1), also decreased significantly and the decline could be associated with TOS. A significant increase in

bilirubin and reduced glutathione (GSH) level was noticed in standard therapy group. CONCLUSION: These data suggest that the improvement in lung function and quality of life in COPD patients may probably be attributed to the antioxidant, anti-inflammatory and anti-MMP activity of doxycycline. The potential therapeutic role of long-term doxycycline, in addition to its traditional antibiotic effect, definitely warrants further attention.

https://www.sciencedirect.com/science/article/pii/S1094553919301191?via%3Dihub

Singh, D., G. Fahim, et al. (2019). **"Effects of Pharmacist-Conducted Medication Reconciliation at Discharge on 30-Day Readmission Rates of Patients With Chronic Obstructive Pulmonary Disease."** J Pharm Pract: 897190019867241.

PURPOSE: To analyze effect of pharmacist-conducted medication reconciliation on 30-day readmission rates in chronic obstructive pulmonary disease (COPD) and identify common medication errors among patient with readmissions. METHODS: Pharmacists were educated on discharge medication reconciliation for patients with COPD. A retrospective chart review was conducted on patients who underwent pharmacist-conducted discharge medication reconciliation to determine 30-day readmissions. Medication errors analyzed included medication omissions and dose or frequency errors. Previously collected internal research without pharmacist-conducted medication reconciliation served as the control. RESULTS: There were 65 patients in the control group and 50 in the intervention group. About 25% of patients in the control group and 26% of patients in the intervention group had any cause readmissions within 30 days of discharge (P = .87). Both the control and the intervention group had similar COPD-related readmissions of 12.3% and 12.6%, respectively. Medication dose or frequency errors consisted of 68.9% and 46.7% of total errors in the control and the intervention groups, respectively. Long-acting muscarinic antagonist (LAMA) or long-acting beta 2-agonist (LABA) were the most common drug classes to be incorrectly dosed or omitted at discharge. In the intervention group, 30 errors were identified. Due to inability to coordinate discharges, pharmacists intervened on 13 errors, 7 of which were accepted by the prescriber. CONCLUSION: Pharmacist-conducted medication reconciliation at discharge did not affect 30-day readmission rates of patients with COPD. Confounding factors included a small sample size, passive pharmacist education, and discharge issues. The most common medication errors at discharge were dosing or frequency errors of LABAs or LAMAs.

https://journals.sagepub.com/doi/10.1177/0897190019867241

Sirois, C., A. Ouali, et al. (2019). **"Polypharmacy among Older Individuals with COPD: Trends between 2000 and 2015 in Quebec, Canada."** Copd **16**(3-4): 234-239.

The treatment of chronic obstructive pulmonary disease (COPD) and concomitant diseases requires several medications. Yet there is little data on how the pharmacological burden progressed over time among older individuals with COPD. We aimed to: 1) describe the proportion of older adults with COPD in Quebec, Canada, that were exposed to polypharmacy (>/=10, >/=15 or >/=20 medications/year) between 2000 and 2015; 2) calculate the proportion of individuals receiving specific prescriptions for COPD during this period. We conducted a population-based cohort study with the Quebec Integrated Chronic Disease Surveillance System. Individuals aged >/=66 years with COPD and covered by the universal public drug plan were included. We calculated the total number of drugs used at least once by each individual during each of the studied years, and used age-standardized proportions to compare proportions of users between the years. The average number of drugs used increased from 12.0 in 2000 to 14.8 in 2015. The proportion of individuals exposed to polypharmacy increased (>/=10 drugs: 62.0% to 74.6%;>/=15 drugs: 31.2% to 45.4%; >/=20 drugs: 12.3% to 22.4%). The proportion of individuals receiving long-acting bronchodilators increased from 18.7% in 2000 to 69.6% in 2015. The use of short-acting bronchodilators decreased from 81.5% to 67.9%, and that of inhaled corticosteroids from 60.6% to 26.0%. The proportion of users of methylxanthines decreased from 15.0% to 1.9%. Older individuals with COPD are increasingly exposed to polypharmacy. Identifying which polypharmacy is beneficial is a priority.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1646716

Slebos, D. J., P. L. Shah, et al. (2019). **"Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe COPD (AIRFLOW): A Multicenter Randomized Controlled Trial."** Am J Respir Crit Care MedRATIONALE: Targeted Lung Denervation (TLD) is a bronchoscopic radiofrequency ablation therapy for COPD, which durably disrupts parasympathetic pulmonary nerves to decrease airway resistance and mucous hyper-secretion. OBJECTIVE: To determine the safety and impact of TLD on respiratory adverse events. METHODS: A multicenter, randomized sham-bronchoscopy controlled, double-blinded trial, with symptomatic (mMRC>/=2 or CAT>/=10) COPD (FEV1 30-60%pred) patients. Primary endpoint was the rate of respiratory adverse events between 3 and 6.5 months post-randomization (defined as COPD exacerbation, tachypnea, wheezing, worsening bronchitis, worsening dyspnea, influenza, pneumonia, other respiratory infections, respiratory failure, or airway effects requiring therapeutic intervention). Blinding was maintained through 12.5 months. RESULTS: Eighty-two patients (50% female, 63.7 years +/-6.8, FEV1 41.6 +/-7.3%pred, mMRC 2.2 +/-0.7, and CAT 18.4 +/-6.1) were 1:1 randomized. During the pre-defined 3-6.5m window, patients in the TLD group experienced a significantly lower number of respiratory adverse events compared to sham (32% vs. 71%, p=0.008; odds ratio 0.19, 95%CI [0.0750, 0.4923], p=0.0006). Between 0-12.5m, these were not different (83% vs. 90%, p=0.52). The time to first COPD exacerbation requiring hospitalization in the 0 to 12.5 month window was significantly lower in the TLD group compared to sham (hazard ratio 0.35; 95%CI [0.13, 0.99] p=0.039). There was no statistical difference in the time to first moderate or severe COPD exacerbation, patient reported symptoms, or other physiologic measures over the 12.5 months of follow up. CONCLUSIONS: Patients with symptomatic COPD treated with TLD combined with optimal pharmacotherapy had fewer study defined respiratory adverse events, including hospitalizations for COPD exacerbation. Clinical trial registration available at clinicaltrials.gov, ID: NCT02058459.

Steriade, A. T., S. Johari, et al. (2019). **"Predictors of outcome of noninvasive ventilation in severe COPD exacerbation."** BMC Pulm Med **19**(1): 131.

BACKGROUND: Noninvasive ventilation (NIV) reduces the rate of endotracheal intubation (ETI) and overall mortality in severe acute exacerbation of COPD (AECOPD) with acute respiratory failure and is increasingly applied in respiratory intermediate care units. However, inadequate patient selection and incorrect management of NIV increase mortality. We aimed to identify factors that predict the outcome of NIV in AECOPD. Also, we looked for factors that influence ventilator settings and duration. METHODS: A prospective cohort study was undertaken in a respiratory intermediate care unit in an academic medical center between 2016 and 2017. Age, BMI, lung function, arterial pH and pCO2 at admission (t0), at 1-2 h (t1) and 4-6 h (t2) after admission, creatinine clearance, echocardiographic data (that defined left heart dysfunction), mean inspiratory pressure during the first 72 h (mIPAP-72 h) and hours of NIV during the first 72 h (dNIV-72 h) were recorded. Main outcome was NIV failure (i.e., ETI or in-hospital death). Secondary outcomes were in-hospital mortality, length of stay (LOS), duration of NIV (days), mIPAP-72 h, and dNIV-72 h. RESULTS: We included 89 patients (45 male, mean age 67.6 years) with AECOPD that required NIV. NIV failure was 12.4%, and in-hospital mortality was 11.2%. NIV failure was correlated with days of NIV, LOS, in-hospital mortality ($p < 0.01$), and kidney dysfunction ($p < 0.05$). In-hospital mortality was strongly associated with days of NIV (OR 1.27, 95%CI: 1.07-1.5, $p < 0.01$) and with FEV1 ($p < 0.05$). All other investigated parameters (including left heart dysfunction, dNIV-72 h, mIPAP-72 h, pH, etc.) did not influence NIV failure or mortality. dNIV-72 h and days of NIV were independent predictors of LOS ($p < 0.01$). Regarding the secondary outcomes, left heart dysfunction and pH at 1-2 h independently predicted NIV duration (dNIV-72 h, $p < 0.01$), while BMI and baseline pCO2 predicted NIV settings (mIPAP-72 h, $p < 0.01$). CONCLUSION: In-hospital mortality and NIV failure were not influenced by BMI, left heart dysfunction, age, nor by arterial blood gas values in the first 6 h of NIV. Patients with

severe acidosis and left heart dysfunction required prolonged use of NIV. BMI and pCO2 levels influence the NIV settings in AECOPD regardless of lung function.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6639947/pdf/12890_2019_Article_892.pdf

Sun, H. B., X. S. Jing, et al. (2019). **"Preliminary Study of Obese Patients with Chronic Obstructive Pulmonary Disease Suffering from Painful Osteoporotic Vertebral Compression Fracture Treated by Percutaneous Vertebroplasty in Improved Prone Position and Right Lateral Position."** World Neurosurg **130**: e933-e940.

OBJECTIVE: To assess outcomes in obese patients with chronic obstructive pulmonary disease (COPD) who sustained an osteoporotic vertebral compression fracture (OVCF) treated by percutaneous vertebroplasty (PVP) in the improved prone position and right lateral position. METHODS: Between January 2015 and May 2016, a total of 60 patients were enrolled in this randomized controlled study. Patients in group A were placed in the improved prone position for a bilateral transpedicular technique, and those in group B were placed in the right lateral position for a left transverse process-pedicle approach. Clinical and radiologic outcomes were assessed and compared between the 2 groups during the 12-month follow-up period. RESULTS: All operations were successfully completed without any serious sequelae. The operation time, fluoroscopic time, scores for respiratory condition during the operation, intravertebral cement volume, and incidence of cement leakage were significantly greater in group A compared with group B ($P < 0.01$). During the follow-up period, all patients in both groups experienced significant improvement in pain relief. Satisfactory functional improvement was obtained at 3 months postoperatively. CONCLUSIONS: Treatment of obese patients with COPD suffering from painful OVCF by PVP in both the improved prone position with a bilateral technique and the right lateral position with a unilateral technique was relatively safe and effective. However, unilateral PVP in the right lateral position was associated with a shorter operation time, limited fluoroscopic time, and minimal cement leakage.

https://www.sciencedirect.com/science/article/abs/pii/S1878875019319461?via%3Dihub

Tangedal, S., R. Nielsen, et al. (2019). **"Sputum microbiota and inflammation at stable state and during exacerbations in a cohort of chronic obstructive pulmonary disease (COPD) patients."** PLoS One **14**(9): e0222449.

BACKGROUND: Exacerbations of chronic obstructive pulmonary disease (COPD) are debilitating events and spur disease progression. Infectious causes are frequent; however, it is unknown to what extent exacerbations are caused by larger shifts in the airways' microbiota. The aim of the current study was to analyse the changes in microbial composition between stable state and during exacerbations, and the corresponding immune response. METHODS: The study sample included 36 COPD patients examined at stable state and exacerbation from the Bergen COPD Cohort and Exacerbations studies, and one patient who delivered sputum on 13 different occasions during the three-year study period. A physician examined the patients at all time points, and sputum induction was performed by stringent protocol. Only induced sputum samples were used in the current study, not spontaneously expectorated sputum. Sputum inflammatory markers (IL-6, IL-8, IL-18, IP-10, MIG, TNF-alpha) and antimicrobial peptides (AMPs, i.e. LL-37/hCAP-18, SLPI) were measured in supernatants, whereas target gene sequencing (16S rRNA) was performed on corresponding cell pellets. The microbiome bioinformatics platform QIIME2TM and the statistics environment R were applied for bioinformatics analyses. RESULTS: Levels of IP-10, MIG, TNF-alpha and AMPs were significantly different between the two disease states. Of 36 sample pairs, 24 had significant differences in the 12 most abundant genera between disease states. The diversity was significantly different in several individuals, but not when data was analysed on a group level. The one patient case study showed longitudinal dynamics in microbiota unrelated to disease state. CONCLUSION: Changes in the sputum microbiota with changing COPD disease states are common, and are accompanied by changes in inflammatory markers. However, the changes are highly individual and heterogeneous events.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6748569/pdf/pone.0222449.pdf

Tavakoli, H., K. M. Johnson, et al. (2019). **"Trends in prescriptions and costs of inhaled medications in chronic obstructive pulmonary disease: a 19-year population-based study from Canada."** Int J Chron Obstruct Pulmon Dis **14**: 2003-2013.

Background: The patterns of medication use in chronic obstructive pulmonary disease (COPD) may change over time due to the availability of new medications, updates in guideline-based recommendations, and changes in patient and care provider preferences. Objectives: To document population-level trends of filled prescriptions and costs for major classes of inhaled COPD therapies. Method: We used administrative health databases of the province of British Columbia, Canada, from 1997 to 2015, to create a retrospective cohort of COPD patients. We documented the percentage of patients receiving major inhaled COPD-related medications, including short-acting beta-2 adrenoreceptor agonists (SABA), long-acting beta-2 adrenoreceptor agonists (LABA), inhaled corticosteroids (ICS), short-acting muscarinic receptor antagonists (SAMA), and long-acting muscarinic receptor antagonists (LAMA). We quantified the average, and relative annual change in, dispensed quantities and costs (in 2015 Canadian dollars [$]) of medications. Combination therapy was assessed as the proportion of time covered by two or more long-acting medications of different classes. Results: A total of 176,338 patients were included in the final cohort (mean age at entry 68.7, 48.5% female). In 2015, the most common medication was ICS (45.7% of the patients), followed by LABA (36.5%). LAMA was the least used medication (18.9%). The number of filled prescriptions per patient per year for LAMA (+7.8% per year) and LABA (+4.9%) increased, while they decreased for SAMA (-6.3%) and SABA (-3.8%), and remained relatively constant for ICS. The average annual per-patient costs of inhaled medications were $570.8 in 2015, which was double the costs from 1997. Single-inhaler ICS/LABA had the highest rate of increase (11.6% per year), and comprised 53.7% of the total costs of inhalers in 2015. In 2015, 28.5% of the patient time was on combination therapies, with 7.1% on triple ICS/LABA/LAMA therapy. Conclusion: Utilization of inhaled therapies for COPD has changed significantly over time. The low utilization of LAMA and high utilization of combination therapies (particularly those containing ICS) do not seem to be aligned with COPD treatment guidelines.

https://www.dovepress.com/getfile.php?fileID=52490

van Velzen, P., P. Brinkman, et al. (2019). **"Exhaled Breath Profiles Before, During and After Exacerbation of COPD: A Prospective Follow-Up Study."** Copd: 1-8.

Many patients with chronic obstructive lung disease (COPD) experience exacerbations. The diagnosis of an exacerbation is solely based on symptoms. We hypothesized that exhaled breath profiles, measured by Gas Chromatography-Mass Spectrometry (GC-MS) or electronic nose (eNose), are different between stable disease and exacerbations and may have the potential to serve as biomarkers for COPD exacerbations. In this prospective follow-up study, breath samples were taken during stable COPD, during a subsequent exacerbation and after recovery. Samples were analyzed by GC-MS and eNose. CCQ symptom scores were associated with univariate outcomes of GC-MS and eNose using analysis of covariance (ANCOVA). After multivariate modeling by Principal Component Analysis (PCA), paired student t-tests were performed. Sixty-eight patients were included, 31 had an exacerbation and 16 patients had breath sampled at all three time points. Significant differences were found in breathprints taken during exacerbation as compared to baseline and recovery for both GC-MS and eNose. Breath profiles obtained by GC-MS as well as by eNose showed a correct classification of 71% (10/14) for baseline vs exacerbation and of 78% (11/14) for exacerbation vs recovery. These results provide proof of principle that exhaled breath can serve as a noninvasive biomarker for the diagnosis of COPD exacerbations.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2019.1669550?needAccess=true

Vasiljevic, S., M. Petrovic, et al. (2019). **"Relationship between incidence of chronic obstructive pulmonary disease and lung cancer as comorbidity in primary health care in two Belgrade communities."** J buon **24**(3): 963-966.

PURPOSE: To investigate the recent trends in the incidence of chronic obstructive pulmonary disease (COPD) and lung cancer as comorbidity in primary health care (Community Health Center, Zemun, Belgrade, which covers two municipalities - Surchin and Zemun), during the period 2014-2017. METHODS: This retrospective study analyzed the incidence of COPD and lung cancer as comorbidity in a 4-year period. Data were derived from the Heliant information system. Descriptive statistics -frequencies and percentages - were used, and differences between groups were tested by x2 test. RESULTS: The number of patients with COPD was slightly, but insignificantly, higher each consecutive year. Lung cancer as comorbidity appeared in about 11% of these patients. As for gender, male and female patients contributed equally to the number of patients with CORD. CONCLUSION: The number of patients with COPD registered in primary health care was similar in all investigated years. Lung cancer as comorbidity was found in a significantly smaller number of these patients.

Vikgren, J., M. Khalil, et al. (2019). **"Visual and Quantitative Evaluation of Emphysema: A Case-Control Study of 1111 Participants in the Pilot Swedish CArdioPulmonary BioImage Study (SCAPIS)."** Acad RadiolRATIONALE AND OBJECTIVES: Emphysema is a hallmark of chronic obstructive pulmonary disease. The primary aim of this study was to investigate inter- and intraobserver agreement of visual assessment of mild emphysema in low-dose multidetector computed tomography of subjects in the pilot SCAPIS in order to certify consistent detection of mild emphysema. The secondary aim was to investigate the performance of quantitative densitometric measurements in the cohort. MATERIALS AND METHODS: Participants with emphysema (n=100, 56 males and 44 females) reported in the electronic case report form of pilot SCAPIS and 100 matched controls (gender, age, height, and weight) without emphysema were included. To assess interobserver variability the randomized examinations were evaluated by two thoracic radiologists. For intraobserver variability three radiologists re-evaluated randomized examinations which they originally evaluated. The results were evaluated statistically by Krippendorff's alpha. The dataset was also assessed quantitively for % lung attenuation value -950 HU (LAV950), mean lung density and total lung volume by commercially available software. RESULTS: Emphysema was visually scored as mild and Krippendorff's alpha was >/=0.8 for both the inter- and intraobserver agreement regarding presence of emphysema and approaching 0.8 regarding presence and extent of emphysema by location in the upper lobes. Mean LAV950 was not different between the emphysematous and the nonemphysematous participants; 8.3% and 8.4%, respectively. CONCLUSION: The inter- and intraobserver agreement for visual detection of mild emphysema in low-dose multidetector computed tomography was good. Surprisingly, quantitative analysis could not reliably identify participants with mild emphysema, which hampers the use of automatic evaluation.

https://www.academicradiology.org/article/S1076-6332(19)30325-3/pdf

Vogelmeier, C. F., K. Kostikas, et al. (2019). **"Evaluation of exacerbations and blood eosinophils in UK and US COPD populations."** Respir Res **20**(1): 178.

BACKGROUND: Blood eosinophil counts and history of exacerbations have been proposed as predictors of patients with chronic obstructive pulmonary disease (COPD) who may benefit from triple therapy (inhaled corticosteroid, long-acting beta2-agonist and long-acting muscarinic antagonist). METHODS: In a retrospective cohort analysis we examined the profiles of COPD patients from the UK Clinical Practice Research Datalink (CPRD) and US Optum Clinformatics Data Mart (Optum) databases with reference to exacerbation frequency and blood eosinophil distribution. RESULTS: Of the 31,437 (CPRD) and 383,825

(Optum) patients with COPD, 15,364 (CPRD) and 139,465 (Optum) met the eligibility criteria and were included. Among patients with >/=2 exacerbations and available eosinophil counts in the baseline period (CPRD, n = 3089 and Optum, n = 13414), 17.0 and 13.3% respectively had eosinophil counts >/=400 cells/muL. Patients with >/=2 exacerbations or eosinophil count >/=400 cells/muL during first year, exacerbated at least once (CPRD, 82.8% vs Optum, 80.6%) or continued to have eosinophil count >/=300 cells/muL (76.8% vs 76.5%), respectively in the follow-up year. In both years, a higher variability in the number of exacerbations and eosinophil count was observed in patients with one exacerbation and eosinophil counts between 300 and 400 cells/muL; patients with eosinophil count < 150 cells/muL had the lowest variability. Approximately 10% patients had both >/=2 exacerbations and eosinophil count >/=300 cells/muL across the databases. CONCLUSION: A high variability in blood eosinophil counts over two consecutive years was observed in UK and US patients with COPD and should be considered while making treatment decisions. A small proportion of COPD patients had frequent exacerbations and eosinophil count >/=300 cells/muL.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6686508/pdf/12931_2019_Article_1130.pdf

Vozoris, N. T., Z. Yao, et al. (2019). **"Prescription Synthetic Oral Cannabinoid use Among Older Adults with Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study."** Drugs AgingBACKGROUND: Synthetic oral cannabinoids (nabilone and dronabinol) may have adverse respiratory effects. Our purpose was to describe the scope, pattern, and patient characteristics associated with incident off-label synthetic oral cannabinoid use among older adults with chronic obstructive pulmonary disease (COPD) compared to older adults without COPD. METHODS: This was a retrospective, population-based, cohort study using Ontario, Canada, heath administrative data. Individuals aged 66 years or older were included, and physician-diagnosed COPD was identified using a previously validated, highly specific algorithm. Incident off-label oral cannabinoid use was examined between April 1, 2005 and March 31, 2015. Descriptive statistics were used to describe drug use patterns. Multiple logistic regression was used to identify patient characteristics associated with incident drug use. RESULTS: There were 172,282 older adults with COPD and 1,068,256 older adults without COPD identified between April 1, 2005 and March 31, 2015. Incident synthetic oral cannabinoid use during this period occurred with significantly greater ($p < 0.001$) frequency among older adults with COPD (0.6%) versus older adults without COPD (0.3%). Compared to those without COPD, older adults with COPD used synthetic cannabinoids for significantly longer durations and more frequently at higher doses. CONCLUSIONS: Although incident off-label oral cannabinoid use was relatively low among all older Ontarian adults, this drug class was used with greater frequency and more often in potentially concerning ways among older adults with COPD. These findings raise possible safety concerns, but further research on the respiratory safety of oral cannabinoids among individuals with COPD is needed.

https://link.springer.com/article/10.1007%2Fs40266-019-00707-3

Wan, E. S., R. L. Goldstein, et al. (2019). **"Telomere length in COPD: Relationships with physical activity, exercise capacity, and acute exacerbations."** PLoS One **14**(10): e0223891.

RATIONALE: Shorter leukocyte telomere length (LTL) is associated with reduced health-related quality of life and increased risk for acute exacerbations (AEs) and mortality in chronic obstructive pulmonary disease (COPD). Increased physical activity and exercise capacity are associated with reduced risk for AEs and death. However, the relationships between LTL and physical activity, exercise capacity, and AEs in COPD are unknown. METHODS: Data from 3 COPD cohorts were examined: Cohort 1 (n = 112, physical activity intervention trial), Cohorts 2 and 3 (n = 182 and 294, respectively, separate observational studies). Subjects completed a 6-minute walk test (6MWT) and provided blood for LTL assessment using real-time PCR. Physical activity was measured as average daily step count using an accelerometer or pedometer. Number of self-reported AEs was available for 1) the year prior to enrollment (Cohorts 1 and 3) and 2) prospectively after enrollment (all cohorts). Multivariate models examined associations between LTL and average daily step count, 6MWT distance, and AEs. RESULTS: A significant association

between longer LTL and increased 6MWT distance was observed in the three combined cohorts (beta = 3x10-5, p = 0.045). No association between LTL and average daily step count was observed. Shorter LTL was associated with an increased number of AEs in the year prior to enrollment (Cohorts 1 and 3 combined, beta = -1.93, p = 0.04) and with prospective AEs (Cohort 3, beta = -1.3388, p = 0.0003). CONCLUSIONS: Among COPD patients, increased LTL is associated with higher exercise capacity, but not physical activity. Shorter LTL was associated with AEs in a subgroup of cohorts.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6797105/pdf/pone.0223891.pdf

Wang, H. and J. An (2019). **"Orbital Emphysema After Repair of Orbital Fracture."** J Craniofac Surg **30**(7): e687-e688.

Orbital emphysema is a rare postoperative complication that can cause diplopia and even visual loss. Therefore, immediate diagnosis and treatment are crucial. In this study, a healthy male patient sustained left facial trauma caused by a fall 2 months ago; orbit emphysema occurred when the patient sneezed on the 5th day after surgery. The patient was treated conservatively with oral antibiotics and oral dexamethasone. Sixth-month follow-up showed no residual lesion.

Washko, G. R., P. Nardelli, et al. (2019). **"Arterial Vascular Pruning, Right Ventricular Size, and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. A Longitudinal Observational Study."** Am J Respir Crit Care Med **200**(4): 454-461.

Rationale: Cor pulmonale (right ventricular [RV] dilation) and cor pulmonale parvus (RV shrinkage) are both described in chronic obstructive pulmonary disease (COPD). The identification of emphysema as a shared risk factor suggests that additional disease characterization is needed to understand these widely divergent cardiac processes.Objectives: To explore the relationship between computed tomography measures of emphysema and distal pulmonary arterial morphology with RV volume, and their association with exercise capacity and mortality in ever-smokers with COPD enrolled in the COPDGene Study.Methods: Epicardial (myocardium and chamber) RV volume (RVEV), distal pulmonary arterial blood vessel volume (arterial BV5: vessels <5 mm(2) in cross-section), and objective measures of emphysema were extracted from 3,506 COPDGene computed tomography scans. Multivariable linear and Cox regression models and the log-rank test were used to explore the association between emphysema, arterial BV5, and RVEV with exercise capacity (6-min-walk distance) and all-cause mortality.Measurements and Main Results: The RVEV was approximately 10% smaller in Global Initiative for Chronic Obstructive Lung Disease stage 4 versus stage 1 COPD (P < 0.0001). In multivariable modeling, a 10-ml decrease in arterial BV5 (pruning) was associated with a 1-ml increase in RVEV. For a given amount of emphysema, relative preservation of the arterial BV5 was associated with a smaller RVEV. An increased RVEV was associated with reduced 6-minute-walk distance and in those with arterial pruning an increased mortality.Conclusions: Pulmonary arterial pruning is associated with clinically significant increases in RV volume in smokers with COPD and is related to exercise capacity and mortality in COPD.Clinical trial registered with www.clinicaltrials.gov (NCT00608764).

Westcott, A., D. P. I. Capaldi, et al. (2019). **"Chronic Obstructive Pulmonary Disease: Thoracic CT Texture Analysis and Machine Learning to Predict Pulmonary Ventilation."** Radiology: 190450.

Background Fixed airflow limitation and ventilation heterogeneity are common in chronic obstructive pulmonary disease (COPD). Conventional noncontrast CT provides airway and parenchymal measurements but cannot be used to directly determine lung function. Purpose To develop, train, and test a CT texture

analysis and machine-learning algorithm to predict lung ventilation heterogeneity in participants with COPD. Materials and Methods In this prospective study (ClinicalTrials.gov: NCT02723474; conducted from January 2010 to February 2017), participants were randomized to optimization (n = 1), training (n = 67), and testing (n = 27) data sets. Hyperpolarized (HP) helium 3 ((3)He) MRI ventilation maps were co-registered with thoracic CT to provide ground truth labels, and 87 quantitative imaging features were extracted and normalized to lung averages to generate 174 features. The volume-of-interest dimension and the training data sampling method were optimized to maximize the area under the receiver operating characteristic curve (AUC). Forward feature selection was performed to reduce the number of features; logistic regression, linear support vector machine, and quadratic support vector machine classifiers were trained through fivefold cross validation. The highest-performing classification model was applied to the test data set. Pearson coefficients were used to determine the relationships between the model, MRI, and pulmonary function measurements. Results The quadratic support vector machine performed best in training and was applied to the test data set. Model-predicted ventilation maps had an accuracy of 88% (95% confidence interval [CI]: 88%, 88%) and an AUC of 0.82 (95% CI: 0.82, 0.83) when the HP (3)He MRI ventilation maps were used as the reference standard. Model-predicted ventilation defect percentage (VDP) was correlated with VDP at HP (3)He MRI (r = 0.90, P < .001). Both model-predicted and HP (3)He MRI VDP were correlated with forced expiratory volume in 1 second (FEV1) (model: r = -0.65, P < .001; MRI: r = -0.70, P < .001), ratio of FEV1 to forced vital capacity (model: r = -0.73, P < .001; MRI: r = -0.75, P < .001), diffusing capacity (model: r = -0.69, P < .001; MRI: r = -0.65, P < .001), and quality-of-life score (model: r = 0.59, P = .001; MRI: r = 0.65, P < .001). Conclusion Model-predicted ventilation maps generated by using CT textures and machine learning were correlated with MRI ventilation maps (r = 0.90, P < .001). (c) RSNA, 2019 Online supplemental material is available for this article. See also the editorial by Fain in this issue.

Wurtz, E. T., C. Brasch-Andersen, et al. (2019). **"Heme oxygenase 1 polymorphism, occupational vapor, gas, dust, and fume exposure and chronic obstructive pulmonary disease in a Danish population-based study."** Scand J Work Environ HealthObjectives The number of dinucleotide repeats (GT) nmodulate expression of heme oxygenase 1 (HMOX1), a stress response gene. Multiple repeats might affect chronic obstructive pulmonary disease (COPD) susceptibility. We aimed to investigate the association of this polymorphism with COPD and its interaction with occupational exposures (vapor, gas, dust, or fumes). Methods This population-based cross-sectional study included 4703 Danes, aged 45-84 years. HMOX1 (GT) nwas genotyped and grouped as short: </=26, medium: 27-32 and long: >/=33 alleles. COPD was defined by the lower limit of normal (2.5 (th)FEV 1/FVC and FEV 1centiles). Occupational exposure was defined as ever exposed to vapor, gas, dust, or fume in expert-selected jobs. Associations were analyzed by adjusted mixed logistic regression. Results The population included 6% with COPD, 48% who had smoked >/=10 pack-years, and 46% with occupational exposure. HMOX1 was genotyped in 4423 participants. The adjusted odds ratio (OR) for the association between HMOX1 long allele and COPD was 1.75 [95% confidence interval (CI) 1.18-2.60]. An interaction was evident between HMOX1 long allele and occupational exposure, OR 2.38 (95% CI 1.04-5.46), versus HMOX1 short/medium without exposure. Analyses were replicated in another cohort, aged 20-44 years, N=1168, including 3% with COPD, 25% who had smoked >/=10 pack-years and 20% with occupational exposure. No associations were seen between COPD and HMOX1 long allele here. Conclusions Long alleles in HMOX1 alone and in interaction with occupational exposure seem to be associated with COPD. Failure to replicate data may be due to premature age for COPD development and low occupational exposure prevalence. We propose this long allele may be a genetic contributor to the COPD pathogenesis.

Xu, L., B. Chen, et al. (2019). **"A Higher Rate of Pulmonary Fungal Infection in Chronic Obstructive Pulmonary Disease Patients with Influenza in a Large Tertiary Hospital."** Respiration: 1-10.

BACKGROUND: Influenza is considered a self-limiting disease. However, in patients with chronic obstructive pulmonary disease (COPD), it may result in serious outcomes during the flu season. OBJECTIVES: The aims of this retrospective study were to explore the characteristics of hospitalized patients with COPD complicated by influenza and determine the factors affecting the prognosis of these patients. METHOD: Demographic and clinical data were collected for 278 patients totally from the West China Hospital between January 1, 2016 and February 28, 2018. RESULTS: Among the patients with influenza, the positive fungal culture rate, and the rates of antifungal drug and systemic corticosteroids use were higher for those with COPD than for those without COPD. Respiratory failure was more common in patients with influenza and COPD than in patients with influenza only, while the proportion of severe cases was higher among the former than among the latter. Among the patients with COPD, the positive fungal culture rate, particularly for Aspergillus, and the rate of systemic corticosteroids use were higher for those with influenza than for those without influenza. Multivariate analysis revealed that a COPD history of >20 years and smoking for >20 pack-years were independent factors for susceptibility of COPD patients to influenza. CONCLUSIONS: Aspergillus infection seems to be more common in patients with influenza and COPD. In addition, COPD complicated by influenza during the seasonal outbreak can easily progress to a severe disease state. Heavy smokers and patients with a prolonged COPD history are more likely to be infected by influenza.

https://www.karger.com/Article/Abstract/501410

Xu, L., Y. Chen, et al. (2019). **"High hemoglobin is associated with increased in-hospital death in patients with chronic obstructive pulmonary disease and chronic kidney disease: a retrospective multicenter population-based study."** BMC Pulm Med **19**(1): 174.

BACKGROUND: Chronic kidney disease (CKD) is a common comorbidity of chronic obstructive pulmonary disease (COPD). Although high hemoglobin (Hb) is detrimental to CKD patients, its relationship with poor outcomes in the COPD population has not been reported. This study aimed to investigate the relationship between high Hb and in-hospital mortality and to explore reference Hb intervals in patients with COPD and CKD. METHODS: This retrospective study was multicenter population-based. A total of 47,209 patients who presented with COPD between January 2012 and December 2016 were included. The average Hb level during hospitalization was used as the Hb level. CKD and advanced CKD were defined as estimated glomerular filtration rates < 60 and < 30 ml/min/1.73 m(2), respectively. The association between Hb level (measured in 1 g/dL intervals) and in-hospital mortality was analyzed in different multivariable logistic regression models by CKD stratification. RESULTS: The Hb level was decreased in the CKD subgroup. In the non-CKD group, a higher Hb level was not associated with an increased risk of in-hospital death. However, the Hb level and mortality showed a U-shaped relationship in the CKD group. After adjusting for age and Charlson Comorbidity Index, multivariable regression analysis showed that an Hb level > 17 g/dL was associated with an increased risk of death in the CKD group with an odds ratio (OR) of 2.085 (95% CI, 1.019-4.264). Hb > 14 g/dL was related to an increased risk of death in advanced CKD patients (OR, 4.579 (95% CI, 1.243-16.866)). CONCLUSIONS: High Hb is associated with an increased risk of in-hospital death in COPD patients with CKD, especially among those with advanced CKD. In this group of patients, attention should be paid to those with high Hb levels.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6749661/pdf/12890_2019_Article_933.pdf

Xu, L., T. Ye, et al. (2019). **"Identification of relevant variables and construction of a multidimensional index for predicting mortality in COPD patients."** Int J Chron Obstruct Pulmon Dis **14**: 1703-1711.

Background and objective: The Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index is a well-known metric for chronic obstructive pulmonary disease (COPD), but it is inadequate for predicting mortality. This study proposed a new index that combines inspiratory muscle training with the BODE index and verified its ability to predict mortality in patients with COPD. Methods: Cox regression identified predictors of mortality, which were then included in the new index. The receiver operating

characteristic (ROC) curve verified the ability of the new index to predict mortality. The Kaplan-Meier curves compared the survival rates of patients with different scores on the new index. Results: Among the 326 patients, 48 died during follow-up (1-59 months). Cox regression showed that the fat-free mass index (FFMI), forced expiratory volume in one second/the predicted value (FEV1%), modi fi ed Medical Research Council (mMRC) score, six-minute-walk test (6MWT) distance, and maximal inspiratory pressure were predictors of mortality (P<0.05); these variables were included in the FODEP index. The AUC of the FODEP index (0.860, 95% CI: 95% CI: 0.817-0.896) was greater than that of the BODE index (0.778, 95% CI: 0.729-0.822). The Kaplan-Meier curves suggested that as the FODEP score increased, so did the risk of morality in patients with COPD. The cumulative survival in the group with the highest FODEP-value was significantly lower than that in the other groups (P<0.01). Conclusion: The FODEP index was more effective than the BODE index at predicting the risk of mortality in patients with COPD.

https://www.dovepress.com/getfile.php?fileID=51696

Yoon, H. Y., S. Y. Park, et al. (2019). **"Prediction of first acute exacerbation using COPD subtypes identified by cluster analysis."** Int J Chron Obstruct Pulmon Dis **14**: 1389-1397.

Purpose: In patients with COPD, acute exacerbation (AE) is not only an important determinant of prognosis, but also an important factor in choosing therapeutic agents. In this study, we evaluated the usefulness of COPD subtypes identified through cluster analysis to predict the first AE. Patients and methods: Among COPD patients in the Korea COPD Subgroup Study (KOCOSS) cohort, 1,195 who had follow-up data for AE were included in our study. We selected seven variables for cluster analysis - age, body mass index, smoking status, history of asthma, COPD assessment test (CAT) score, post-bronchodilator (BD) FEV1 % predicted, and diffusing capacity of carbon monoxide % predicted. Results: K-means clustering identified four clusters for COPD that we named putative asthma-COPD overlap (ACO), mild COPD, moderate COPD, and severe COPD subtypes. The ACO group (n=196) showed the second-best post-BD FEV1 (75.5% vs 80.9% [mild COPD, n=313] vs 52.4% [moderate COPD, n=345] vs 46.7% [severe COPD, n=341] predicted), the longest 6-min walking distance (424 m vs 405 m vs 389 m vs 365 m), and the lowest CAT score (12.2 vs 13.7 vs 15.6 vs 17.5) among the four groups. ACO group had greater risk for first AE compared to the mild COPD group (HR, 1.683; 95% CI, 1.175-2.410). The moderate COPD and severe COPD group HR values were 1.587 (95% CI, 1.145-2.200) and 1.664 (95% CI, 1.203-2.302), respectively. In addition, St. George's Respiratory Questionnaire score (HR: 1.019; 95% CI, 1.014-1.024) and gastroesophageal reflux disease were independent factors associated with the first AE (HR: 1.535; 95% CI, 1.116-2.112). Conclusion: Our cluster analysis revealed an exacerbator subtype of COPD independent of FEV1. Since these patients are susceptible to AE, a more aggressive treatment strategy is needed in these patients.

https://www.dovepress.com/getfile.php?fileID=50752

Yormaz, B., H. Cebeci, et al. (2019). **"Bone mineral density in emphysema and chronic bronchitis phenotypes in hospitalized male COPD patients."** Clin Respir JINTRODUCTION: Risk of osteoporosis known to increase in COPD, but is usually overlooked, especially in male patients. OBJECTIVES: The present study compares the bone mineral density (BMD) measurements of male COPD patients with emphysema and the chronic bronchitis phenotype, and evaluates the association between density of emphysema and osteoporosis. METHODS: 94 patients with COPD, and with emphysema and the chronic bronchitis phenotype were included in the prospective study. A high resolution computed tomography (HRCT) was used for the diagnosis of emphysema, dual X-ray absorptiometry was used to measure the BMD of the lumbar vertebrae and neck of the femur. RESULTS: Emphysema phenotype 45.75% and chronic bronchitis phenotype 54.25%, based on their clinical findings and a quantitative volumetric analysis by HRCT. Osteoporosis was found 60.47% and 17.65% of patients with emphysema and bronchitis, while osteopenia was detected 27.91% and 41.18% of patients with emphysema and bronchitis. A negative correlation was found between HRCT emphysema density and the bone densitometer t-score in patients with osteoporosis. Among the patients with osteoporosis, a positive correlation was found between BMI

and the bone densitometer t-score. Only BMI and emphysema score were found to be independent risk factors for a low BMD. One unit drop in BMI increased the risk of osteoporosis by 28% (OR=1.28, 95% CI 1.14-1.45) (p<0.001). One unit increase in emphysema score increased the risk of osteoporosis by 6% (OR=1.06, 95% CI 1.03-1.09) (p<0.001). CONCLUSION: Especially male patients with emphysema, high dyspnea score, low BMI and frequent exacerbations should be evaluated for osteoporosis.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13099

Zhong, S., C. Chen, et al. (2019). **"Overexpression Of hsa-miR-664a-3p Is Associated With Cigarette Smoke-Induced Chronic Obstructive Pulmonary Disease Via Targeting FHL1."** Int J Chron Obstruct Pulmon Dis **14**: 2319-2329.

Background: Chronic obstructive pulmonary disease (COPD) is recognized as a chronic lung disease with incomplete reversible airflow limitation, but its pathophysiology was still not clear. This study aimed at investigating regulatory roles of special miRNA-mRNA axis in COPD development. Methods: Differentially expressed miRNAs and downstream mRNAs were screened from the Gene Expression Omnibus (GEO) dataset by using the LIMMA package in R software. Weighted Gene Co-expression Network Analysis (WGCNA) was used to construct a co-expression network for COPD. The correlation of dysregulated miRNA(s) and COPD was analyzed, and miRNAs with significant differences were validated in peripheral blood mononuclear cells (PBMCs) from COPD patients by real-time PCR. Regulatory roles of candidate miRNAs and targeted mRNAs were investigated in vitro study. Results: Thirteen modules of co-expressed miRNAs and mRNAs were constructed from a selected cohort with WGCNA. Turquoise module with 12 differentially expressed miRNAs and 120 mRNAs was significantly correlated with COPD. The expression of hsa-miR-664a-3p, an upregulated miRNA in the module, was increased both in lung tissue and PBMCs from COPD patients, whereas that targeted four and a half LIM domains 1 (FHL1) gene was decreased and positively correlated with forced expiratory volume in 1 sec (FEV1)/forced vital capacity (FVC%) ($r = 0.59$, $p < 0.01$). In vitro, luciferase activity assay revealed FHL1 as a target of hsa-miR-664a-3p and it could be directly downregulated by overexpression of hsa-miR-664a-3p. Furthermore, cigarette smoke extract could increase hsa-miR-664a-3p level and decrease FHL1 level in Beas-2B cells. Conclusion: The present study validated significant upregulation of hsa-miR-664a-3p in COPD patients, and its target gene FHL1 was downregulated and positively correlated with FEV1/FVC%; both hsa-miR-664a-3p and FHL1 could be regulated by cigarette smoke extract. Results of bioinformatic analyses and expanded validation suggest that the axis from hsa-miR-664a-3p to FHL1 might play a key role in cigarette smoke-induced COPD, and the exact mechanism should be confirmed in further studies.

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Zvizdic, F., E. Begic, et al. (2019). **"Beta-blocker Use in Moderate and Severe Chronic Obstructive Pulmonary Disease."** Med Arch **73**(2): 72-75.

Introduction: The most appropriate choice of pharmacological treatment of heart rhythm disorders occurring in patients with chronic obstructive pulmonary disease (COPD) and cardiovascular comorbidity is often a topic of debate between pulmonologists and cardiologists in clinical practice, although numerous studies and clinical trials have demonstrated evidence to support the use of selective beta-blockers (BBs) in these patients. Aim: To examine the difference in the number of exacerbations in patients treated with a combination of verapamil and digoxin or BB alone in patients with different COPD stages. Patients and methods: The study included 68 patients (n = 68) diagnosed with COPD who were followed-up during a 12-month period, and the number of exacerbations were analyzed. The patients were divided into two groups according to the stage of COPD: GOLD II (moderate), and GOLD III (severe), and in each group a subdivision was established in relation to the use of either a combination of verapamil and digoxin or the use of BBs alone in pharmacological treatment. The inclusion criteria for patients were defined as following: a) established diagnosis of COPD according to present or deteriorated relevant clinical symptoms and signs, b) the ejection fraction (EF) of a left ventricle (LV) >35%, and c) spirometric cut-points classified as GOLD II (FEV1 / FVC <0.7, FEV1 predicted 50-80%), or GOLD III (FEV1/FVC <0.7, FEV1

predicted 30-50%) stage of the COPD. The exclusion criteria were EF of LV <35% and a lethal outcome during a follow-up period (2 patients were encountered). Exacerbation was defined as functional deterioration of the COPD symptoms verified by spirometric functional testing, frequency of hospitalizations according to GOLD stage assignment or verified clinical symptoms deterioration. Results: Regardless the pharmacological treatment, there is a statistically significant increase in the number of COPD exacerbations, in a 12-month period follow-up, in the GOLD III group (severe) compared to the GOLD II group (moderate). In the group of patients taking verapamil and digoxin, a two-tailed t-test was used to analyze the results between the GOLD II and GOLD III stage groups, p = 0.01, and 2. In the group of patients taking BBs, a two-tailed t-test was also used to analyze the results between the GOLD II and GOLD III stage groups, p = 0.003). Within the COPD GOLD II stage group, there appears to be no statistically significant difference in the number of exacerbations between the patients taking verapamil and digoxin (n = 24) and the patients taking BBs alone (n = 15), although, in patients taking BBs alone, there appears to be a trend towards a decrease in the exacerbations compared to the number of exacerbations in patients taking verapamil and digoxin (p = 0.007). Within the COPD GOLD III stage group, there is no difference in the number of exacerbations between the patients taking verapamil and digoxin (n = 20), and the patients taking BBs alone (n = 9), as analyzed by a two-tailed t-test, p = 0.577. Conclusion: Use of selective BBs in the treatment of cardiovascular comorbidity in patients with COPD represents a far better choice of pharmacological approach in the treatment of patients diagnosed with COPD GOLD II (moderate) stage.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6643359/pdf/medarch-73-72.pdf

Zysman, M., P. R. Burgel, et al. (2019). **"Relationship between gender and survival in a real-life cohort of patients with COPD."** Respir Res **20**(1): 191.

BACKGROUND: Although COPD affects both men and women, its prevalence is increasing more rapidly in women. Disease outcomes appear different among women with more frequent dyspnea and anxiety or depression but whether this translates into a different prognosis remains to be determined. Our aim was to assess whether the greater clinical impact of COPD in women was associated with differences in 3-year mortality rates. METHODS: In the French Initiatives BPCO real-world cohort, 177 women were matched up to 458 menon age (within 5-year intervals) and FEV1 (within 5% predicted intervals). 3-year mortality rate and survival were analyzed. Univariate and multivariate logistic regression analyses were performed. RESULTS: For a given age and level of airflow obstruction, women with COPD had more severe dyspnea, lower BMI, and were more likely to exhibit anxiety. Nevertheless, three-year mortality rate was comparable among men and women, respectively 11.2 and 10.8%. In a multivariate model, the only factors significantly associated with mortality were dyspnea and malnutrition but not gender. CONCLUSION: Although women with COPD experience higher levels of dyspnea and anxiety than men at comparable levels of age and FEV1, these differences do not translate into variations in 3-year mortality rates. TRIAL REGISTRATION: 04-479.

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