COPD/Emphysema PubMed search results covering the period 26/04/2019-19/07/2019

Cohort and case-control studies

Search strategy: ("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR "emphysema"[MeSH Major Topic]) AND ("Cohort Studies"[MeSH Terms] OR "Case-Control Studies"[MeSH Terms]) AND English[lang] AND ("2019/04/26"[CDAT] : "3000"[CDAT])

Aggarwal, T., R. Wadhwa, et al. (2018). **"Biomarkers of oxidative stress and protein-protein interaction in chronic obstructive pulmonary disease."** Arch Physiol Biochem **124**(3): 226-231.

CONTENT: The increased oxidative stress in chronic obstructive pulmonary disease (COPD) patients is the result of increased inhaled oxidants, generated by various cells of the airways. OBJECTIVE: The investigation included measurements of malondiadehyde (MDA), uric acid, ascorbic acid, and matrix metalloproteinase-12 (MMP-12) in COPD patient. We also performed genetic analysis for protein-protein interaction (PPI) network. MATERIALS AND METHODS: The study was conducted on healthy subjects with normal lung function (NS, 14 subjects) and 28 patients (Global Initiative for Chronic Obstructive Lung Disease (Gold) 1 and Gold 2) with COPD. RESULTS: There was significant ($p < .001$) increase in MMP-12, MDA and uric acid levels as compared to healthy controls. A significant ($p < .001$) decline in ascorbic acid level was observed in COPD patients. The PPI was found to be 0.833 which indicated that proteins present in COPD are linked. DISCUSSION AND CONCLUSION: This study suggests oxidative stress plays an important role in COPD and the PPI provide indication that proteins present in COPD are linked.

https://www.tandfonline.com/doi/full/10.1080/13813455.2017.1387796

Andrijevic, I., S. Milutinov, et al. (2018). **"N-Terminal Prohormone of Brain Natriuretic Peptide (NT-proBNP) as a Diagnostic Biomarker of Left Ventricular Systolic Dysfunction in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)."** Lung **196**(5): 583-590.

INTRODUCTION: Left ventricular systolic dysfunction (LVSD) and cardiac decompensation often accompany AECOPD. Differentiation between the two is difficult and mainly relies on clinical and echocardiographic diagnostic procedures. The value of biomarkers, such as NT-proBNP, as diagnostic tools is still insufficiently investigated. The main goals of this trial were to investigate the value of NT-proBNP as a diagnostic tool for LVSD in AECOPD patients and determine its cut-off value which could reliably diagnose LVSD during AECOPD. PATIENTS AND METHODS: This trial prospectively enrolled 209 patients with AECOPD. The patients were divided into four groups-AECOPD plus chronic pulmonary heart disease (CPHD) with or without left ventricular compromise (LVSD), and AECOPD patients without CPHD with or without LVSD. NT-proBNP was measured within first 48 h of hospitalization. RESULTS: Majority of patients were male (61%) active smokers (41.6%), average age of 68 years. High quality of echocardiography was obtained in 63.3 and 22.5% of the patients had LVSD. Average value of NT-proBNP in patients with LVSD was 3303.2 vs. 1092.5 pg/mL in patients without LVSD. Significant differences in NT-proBNP value ($p = 0.0001$) were determined between observed patient groups. At the cut-off value of 1505 pg/mL, sensitivity, specificity, and positive and negative predictive values are 76.6, 83.3, 57.1, and 92.47%, respectively. CONCLUSION: At the cut-off value of 1505 pg/mL NT-proBNP could be used as a diagnostic marker for LVSD in acute exacerbation of COPD.

https://link.springer.com/article/10.1007%2Fs00408-018-0137-3

Bahtouee, M., N. Maleki, et al. (2018). **"The prevalence of chronic obstructive pulmonary disease in hookah smokers."** Chron Respir Dis **15**(2): 165-172.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Hookah smoking is growing worldwide and particularly in Iran. The aim of this study was to determine the prevalence of obstructive pulmonary dysfunction in hookah smokers. We conducted a population-based study in Bushehr Province, Iran. A total of 245 subjects aged 35 years or older who were taking hookah for at least 15 years and 245 healthy controls were enrolled in the study and spirometry was done. Statistical analyses were performed using SPSS for windows software version 19. The prevalence of COPD among the exposed group of hookah smoke was 10.2%, with the rate being significantly higher in the patients with older age (p < 0.001), duration of hookah smoking (p < 0.001), men (p = 0.026), >/=3 hookahs/day (p = 0.006), history of cough for >/=2 years (p = 0.002), in patients with a history of sputum for >/=2 years (p = 0.031), and in patients with a history of dyspnea for >/=2 years (p = 0.001). The results of the logistic regression analysis demonstrated that older age, male gender, smoking, and occupational exposure were independent predictive factors for COPD. The results of our study suggest that hookah smoking significantly increases the risk of COPD. Given the importance of COPD in the global burden of diseases, it is necessary to carry out further studies on the relationship between hookah use and COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5958464/pdf/10.1177_1479972317709652.pdf

Bashir, A., Y. M. Hazari, et al. (2018). **"SERPINA1 Hepatocyte-Specific Promoter Polymorphism Associate with Chronic Obstructive Pulmonary Disease in a Study of Kashmiri Ancestry Individuals."** Lung **196**(4): 447-454.

PURPOSE: Different mutations in coding and non-coding sequences of the SERPINA1 gene have been implicated in the pathogenesis of COPD. However, - 10T/C mutation in the hepatocyte-directed promoter region has not been associated with COPD pathogenesis so far. Here, we report an increased frequency of - 10C genotype that is associated with decreased levels of serum alpha1-antitrypsin (alpha1AT) in COPD patients. METHODS: The quantification of serum alpha1AT was done by ELISA, the phenol-chloroform method was used for DNA extraction, PCR products were directly sequenced. The IBM SPSS Statistics v21 software was used for statistical analyses of the data. RESULTS: The mean serum alpha1AT level was found to be 1.203+0.239 and 3.162+0.160 g/L in COPD cases and in control, respectively. The - 10C allele is associated with an increased risk of COPD [OR, 3.50 (95%CI, 1.86-6.58); p < 0.001]. The combined variant genotype (TT+CC) was significantly found associated with an increased risk of COPD [OR, 3.20 (95% CI, 1.47-6.96); p = 0.003]. A significant association of the family history with COPD (overall p value= 0.0331) suggests that genetics may play an important role in the pathogenesis of COPD. CONCLUSION: The polymorphism associated with hepatocyte-specific promoter region (- 10T/C) is likely to be associated with the pathogenesis of COPD. It is quite possible that the change of the base in the hepatocyte-specific promoter of the SERPINA1 gene can modulate its strength, thereby driving the reduced expression of alpha1AT.

https://link.springer.com/article/10.1007%2Fs00408-018-0124-8

Bchir, S., H. Ben Nasr, et al. (2018). **"MMP-3 (-1171 5A/6A; Lys45Glu) variants affect serum levels of matrix metalloproteinase (MMP)-3 and correlate with severity of COPD: A study of MMP-3, MMP-7 and MMP-12 in a Tunisian population."** J Gene Med **20**(1)BACKGROUND: The present study aimed to examine the role of matrix metalloproteinase (MMP)-3 [(-1171) 5A/6A; Lys45Glu (A/G)], MMP-7 [(-181) A/G] and MMP-12 [(-82) A/G; Asn357Ser (A/G)] variants in the development and severity of chronic obstructive pulmonary disease (COPD) in Tunisians. METHODS: Plethysmography was performed in all participants to measure forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and FEV1/FVC parameters. Genotyping of MMP-3, MMP-7 and MMP-12 polymorphisms was carried out in 138 patients with COPD and 216 healthy controls using a polymerase chain reaction-restriction fragment length polymorphism. Serum levels of MMPs and cytokines (interleukin-6, tumor necrosis factor-alpha) were

determined by an enzyme-linked immunosorbent assay. RESULTS: No significant correlations were observed between genetic variations in MMP-3, MMP-7 and MMP-12 and the risk of development of COPD. Additionally, no impact of MMP-7 (-181) A/G and MMP-12 [(-82) A/G; Asn357Ser (A/G)] polymorphisms was observed on the respective protein levels and clinical parameters of the disease. Interestingly, both MMP-3 (-1171) 5A/6A and Lys45Glu (A/G) variants were associated with respiratory function, as well as with serum levels of MMP-3 in COPD patients. A relationship was found between the (-1171) 6A and 45Glu (G) alleles of the MMP-3 gene and enhanced airflow limitation among COPD patients. Additionally, carriers of the 6A6A and 45 GG genotypes present higher MMP-3 levels than noncarriers. CONCLUSIONS: MMP-3 (-1171) 5A/6A and Lys45Glu (A/G) polymorphisms were associated with the decline of lung function among COPD patients. These results could be linked to the upregulation of MMP-3 in serum from COPD patients carrying the (-1171) 6A and 45 G homozygous genotypes.

https://onlinelibrary.wiley.com/doi/abs/10.1002/jgm.2999

Behr, G., E. Mema, et al. (2018). **"Proportion and Clinical Relevance of Intraspinal Air in Patients With Pneumomediastinum."** AJR Am J Roentgenol **211**(2): 321-326.

OBJECTIVE: The purposes of this study were to determine the incidence of pneumorrhachis among patients with pneumomediastinum, determine whether its proportion correlates with the extent of pneumomediastinum, and ascertain its clinical relevance. MATERIALS AND METHODS: The radiologic database was searched for CT reports between January 2009 and September 2013 containing the term "pneumomediastinum" or "mediastinal air." Scans were examined for pneumomediastinum, pneumorrhachis, pneumothorax, sternotomy, and distribution of pneumomediastinum. The age and sex of the patient and probable cause of the abnormality were recorded. Cases that might have had another cause were excluded. RESULTS: The search yielded 422 CT scans. Among these, 242 instances of pneumomediastinum in 241 patients were found. Fifteen of these patients had pneumorrhachis. One was excluded because of recent traumatic spinal penetration. There was no significant difference in age or sex between patients with and those without pneumorrhachis. After application of the exclusion criteria, there were 14 cases of pneumorrhachis, yielding a proportion of 5.8%. Pneumorrhachis was observed more frequently in cases of the most severe grade (grade C) of pneumomediastinum; however, that relationship was not statistically significant (11 cases [8.2%]; $p = 0.304$). Pneumorrhachis was found significantly more frequently in patients with distribution of air in all three mediastinal compartments (13 cases, 16.2%, $p < 0.001$). Pneumorrhachis was overrepresented among subjects with spontaneous compared with those with secondary pneumomediastinum, although the trend did not reach statistical significance. CONCLUSION: Pneumorrhachis was present in 5.8% of patients. It is significantly more common in patients with the broadest distributions of mediastinal air and nonsignificantly more common in association with spontaneous as opposed to secondary pneumomediastinum. Pneumorrhachis in patients with pneumomediastinum is a generally benign, self-resolving condition.

Bernardi, E., C. Merlo, et al. (2018). **"Endothelial Function in COPD Is in an Intermediate Position Between Healthy Subjects and Coronary Artery Disease Patients and Is Related to Physical Activity."** Lung **196**(6): 669-672.

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of ischemic heart disease. Endothelial dysfunction may play a role in the onset of cardiovascular event. Previous studies showed an impaired endothelial function (measured by flow-mediated dilation, FMD) in COPD patients compared to healthy subjects. To the best of our knowledge no study has compared FMD in COPD and in cardiac (coronary artery disease, CAD) patients. We aimed to assess FMD in healthy subjects, COPD, CAD, and COPD + CAD. The main result is that FMD in COPD is reduced and is in an intermediate position between healthy subjects and CAD or COPD + CAD; this impairment can contribute to explain the higher prevalence of cardiovascular disease in COPD. The only determinant independently associated with FMD

in all subjects is the physical activity level, irrespective of the traditional risk factors (i.e., smoke, dyslipidemia, hypertension).

https://link.springer.com/article/10.1007%2Fs00408-018-0168-9

Bhatt, S. P., P. P. Balte, et al. (2019). **"Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality."** Jama **321**(24): 2438-2447.

Importance: According to numerous current guidelines, the diagnosis of chronic obstructive pulmonary disease (COPD) requires a ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV1:FVC) of less than 0.70, yet this fixed threshold is based on expert opinion and remains controversial. Objective: To determine the discriminative accuracy of various FEV1:FVC fixed thresholds for predicting COPD-related hospitalization and mortality. Design, Setting, and Participants: The National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study harmonized and pooled data from 4 US general population-based cohorts (Atherosclerosis Risk in Communities Study; Cardiovascular Health Study; Health, Aging, and Body Composition Study; and Multi-Ethnic Study of Atherosclerosis). Participants aged 45 to 102 years were enrolled from 1987 to 2000 and received follow-up longitudinally through 2016. Exposures: Presence of airflow obstruction, which was defined by a baseline FEV1:FVC less than a range of fixed thresholds (0.75 to 0.65) or less than the lower limit of normal as defined by Global Lung Initiative reference equations (LLN). Main Outcomes and Measures: The primary outcome was a composite of COPD hospitalization and COPD-related mortality, defined by adjudication or administrative criteria. The optimal fixed FEV1:FVC threshold was defined by the best discrimination for these COPD-related events as indexed using the Harrell C statistic from unadjusted Cox proportional hazards models. Differences in C statistics were compared with respect to less than 0.70 and less than LLN thresholds using a nonparametric approach. Results: Among 24207 adults in the pooled cohort (mean [SD] age at enrollment, 63 [10.5] years; 12990 [54%] women; 16794 [69%] non-Hispanic white; 15181 [63%] ever smokers), complete follow-up was available for 11077 (77%) at 15 years. During a median follow-up of 15 years, 3925 participants experienced COPD-related events over 340757 person-years of follow-up (incidence density rate, 11.5 per 1000 person-years), including 3563 COPD-related hospitalizations and 447 COPD-related deaths. With respect to discrimination of COPD-related events, the optimal fixed threshold (0.71; C statistic for optimal fixed threshold, 0.696) was not significantly different from the 0.70 threshold (difference, 0.001 [95% CI, -0.002 to 0.004]) but was more accurate than the LLN threshold (difference, 0.034 [95% CI, 0.028 to 0.041]). The 0.70 threshold provided optimal discrimination in the subgroup analysis of ever smokers and in adjusted models. Conclusions and Relevance: Defining airflow obstruction as FEV1:FVC less than 0.70 provided discrimination of COPD-related hospitalization and mortality that was not significantly different or was more accurate than other fixed thresholds and the LLN. These results support the use of FEV1:FVC less than 0.70 to identify individuals at risk of clinically significant COPD.

https://jamanetwork.com/journals/jama/article-abstract/2736562

Braunlich, J. and H. Wirtz (2018). **"Oral Versus Nasal High-Flow Bronchodilator Inhalation in Chronic Obstructive Pulmonary Disease."** J Aerosol Med Pulm Drug Deliv **31**(4): 248-254.

BACKGROUND: Nasal high flow (NHF) alters breathing patterns, stabilizes fraction of inspired oxygen (FiO2) during respiratory distress, helps to keep up hemostasis in the airways, and washes out the upper airways. Particularly the support of inspiratory flow and decrease in functional dead space are interesting mechanisms of action with regard to aerosol delivery. Several laboratory investigations have studied aerosol delivery via the nasal route by using NHF, whereas clinical benefits are poorly evaluated. METHODS: Thirty patients with stable chronic obstructive pulmonary disease Gold D were recruited. In a randomized order, they inhaled a salbutamol 2.5 mg/ipratropium bromide 500 mug solution oral or NHF adapted on the second study day. A jet nebulizer was used as aerosol delivery device. The chosen flow rate was 35 L/min. RESULTS: Four patients refused to repeat the procedure, for example, for inconvenience or fear of delayed discharge, and were not included in the intention-to-treat analysis. All

remaining patients tolerated both inhalation systems well. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), airway resistance (Rtot), and residual volume (RV) were significantly altered after bronchodilator inhalation with each of the both devices. The two different ways of combined bronchodilator inhalation resulted in very comparable changes in FVC, FEV1, relative 1 second-capacity (FEV1%FVC), Rtot, total lung capacity (TLC), RV, and residual volume expressed as percent of TLC (RV%TLC). However, in between devices, no difference was observed on comparing the postinhalational measurements of FVC, FEV1, Rtot, and RV. CONCLUSIONS: We conclude from this proof-of-principle kind of study that inhalation of combined bronchodilators adapted to an NHF device is similarly effective to inhalation with a standard oral aerosol nebulizer. (Clinical Trails NCT02885103).

Button, B. M., A. E. Holland, et al. (2019). **"Prevalence, impact and specialised treatment of urinary incontinence in women with chronic lung disease."** Physiotherapy **105**(1): 114-119.

OBJECTIVES: To determine in women with clinically stable chronic lung disease (CLD) and healthy women; (1) prevalence of urinary incontinence; (2) risk factors for urinary incontinence; (3) effects of a standard course of specialised physiotherapy treatment (PT) in women with CLD. DESIGN: Prospective prevalence study; PT study in CLD subgroup. SETTING: Tertiary metropolitan public hospital. PARTICIPANTS: Women with cystic fibrosis (CF, n=38), chronic obstructive pulmonary disease (COPD, n=27) and 69 healthy women without CLD. PT study - 10 women with CLD. INTERVENTIONS: Five continence PT sessions over 3 months. MAIN OUTCOME MEASURES: Prevalence and impact of incontinence (questionnaire), number of leakage episodes (7-day accident diary), pelvic floor muscle function (ultrasound imaging) and quality of life (King's Health Questionnaire). RESULTS: The majority of women in all three groups reported episodes of incontinence (CF 71%; COPD 70%; healthy women 55%). Compared to age-matched healthy controls, women with CF reported more episodes of incontinence (P=0.006) and more commonly reported stress incontinence (P=0.001). A logistic regression model revealed that women with CLD were twice as likely to develop incontinence than healthy women (P=0.05). Women with COPD reported significantly more 'bother' with incontinence than age-matched women with incontinence. There was a significant reduction in incontinence episodes following treatment, which was maintained after three months. CONCLUSIONS: The presence of CLD is an independent predictor of incontinence in women. In older women this is associated with more distress than in age-matched peers without CLD. Larger treatment studies are indicated for women with CLD and incontinence.

https://www.physiotherapyjournal.com/article/S0031-9406(18)30155-X/pdf

Byers, D. E., K. Wu, et al. (2018). **"Triggering Receptor Expressed on Myeloid Cells-2 Expression Tracks With M2-Like Macrophage Activity and Disease Severity in COPD."** Chest **153**(1): 77-86.

BACKGROUND: Cell and animal models show a key role for Triggering Receptor Expressed on Myeloid Cells (TREM)-2 in chronic airway disease after viral infection, but comparable evidence in humans still needs to be established. METHODS: Lung tissue samples were obtained from lung transplant recipients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV COPD (n = 16), nontransplantable donor lung tissues (n = 7), and resected lung tissues from patients at risk or with GOLD stage I through IV (n = 55) and were assessed for TREM-2 and TREM-1 messenger RNA (mRNA), protein expression, and other markers of a type 2 immune response. RESULTS: TREM2 (but not TREM1) mRNA levels were increased in GOLD stage IV COPD lung tissues compared with non-COPD lung tissues. TREM2 mRNA was coexpressed with its signaling molecule DAP12 and the macrophage marker CD68 and M2-macrophage markers CD206 and CHIT1. TREM-2 protein was also increased in COPD lung tissues and was localized to CD14(+) macrophages by flow cytometry and CD68(+) and CCR2(+) macrophages by tissue immunostaining. In lung samples from patients at risk and with GOLD stage I through IV COPD, TREM2 but not TREM1 mRNA levels were also increased, and the ratio of TREM2/TREM1 mRNA levels was associated with increases in CHIT1 mRNA and decreases in FEV1 and FEV1/FVC. CONCLUSIONS: TREM-2 expression is increased in lung macrophages in COPD, particularly in comparison with TREM-1.

Therefore, TREM-2 levels and the ratio of TREM-2/TREM-1 signifies M2 activation in COPD lung tissues and may help to guide therapeutics directed against the type 2 immune response in patients with this disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5812763/pdf/main.pdf

Cabrera Lopez, C., C. Casanova Macario, et al. (2018). **"Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes."** Am J Respir Crit Care Med **197**(4): 463-469.

RATIONALE: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document has modified the grading system directing pharmacotherapy, but how this relates to the previous one from 2015 and to comorbidities, hospitalizations, and mortality risk is unknown. OBJECTIVES: The aim of this study was to evaluate the changes in the GOLD groups from 2015 to 2017 and to assess the impact on severity, comorbidities, and mortality within each group. METHODS: We prospectively enrolled and followed, for a mean of 5 years, 819 patients with chronic obstructive pulmonary disease (84% male) in clinics in Spain and the United States. We determined anthropometrics, lung function (FEV1%), dyspnea score (modified Medical Research Council scale), ambulatory and hospital exacerbations, and the body mass index, obstruction, dyspnea, and exercise capacity (BODE) and Charlson indexes. We classified patients by the 2015 and 2017 GOLD ABCD system, and compared the differential realignment of the same patients. We related the effect of the reclassification in BODE and Charlson distribution as well as chronic obstructive pulmonary disease and all-cause mortality between the two classifications. MEASUREMENTS AND MAIN RESULTS: Compared with 2015, the 2017 grading decreased by half the proportion of patients in groups C and D (20.5% vs. 11.2% and 24.6% vs. 12.9%; $P < 0.001$). The distribution of Charlson also changed, whereas group D was higher than B in 2015, they become similar in the 2017 system. In 2017, the BODE index and risk of death were higher in B and D than in A and C. The mortality risk was better predicted by the 2015 than the 2017 system. CONCLUSIONS: Compared with 2015, the GOLD ABCD 2017 classification significantly shifts patients from grades C and D to categories A and B. The new grading system equalizes the Charlson comorbidity score in all groups and minimizes the differences in BODE between groups B and D, making the risk of death similar between them.

Callahan, C. L., P. A. Stewart, et al. (2019). **"Extended Mortality Follow-up of a Cohort of Dry Cleaners."** Epidemiology **30**(2): 285-290.

BACKGROUND: Dry cleaning workers are commonly exposed to tetrachloroethylene, a suspected bladder carcinogen, and other organic solvents. The health risks associated with solvent exposures in this industry are unclear. METHODS: We extended mortality follow-up of 5,369 dry cleaning union members in St. Louis to further investigate solvent-related risks. We added 22 years of follow-up, from 1993 through 2014, via linkage to the National Death Index. Using Cox proportional hazards modeling, we computed hazard ratios (HRs) and 95% confidence intervals (CIs) relating cause-specific mortality with levels of a solvent exposure index previously developed by an industrial hygienist based on workers' job titles from union records. The models were fit adjusting for age, sex, and decade of union enrollment, and assuming different exposure lags. RESULTS: In internal analyses of estimated solvent exposure with a 20-year lag, we observed exposure-response relationships for bladder cancer (HR medium exposure = 4.2; 95% CI = 0.7, 24.5 and HR high exposure = 9.2; 95% CI = 1.1, 76.7 vs. no exposure; Ptrend = 0.08) and kidney cancer (HR = 4.1; 95% CI = 0.7, 22.5 and 24.4; 2.9, 201.6; Ptrend = 0.004). High exposure was also associated with heart disease (HR = 1.6; 95% CI = 1.1, 2.2) and lymphatic/hematopoietic malignancies (HR = 4.3; 95% CI = 1.4, 13.6). CONCLUSIONS: These findings are, to the best of our knowledge, the first cohort evidence relating solvent exposure levels among dry cleaners to elevated risks of selected cancers and heart disease. Additional studies employing solvent-specific exposure assessment are needed to clarify cancer risks associated with tetrachloroethylene.

Campos, M. A., M. C. Runken, et al. (2018). **"Impact of a Health Management Program on Healthcare Outcomes among Patients on Augmentation Therapy for Alpha 1-Antitrypsin Deficiency: An Insurance Claims Analysis."** Adv Ther **35**(4): 467-481.

INTRODUCTION: Alpha 1-antitrypsin deficiency (AATD) is a genetic disorder which reduces serum alpha 1-antitrypsin (AAT or alpha1-proteinase inhibitor, A1PI) and increases the risk of chronic obstructive pulmonary disease (COPD). Management strategies include intravenous A1PI augmentation, and, in some cases, a health management program (Prolastin Direct((R)); PD). OBJECTIVES: This study compared clinical and economic outcomes between patients with and without PD program participation. METHODS: This retrospective study included commercial and Medicare Advantage health insurance plan members with >/= 1 claim with diagnosis codes for COPD and >/= 1 medical or pharmacy claim including A1PI (on index date). Outcomes were compared between patients receiving only Prolastin((R)) or Prolastin((R))-C (PD cohort) and patients who received a different brand without PD (Comparator cohort). Demographic and clinical characteristics were captured during 6 months pre-index. Post-index exacerbation episodes and healthcare utilization and costs were compared between cohorts. RESULTS: The study sample comprised 445 patients (n = 213 in PD cohort; n = 232 in Comparator cohort), with a mean age 55.5 years, 50.8% male, and 78.9% commercially insured. The average follow-up was 822 days (2.25 years), and the average time on A1PI was 747 days (2.04 years). Few differences were observed in demographic or clinical characteristics. Adjusting for differences in patient characteristics, the rate of severe exacerbation episodes was reduced by 36.1% in the PD cohort. Adjusted total annual all-cause costs were 11.4% lower, and adjusted mean respiratory-related costs were 10.6% lower in the PD cohort than the Comparator cohort. Annual savings in all-cause total costs in the PD cohort relative to the Comparator cohort was US$25,529 per patient, largely due to significantly fewer and shorter hospitalizations. CONCLUSIONS: These results suggest that comprehensive health management services may improve both clinical and economic outcomes among patients with COPD and AATD who receive augmentation therapy. FUNDING: Grifols Shared Services of North America, Inc.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5910458/pdf/12325_2018_Article_690.pdf

Cappa, V., A. Marcon, et al. (2019). **"Health-related quality of life varies in different respiratory disorders: a multi-case control population based study."** BMC Pulm Med **19**(1): 32.

BACKGROUND AND OBJECTIVE: Health-related quality of life (HRQL) in respiratory diseases has been generally investigated in clinical settings, focusing on a single disorder. In this study on a general population sample, we assessed the relationship between HRQL and several respiratory diseases studied simultaneously (COPD, current (CA) and past (PA) asthma, allergic (AR) and non-allergic (NAR) rhinitis and chronic bronchitis (CB). METHODS: Controls (n = 328) and cases of NAR (n = 95), AR (n = 163), CB (n = 48), CA (n = 224), PA (n = 126) and COPD (n = 28) were recruited in the centre of Verona in the frame of the Italian multi-case control GEIRD (Gene Environment Interactions in Respiratory Diseases) study; HRQL was measured through the SF-36 questionnaire. The relationships between HRQL (in terms of Physical (PCS) and Mental Component Scores (MCS)), respiratory diseases, and covariates were evaluated. RESULTS: With respect to controls, the adjusted PCS median score was worse in subjects suffering from current asthma (- 1.7; 95%CI:-2.8;-0.6), CB (- 3.8; 95%CI:-5.7;-1.9), and COPD (- 5.6; 95%CI:-8.1;-3.1). MCS was worse in current asthmatics (- 2.2; 95%CI:-4.1;-0.3), CB (- 5.5; 95%CI:-8.7;-2.2), and COPD cases (- 4.6; 95%CI:-8.8;-0.5) as well. CONCLUSIONS: To our knowledge, this is the first study in the general population that analyzed HRQL performing a simultaneous comparison of HRLQ in several respiratory disorders. We found that subjects suffering from COPD, CA, and CB had the poorest HRQL. Clinicians should carefully consider the possible impact of respiratory disorders as CB and not only that of CA and COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6367788/pdf/12890_2019_Article_796.pdf

Chan, H. F., N. J. Stewart, et al. (2018). **"3D diffusion-weighted (129) Xe MRI for whole lung morphometry."** Magn Reson Med **79**(6): 2986-2995.

PURPOSE: To obtain whole lung morphometry measurements from (129) Xe in a single breath-hold with 3D multiple b-value (129) Xe diffusion-weighted MRI (DW-MRI) with an empirically optimized diffusion time and compressed sensing for scan acceleration. METHODS: Prospective three-fold undersampled 3D multiple b-value hyperpolarized (129) Xe DW-MRI datasets were acquired, and the diffusion time (Delta) was iterated so as to provide diffusive length scale (LmD) estimates from the stretched exponential model (SEM) that are comparable to those from (3) He. The empirically optimized (129) Xe diffusion time was then implemented with a four-fold undersampling scheme and was prospectively benchmarked against (3) He measurements in a cohort of five healthy volunteers, six ex-smokers, and two chronic obstructive pulmonary disease patients using both SEM-derived LmD and cylinder model (CM)-derived mean chord length (Lm). RESULTS: Good agreement between the mean (129) Xe and (3) He LmD (mean difference, 2.2%) and Lm (mean difference, 1.1%) values was obtained in all subjects at an empirically optimized (129) Xe Delta = 8.5 ms. CONCLUSION: Compressed sensing has facilitated single-breath 3D multiple b-value (129) Xe DW-MRI acquisitions, and results at (129) Xe Delta = 8.5 ms indicate that (129) Xe provides a viable alternative to (3) He for whole lung morphometry mapping with either the SEM or CM. Magn Reson Med 79:2986-2995, 2018. (c) 2017 The Authors Magnetic Resonance in Medicine published by Wiley Periodicals, Inc. on behalf of International Society for Magnetic Resonance in Medicine. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5888195/pdf/MRM-79-2986.pdf

Chen, Y. C., M. C. Lin, et al. (2018). **"Defective formyl peptide receptor 2/3 and annexin A1 expressions associated with M2a polarization of blood immune cells in patients with chronic obstructive pulmonary disease."** J Transl Med **16**(1): 69.

BACKGROUND: Controversy exists in previous studies on macrophage M1/M2 polarization in chronic obstructive pulmonary disease (COPD). We hypothesized that formyl peptide receptor (FPR), a marker of efferocytosis and mediator of M1/M2 polarization, may be involved in the development of COPD. METHODS: We examined FPR 1/2/3 expressions of blood M1/M2a monocyte, neutrophil, natural killer (NK) cell, NK T cell, T helper (Th) cell, and T cytotoxic (Tc) cell by flowcytometry method in 40 patients with cigarette smoking-related COPD and 16 healthy non-smokers. Serum levels of five FPR ligands were measured by ELISA method. RESULTS: The COPD patients had lower M2a percentage and higher percentages of NK, NK T, Th, and Tc cells than the healthy non-smokers. FPR2 expressions on Th/Tc cells, FPR3 expressions of M1, M2a, NK, NK T, Th, and Tc cells, and serum annexin A1 (an endogenous FPR2 ligand) levels were all decreased in the COPD patients as compared with that in the healthy non-smokers. FPR1 expression on neutrophil was increased in the COPD patient with a high MMRC dyspnea scale, while FPR2 expression on neutrophil and annexin A1 were both decreased in the COPD patients with a history of frequent moderate exacerbation (>/= 2 events in the past 1 year). In 10 COPD patients whose blood samples were collected again after 1-year treatment, M2a percentage, FPR3 expressions of M1/NK/Th cells, FPR2 expression on Th cell, and FPR1 expression on neutrophil were all reversed to normal, in parallel with partial improvement in small airway dysfunction. CONCLUSIONS: Our findings provide evidence for defective FPR2/3 and annexin A1 expressions that, associated with decreased M2a polarization, might be involved in the development of cigarette smoking induced persistent airflow limitation in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5856198/pdf/12967_2018_Article_1435.pdf

Christensen, C. H., B. Rostron, et al. (2018). **"Association of Cigarette, Cigar, and Pipe Use With Mortality Risk in the US Population."** JAMA Intern Med **178**(4): 469-476.

Importance: Tobacco products have changed in recent years. Contemporary mortality risk estimates of combustible tobacco product use are needed. Objective: To investigate the mortality risks associated with current and former use of cigars, pipes, and cigarettes. Design, Setting, and Participants: The National Longitudinal Mortality Study is a longitudinal population-based, nationally representative health survey with mortality follow-up that includes demographic and other information from the Current Population Survey, tobacco product use information from the Tobacco Use Supplement, and mortality data from the National Death Index. In this study, participants provided tobacco use information at baseline in surveys starting from 1985 and were followed for mortality through the end of 2011. The study includes 357420 participants who reported exclusively using cigar, pipes, or cigarettes or reported never using any type of tobacco product. Exposures: Current or former exclusive use of any cigar (little cigar, cigarillos, large cigar), traditional pipe, or cigarette and never tobacco use. Information on current daily and nondaily use was also collected. Estimates adjusted for age, sex, race/ethnicity, education, and survey year. Main Outcomes and Measures: All-cause and cause-specific mortality as identified as the primary cause of death from death certificate information. Results: Of the 357420 persons included in the analysis, the majority of current and former cigar and pipe smokers were male (79.3%-98.0%), and smokers were more evenly divided by sex (46% of current daily smokers were male). There were 51 150 recorded deaths during follow-up. Exclusive current cigarette smokers (hazard ratio [HR], 1.98; 95% CI, 1.93-2.02) and exclusive current cigar smokers (HR, 1.20; 95% CI, 1.03-1.38) had higher all-cause mortality risks than never tobacco users. Exclusive current cigarette smokers (HR, 4.06; 95% CI, 3.84-4.29), exclusive current cigar smokers (HR, 1.61; 95% CI, 1.11-2.32), and exclusive current pipe smokers (HR, 1.58; 95% CI, 1.05-2.38) had an elevated risk of dying from a tobacco-related cancer (including bladder, esophagus, larynx, lung, oral cavity, and pancreas). Among current nondaily cigarette users, statistically significant associations were observed with deaths from lung cancer (HR, 6.24; 95% CI, 5.17-7.54), oral cancer (HR, 4.62; 95% CI, 1.84-11.58), circulatory death (HR, 1.43; 95% CI, 1.30-1.57), cardiovascular death (HR, 1.24; 95% CI, 1.11-1.39), cerebrovascular death (stroke) (HR, 1.39; 95% CI, 1.12-1.74), and chronic obstructive pulmonary disease (HR, 7.66; 95% CI, 6.09-9.64) as well as for daily smokers. Conclusions and Relevance: This study provides further evidence that exclusive use of cigar, pipes, and cigarettes each confers significant mortality risks.

https://jamanetwork.com/journals/jamainternalmedicine/articlepdf/2672576/jamainternal_christensen_2018_oi_170133.pdf

Cleutjens, F., M. A. Spruit, et al. (2018). **"Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease."** Chron Respir Dis **15**(2): 91-102.

We aimed to investigate (1) the relationship between cognitive impairment (CI) and disease severity and (2) the potential differences in exercise performance, daily activities, health status, and psychological well-being between patients with and without CI. Clinically stable chronic obstructive pulmonary disease (COPD) patients, referred for pulmonary rehabilitation, underwent a neuropsychological examination. Functional exercise capacity (6-minute walk test [6MWT]), daily activities (Canadian Occupational Performance Measure [COPM]), health status (COPD Assessment Test [CAT]) and St George's Respiratory Questionnaire-COPD specific [SGRQ-C]), and psychological well-being (Hospital Anxiety and Depression Scale [HADS], Beck Depression Inventory [BDI], and Symptom Checklist 90 [SCL-90]) were compared between patients with and without CI. Of 183 COPD patients (mean age 63.6 (9.4) years, FEV1 54.8 (23.0%) predicted), 76 (41.5%) patients had CI. The prevalence was comparable across Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1-4 (44.8%, 40.0%, 41.0%, 43.5%, respectively, p = 0.97) and GOLD groups A-D (50.0%, 44.7%, 33.3%, 40.2%, respectively, p = 0.91). Patients with and without CI were comparable for demographics, smoking status, FEV1% predicted, mMRC, 6MWT, COPM, CAT, HADS, BDI, and SCL-90 scores. Clinical characteristics of COPD patients with and without CI are comparable. Assessment of CI in COPD, thus, requires an active case-finding approach.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5958463/pdf/10.1177_1479972317709651.pdf

Cuthbert, J. J., J. W. Kearsley, et al. (2019). **"The impact of heart failure and chronic obstructive pulmonary disease on mortality in patients presenting with breathlessness."** Clin Res Cardiol **108**(2): 185-193.
BACKGROUND: Differentiating heart failure from chronic obstructive pulmonary disease (COPD) in a patient presenting with breathlessness is difficult but may have implications for outcome. We investigated the prognostic impact of diagnoses of COPD and/or heart failure in consecutive patients presenting to a secondary care clinic with breathlessness. METHODS: In patients with left ventricular systolic dysfunction (LVSD) by visual estimation, N-terminal pro B-type natriuretic peptide (NTproBNP) levels and spirometry were evaluated (N = 4986). Heart failure was defined as either LVSD worse than mild (heart failure with reduced ejection fraction) or LVSD mild or better and raised NTproBNP levels (> 400 ng/L) (heart failure with normal ejection fraction). COPD was defined as forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio < 0.7. The primary outcome was all-cause mortality. RESULTS: 1764 (35%) patients had heart failure alone, 585 (12%) had COPD alone, 1751 (35%) had heart failure and COPD, and 886 (18%) had neither. Compared to patients with neither diagnosis, those with COPD alone [hazard ratio (HR) = 1.84 95% confidence interval (CI) 1.40-2.43], heart failure alone [HR = 4.40 (95% CI 3.54-5.46)] or heart failure and COPD [HR = 5.44 (95% CI 4.39-6.75)] had a greater risk of death. COPD was not associated with increased risk of death in patients with heart failure on a multivariable analysis. CONCLUSION: While COPD is associated with increased risk of death compared to patients with neither heart failure nor COPD, it has a negligible impact on prognosis amongst patients with heart failure.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6510798/pdf/392_2018_Article_1342.pdf

De Miguel-Diez, J., A. Lopez-De-Andres, et al. (2019). **"Chronic obstructive pulmonary disease is not associated with worse in-hospital outcomes after surgical aortic valve replacement in Spain (2001-2015)."** J Cardiovasc Surg (Torino) **60**(3): 413-421.
BACKGROUND: The aims of this study were: 1) to examine incidence, characteristics and in-hospital outcomes of surgical aortic valve replacement (SAVR) among patients with or without COPD; 2) to compare both groups matched by sex, age, year hospitalized for SAVR and implanted valve type; and 3) to identify factors associated with in-hospital mortality (IHM) among chronic obstructive pulmonary disease (COPD) patients. METHODS: We used the Spanish National Hospital Discharge Database for patients aged >/=40 years from 2001 to 2015. We selected patients whose medical procedures included SAVR. We grouped hospitalizations by COPD status. Main outcomes were incidences and IHM. Covariates included comorbidities and concomitant procedures. RESULTS: We identified 78,223 hospitalizations with SAVR and COPD accounted for 9.14% (6028 men and 1125 women). Incidence of hospitalizations for SAVR increased overtime in patients without COPD, but not in COPD sufferers. COPD patients were more likely to receive bioprosthetic valves than those without COPD. The proportion of mechanical valves implanted decreased as the bioprosthetic valves increased overtime in both groups. Crude IHM was 6.77% for COPD patients and 6.48% for non-COPD (P=0.17). IHM decreased significantly over time in both groups of patients. After matching no differences were found in IHM between COPD and matched not-COPD patients who received a mechanical or bioprosthetic SAVR. Among COPD patients, IHM was associated with older age, more comorbidities and concomitant coronary artery bypass graft. CONCLUSIONS: Our analysis suggest that COPD per se should not represent a contraindication to SAVR. No differences were found for IHM between patients with and without COPD beside the type of valve used.

Dunican, E. M., B. M. Elicker, et al. (2018). **"Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction."** J Clin Invest **128**(3): 997-1009.
BACKGROUND: The link between mucus plugs and airflow obstruction has not been established in chronic severe asthma, and the role of eosinophils and their products in mucus plug formation is unknown. METHODS: In clinical studies, we developed and applied a bronchopulmonary segment-based scoring system to

quantify mucus plugs on multidetector computed tomography (MDCT) lung scans from 146 subjects with asthma and 22 controls, and analyzed relationships among mucus plug scores, forced expiratory volume in 1 second (FEV1), and airway eosinophils. Additionally, we used airway mucus gel models to explore whether oxidants generated by eosinophil peroxidase (EPO) oxidize cysteine thiol groups to promote mucus plug formation. RESULTS: Mucus plugs occurred in at least 1 of 20 lung segments in 58% of subjects with asthma and in only 4.5% of controls, and the plugs in subjects with asthma persisted in the same segment for years. A high mucus score (plugs in >/= 4 segments) occurred in 67% of subjects with asthma with FEV1 of less than 60% of predicted volume, 19% with FEV1 of 60%-80%, and 6% with FEV1 greater than 80% (P < 0.001) and was associated with marked increases in sputum eosinophils and EPO. EPO catalyzed oxidation of thiocyanate and bromide by H_2O_2 to generate oxidants that crosslink cysteine thiol groups and stiffen thiolated hydrogels. CONCLUSION: Mucus plugs are a plausible mechanism of chronic airflow obstruction in severe asthma, and EPO-generated oxidants may mediate mucus plug formation. We propose an approach for quantifying airway mucus plugging using MDCT lung scans and suggest that treating mucus plugs may improve airflow in chronic severe asthma. TRIAL REGISTRATION: Clinicaltrials.gov NCT01718197, NCT01606826, NCT01750411, NCT01761058, NCT01761630, NCT01759186, NCT01716494, and NCT01760915. FUNDING: NIH grants P01 HL107201, R01 HL080414, U10 HL109146, U10 HL109164, U10 HL109172, U10 HL109086, U10 HL109250, U10 HL109168, U10 HL109257, U10 HL109152, and P01 HL107202 and National Center for Advancing Translational Sciences grants UL1TR0000427, UL1TR000448, and KL2TR000428.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5824874/pdf/jci-128-95693.pdf

Durmus, U., N. O. Dogan, et al. (2018). **"The value of lactate clearance in admission decisions of patients with acute exacerbation of COPD."** Am J Emerg Med **36**(6): 972-976.

BACKGROUND: Lactate and lactate clearance are being used as biomarkers in several critical conditions. The aim of this study was to examine the value of sixth hour lactate clearance in patients who were hospitalized with chronic obstructive pulmonary disease (COPD) exacerbations. METHODS: This single-center, cross-sectional study was conducted in a tertiary emergency department (ED) on patients who presented with acute exacerbation of COPD. Discharge or admission decisions were specified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and the clinician's decision. In the study, lactate clearance was defined as the percent decrease in lactate from the time of presentation to the ED to the sixth hour. RESULTS: A total of 495 patients were evaluated and 397 patients were excluded. Among included patients, 53 (54.1%) were admitted to the hospital and 45 (45.9%) were discharged. The median lactate clearance was found to be -11.8% (95% CI: -50.0 to 34.5) in the admitted group and 14.7% (95% CI: -11.3 to 42.3) in the discharged group. Between the two groups, the median difference of lactate clearance was found to be 26.5% (95% CI: 0.6 to 52.4). Multivariate logistic regression analysis revealed that the delta lactate value can determine the hospitalization need of patients (OR: 0.91, 95% CI: 0.85 to 0.97). CONCLUSION: Lactate clearance can be evaluated as a useful marker in patients with COPD exacerbations. This study suggests that lactate monitoring in the ED has clinical benefits in addition to GOLD guidelines when deciding whether to discharge or hospitalize a patient.

https://www.ajemjournal.com/article/S0735-6757(17)30910-5/fulltext

Evans, R. A. and M. C. Steiner (2017). **"Pulmonary Rehabilitation: The Lead Singer of COPD Therapy but Not a "One-Man Band"."** Chest **152**(6): 1103-1105.

https://journal.chestnet.org/article/S0012-3692(17)31250-3/pdf

Farahani, P., R. Halabian, et al. (2017). **"Increased Genes Expression Levels of Cytokines Related to Th17/Treg Cells in Peripheral Blood Mononuclear Cell Correlate with Clinical Severity in COPD and Mustard Gas-exposed Patients."** Iran J Allergy Asthma Immunol **16**(5): 396-403.

The long lasting inflammation and immune dysregulation is one of the main mechanisms involved in lung complication of veterans exposed to sulfur mustard (SM) gas. Th17/Treg cells have an important role in immunopathogenesis of chronic obstructive pulmonary disease (COPD) and mustard lung disease. In this study, expression of cytokines genes levels related to Th17/Treg cells was determined in peripheral blood mononuclear (PBMC) of mustard lung patients and was compared with COPD patients and healthy controls (HC). Real time-polymerase chain reaction was used to assay genes expression levels of Th17 related cytokines (IL-17, IL-6 and TGF-beta) and Treg related cytokines (IL-10, TGF-beta). IL-17 gene expression level considerably was higher in SM patients (9.98+/-0.65, p<0.001), and COPD (4.75+/-0.71, p<0.001), compare to HC group. Also, gene expression level of IL-6 in the SM group (3.31+/-0.93, p<0.001) and COPD group (2.93+/-0.21, p<0.001) were significantly higher than the HC group. The IL-10 gene expression level showed a high increase in SM patients (4.12+/-0.91, p<0.01), and COPD (2.1+/-0.45, p<0.01). Finally, the TGF-beta gene expression level was increased in SM patients (4.91+/-0.69, p<0.001) as well as in COPD group (5.41+/-0.78, p<0.001). In SM patients, IL-17 (R=-0.721, p<0.05), IL-6 (R=-0.621, p<0.05) and TGF-beta (R=-0.658, p<0.05) had significant negative association with FEV1 (%). Inversely, Il-10 showed positive correlation (R=0.673) with FEV1 (%). Th17/Treg cells related cytokines genes were highly expressed and imbalanced in peripheral blood mononuclear cells of SM and COPD patients which correlated with pulmonary dysfunction.

http://ijaai.tums.ac.ir/index.php/ijaai/article/download/1236/765

Fernandes, L. and A. M. Mesquita (2017). **"The success and safety profile of sputum induction in patients with chronic obstructive pulmonary disease: An Indian experience."** Indian J Tuberc **64**(3): 201-205.

BACKGROUND: Neutrophilic inflammation is common in chronic obstructive pulmonary disease while Asthma COPD overlap syndrome has eosinophilic predominance. Identifying the type of inflammation will aid in better management of COPD, but published studies show that induced sputum examination is more frequently used in asthma than COPD, with safety being the limiting factor. We aimed to determine the success and safety of sputum induction (SI) in COPD patients. METHODS: 116 stable COPD patients underwent SI. Success was defined as adequate sputum sample resulting in a cytospin sufficient to assess differential count while safety by the fall in FEV1. RESULTS: The mean (SD) FEV1% predicted post bronchodilator was 58.8 (17.8) and 59 (51.8%) patients had moderate COPD. Success was 98.28%. The procedure was safe with overall fall in FEV1 of 11.1% (5.1, 15.2). >/=20% fall was noted in 13 (11.4%) patients, 10-20% in 24 (21.0%) patients, and less than 10% in 29 (25.4%) patients while 48 (42.1%) had no fall. There was an inverse correlation between reversibility in FEV1 and percentage fall in FEV1; r=-0.437 and p=0.001. Stepwise multivariate linear regression showed reversibility as an independent predictor of fall in FEV1; R(2)=0.137. CONCLUSIONS: Sputum induction is successful and safe in COPD. Even a fall in FEV1>20% is reversible.

https://www.sciencedirect.com/science/article/pii/S0019570716302426?via%3Dihub

Frenkel, A., E. Kachko, et al. (2018). **"Estimations of a degree of steroid induced leukocytosis in patients with acute infections."** Am J Emerg Med **36**(5): 749-753.

BACKGROUND: Glucocorticosteroids (GCS) are known to cause the hematologic effect of leukocytosis and neutrophilia. Leukocytosis is a key parameter in establishing the diagnosis of sepsis and in the estimation of its severity. OBJECTIVE: To quantify the effect of chronic or acute GCS treatment on the level of leukocytosis in patients with acute infectious process. METHODS: We conducted a retrospective cohort study of patients with an acute infection hospitalized in tertiary medical center between the years 2003-2014. Patients were classified into three categories: chronic GCS treatment, acute GCS treatment, no GCS treatment. The primary outcome was the maximal WBC count within the first 24h from admission. RESULTS: We identified 5468 patients with acute infection: 333 of them with chronic GCS

treatment, 213 with acute GCS treatment and 4922 with no GCS treatment. The overall maximal leukocytes count was higher in GCS therapy groups: 15.4+/-8.3x10(9)/L for the acute GCS treatment, 14.9+/-7.4x10(9)/L for chronic GCS treatment and 12.9+/-6.4x10(9)/L for the no GCS group (P<0.001). CONCLUSION: In patients with acute infections chronically treated with GCS, an increase in the WBC is at average of 5x10(9)/L. These data must be taken into consideration while using the level of leukocytosis as a parameter in the diagnosis of the infectious process.

https://www.ajemjournal.com/article/S0735-6757(17)30805-7/fulltext

Frykholm, E., P. Klijn, et al. (2019). **"Effect and feasibility of non-linear periodized resistance training in people with COPD: study protocol for a randomized controlled trial."** Trials **20**(1): 6.

BACKGROUND: In people with chronic obstructive pulmonary disease (COPD), limb-muscle dysfunction is one of the most troublesome systemic manifestations of the disease, which at the functional level is evidenced by reduced strength and endurance of limb muscles. Improving limb-muscle function is an important therapeutic goal of COPD management, for which resistance training is recommended. However, current guidelines for resistance training in COPD mainly focus on improving muscle strength which only reflects one aspect of limb-muscle function and does not address the issue of reduced muscle endurance. The latter is of importance considering that the reduction in limb-muscle endurance often is greater than that of muscle weakness, and also, limb-muscle endurance seems to be closer related to walking capacity as well as arm function than to limb-muscle strength within this group of people. Thus, strategies targeting multiple aspects of the decreased muscle function are warranted to increase the possibility for an optimal effect for the individual patient. Periodized resistance training, which represents a planned variation of resistance training variables (i.e., volume, intensity, frequency, etc.), is one strategy that could be used to target limb-muscle strength as well as limb-muscle endurance within the same exercise regimen. METHODS: This is an international, multicenter, randomized controlled trial comparing the effect and feasibility of non-linear periodized resistance training to traditional non-periodized resistance training in people with COPD. Primary outcomes are dynamic limb-muscle strength and endurance. Secondary outcomes include static limb-muscle strength and endurance, functional performance, quality of life, dyspnea, intramuscular adaptations as well as the proportion of responders. Feasibility of the training programs will be assessed and compared on attendance rate, duration, satisfaction, drop-outs as well as occurrence and severity of any adverse events. DISCUSSION: The proposed trial will provide new knowledge to this research area by investigating and comparing the feasibility and effects of non-linear periodized resistance training compared to traditional non-periodized resistance training. If the former strategy produces larger physiological adaptations than non-periodized resistance training, this project may influence the prescription of resistance training in people with COPD. TRIAL REGISTRATION: ClinicalTrials.gov, ID: NCT03518723 . Registered on 13 April 2018.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6318913/pdf/13063_2018_Article_3129.pdf

Galizia, G., G. Balestrieri, et al. (2018). **"Role of rehabilitation in the elderly after an acute event: insights from a real-life prospective study in the subacute care setting."** Eur J Phys Rehabil Med **54**(6): 934-938.

BACKGROUND: Any acute event, either primary or secondary to a chronic disease, is generally followed by some degree of physical impairment. Subacute care (SAC) represents one of the inpatient intermediate care settings aimed at completing recovery and restoring functional capacity. Debate exists on the role of the rehabilitation treatment in the SAC setting. AIM: The aim of this study was to compare the outcomes of patients managed in two different SAC Units where A) patients undergo an individualized rehabilitation program on top of optimal medical therapy (OMT) B) patients receive OMT only. DESIGN: Real-life prospective study. SETTING: SAC units. POPULATION: Seventy-five chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) patients transferred after an acute hospitalization. METHODS: Upon SAC admission, the following scales were obtained: cumulative illness rating scale comorbidity and severity (CIRSC and CIRSS), mini mental state examination (MMSE), Performance-

Oriented Mobility Assessment (POMA), Barthel Index (BI), the 10-meter walking test (10MWT). Pre-admission BI was also collected based on history. Upon SAC discharge, BI, POMA, and 10MWT were repeated. RESULTS: Patients (44 in Group A, 31 in Group B) were similar with regard to age, gender, MMSE, clinical complexity, pre-admission BI, admission 10MWT, POMA, and bedrest conditions. Admission BI was lower in Group A. In both groups BI was lower when compared to the respective pre-admission score. Upon discharge, Group A patients were characterized by a higher BI and POMA compared to Group B. Indeed, BI and POMA improved at discharge only in Group A patients. Only this latter group reached the pre-morbid BI. Upon discharge the number of bedrest patients decreased only in Group A. The percentage of patients discharged home was also much higher in Group A, while a greater number of Group B patients were transferred to a rehabilitation ward or were enrolled in an integrated home care assistance program. CONCLUSIONS: In a real-life prospective experience, a better outcome is demonstrated in elderly CHF and COPD patients undergoing a rehabilitative approach during their in-hospital SAC stay. CLINICAL REHABILITATION IMPACT: An individualized rehabilitation program should integrate medical treatment of CHF and BPCO patients in the SAC setting. This approach demonstrates a better cost-effectiveness management of these patients.

Grigoryeva, N. Y., C. Maiorova capital Em, et al. (2019). **"capital ES, Cyrillicomorbidity and polymorbidity of the patient with chronic obstructive pulmonary disease and cardiovascular diseases."** Ter Arkh **91**(1): 44-47.

AIM: the study of comorbid status and characteristics of clinical course of ischemic heart disease (IHD) in patients with chronic obstructive pulmonary disease (COPD). MATERIALS AND METHODS: We conducted a retrospective analysis of case histories of 958 IHD patients aged 32 to 93 years (mean age of 60.8+/-10.2 years), including men - 525 (54.8%), women - 433 (45.2%) who were treated in the cardiology Department of city clinical hospital numero sign5 of Nizhny Novgorod. Related COPD was diagnosed in 251 patients (26.3%). We compared two groups patients: with IHD and COPD, and the second - persons suffering from only IHD (without COPD). RESULTS: Myocardial infarction was transferred by 62.2% of patients in Group 1, which is 16.3% more than in Group 2 (p<0.05). Arterial hypertension in patients with COPD was 13.6% more frequent than in patients without COPD (p<0.05), and 6.4% more often (p<0.05), with comorbid pathology there was a chronic and paroxysmal forms of atrial fibrillation. In patients with IHD in combination with COPD it is 21.5% more often (p<0.05) than in IHD without COPD, there was shortness of breath and 32.1% more often (p<0.05) of the heartbeat. In patients with IHD with COPD, a higher level of was C-reactive protein detected (p<0.05) and more pronounced violations of the lipid profile (p<0.05). CONCLUSION: COPD makes a significant contribution to the development of the cardiovascular continuum, modifying its course. A modern patient with COPD is a high-risk patient with severe cardiovascular comorbidity and various polymorbidity.

Hamad, G. A., W. Cheung, et al. (2018). **"Eosinophils in COPD: how many swallows make a summer?"** Eur Respir J **51**(1)
https://erj.ersjournals.com/content/51/1/1702177

Hassan, T., C. de Santi, et al. (2017). **"Alpha-1 antitrypsin augmentation therapy decreases miR-199a-5p, miR-598 and miR-320a expression in monocytes via inhibition of NFkappaB."** Sci Rep **7**(1): 13803.

Alpha-1 antitrypsin (AAT) augmentation therapy involves infusion of plasma-purified AAT to AAT deficient individuals. Whether treatment affects microRNA expression has not been investigated. This study's objectives were to evaluate the effect of AAT augmentation therapy on altered miRNA expression in

monocytes and investigate the mechanism. Monocytes were isolated from non-AAT deficient (MM) and AAT deficient (ZZ) individuals, and ZZs receiving AAT. mRNA (qRT-PCR, microarray), miRNA (miRNA profiling, qRT-PCR), and protein (western blotting) analyses were performed. Twenty one miRNAs were differentially expressed 3-fold between ZZs and MMs. miRNA validation studies demonstrated that in ZZ monocytes receiving AAT levels of miR-199a-5p, miR-598 and miR-320a, which are predicted to be regulated by NFkappaB, were restored to levels similar to MMs. Validated targets co-regulated by these miRNAs were reciprocally increased in ZZs receiving AAT in vivo and in vitro. Expression of these miRNAs could be increased in ZZ monocytes treated ex vivo with an NFkappaB agonist and decreased by NFkappaB inhibition. p50 and p65 mRNA and protein were significantly lower in ZZs receiving AAT than untreated ZZs. AAT augmentation therapy inhibits NFkappaB and decreases miR-199a-5p, miR-598 and miR-320a in ZZ monocytes. These NFkappaB-inhibitory properties may contribute to the anti-inflammatory effects of AAT augmentation therapy.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5653852/pdf/41598_2017_Article_14310.pdf

Hernandez Zenteno, R. J., D. F. Lara, et al. (2018). **"Varenicline for long term smoking cessation in patients with COPD."** Pulm Pharmacol Ther **53**: 116-120.

BACKGROUND: Quitting smoking is key for patients with Chronic Obstructive Pulmonary Disease (COPD). Standard recommendations for quitting smoking are implemented for COPD as well. Varenicline Tartrate (VT) is the most effective drug to help quit smoking, but few studies have analysed its effectiveness. AIM OF THE STUDY: To determine the Abstinence Rate (AR) at 12 months, in COPD and non-COPD smokers. METHODS: Observational study in 31 COPD (post bronchodilator-BD FEV1/FVC <0.70) and in 63 non-COPD smokers, were invited to receive treatment with Varenicline Tartrate (VT). Fourteen subjects with COPD and 46 non-COPD subjects received additionally Cognitive-Behavioral Therapy (CBT). Abstinence rate (AR) was validated by exhaled carbon monoxide CO (COe), in addition to a phone or face-to-face interview. Motivation score was measured with a visual analogue scale (MS). RESULTS: Differences between COPD and non-COPD, mean FEV1/FVC ratio 0.52+/-0.10 vs. 0.90+/-0.15, age 60+/-10 vs. 47+/-10 years, smoking pack-years 37+/-3.5 vs. 22+/-12, and COe 16+/-11 vs. 12+/-9ppm were statistically significant ($p<0.05$); for MS the score was 93+/-11 vs. 93+/-11 and for attempts to quit (AQ) 2+/-2 vs. 2+/-3 were not. AR was not significantly different at 12 months (61.2 vs. 42.8% $p=0.072$). Motivation was the only significant one-year AR predictor. CONCLUSIONS: COPD smokers had a similar response (higher tendency) to VT regardless of the presence of airflow obstruction and stronger nicotine addiction.

https://www.sciencedirect.com/science/article/pii/S1094553918300427?via%3Dihub

Hsu, A. C., K. Dua, et al. (2017). **"MicroRNA-125a and -b inhibit A20 and MAVS to promote inflammation and impair antiviral response in COPD."** JCI Insight **2**(7): e90443.

Influenza A virus (IAV) infections lead to severe inflammation in the airways. Patients with chronic obstructive pulmonary disease (COPD) characteristically have exaggerated airway inflammation and are more susceptible to infections with severe symptoms and increased mortality. The mechanisms that control inflammation during IAV infection and the mechanisms of immune dysregulation in COPD are unclear. We found that IAV infections lead to increased inflammatory and antiviral responses in primary bronchial epithelial cells (pBECs) from healthy nonsmoking and smoking subjects. In pBECs from COPD patients, infections resulted in exaggerated inflammatory but deficient antiviral responses. A20 is an important negative regulator of NF-kappaB-mediated inflammatory but not antiviral responses, and A20 expression was reduced in COPD. IAV infection increased the expression of miR-125a or -b, which directly reduced the expression of A20 and mitochondrial antiviral signaling (MAVS), and caused exaggerated inflammation and impaired antiviral responses. These events were replicated in vivo in a mouse model of experimental COPD. Thus, miR-125a or -b and A20 may be targeted therapeutically to inhibit excessive inflammatory responses and enhance antiviral immunity in IAV infections and in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5374076/pdf/jciinsight-2-90443.pdf

Huang, T. H., T. R. Hsiue, et al. (2018). **"Comparison of different staging methods for COPD in predicting outcomes."** Eur Respir J **51**(3)Chronic obstructive pulmonary disease (COPD) is commonly staged according to the percentage of predicted forced expiratory volume in 1 s (FEV1 % pred), but other methods have been proposed. In this study we compared the performance of seven staging methods in predicting outcomes.We retrospectively studied 296 COPD outpatients. For each patient the disease severity was staged by separately applying the following methods: the criteria proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), quartiles of FEV1 % pred and z-score of FEV1, quartiles and specified cut-off points of the ratio of FEV1 over height squared ((FEV1.Ht(-2))A and (FEV1.Ht(-2))B, respectively), and quartiles of the ratio of FEV1 over height cubed (FEV1.Ht(-3)) and of FEV1 quotient (FEV1Q). We evaluated the performance of these methods in predicting the risks of severe acute exacerbation and all-cause mortality.Overall, staging based on the reference-independent FEV1Q performed best in predicting the risks of severe acute exacerbation (including frequent exacerbation) and mortality, followed by (FEV1.Ht(-2))B The performance of staging methods could also be influenced by the choice of cut-off values. Future work using large and ethnically diverse populations to refine and validate the cut-off values would enhance the prediction of outcomes.

https://erj.ersjournals.com/content/51/3/1700577

Jaen-Moreno, M. J., N. Feu, et al. (2019). **"Smoking cessation opportunities in severe mental illness (tobacco intensive motivational and estimate risk - TIMER-): study protocol for a randomized controlled trial."** Trials **20**(1): 47.

BACKGROUND: There is an increased risk of premature death in people with severe mental illness (SMI). Respiratory disorders and cardiovascular disease are leading causes of increased mortality rates in these patients, and tobacco consumption remains the most preventable risk factor involved. Developing new tools to motivate patients towards cessation of smoking is a high priority. Information on the motivational value of giving the lung age and prevention opportunities is unknown in this high-risk population. METHODS/DESIGN: This article describes in detail a protocol developed to evaluate an intensive motivational tool, based on the individual risks of pulmonary damage and prevention opportunities. It is designed as a randomized, 12-month, follow-up, multicenter study. A minimum of 204 smokers will be included, aged 40 years and older, all of whom are patients diagnosed with either schizophrenia or bipolar disorder (BD). Chronic obstructive pulmonary disease (COPD) will be evaluated using spirometry, and the diagnosis will then be validated by a pneumologist and the lung age estimated. Based on this value, a motivational message about prevention will be issued for the intervention group, which will be reinforced by individualized text messages over a period of 3 months. The efficacy of the method and the pulmonary damage variables will be evaluated: smoking cessation at the end of follow-up will be confirmed by cooximetry, and the COPD diagnosis and the severity of the staging for disease will be assessed. DISCUSSION: In the context of community care, screening and early detection of lung damage could potentially be used, together with mobile technology, in order to produce a prevention message, which may provide patients with SMI with a better chance of quitting smoking. TRIAL REGISTRATION: ClinicalTrials.gov, ID: NCT03583203 . Registered on 11 July 2018. Trial status: recruitment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6332915/pdf/13063_2018_Article_3139.pdf

Jia, Q., J. Chang, et al. (2018). **"MiR-212-5p exerts a protective effect in chronic obstructive pulmonary disease."** Discov Med **26**(144): 173-183.

Chronic obstructive pulmonary disease (COPD) is a common respiratory tract disease with an incompletely understood pathogenesis. According to previous reports, miRNAs play a crucial pathophysiological role in COPD. MiR-212 was reported to be downregulated in COPD patients; however, the role of miR-212 in COPD remains unknown. In this study, the expression level of miR-212-5p and miR-223 decreased significantly in COPD patients compared to healthy controls. In vitro experiments showed that cigarette smoke extract (CSE) induced NCI-H292 cell apoptosis and inhibited cell proliferation. Inflammation and COPD related genes were also upregulated by CSE, while miR-212-5p inhibited the overexpression of these genes. Furthermore, miR-212-5p promoted cell proliferation and inhibited IGFBP3 expression which was induced by CSE. The expression of p-Akt was also inhibited by CSE, while miR-212-5p significantly promoted the phosphorylation of Akt. In summary, our data suggest that miR-212-5p exerts a protective effect in COPD, and may serve as a prognostic biomarker and potential therapeutic target for COPD.

Kalchiem-Dekel, O. and R. M. Reed (2017). **"Statins in COPD: Life After STATCOPE."** Chest **152**(3): 456-457.

https://journal.chestnet.org/article/S0012-3692(17)30731-6/pdf

Khan, N., J. Vestbo, et al. (2018). **"The Manchester Respiratory-related Sleep Symptoms scale for patients with COPD: development and validation."** Int J Chron Obstruct Pulmon Dis **13**: 3885-3894.

Background: In COPD disturbed sleep is related to exacerbation frequency, poor quality of life, and early mortality. We developed the Manchester Respiratory-related Sleep Symptoms scale (MaRSS) to assess sleep-time symptoms in COPD. Methods: Focus groups including COPD and age-matched controls were used to develop an item-list, which was then administered to COPD patients and age-matched controls in a cross-sectional study. Hierarchical and Rasch analysis informed item selection and scale unidimensionality. Construct validity was examined using Pearson's correlation with the Sleep Problems Index, St George's Respiratory Questionnaire (SGRQ), and FACIT-Fatigue scale. MaRSS change scores from baseline (stable) to exacerbation were assessed in a separate sub-study of COPD patients. Results: Thirty-six COPD patients and nine age-matched controls produced an initial 26-item list. The cross-sectional study involved 203 COPD patients (male: 63%, mean age 64.7 years) and 50 age-matched controls (male: 56%, mean age 65.8 years). Eighteen items were removed to develop an eight-item unidimensional scale covering breathlessness, chest tightness, cough, sputum production, lack of sleep, and medication use. MaRSS scores significantly correlated with sleep problems, SGRQ Total, and FACIT-Fatigue (r=0.58-0.62) and demonstrated a good fit to the Rasch model (chi-squared=29.2; P=0.04). In the substudy, MaRSS scores demonstrated a moderate effect size from baseline to exacerbation visit in 27 patients with 32 exacerbation episodes (Cohen's d=0.6). Conclusion: The MaRSS is a reliable, valid, and clinically responsive measure of respiratory-related symptoms that disturb sleep. It is simple to use and score, making it suitable for research and clinical practice.

https://www.dovepress.com/getfile.php?fileID=46620

Kisialiou, A., G. Prinzi, et al. (2019). **"Pharmacological Management of Chronic Obstructive Lung Disease (COPD). Evidence from a Real-World Perspective - Part 2."** Curr Med Chem **26**(10): 1734-1745.

BACKGROUND: We report a comprehensive overview of current COPD therapies from a real-world experience. OBJECTIVE: Critically review the opportunities and the challenges occurring in the real-world treatment of COPD. METHODS: This is a review that also report results from COPD patients treated with standardized therapy including pulmonary rehabilitation (Real World Data - RWD). CONCLUSION: Comprehensive assessment of COPD management requires strategies able to evaluate efficacy and

usefulness in a real-world population, that take into account the interaction between experience and academic training, research, adherence to guidelines and judgments in order to plan the appropriate and optimum use of available strategies.

http://www.eurekaselect.com/166776/article

Koo, H. K., D. M. Vasilescu, et al. (2018). **"Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study."** Lancet Respir Med **6**(8): 591-602.

BACKGROUND: The concept that small conducting airways less than 2 mm in diameter become the major site of airflow obstruction in chronic obstructive pulmonary disease (COPD) is well established in the scientific literature, and the last generation of small conducting airways, terminal bronchioles, are known to be destroyed in patients with very severe COPD. We aimed to determine whether destruction of the terminal and transitional bronchioles (the first generation of respiratory airways) occurs before, or in parallel with, emphysematous tissue destruction. METHODS: In this cross-sectional analysis, we applied a novel multiresolution CT imaging protocol to tissue samples obtained using a systematic uniform sampling method to obtain representative unbiased samples of the whole lung or lobe of smokers with normal lung function (controls) and patients with mild COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage 1), moderate COPD (GOLD 2), or very severe COPD (GOLD 4). Patients with GOLD 1 or GOLD 2 COPD and smokers with normal lung function had undergone lobectomy and pneumonectomy, and patients with GOLD 4 COPD had undergone lung transplantation. Lung tissue samples were used for stereological assessment of the number and morphology of terminal and transitional bronchioles, airspace size (mean linear intercept), and alveolar surface area. FINDINGS: Of the 34 patients included in this study, ten were controls (smokers with normal lung function), ten patients had GOLD 1 COPD, eight had GOLD 2 COPD, and six had GOLD 4 COPD with centrilobular emphysema. The 34 lung specimens provided 262 lung samples. Compared with control smokers, the number of terminal bronchioles decreased by 40% in patients with GOLD 1 COPD (p=0.014) and 43% in patients with GOLD 2 COPD (p=0.036), the number of transitional bronchioles decreased by 56% in patients with GOLD 1 COPD (p=0.0001) and 59% in patients with GOLD 2 COPD (p=0.0001), and alveolar surface area decreased by 33% in patients with GOLD 1 COPD (p=0.019) and 45% in patients with GOLD 2 COPD (p=0.0021). These pathological changes were found to correlate with lung function decline. We also showed significant loss of terminal and transitional bronchioles in lung samples from patients with GOLD 1 or GOLD 2 COPD that had a normal alveolar surface area. Remaining small airways were found to have thickened walls and narrowed lumens, which become more obstructed with increasing COPD GOLD stage. INTERPRETATION: These data show that small airways disease is a pathological feature in mild and moderate COPD. Importantly, this study emphasises that early intervention for disease modification might be required by patients with mild or moderate COPD. FUNDING: Canadian Institutes of Health Research.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30196-6/fulltext

Kubota, Y., A. R. Folsom, et al. (2018). **"Prospective study of lung function and abdominal aortic aneurysm risk: The Atherosclerosis Risk in Communities study."** Atherosclerosis **268**: 225-230.

BACKGROUND AND AIMS: No prospective study has investigated whether individuals with respiratory impairments, including chronic obstructive pulmonary disease (COPD) and restrictive lung disease (RLD), are at increased risk of abdominal aortic aneurysm (AAA). We aimed to prospectively investigate whether those respiratory impairments are associated with increased AAA risk. METHODS: In 1987-1989, the Atherosclerosis Risk in Communities (ARIC) study followed 14,269 participants aged 45-64 years, without a history of AAA surgery, through 2011. Participants were classified into four groups, "COPD" [forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <lower limit of normal (LLN)], "RLD" (FEV1/FVC >/= LLN and FVC < LLN), "respiratory symptoms with normal spirometry" (without RLD or COPD), and "normal" (without respiratory symptoms, RLD or COPD, reference group). RESULTS: During the 284,969 person-years of follow-up, 534 incident AAA events were documented. In an age, sex, and

race-adjusted proportional hazards model, individuals with respiratory impairments had a significantly higher risk of AAA than the normal reference group. After adjustment for AAA risk factors, including smoking status and pack-years of smoking, AAA risk was no longer significant in the respiratory symptoms with normal spirometry group [HR (95% CI), 1.25 (0.98-1.60)], but was still increased in the other two groups [RLD: 1.45 (1.04-2.02) and COPD: 1.66 (1.34-2.05)]. Moreover, continuous measures of FEV1/FVC, FEV1 and FVC were associated inversely with risk of AAA. CONCLUSIONS: In the prospective population-based cohort study, obstructive and restrictive spirometric patterns were associated with increased risk of AAA independent of smoking, suggesting that COPD and RLD may increase the risk of AAA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785925/pdf/nihms935283.pdf

Lai, T., Y. Li, et al. (2018). **"Heparin-binding epidermal growth factor contributes to COPD disease severity by modulating airway fibrosis and pulmonary epithelial-mesenchymal transition."** Lab Invest **98**(9): 1159-1169.

Although airway fibrosis and epithelial-mesenchymal transition (EMT) contribute to airway remodeling in chronic obstructive pulmonary disease (COPD), the mechanisms underlying their development have not been fully elucidated. In the present study, we aimed to assess heparin-binding epidermal growth factor (HB-EGF) expression in the airways of patients with COPD and to elucidate the possible role of HB-EGF in the pathology of COPD. Sputum and lung tissue HB-EGF expression was evaluated in control subjects and patients with COPD. The relationships between HB-EGF expression, disease severity, collagen deposition (fibrosis), and EMT were investigated. In vitro, human bronchial epithelial (HBE) cells and lung fibroblast cells exposed to the recombinant HB-EGF, collagen deposition and EMT were assessed. We found that sputum HB-EGF expression was significantly increased in patients with COPD compared with non-smokers and smokers without COPD. There was a significant positive correlation between sputum HB-EGF and COPD assessment test (CAT) score. HB-EGF expression was significantly increased in the lung tissue samples of patients with COPD and associated with collagen deposition and N- and E-cadherin, and vimentin expression. In vitro, HB-EGF promoted collagen production in lung fibroblasts. Moreover, HB-EGF induced the EMT process through induction of N-and E-cadherin, and vimentin expression in HBE cells. Collectively, HB-EGF induces airway remodeling by modulating airway fibrosis and pulmonary EMT, and contributes to the COPD severity. The current data may provide insight into the underlying pathogenesis of COPD, in which HB-EGF has an important pathogenic role.

https://www.nature.com/articles/s41374-018-0049-0

Landis, S., R. Suruki, et al. (2018). **"Demographic and Clinical Characteristics of COPD Patients at Different Blood Eosinophil Levels in the UK Clinical Practice Research Datalink."** Copd **15**(2): 177-184.

Blood eosinophil count may be a useful biomarker for predicting response to inhaled corticosteroids and exacerbation risk in chronic obstructive pulmonary disease (COPD) patients. The optimal cut point for categorizing blood eosinophil counts in these contexts remains unclear. We aimed to determine the distribution of blood eosinophil count in COPD patients and matched non-COPD controls, and to describe demographic and clinical characteristics at different cut points. We identified COPD patients within the UK Clinical Practice Research Database aged >/=40 years with a FEV1/FVC <0.7, and >/=1 blood eosinophil count recorded during stable disease between January 1, 2010 and December 31, 2012. COPD patients were matched on age, sex, and smoking status to non-COPD controls. Using all blood eosinophil counts recorded during a 12-month period, COPD patients were categorized as "always above," "fluctuating above and below," and "never above" cut points of 100, 150, and 300 cells/muL. The geometric mean blood eosinophil count was statistically significantly higher in COPD patients versus matched controls (196.6 cells/microL vs. 182.1 cells/microL; mean difference 8%, 95% CI: 6.8, 9.2), and in COPD patients with versus without a history of asthma (205.0 cells/microL vs. 192.2 cells/microL; mean difference 6.7%, 95%, CI: 4.9, 8.5). About half of COPD patients had all blood eosinophil counts above 150 cells/muL; this persistent higher eosinophil phenotype was associated with being male, higher body

mass index, and history of asthma. In conclusion, COPD patients demonstrated higher blood eosinophil count than non-COPD controls, although there was substantial overlap in the distributions. COPD patients with a history of asthma had significantly higher blood eosinophil count versus those without.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1441275

Liao, K. M. and C. Y. Chen (2019). **"The association between adherence and dementia in chronic obstructive pulmonary disease."** Medicine (Baltimore) **98**(20): e15646.

Our previous studies have shown that patients with chronic obstructive pulmonary disease (COPD) have an increased risk of dementia and that COPD combined with dementia confers an increased risk of acute respiratory dysfunction, severe sepsis, and hospital mortality. The aim of this study was to investigate whether medication adherence can decrease the risk of dementia in COPD.This retrospective study enrolled COPD patients from 1 million beneficiaries randomly sampled from all beneficiaries in Taiwan. We excluded COPD patients not prescribed a bronchodilator or those using theophylline or short-acting beta2-agonists for <1 year. To ensure a sufficient observation period, we excluded patients diagnosed with dementia within 1 year after the diagnosis of COPD or those prescribed bronchodilators after the diagnosis of dementia. Patients with COPD and a history of severe mental disorders were also excluded.There was a total of 13,015 first diagnoses of COPD from 1998 to 2012, of whom 9,489 had a proportion of days covered (PDC) <80% and 1,206 had a PDC >/=80% before matching. In the high PDC group, 226 (18.74%) patients had acute exacerbations of COPD and were hospitalized within 1 year after diagnosis. Compared with the PDC <80% group, the PDC >/=80% group had a risk of dementia with an adjusted hazard ration of 0.88, but there were no statistically significant differences (95% confidence interval, 0.57-1.35).Medication adherence to bronchodilators may not modify the risk of dementia in patients with COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6531282/pdf/medi-98-e15646.pdf

Makino, Y., Y. Shimada, et al. (2018). **"Assessment of emphysema severity as measured on three-dimensional computed tomography images for predicting respiratory complications after lung surgery."** Eur J Cardiothorac Surg **54**(4): 671-676.

OBJECTIVES: Emphysema is one of the main causes of respiratory complications in patients operated on for lung cancer. We have used three-dimensional computed tomography (3D CT) for surgical simulations, as well as for depicting emphysematous areas as low attenuation areas (LAAs) and visual scores based on the Goddard classification (Goddard score), which is a visual scale of the area of vascular disruption and LAA for each lung field. This study aimed to investigate the effectiveness of the 3D CT function for assessing emphysema severity and its association with respiratory complications. METHODS: The study included 504 lung cancer patients who had preoperative 3D CT from October 2010 to March 2015. Goddard score and LAA% (LAA/total lung volume) were measured using 3D CT data. The relationship between respiratory complications and independent variables was investigated. RESULTS: Postoperative respiratory complications were observed in 69 (13.6%) patients. The receiver operating characteristic curves for respiratory complications determined using the Goddard score and LAA% dichotomized at each cut-off level (1 and 0.7%, respectively) showed that the events were observed in 32% of the patients with a Goddard score >/=1 and in 25% of the patients with an LAA% >/=0.7. On multivariable analyses, the Goddard score was significantly correlated with postoperative respiratory complications (P < 0.001). CONCLUSIONS: Preoperative measurement of the Goddard score and LAA% using 3D CT in patients with lung cancer, particularly with the coexistence of emphysema, was beneficial for predicting postoperative respiratory complications.

https://academic.oup.com/ejcts/article-abstract/54/4/671/4930723?redirectedFrom=fulltext

Maniscalco, M., D. Paris, et al. (2018). **"Differential diagnosis between newly diagnosed asthma and COPD using exhaled breath condensate metabolomics: a pilot study."** Eur Respir J **51**(3) https://erj.ersjournals.com/content/51/3/1701825

Miyamoto, A., A. Kurosaki, et al. (2019). **"Reduced area of the normal lung on high-resolution computed tomography predicts poor survival in patients with lung cancer and combined pulmonary fibrosis and emphysema."** Respir Investig **57**(2): 140-149.

BACKGROUND: This study aimed to determine the radiologic predictors and clarify the clinical features related to survival in patients with combined pulmonary fibrosis and emphysema (CPFE) and lung cancer. METHODS: We retrospectively reviewed the medical chart data and high-resolution computed tomography (HRCT) findings for 81 consecutive patients with CPFE and 92 primary lung cancers (70 men, 11 women; mean age, 70.9 years). We selected 8 axial HRCT images per patient, and visually determined the normal lung, modified Goddard, and fibrosis scores. Multivariate analysis was performed using the Cox proportional hazards regression model. RESULTS: The major clinical features were a high smoking index of 54.8 pack-years and idiopathic pulmonary fibrosis (n = 44). The major lung cancer profile was a peripherally located squamous cell carcinoma (n = 40) or adenocarcinoma (n = 31) adjacent to emphysema in the upper/middle lobe (n = 27) or fibrosis in the lower lobe (n = 26). The median total normal lung, modified Goddard, and fibrosis scores were 10, 8, and 8, respectively. TNM Classification of malignant tumors (TNM) stage I, II, III, and IV was noted in 37, 7, 26, and 22 patients, respectively. Acute exacerbation occurred in 20 patients. Multivariate analysis showed that a higher normal lung score and TNM stage were independent radiologic and clinical predictors of poor survival at the time of diagnosis of lung cancer. CONCLUSIONS: A markedly reduced area of normal lung on HRCT was a relevant radiologic predictor of survival.

https://www.sciencedirect.com/science/article/abs/pii/S2212534518301503?via%3Dihub

Mohamed Hoesein, F. A. A. and P. Zanen (2017). **"Don't Forget Symptomatic Smokers without Airflow Obstruction."** Ann Am Thorac Soc **14**(5): 615-616.

Murakami, J., K. Ueda, et al. (2018). **"Grading of Emphysema Is Indispensable for Predicting Prolonged Air Leak After Lung Lobectomy."** Ann Thorac Surg **105**(4): 1031-1037.

BACKGROUND: The aim of this study was to assess the utility of quantitative computed tomography-based grading of emphysema for predicting prolonged air leak after thoracoscopic lobectomy. METHODS: A consecutive series of 284 patients undergoing thoracoscopic lobectomy for lung cancer was retrospectively reviewed. Prolonged air leak was defined as air leaks lasting 7 days or longer. The grade of emphysema (emphysema index) was defined by the proportion of the emphysematous lung volume (less than -910 HU) to the total lung volume (-600 to -1,024 HU) by a computer-assisted histogram analysis of whole-lung computed tomography scans. RESULTS: The mean length of chest tube drainage was 1.5 days. Fifteen patients (5.3%) presented with prolonged air leak. According to a receiver-operating characteristics curve analysis, the emphysema index was the best predictor of prolonged air leak, with an area under the curve of 0.85 (95% confidence interval: 0.73 to 0.98). An emphysema index of 35% or greater was the best cutoff value for predicting prolonged air leak, with a negative predictive value of 0.99. The emphysema index was the only significant predictor for the length of postoperative chest tube drainage among conventional variables, including the pulmonary function and resected lobe, in both univariate and multivariate analyses. Prolonged air leak resulted in an increased duration of hospitalization ($p < 0.001$) and was frequently accompanied by pneumonia or empyema ($p < 0.001$).

CONCLUSIONS: The grade of emphysema on computed tomography scan is the best predictor of prolonged air leak that adversely influences early postoperative outcomes. We must take new measures against prolonged air leak in quantitative computed tomography-based high-risk patients.

https://www.annalsthoracicsurgery.org/article/S0003-4975(17)31631-4/pdf

Nagatani, Y., M. Hashimoto, et al. (2018). **"Continuous quantitative measurement of the main bronchial dimensions and lung density in the lateral position by four-dimensional dynamic-ventilation CT in smokers and COPD patients."** Int J Chron Obstruct Pulmon Dis **13**: 3845-3856.

Purpose: The purpose of this study was to measure changes in lung density and airway dimension in smokers in the lateral position using four-dimensional dynamic-ventilation computed tomography (CT) during free breathing and to evaluate their correlations with spirometric values. Materials and methods: Preoperative pleural adhesion assessments included dynamic-ventilation CT of 42 smokers (including 22 patients with COPD) in the lateral position, with the unoperated lung beneath (dependent lung). The scanned lungs' mean lung density (MLD) and the bilateral main bronchi's luminal areas (Ai) were measured automatically (13-18 continuous image frames, 0.35 seconds/frame). Calculations included cross-correlation coefficients (CCCs) between the MLD and Ai time curves, and correlations between the quantitative measurements and spirometric values were evaluated by using Spearman's rank coefficient. Results: The DeltaMLD1.05 (from the peak inspiration frame to the third expiratory frame, 1.05 seconds later) in the nondependent lung negatively correlated with FEV1/FVC ($r=-0.417$, $P<0.01$), suggesting that large expiratory movement of the nondependent lung would compensate limited expiratory movement of the dependent lung due to COPD. The DeltaAi1.05 negatively correlated with the FEV1/FVC predicted in both the lungs ($r=-0.465$ and -0.311, $P<0.05$), suggesting that early expiratory collapses of the main bronchi indicate severe airflow limitation. The CCC correlated with FEV1/FVC in the dependent lung ($r=-0.474$, $P<0.01$), suggesting that reduced synchrony between the proximal airway and lung occurs in patients with severe airflow limitation. Conclusion: In COPD patients, in the lateral position, the following abnormal dynamic-ventilation CT findings are associated with airflow limitation: enhanced complementary ventilation in the nondependent lung, early expiratory airway collapses, and reduced synchrony between airway and lung movements in the dependent lung.

https://www.dovepress.com/getfile.php?fileID=46548

Nagy, P., C. Antony, et al. (2018). **"Same-day Routine Chest-X Ray After Thoracic Surgery is Not Necessary!"** Zentralbl Chir **143**(1): 96-101.

INTRODUCTION: Performing a routine postoperative chest X-ray (CXR) after general thoracic surgery is daily practice in many thoracic surgery departments. The quality, frequency of pathological findings and the clinical consequences have not been well evaluated. Furthermore, exposure to ionising radiation should be restricted to a minimum and therefore routine practice can be questioned. METHODS: As a hospital standard, each patient was given a routine CXR after opening of the pleura and inserting a chest tube. From October 2015 to March 2016, each postoperative patient with a routine CXR was included in a prospective database, including film quality, pathological findings, clinical and laboratory results and cardiorespiratory monitoring, as well as clinical consequences. RESULTS: 546 patients were included. Risk factors for postoperative complications were obesity in 50 patients (9.2%), emphysema in 127 patients (23.3%), coagulopathy in 34 patients (6.2%), longer operation time (more than two hours) in 242 patients (44.3%) and previous lung irradiation in 29 (5.3%) of patients. Major lung resections were performed in 191 patients (35.9%). 263 (48.2%) patients had procedures with minimally invasive access. The quality of the X-ray film was insufficient in 8.2% of patients. 90 (16.5%) of CXRs were found to show pathological findings, with a trend for more pathological findings after open surgery (55/283; 19.4%) compared to minimally invasive surgery (35/263; 13.3%) ($p = 0.064$). 11 (2.0%) patients needed a surgical or clinical intervention during postoperative observation; this corresponds to 12.2% of patients with a pathological finding on CXR. Nine of these 11 patients were clinically symptomatic and only two (0.37%) patients were asymptomatic with a relevant pneumothorax. CONCLUSIONS: Our study cannot support routine

postoperative CXR after general thoracic procedures and we believe that restriction to clinically symptomatic cases should be a safe option.

https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0043-117174

Ngo, C. Q., T. Thi Bui, et al. (2018). **"Direct Hospitalization Cost of Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Vietnam."** Int J Environ Res Public Health **16**(1)Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have been found to contribute, predominantly, to increasing costs of COPD-a major public health issue. This study aimed to fill the gap in literature concerning costs of AECOPD in Vietnam, by examining the direct cost of AECOPD hospitalization and determining potentially associated factors. A cross-sectional study was conducted at the Respiratory Center of Bach Mai Hospital, Hanoi. A total of 57 participants were selected. Information regarding sociodemographic features, clinical characteristics, and hospitalization costs were collected. A multivariate generalized linear regression model was utilized to determine the factors associated with hospitalization costs. The mean total and daily hospitalization cost were 18.3 million VND (SD = 12.9) and 2.5 million VND (SD = 3.2), respectively. Medication cost accounted for 53.9% of hospitalization cost (from 44.0% in the Global Initiative for Chronic Obstructive Lung Disease Classification A (GOLD A) to 55.3% in GOLD C). Patients having GOLD D COPD (Coef. = 5.78; 95% CI = 0.73(-)10.83), higher age (Coef. = 0.37; 95% CI = 0.13(-)0.61), and higher duration of hospitalization (Coef. = 1.91; 95% CI = 1.28(-)2.53) had higher hospitalization costs ($p < 0.05$). This study suggested that interventions to screen COPD patients as well as provide timely treatment should be conducted widely in the community in order to avoid any unnecessary hospitalization cost, consequently reducing the economic burden of COPD.

https://res.mdpi.com/ijerph/ijerph-16-00088/article_deploy/ijerph-16-00088.pdf?filename=&attachment=1

Novotna, B., M. Abdel-Hamid, et al. (2018). **"A pilot data analysis of a metabolomic HPLC-MS/MS study of patients with COPD."** Adv Clin Exp Med **27**(4): 531-539.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition with multiple clinical faces. Metabolomic profiling studies small molecules present in biological samples by combined use of chromatography with mass spectrometry. OBJECTIVES: The goal of our work was to perform a high performance liquid chromatography combined with tandem mass spectrometry (HPLC-MS/MS) metabolomic study to compare the concentrations of metabolites in COPD patients and in controls. MATERIAL AND METHODS: Participants were recruited at the University Hospital, Hradec Kralove, Czech Republic, with the approval of the ethics committee. The analysis of blood samples was performed at Health Sciences Center (HSC) in Kuwait. The blood samples were analyzed for concentrations of acylcarnitines and amino acids by high performance liquid chromatography (Waters 2690 HPLC; Waters, Milford, USA) and a triple-quadruple tandem mass spectrometer (Quattro LC, Micromass, Manchester, United Kingdom). RESULTS: Groups of 10 subjects with COPD and 10 healthy controls were analyzed. Carnitine analysis showed that the free carnitine to acylcarnitine ratio (C0/AC ratio) was significantly lower in COPD (0.58 muM/L) compared to the controls (0.73 muM/L; $p = 0.002$). The mean C8/C2 ratio in the COPD group was significantly higher (0.03 muM/L) - in the control group it was 0 muM/L ($p = 0.03$). Amino acid analysis showed lower levels of phenylalanine in the COPD group (22.05 muM/L) compared to the controls (30.05 muM/L; $p = 0.008$). The alanine concentrations were significantly lower in the COPD group (173 muM/L) than in the control group (253 muM/L; $p = 0.001$). The pyroglutamate levels were higher in COPD (1.58 muM/L) than in the controls (1 muM/L; $p = 0.040$). CONCLUSIONS: The carnitine and acylcarnitine levels in COPD subjects in this study possibly indicate a predisposition to atherosclerosis as a result of inadequate beta-oxidation of fatty acids and show the presence of oxidative stress. Furthermore, the high sensitivity to changes in circulating amino acid levels may allow us to detect subclinical malnutrition and take early preventative interventions such as nutritional supplementation and patient education.

Olivares, A., M. Vitacca, et al. (2018). **"Combining the Pulmonary Rehabilitation Decisional Score with the Bode Index and Clinical Opinion in Assigning Priority for Pulmonary Rehabilitation."** Copd **15**(3): 238-244.

Combining objective tools with clinical decision (CD) may help clinicians identify the priority for pulmonary rehabilitation (PR) in patients with COPD. We aimed to assess the specificity, sensitivity and efficiency of a new tool, the Pulmonary Rehabilitation Decisional Score (PRDS), and its correlation with the BODE index (BI) and CD in assigning PR priority. We retrospectively compared the three methods (CD vs. PRDS vs. BI) in 124 patients. We assigned low priority (LP), high priority (HP) and very high priority (VHP) to PR based on a priori scores of PRDS (LP = 0-10; HP = 11-17; VHP >/=18) and BI (LP = 0-2; HP = 3-5; VHP >/=6) and compared these with CD. PR priority assigned by the different methods was similar among groups, but did not often refer to the same subjects. PRDS and BI showed very high concordance with CD in defining VHP (97.8% and 95.6% for PRDS and BI, respectively), but were less concordant with CD in assigning LP and HP. Both PRDS and BI differently evaluated 38/124 cases compared to CD (PRDS underprescribed 18 and overprescribed 20; BI underprescribed 19 and overprescribed 19). However, a direct comparison between PRDS and BI showed that the discordance decreased to 8 underprescriptions and 10 overprescriptions (efficiency approximately 85%). An objective instrument such as the PRDS can enhance CD with additional information on new aspects such as disability and fragility. PRDS and BI are nonetheless equally efficient at detecting discrepancies versus CD alone, especially when the priority for PR is defined as low or very high.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1531389

Paschos, K. A. and A. Chatzigeorgiadis (2019). **"Cervicofacial Emphysema, Pneumomediastinum and Pneumothorax Caused by a Dental Procedure."** J Coll Physicians Surg Pak **29**(2): 191-192.

Pedraza-Serrano, F., R. Jimenez-Garcia, et al. (2019). **"Characteristics and outcomes of patients hospitalized with interstitial lung diseases in Spain, 2014 to 2015."** Medicine (Baltimore) **98**(21): e15779.

To assess characteristics and outcomes of patients hospitalized with interstitial lung diseases (ILD) and to analyze patient's comorbidities, procedures, and in-hospital outcomes.We identified patients hospitalized with idiopathic pulmonary fibrosis and others ILD such as hypersensitivity pneumonitis, cryptogenic organizing pneumonia, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, and sarcoidosis in Spain during 2014 and 2015.We identified 14,565 discharges among patients admitted for ILD in Spain during the study period: idiopathic pulmonary fibrosis (IPF) in 42.32% (n = 6164), sarcoidosis in 37.65% (n = 5484), hypersensitivity pneumonitis in 10.55% (n = 1538), cryptogenic organizing pneumonia in 7.06% (n = 1028), pulmonary Langerhans cell histiocytosis in 1.48% (n = 215), and lymphangioleiomyomatosis in 0.94% (n = 136). The most common associated comorbidities according to those included in the Charlson Comorbidity Index (CCI) were COPD, diabetes, and congestive heart disease. The presence of pulmonary hypertension increased the probability of dying in patients with idiopathic pulmonary fibrosis (OR 1.36; 95%CI 1.06-1.73). Patients with cryptogenic organizing pneumonia had the longest length of hospital stay and the highest percentage of hospital readmissions (23.64%). The highest IHM corresponded to the idiopathic pulmonary fibrosis (14.94%). Computed tomography of the chest was the procedure more used during admissions for ILD.IPF was responsible for larger percentage of hospital admission among ILD in our study. In addition, the IHM were higher in IPF patients in comparison with those with other ILD. The most common associated comorbidity in ILD according to those included in the CCI was COPD. Computed tomography of the chest was the procedure more frequently used.

Pornsuriyasak, P., M. Rambod, et al. (2018). **"Oxygen Uptake and Lactate Kinetics in Patients with Chronic Obstructive Pulmonary Disease during Heavy Intensity Exercise: Role of Pedaling Cadence."** Copd **15**(3): 283-293.

Oxygen uptake slow component ([Formula: see text]sc) is associated with lactate accumulation, likely a contribution of poorly oxidative muscle fibers. We aimed to test the hypothesis that higher muscle tension during slow pedaling rates would yield more prominent [Formula: see text]sc in healthy subjects, but not in COPD patients. Eight severe COPD patients and 8 age-matched healthy individuals performed 4 rest-heavy exercise transitions at 40 and 80 RPM. Work rates at the two cadences were balanced. Venous blood was sampled for measurement of lactate concentration at rest and every 2 minutes until the end of exercise. [Formula: see text] kinetics were analyzed utilizing nonlinear regression. [Formula: see text] phase II amplitudes at the two cadences were similar in both groups. In healthy individuals, [Formula: see text]sc was steeper at 40 than 80 RPM (46.6 +/- 12.0 vs. 29.5 +/- 11.7 mL/min(2), p = 0.002) but not in COPD patients (16.2 +/- 14.7 vs. 13.3 +/- 7.6 mL/min(2)). End-exercise lactate concentration did not differ between cadences in either group. In healthy individuals, greater slow-cadence [Formula: see text]sc seems likely related to oxidative muscle fiber recruitment at higher muscular tension. COPD patients, known to have fast-twitch fiber predominance, might be unable to recruit oxidative fibers at high muscle tension, blunting [Formula: see text]sc response.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1487391

Prokopenko, D., P. Sakornsakolpat, et al. (2018). **"Whole-Genome Sequencing in Severe Chronic Obstructive Pulmonary Disease."** Am J Respir Cell Mol Biol **59**(5): 614-622.

Genome-wide association studies have identified common variants associated with chronic obstructive pulmonary disease (COPD). Whole-genome sequencing (WGS) offers comprehensive coverage of the entire genome, as compared with genotyping arrays or exome sequencing. We hypothesized that WGS in subjects with severe COPD and smoking control subjects with normal pulmonary function would allow us to identify novel genetic determinants of COPD. We sequenced 821 patients with severe COPD and 973 control subjects from the COPDGene and Boston Early-Onset COPD studies, including both non-Hispanic white and African American individuals. We performed single-variant and grouped-variant analyses, and in addition, we assessed the overlap of variants between sequencing- and array-based imputation. Our most significantly associated variant was in a known region near HHIP (combined P = 1.6 x 10(-9)); additional variants approaching genome-wide significance included previously described regions in CHRNA5, TNS1, and SERPINA6/SERPINA1 (the latter in African American individuals). None of our associations were clearly driven by rare variants, and we found minimal evidence of replication of genes identified by previously reported smaller sequencing studies. With WGS, we identified more than 20 million new variants, not seen with imputation, including more than 10,000 of potential importance in previously identified COPD genome-wide association study regions. WGS in severe COPD identifies a large number of potentially important functional variants, with the strongest associations being in known COPD risk loci, including HHIP and SERPINA1. Larger sample sizes will be needed to identify associated variants in novel regions of the genome.

Qin, J., X. Deng, et al. (2019). **"Correlation between hypocalcemia and acute exacerbation of chronic obstructive pulmonary disease in the elderly."** Postgrad Med **131**(5): 319-323.

Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an important disease of hospitalized elderly patients, who often have electrolyte imbalances. This study was performed to analyze total serum calcium levels in elderly patients with AECOPD and identify the correlation between hypocalcemia and AECOPD. Methods: 153 elderly patients with AECOPD served as the observation group, and 115 healthy elderly people undergoing physical examinations served as the control group. Differences in the corrected serum calcium, albumin (ALB), and neutrophil/lymphocyte ratio (NLR) were analyzed between the observation and control groups before and after treatment. The incidence of hypocalcemia was compared among patients at different ages and with different pulmonary function classifications before treatment. The relationship between hypocalcemia and respiratory infection was analyzed. Differences in the pretreatment NLR, ALB, logarithm of the serum C-reactive protein level (LogCRP), and hospital stay were compared between patients with and without hypocalcemia. Results: The corrected serum calcium level ($P < 0.001$), NLR ($P = 0.001$) and albumin level ($P < 0.001$) were significantly different among the pretreatment group, post-treatment group, and control group. The serum calcium level, LogCRP, and NLR were significantly lower after than before treatment ($P < 0.05$). Significant differences in the incidence of hypocalcemia were found among patients of different ages ($P = 0.002$). The respiratory infection rate ($P < 0.001$), hospital stay ($P < 0.001$), NLR ($P = 0.007$), and LogCRP ($P < 0.001$) was higher in patients with than without hypocalcemia. However, the albumin level was lower in patients with than without hypocalcemia ($P < 0.001$). Conclusions: In elderly patients with AECOPD, hypocalcemia may be related to the disease progression, respiratory infection rate, and hospital stay of patients with AECOPD.

https://www.tandfonline.com/doi/full/10.1080/00325481.2019.1585689

Ronit, A., T. Kristensen, et al. (2018). **"Computed tomography quantification of emphysema in people living with HIV and uninfected controls."** Eur Respir J **52**(1)People living with HIV (PLWH) may be more susceptible to the development of emphysema than uninfected individuals. We assessed prevalence and risk factors for emphysema in PLWH and uninfected controls. Spirometry and chest computed tomography scans were obtained in PLWH from the Copenhagen Comorbidity in HIV Infection (COCOMO) study and in uninfected controls from the Copenhagen General Population Study (CGPS) who were >40 years. Emphysema was quantified using a low attenuation area < -950 Hounsfield units (%LAA-950) and the 15th percentile density index (PD15) and assessed by semi-quantitative visual scales. Of 742 PLWH, 21.2% and 4.7% had emphysema according to the %LAA-950 threshold with cut-offs at 5% and 10%, respectively. Of 470 uninfected controls, these numbers were 24.3% (p=0.23) and 4.0% (p=0.68). HIV was not associated with emphysema (adjusted OR 1.25, 95% CI 0.68-2.36 for %LAA-950 >10%) by PD15 or by visually assessed emphysema. We found no interaction between HIV and cumulative smoking. Breathlessness and sputum production were more common in PLWH with emphysema, and emphysema seemed to be more prevalent in PLWH with airflow limitation. HIV was therefore not independently associated with emphysema, but the clinical impact of emphysema was greater in PLWH than in uninfected controls.

https://erj.ersjournals.com/content/52/1/1800296

Sandri, B. J., A. Kaplan, et al. (2018). **"Multi-omic molecular profiling of lung cancer in COPD."** Eur Respir J **52**(1)Chronic obstructive pulmonary disease (COPD) is a known risk factor for developing lung cancer but the underlying mechanisms remain unknown. We hypothesise that the COPD stroma contains molecular mechanisms supporting tumourigenesis.We conducted an unbiased multi-omic analysis to identify gene expression patterns that distinguish COPD stroma in patients with or without lung cancer. We obtained lung tissue from patients with COPD and lung cancer (tumour and adjacent non-malignant tissue) and those with COPD without lung cancer for profiling of proteomic and mRNA (both cytoplasmic and polyribosomal). We used the Joint and Individual Variation Explained (JIVE) method to integrate and analyse across the three datasets.JIVE identified eight latent patterns that robustly distinguished and separated the three groups of tissue samples (tumour, adjacent and control).

Predictive variables that associated with the tumour, compared to adjacent stroma, were mainly represented in the transcriptomic data, whereas predictive variables associated with adjacent tissue, compared to controls, were represented at the translatomic level. Pathway analysis revealed extracellular matrix and phosphatidylinositol-4,5-bisphosphate 3-kinase-protein kinase B signalling pathways as important signals in the tumour adjacent stroma.The multi-omic approach distinguishes tumour adjacent stroma in lung cancer and reveals two stromal expression patterns associated with cancer.

https://erj.ersjournals.com/content/52/1/1702665

Satici, C., B. Arpinar Yigitbas, et al. (2018). **"Does Adherence to Domiciliary NIMV Decrease the Subsequent Hospitalizations Rates and Cost for Patients Diagnosed with COPD?"** Copd **15**(3): 303-309.

Domiciliary noninvasive mechanical ventilation (NIMV) is used for treating patients with hypercapnic chronic obstructive pulmonary disease (COPD). We aimed to evaluate the association between adherence to the treatment and subsequent hospitalizations and costs. Data from 54 (27 adherent; 27 non-adherent) patients with COPD who were undergoing NIMV treatment at home for 6 months. We assessed adherence based on digitally recorded data and checked hospital records for clinical and laboratory data, rehospitalization rates, and costs during the following 6 months. Nocturnal NIMV usage, mean daily usage of the device, and time to first hospitalization were higher in the treatment-adherent group ($p < .001$, $p < .001$, and $p=.006$, respectively). The percentage of active smokers, device leaks above 30 L/min, length of hospital stay, rehospitalization rates, and costs were significantly higher in the treatment-non-adherent group ($p = 05$, $p = 006$, $p = 004$, $p = 006$, and $p = 01$, respectively). The most frequent reasons for not using NIMV in the treatment-non-adherent group were a decreased need, dry mouth, mask incompatibility, and gastrointestinal complaints. Adherence to NIMV treatment decreases the subsequent hospitalizations rates and noncompliance leads to complications. Findings of this study may help physicians in convincing patients diagnosed with COPD of the need for correct NIMV use to prevent hospitalizations and reduce the costs of COPD treatment.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1500532

Seijo, L. M., J. B. Soriano, et al. (2019). **"New evidence on the chemoprevention of inhaled steroids and the risk of lung cancer in COPD."** Eur Respir J **53**(6)

https://erj.ersjournals.com/content/erj/53/6/1900717.full.pdf

Shevcova, V. I., A. A. Zujkova, et al. (2018). **"Verification of zinc role in pathophysiology of chronic obstructive pulmonary disease."** Ter Arkh **90**(3): 33-37.

AIM: Determination of the level of zinc and its fractions, as well as the enzyme neutrophilic elastase and albumin in persons suffering from chronic obstructive pulmonary disease (COPD), as well as smoking actively and passively. MATERIALS AND METHODS: The study involved 30 patients with a diagnosis of COPD and 90 healthy persons (60 of them smoking at the present time, 30 - no) who underwent spirometry and determination of zinc levels and its pools, albumin, and neutrophil elastase. All data are subject to statistical processing. RESULTS: It is determined that the studied parameters differ significantly in the groups of smokers with COPD, healthy smokers and non-smokers, and correlate with the volume of forced exhalation for 1 second as a percentage of the due. CONCLUSION: The revealed regularities make it possible to consider the indicator "share of bound zinc fraction" introduced in the study as a screening criterion in diagnosing COPD in smokers.

Swigris, J. (2017). **"Caution against Extrapolating Results from the Trial of Long-Term Oxygen for Chronic Obstructive Pulmonary Disease."** Ann Am Thorac Soc **14**(2): 296.

Tanabe, N., D. M. Vasilescu, et al. (2018). **"Analysis of airway pathology in COPD using a combination of computed tomography, micro-computed tomography and histology."** Eur Respir J **51**(2)The small conducting airways are the major site of obstruction in chronic obstructive pulmonary disease (COPD). This study examined small airway pathology using a novel combination of multidetector row computed tomography (MDCT), micro-computed tomography (microCT) and histology.Airway branches visible on specimen MDCT were counted and the dimensions of the third- to fifth-generation airways were computed, while the terminal bronchioles (designated TB), preterminal bronchioles (TB-1) and pre-preterminal bronchioles (TB-2) were examined with microCT and histology in eight explanted lungs with end-stage COPD and seven unused donor lungs that served as controls.On MDCT, COPD lungs showed a decrease in the number of 2-2.5 mm diameter airways and the lumen area of fifth-generation airways, while on microCT there was a reduction in the number of terminal bronchioles as well as a decrease in the luminal areas, wall volumes and alveolar attachments to the walls of TB, TB-1 and TB-2 bronchioles. The combination of microCT and histology showed increased B-cell infiltration into the walls of TB-1 and TB-2 bronchioles, and this change was correlated with a reduced number of alveolar attachments in COPD.Small airways disease extends from 2 mm diameter airways to the terminal bronchioles in COPD. Destruction of alveolar attachments may be driven by a B-cell-mediated immune response in the preterminal bronchioles.

https://erj.ersjournals.com/content/51/2/1701245

Ueda, K., J. Murakami, et al. (2018). **"Predicting the response to a bronchodilator in patients with airflow obstruction and lung cancer."** J Surg Res **228**: 20-26.

BACKGROUND: The aim of the present study was to clarify the predictors of the response of patients with resectable lung cancer and untreated airflow obstruction to tiotropium, an antimuscarinic bronchodilator. METHODS: Tiotropium was administered to 29 preoperative patients with untreated airflow obstruction. The forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured before and after the introduction of tiotropium. The response to tiotropium was determined based on the percentage gain in the FEV1. The volume of the total lung area (TLV) and the low-attenuation area (LAA) was measured by deep inspiratory computed tomography based on the predefined thresholds for attenuation values. RESULTS: The introduction of tiotropium resulted in a 15% gain in the FEV1 ($P < 0.001$). A univariate regression analysis revealed that the FVC/TLV was the best predictor of the gain in FEV1, followed by the FEV1/FVC. Based on the results of a multiple regression analysis, a regression equation to predict a gain in the FEV1 was generated using the FVC, TLV, and LAA. A receiver operating characteristic curve analysis revealed that this equation led to the highest area under the curve for predicting a major response to tiotropium, followed by the FVC/TLV and FEV1/FVC. Postoperatively, six of the 20 minor responders experienced a progression of dyspnea. In contrast, none of the major responders experienced a progression of dyspnea ($P < 0.05$). CONCLUSIONS: We developed an equation for predicting the response to tiotropium using parameters obtained from spirometry and quantitative computed tomography. A large-scale study to validate the usefulness of this equation is warranted.

https://www.journalofsurgicalresearch.com/article/S0022-4804(18)30102-1/fulltext

Vashi, M. T., J. L. Willoughby, et al. (2019). **"Eosinophilic Chronic Obstructive Pulmonary Disease: Implications for Exacerbations, Readmissions, and Treatment."** Am J Respir Crit Care Med **199**(1): 110-112.

Voskrebenzev, A., M. Gutberlet, et al. (2018). **"Feasibility of quantitative regional ventilation and perfusion mapping with phase-resolved functional lung (PREFUL) MRI in healthy volunteers and COPD, CTEPH, and CF patients."** Magn Reson Med **79**(4): 2306-2314.

PURPOSE: In this feasibility study, a phase-resolved functional lung imaging postprocessing method for extraction of dynamic perfusion (Q) and ventilation (V) parameters using a conventional 1H lung MRI Fourier decomposition acquisition is introduced. METHODS: Time series of coronal gradient-echo MR images with a temporal resolution of 288 to 324 ms of two healthy volunteers, one patient with chronic thromboembolic hypertension, one patient with cystic fibrosis, and one patient with chronic obstructive pulmonary disease were acquired at 1.5 T. Using a sine model to estimate cardiac and respiratory phases of each image, all images were sorted to reconstruct full cardiac and respiratory cycles. Time to peak (TTP), V/Q maps, and fractional ventilation flow-volume loops were calculated. RESULTS: For the volunteers, homogenous ventilation and perfusion TTP maps (V-TTP, Q-TTP) were obtained. The chronic thromboembolic hypertension patient showed increased perfusion TTP in hypoperfused regions in visual agreement with dynamic contrast-enhanced MRI, which improved postpulmonary endaterectomy surgery. Cystic fibrosis and chronic obstructive pulmonary disease patients showed a pattern of increased V-TTP and Q-TTP in regions of hypoventilation and decreased perfusion. Fractional ventilation flow-volume loops of the chronic obstructive pulmonary disease patient were smaller in comparison with the healthy volunteer, and showed regional differences in visual agreement with functional small airways disease and emphysema on CT. CONCLUSIONS: This study shows the feasibility of phase-resolved functional lung imaging to gain quantitative information regarding regional lung perfusion and ventilation without the need for ultrafast imaging, which will be advantageous for future clinical translation. Magn Reson Med 79:2306-2314, 2018. (c) 2017 International Society for Magnetic Resonance in Medicine.

https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.26893

Wang, J., H. Shang, et al. (2019). **"Procalcitonin, C-reactive protein, PaCO2, and noninvasive mechanical ventilation failure in chronic obstructive pulmonary disease exacerbation."** Medicine (Baltimore) **98**(17): e15171.

It is unclear whether procalcitonin (PCT) is correlated with noninvasive ventilation (NIV) failure. This retrospective case-control study aimed to compare PCT levels, C-reactive protein (CRP) levels, and PaCO2 in patients (05/2014-03/2015 at the Harrison International Peace Hospital, China) with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and NIV failure/success.This was a retrospective case-control study of patients with AECOPD who required NIV between May 2014 and March 2015. All consecutive patients with AECOPD admitted at the Department of Critical Care Medicine and transferred from the general ward were included in the study. Hemogram, PCT, erythrocyte sedimentation rate (ESR), arterial blood gas (ABG), and CRP levels were measured </=1 hour before NIV was used. NIV was considered to have failed if at least one of the following criteria was met: cardiac arrest or severe hemodynamic instability; respiratory arrest or gasping; mask intolerance; difficulty in clearing bronchial secretions; or worsening of ABGs or sensorium level during NIV. The factors associated with NIV failure were determined.A total of 376 patients were included: 286 with successful NIV and 90 wither NIV failure. The multivariate analysis showed that PCT (OR = 2.0, 95%CI: 1.2-3.2, P = .006), CRP (OR = 1.2, 95%CI: 1.1-1.3, P < .001), and PaCO2 (OR = 1.1, 95%CI: 1.1-1.2, P < .001) </=1 hour before NIV were independently associated with NIV failure. The optimal cutoff were 0.31 ng/mL for PCT (sensitivity, 83.3%; specificity, 83.7%), 15.0 mg/mL for CRP (sensitivity, 75.6%; specificity, 93.0%), and 73.5 mm Hg for PaCO2 (sensitivity, 71.1%; specificity, 100%). The area under the curve (AUC) was 0.854 for PCT, 0.849 for CRP,

and 0.828 for PaCO2. PCT, CRP, and PaCO2 were used to obtain a combined prediction factor, which achieved an AUC of 0.978 (95%CI: 0.961-0.995).High serum PCT, CRP, and PaCO2 levels predict NIV failure for patients with AECOPD. The combination of these three parameters might enable even more accurate prediction.

Zeng, S., A. Tham, et al. (2019). **"Lung volume indices predict morbidity in smokers with preserved spirometry."** Thorax **74**(2): 114-124.

BACKGROUND: Abnormal lung volumes that reflect air trapping are common in COPD. However, their significance in smokers with preserved spirometry (normal FEV1 to FVC ratio) is unclear. METHODS: Using the Veterans Administration Informatics and Computing Infrastructure database, we identified 7479 patients at risk for COPD (ever smokers >40 years of age without restrictive lung disease) who had preserved spirometry and concomitant lung volume measurements, and examined their subsequent health records for clinical diagnoses of COPD, healthcare utilisation, follow-up spirometry and mortality. RESULTS: Air trapping was prevalent, with 31% of patients having residual volume to total lung capacity ratio (RV:TLC) greater than the upper limit of normal (ULN). RV:TLC varied widely from 14% to 77% (51% to 204% of predicted) across the normal ranges of FEV1:FVC and FEV1. Patients with RV:TLC greater than the ULN were more likely to receive subsequent clinical diagnoses of COPD (HR (95% CI)=1.55 (1.42 to 1.70), p<0.001) and had higher all-cause mortality (HR (95% CI)=1.41 (1.29 to 1.54), p<0.001). They had higher rates of respiratory medication prescriptions and hospital and intensive care unit admissions. Other air trapping and static hyperinflation indices showed similar associations with health outcomes. Additionally, high-normal RV:TLC was associated with intermediate adverse health outcomes compared with low-normal and abnormal RV:TLC. Abnormal RV:TLC predicted higher likelihood of progression to spirometric COPD (OR (95% CI)=1.30 (1.03 to 1.65), p=0.027). CONCLUSION: In this study of the Veterans Affairs electronic health records, air trapping was common in smokers with preserved spirometry and predicted adverse respiratory outcomes and progression to overt COPD.

https://thorax.bmj.com/content/74/2/114.long

Zinellu, A., A. G. Fois, et al. (2018). **"Increased kynurenine plasma concentrations and kynurenine-tryptophan ratio in mild-to-moderate chronic obstructive pulmonary disease patients."** Biomark Med **12**(3): 229-237.

AIM: Since an increase in kynurenine (Kyn) plasma concentrations has been proposed as marker of immune system activation, we studied the associations between the Kyn levels and presence and severity of chronic obstructive pulmonary disease (COPD). METHODS & RESULTS: Plasma Kyn, tryptophan (Trp) and Kyn/Trp ratio were measured in 43 COPD patients with clinically defined mild (n = 29) or moderate (n = 14) disease and 43 age- and sex-matched healthy controls. When compared with controls, COPD patients had significantly higher plasma Kyn concentrations and Kyn/Trp ratios. In multiple logistic regression analysis, after adjusting for clinical and demographic confounders, the Kyn/Trp ratio was independently associated with COPD severity. DISCUSSION & CONCLUSION: Kyn and Kyn/Trp ratio might represent a new, sensitive, biomarker of systemic inflammation in COPD patients.

https://www.futuremedicine.com/doi/10.2217/bmm-2017-0280

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]

(2000). **"Rationale and design of the national emphysema treatment trial. A prospective randomized trial of lung volume reduction surgery. The national emphysema treatment trial research group."** J Cardiopulm Rehabil **20**(1): 24-36.

The National Emphysema Treatment Trial is a multicenter, randomized clinical trial of medical therapy vs medical therapy plus lung volume reduction surgery (LVRS) for the treatment of patients with severe bilateral emphysema. LVRS will be accomplished by bilateral stapled excision via median sternotomy or video-assisted thoracoscopic surgery. Every patient will complete 6 to 10 weeks of pulmonary rehabilitation prior to randomization and will participate in a maintenance program of pulmonary rehabilitation after randomization. The primary outcome to be assessed by the trial is survival. Additional outcomes to be assessed are maximum exercise capacity, pulmonary function, oxygen requirement, distance walked in 6 min, quality of life, respiratory symptoms, and health-care utilization and costs. In addition, selected clinics will evaluate lung mechanics and respiratory muscle function, partial and maximal flow-volume curves, gas exchange during maximal exercise, and right heart function. The trial is targeted to enroll patients with severe emphysema who have no significant comorbid conditions; each patient will be randomized to one of the two treatment groups. The study duration is 4.5 years with a close-out period of 6 months.

(2017). **"Erratum: Inhaled Corticosteroids Increase the Risk of Pneumonia in Patients With Chronic Obstructive Pulmonary Disease: A Nationwide Cohort Study: Erratum."** Medicine (Baltimore) **96**(44): e8579.

[This corrects the article DOI: 10.1097/MD.0000000000001723.].

Abubaker, J., F. Zaina, et al. (2019). **"Single Intramuscular Methylprednisolone dose in Asthma and Chronic Obstructive Pulmonary Disease Patients on Discharge."** J Pak Med Assoc **69**(7): 991-994.

OBJECTIVE: In this pilot study we aimed to evaluate the safety of a single intramuscular methylprednisolone (IM) injection at the time of discharge as a replacement for oral steroid therapy for patients in our population with asthma or chronic obstructive pulmonary disease (COPD). METHODS: This proof-of-concept, open label clinical trial without randomisation was conducted at the Pulmonary Department of Ziauddin Hospital and University, Karachi from January 2018 to March 2018. Patients discharged after in-hospital treatment for exacerbations of either asthma or COPD were recruited for this study. Intramuscular injection of methylprednisolone was administered to these patients who were then followed-up after one week and one month. During that period, information was collected of the patients' self-report of any unscheduled emergency room visit, blood sugar and blood pressure control, symptoms suggestive of thrush, increase gastric acidity and weight gain. For the data analysis, frequency and percentages were calculated with SPSS version 21. RESULTS: A total of 30 patients aged 52.83 +/- 14.27 years were recruited for this pilot study. At one month follow-up, no unscheduled emergency room visits were observed in all of the study patients. Symptoms suggestive of oral thrush were recorded in only 2 (6.7%) patients and weight gain was reported by only 5 (16.7%). Controlled blood sugar and blood pressure

was reported by all the patients. No incidence of nocturnal symptoms, awakening and dyspepsia were reported. CONCLUSIONS: A single dose of methylprednisolone injection without any obvious side effects over one month among patients with asthma and COPD demonstrated a safe strategy for them.

Alshabani, K., A. A. Attaway, et al. (2019). **"Electronic inhaler monitoring and healthcare utilization in chronic obstructive pulmonary disease."** J Telemed Telecare: 1357633x19850404.

INTRODUCTION: The effect of electronic inhaler monitoring (EIM) on healthcare utilization in chronic obstructive pulmonary disease (COPD) has not been studied. We hypothesized that the use of EIM in conjunction with a disease management program reduces healthcare utilization in patients with COPD. METHODS: This is a retrospective pre- and post-analysis of a quality improvement project. Patients with COPD and high healthcare utilization (>/=one hospitalization or emergency room visit during the year prior to enrolment) were provided with electronic monitoring devices for monitoring controller and rescue inhaler utilization for one year. Patients were contacted when alerts were triggered, indicating suboptimal adherence to controller inhaler or increased use of rescue inhalers, potentially signalling an impending exacerbation. Healthcare utilization was assessed pre- and post-monitoring, with each subject serving as his/her own control. RESULTS: Patients with COPD and high healthcare utilization (n = 39) were recruited. Mean EIM duration was 280.5 (+/-120.6) days. The mean age was 68.6 (+/-9.9) years, FEV1 (mean forced expiratory volume in one second) was 1.1 (+/-0.4) L, and mean Charlson Comorbidity index was 5.6 (+/-2.7). Average adherence was 44.4% (28.4%). Compared with the year prior to enrolment, EIM was associated with a reduction in COPD-related healthcare utilization per year (2.2 (+/-2.3) versus 3.4 (+/-3.2), p = 0.01). Although there was a reduction in all-cause healthcare utilization, this was not statistically significant (3.4 (+/-2.6) versus 4.7 (+/-4.1), p = 0.06). DISCUSSION: EIM in conjunction with a disease management program may play a role in reducing healthcare utilization in COPD patients with a history of high healthcare utilization.

Bade, B. C., E. C. DeRycke, et al. (2019). **"Sex Differences in Veterans Admitted to the Hospital for Chronic Obstructive Pulmonary Disease Exacerbation."** Ann Am Thorac Soc **16**(6): 707-714.

Rationale: As chronic obstructive pulmonary disease (COPD) prevalence in women has outpaced that in men, COPD-related hospitalization and mortality are now higher in women. Presentation, evaluation, and treatment of COPD differ between women and men. Despite higher smoking rates in Veterans, little work has characterized differences in Veterans with COPD by sex. Objectives: To determine risk factors for 30-day readmission among Veterans hospitalized for COPD exacerbations and how they differed by sex. Methods: We performed a retrospective observational analysis of Veterans receiving primary care in Veterans Health Affairs facilities. We included Veterans Administration-based hospitalizations for Veterans with a COPD exacerbation (identified by International Classification of Disease, Ninth Revision codes) who survived to discharge between fiscal years 2012 and 2015. Primary outcome was 30-day readmission. Predictors ascertained before hospitalization included smoking status (current, former, never), pulmonary function testing, pulmonary medication prescriptions, and medical and psychiatric comorbidities (identified by International Classification of Disease, ninth revision codes). We created combined and sex-stratified multivariate logistic regression models to identify associations with 30-day readmission. Results: Our sample included 48,888 Veterans (4% women). Compared with men, women Veterans were younger, more likely to be nonwhite, and differed in smoking status. Women were more likely to have asthma, drug use, and several psychiatric comorbidities. Before hospitalization, women were less likely to have pulmonary function testing (76% vs. 78%; P = 0.01) or be treated with antimuscarinic (43% vs. 48%) or combined long-acting bronchodilator/inhaled corticosteroid (61% vs. 64%) inhalers. Women were more likely to receive nicotine-replacement therapy (all P < 0.01). Women had shorter length of stay (median days, 2 vs. 3; P = 0.04) and lower 30-day readmission rate (20% vs. 22%; P = 0.01). In adjusted models including both sexes, age, antimuscarinic use, comorbidities, and

diagnosis of drug or alcohol use were associated with readmission; there was no association with sex and readmission risk. In models stratified by sex, associations were similar between women and men. Conclusions: This study suggests differences between women and men hospitalized for COPD regarding presentation, evaluation, and management. Readmission is strongly influenced by comorbidities, suggesting individualized and comprehensive case management may reduce readmission risk for women and men with COPD.

Baillargeon, J., G. Singh, et al. (2019). **"Association of Opioid and Benzodiazepine Use with Adverse Respiratory Events in Older Adults with COPD."** Ann Am Thorac SocRATIONALE: Older adults with 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 and concurrent use of opioid and benzodiazepine medications were associated with hospitalizations for respiratory events; and 2) this association was exacerbated by the presence of obstructive sleep apnea. 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 2 controls (n=6,247) on index date, age, gender, SES, comorbidity, presence of obstructive sleep apnea (OSA), COPD medication, and COPD complexity. RESULTS: In comparison to the referent (no opioid or benzodiazepine use), opioid use alone (aOR= 1.73; 95% 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.

Baldomero, A. K., M. Siddiqui, et al. (2019). **"The relationship between oral health and COPD exacerbations."** Int J Chron Obstruct Pulmon Dis **14**: 881-892.

Introduction: Poor oral health has been implicated as an independent risk factor for the development of COPD, but few studies have evaluated the association between oral health and COPD exacerbations. We aimed to determine if poor oral health is associated with COPD exacerbations and/or worse respiratory health. Methods: We performed a case-control study of oral health among COPD exacerbators and non-exacerbators. Cases (exacerbators) had experienced >/=1 exacerbation in the previous 12 months, while controls (non-exacerbators) had no exacerbations in the previous 24 months. We excluded those with <4 teeth. We evaluated the global oral health assessment, Oral Health Impact Profile (OHIP-5), dental symptoms/habits, and St. George's Respiratory Questionnaire (SGRQ). In a subset, we performed blinded dental exams to measure bleeding on probing, probing depth, clinical attachment loss, periodontitis severity, plaque index, gingival index, and carries risk. We evaluated associations between oral health and COPD exacerbations using logistic regression. Linear regression was used to assess relationships between oral health and SGRQ scores. Results: Screened non-exacerbators (n=118) were significantly

more likely to have <4 teeth, compared to screened exacerbators (n=100) (44% vs 30%, respectively; p=0.046). After excluding those with <4 teeth, there were 70 cases and 66 controls. Self-reported oral health and objective dental exam measures did not vary significantly between cases vs controls. However, the odds of severe COPD exacerbations requiring hospitalizations and/or emergency department visits trended higher in those with worse dental exam compared to those with better dental exam. Worse OHIP-5 was strongly associated with worse SGRQ scores. Conclusions: Oral health status was not related to COPD exacerbations, but was associated with self-reported respiratory health. Non-exacerbators were more likely to be edentate or have </=4 teeth compared to exacerbators. Larger studies are needed to address oral health as a potential method to improve respiratory health in patients with COPD.

https://www.dovepress.com/getfile.php?fileID=49274

Barbetta, C., V. Allgar, et al. (2019). **"Australia-modified Karnofsky Performance Scale and physical activity in COPD and lung cancer: an exploratory pooled data analysis."** BMJ Support Palliat CareOBJECTIVES: Patient-relevant measures of functional status are required in chronic obstructive pulmonary disease (COPD) and lung cancer in clinical practice and research. We explored the relationship between the Australia-modified Karnofsky Performance Scale (AKPS) and measures of functional capacity and physical activity in these patient groups. METHODS: Pooled clinical trial data were analysed to explore the relationship between AKPS and average daily steps (ADS), 6 min walk distance (6MWD), and body mass index, airflow obstruction, dyspnoea and exercise score (COPD group). Receiver operator characteristic curves were produced to compare sensitivity and specificity of cut-offs (no dependency >70, high dependency <60) and area under the curve (AUC). RESULTS: Seven clinical trials included people with COPD (n=79) and lung cancer (n=150). To detect an AKPS of >70, the optimal ADS cut-points were COPD, 3342 steps (AUC 0.88, 95% CI 0.79 to 0.97, sensitivity 82%, specificity 76%), and lung cancer, 3380 steps (AUC 0.72, 95% CI 0.64 to 0.81, sensitivity 61%, specificity 74%), and for 6MWD (COPD only) 242 m (AUC 0.72, 95% CI 0.63 to 0.81, sensitivity 73%, specificity 34%). CONCLUSIONS: An AKPS score is strongly related to ADS in people with COPD and lung cancer. The AKPS may be useful in clinical practice and research to indicate levels of physical activity where ADS and 6 min walk test are not possible. Longitudinal data are needed to confirm these findings.

https://spcare.bmj.com/content/early/2019/07/11/bmjspcare-2019-001869

Barczyk, A., M. Maskey-Warzechowska, et al. (2019). **"Asthma-COPD Overlap-A Discordance Between Patient Populations Defined by Different Diagnostic Criteria."** J Allergy Clin Immunol PractBACKGROUND: The concordance between asthma-chronic obstructive pulmonary disease overlap (ACO) defined according to Global Inititative for Asthma (GINA)/Global Initiative for Chronic Obstructive Lung Disease (GOLD) and other diagnostic criteria is unknown. OBJECTIVE: To assess the concordance between different ACO definitions and to estimate the definition-based ACO prevalence and characteristics. METHODS: A prospective, real-life study based on a 32-item data set was performed in a mixed population of patients with asthma and chronic obstructive pulmonary disease (COPD). Five different definitions of ACO, including the GINA/GOLD criteria, were analyzed. RESULTS: A total of 1609 patients were included in the final analysis. Application of Venn diagram for ACO populations resulted in 31 ACO subpopulations, which were further reduced to 6 separate populations by introducing a rank order for the analyzed definitions to classify patients from intersecting groups. Overall, the level of agreement between different ACO definitions was poor. Cohen kappa coefficient for the agreement between ACO GINA/GOLD definition and other ACO definitions varied from 0.06 to 0.21. Only 2 patients (0.12%) met all the ACO definitions. Definition-based ACO prevalence ranged between 3.8% (Spanish criteria) and 18.4% (clinician's diagnosis). A total of 573 (33.4%) patients met the criteria from at least 1 ACO definition. Patients who could not be classified as suffering from "pure" asthma, "pure" COPD, or ACO accounted for as much as 27.5% of the whole investigated group. The most severe symptoms were observed in patients with ACO defined as COPD and asthma diagnosed at age less than 40 years.

CONCLUSIONS: The current ACO definitions identify distinct populations that share only a small number of common features and present with different disease phenotypes. ACO prevalence is highly variable, depending on the definition applied.

https://www.sciencedirect.com/science/article/abs/pii/S2213219819303952?via%3Dihub

Bari, M. Z. J., I. Patwary, et al. (2019). **"Association of COPD with osteoporosis in male smokers: A case control study in a tertiary medical college hospital in Bangladesh."** J Back Musculoskelet RehabilOBJECTIVES: Chronic obstructive pulmonary disease (COPD) may increase the risk of osteoporosis and resulting fractures can contribute to disability and mortality of patients. We intended to evaluate the frequency of osteoporosis in male smokers with and without COPD and study whether any correlation existed between osteoporosis and COPD. MATERIALS AND METHODS: This case-control study was carried out in the Department of Medicine, Sylhet M.A.G. Osmani Medical College Hospital, Sylhet, Bangladesh between July 2013 and June 2015. Seventy four male smokers with COPD and 66 age-matched male smokers without COPD were enrolled. All individuals underwent Bone Mass Densitometry (BMD) by Dual-Energy X-Ray Absorptiometry (DEXA). RESULTS: COPD and non-COPD groups did not differ regarding age and smoking pack-years. Osteoporosis at femoral neck (48.6% versus 16.7%; p< 0.001) and lumbar spine (68.9% versus 37.9%; p< 0.01) was significantly higher in COPD compared to controls. Osteopenia did not differ significantly. Patients with COPD were 4.5 times more likely to develop osteoporosis than controls after adjusting age, smoking-pack years and BMI (adjusted OR = 4.5; 95% CI = 1.8-11.5). CONCLUSIONS: Osteoporosis is more frequent in male smokers with COPD compared to smokers without COPD. COPD is a risk factor of osteoporosis independent of age, smoking and BMI.

https://content.iospress.com:443/download/journal-of-back-and-musculoskeletal-rehabilitation/bmr181303?id=journal-of-back-and-musculoskeletal-rehabilitation%2Fbmr181303

Boixeda, R., J. Diez-Manglano, et al. (2019). **"Consensus for managing patients with chronic obstructive pulmonary disease according to the CODEX index."** Rev Clin EspThe comorbidity, obstruction, dyspnoea, exacerbations (CODEX) index is the first multicomponent scale designed to predict the risk of readmissions and mortality at 1 year for patients hospitalised for chronic obstructive pulmonary disease (COPD). The index includes the comorbidities (C) (measured by the Charlson index), the degree of obstruction (O) (assessed by the forced expiratory volume in 1 second percentage), dyspnoea (D) (stratified according to the modified Medical Research Council scale) and exacerbations (EX) in the previous year. Our objective was to prepare recommendations based on the index's various components for personalised therapeutic management. To this end, we performed a literature search based on guidelines, consensuses and systematic reviews, as a basis for preparing recommendations on basic concepts, comorbidities, dyspnoea, pulmonary obstruction, exacerbations and follow-up. The recommendations were then subjected to an external assessment process by a multidisciplinary group of 62 experts. In total, 108 recommendations were created, 96 of which achieved consensus, including the recommendation that COPD be considered a high-risk cardiovascular disease, as well as several specific recommendations on managing the various comorbidities. A consensus was reached on the recommended treatments in the guidelines for the various levels of obstruction, dyspnoea and exacerbations, adapted to the CODEX scores. Advice is also offered for patient follow-up after hospital discharge, which includes aspects on assessment, treatment and care coordination.

https://www.sciencedirect.com/science/article/pii/S0014256519300967?via%3Dihub

Bordon, J., M. Slomka, et al. (2019). **"Hospitalization due to community-acquired pneumonia in patients with chronic obstructive pulmonary disease: incidence, epidemiology & 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 U.S. 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 June 1(st), 2014 to May 31(st), 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 U.S. 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, 3,419 pneumonia hospitalizations were documented during the two-year study. The annual incidence was 9,369 patients with pneumonia per 100,000 COPD population, corresponding to an estimated 506,953 adults with COPD hospitalized due to pneumonia in the US. The incidence of CAP in patients without COPD was 509 (95% 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 3,419 (5.6%), 400 of 3,374 (11.9%), 816 of 3,363 (24.3%), and 1,104 of 3349 (33.0%), respectively. CONCLUSIONS: There was an annual incidence of 9,369 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/pdf

Borras-Santos, A., J. Garcia-Aymerich, et al. (2019). **"Determinants of the Appearance and Progression of Early-Onset Chronic Obstructive Pulmonary Disease in Young Adults. A Case-Control Study with Follow-up."** Arch Bronconeumol **55**(6): 312-318.

INTRODUCTION AND OBJECTIVES: Determinants of chronic obstructive pulmonary disease (COPD) in the early stages of its natural history are not well known. Improving our knowledge of these factors will help to design interventions that can modify prognosis. Study objectives are: a) to characterize a COPD population of young adults aged 35-50 years from a multidimensional point of view; b) to compare these patients with smokers with normal lung function; and c) to create a cohort of young adults aged 35-50 years (smokers or former smokers), with and without COPD, who will be followed in the future to improve understanding of the natural history of the disease. PARTICIPANTS AND METHOD: This is a case-control multicenter study aimed at establishing a well-characterized cohort of young adults, smokers or former-smokers, with and without COPD, for subsequent follow-up. A total of 311 participants (101 cases and 210 controls) were selected from approximately 30 primary care settings and 12 hospitals in 8 Spanish regions. Subjects were smokers or former smokers (>10 pack-years) aged 35-50 years. Diagnosis of COPD was based on a post-bronchodilator result of FEV1/FVC<70%. The main study variables were: questionnaires on health, symptoms, exacerbations and daily physical activity, lung function tests, blood and sputum samples, and low-dose computed tomography. In the statistical analysis, COPD patient characteristics will be described and compared with control subjects using a logistic regression analysis.

https://www.sciencedirect.com/science/article/pii/S0300289618303417?via%3Dihub

Bozek, A., J. Jarzab, et al. (2019). **"Fall episodes in elderly patients with asthma and COPD - A pilot study."** J Asthma **56**(6): 627-631.

OBJECTIVE: Evidence of an increased risk of falls in patients with chronic obstructive pulmonary disease (COPD) exists; however, this has not been studied in elderly asthmatic patients. The aim of the study was to determine the incidence of falls in elderly patients who were diagnosed with bronchial asthma compared to subjects with COPD. METHODS: A 12-month prospective observational study in elderly outpatients with diagnosis of either asthma or COPD was conducted. All of the participants were monitored on the following parameters: falls, comorbidities, drug therapy, and The Berg Balance Scale. The rate of falls was shown as an incidence ratio. Cluster analysis for subgroups with similar features was performed on all

patients included in the study. Two clusters of frequent fallers were determined. RESULTS: The fall incidence rate in falls per person per year was 1.41 (95% CI: 0.86-1.96) in asthmatic patients and 1.49 (95% CI: 1.05-2.11) in the COPD group. Frequent fallers were more prevalent in the COPD group, with 32% in this group compared to 28% in the groups of patients with asthma. In cluster analysis, frequent fallers were grouped into two models characterized by polytherapy, depression symptoms, hospitalizations, coronary disease, dementia, and diagnosis of COPD or asthma. CONCLUSION: Elderly asthmatic patients presented a high rate of falls, which is comparable to that of patients with COPD.

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

Butler, C. C., D. Gillespie, et al. (2019). **"C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations."** N Engl J Med **381**(2): 111-120.

BACKGROUND: Point-of-care testing of C-reactive protein (CRP) may be a way to reduce unnecessary use of antibiotics without harming patients who have acute exacerbations of chronic obstructive pulmonary disease (COPD). METHODS: We performed a multicenter, open-label, randomized, controlled trial involving patients with a diagnosis of COPD in their primary care clinical record who consulted a clinician at 1 of 86 general medical practices in England and Wales for an acute exacerbation of COPD. The patients were assigned to receive usual care guided by CRP point-of-care testing (CRP-guided group) or usual care alone (usual-care group). The primary outcomes were patient-reported use of antibiotics for acute exacerbations of COPD within 4 weeks after randomization (to show superiority) and COPD-related health status at 2 weeks after randomization, as measured by the Clinical COPD Questionnaire, a 10-item scale with scores ranging from 0 (very good COPD health status) to 6 (extremely poor COPD health status) (to show noninferiority). RESULTS: A total of 653 patients underwent randomization. Fewer patients in the CRP-guided group reported antibiotic use than in the usual-care group (57.0% vs. 77.4%; adjusted odds ratio, 0.31; 95% confidence interval [CI], 0.20 to 0.47). The adjusted mean difference in the total score on the Clinical COPD Questionnaire at 2 weeks was -0.19 points (two-sided 90% CI, -0.33 to -0.05) in favor of the CRP-guided group. The antibiotic prescribing decisions made by clinicians at the initial consultation were ascertained for all but 1 patient, and antibiotic prescriptions issued over the first 4 weeks of follow-up were ascertained for 96.9% of the patients. A lower percentage of patients in the CRP-guided group than in the usual-care group received an antibiotic prescription at the initial consultation (47.7% vs. 69.7%, for a difference of 22.0 percentage points; adjusted odds ratio, 0.31; 95% CI, 0.21 to 0.45) and during the first 4 weeks of follow-up (59.1% vs. 79.7%, for a difference of 20.6 percentage points; adjusted odds ratio, 0.30; 95% CI, 0.20 to 0.46). Two patients in the usual-care group died within 4 weeks after randomization from causes considered by the investigators to be unrelated to trial participation. CONCLUSIONS: CRP-guided prescribing of antibiotics for exacerbations of COPD in primary care clinics resulted in a lower percentage of patients who reported antibiotic use and who received antibiotic prescriptions from clinicians, with no evidence of harm. (Funded by the National Institute for Health Research Health Technology Assessment Program; PACE Current Controlled Trials number, ISRCTN24346473.).

https://www.nejm.org/doi/full/10.1056/NEJMoa1803185?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

Byng, D., J. I. Lutter, et al. (2019). **"Determinants of healthcare utilization and costs in COPD patients: first longitudinal results from the German COPD cohort COSYCONET."** Int J Chron Obstruct Pulmon Dis **14**: 1423-1439.

Background: In light of overall increasing healthcare expenditures, it is mandatory to study determinants of future costs in chronic diseases. This study reports the first longitudinal results on healthcare utilization and associated costs from the German chronic obstructive pulmonary disease (COPD) cohort COSYCONET. Material and methods: Based on self-reported data of 1904 patients with COPD who attended the baseline and 18-month follow-up visits, direct costs were calculated for the 12 months preceding both examinations. Direct costs at follow-up were regressed on baseline disease severity and other co-

variables to identify determinants of future costs. Change score models were developed to identify predictors of cost increases over 18 months. As possible predictors, models included GOLD grade, age, sex, education, smoking status, body mass index, comorbidity, years since COPD diagnosis, presence of symptoms, and exacerbation history. Results: Inflation-adjusted mean annual direct costs increased by 5% (n.s., euro6,739 to euro7,091) between the two visits. Annual future costs were significantly higher in baseline GOLD grades 2, 3, and 4 (factors 1.24, 95%-confidence interval [1.07-1.43], 1.27 [1.09-1.48], 1.57 [1.27-1.93]). A history of moderate or severe exacerbations within 12 months, a comorbidity count >3, and the presence of dyspnea and underweight were significant predictors of cost increase (estimates ranging between + euro887 and + euro3,679, all $p<0.05$). Conclusions: Higher GOLD grade, comorbidity burden, dyspnea and moderate or severe exacerbations were determinants of elevated future costs and cost increases in COPD. In addition we identified underweight as independent risk factor for an increase in direct healthcare costs over time.

https://www.dovepress.com/getfile.php?fileID=50989

Calderazzo, M. A., M. B. Trujillo-Torralbo, et al. (2019). **"Inflammation and infections in unreported chronic obstructive pulmonary disease exacerbations."** Int J Chron Obstruct Pulmon Dis **14**: 823-832.

Purpose: COPD patients often do not report acute exacerbations to healthcare providers - unreported exacerbations. It is not known whether variances in symptoms, airway obstruction, aetiology and inflammatory responses account for differences in reporting of COPD exacerbations. The aims of the study were to compare symptoms, lung function changes, aetiology and inflammatory markers between exacerbations that were reported to healthcare providers or treated, with those that were unreported and untreated. Patients and methods: We recruited a cohort of COPD patients and collected clinical data and blood and airway samples when stable and during acute exacerbations. Virological and bacterial analyses were carried out and inflammatory markers measured. Results: We found no differences in symptoms, lung function, incidence of infection and inflammatory markers between reported and unreported exacerbations. Subjects who reported all exacerbations had higher BODE scores, lower FEV1 and more exacerbations compared with those who did not. Conclusion: The failure to report exacerbations is not related to the severity, aetiology or inflammatory profile of the exacerbation. Patients with less severe COPD and less frequent exacerbations are less likely to report exacerbations. The decision to report an exacerbation is not an objective marker of exacerbation severity and therefore studies that do not count unreported exacerbations will underestimate the frequency of clinically significant exacerbations. A better understanding of the factors that determine non-reporting of exacerbations is required to improve exacerbation reporting. Trial registration: ClinicalTrials.gov Identifier: NCT01376830. Registered June 17, 2011.

https://www.dovepress.com/getfile.php?fileID=49021

Cao, F. T., Y. Cui, et al. (2019). **"Application of Non-invasive Positive Pressure Ventilation Combined with PetCO(2) Monitoring for Patients with Chronic Obstructive Pulmonary Disease Combined with Severe Respiratory Failure."** J Coll Physicians Surg Pak **29**(6): 545-548.

OBJECTIVE: To investigate the role of PetCO(2) monitoring in non-invasive positive pressure ventilation (NPPV) treatment for chronic obstructive pulmonary disease (COPD) patients combined with severe respiratory failure. STUDY DESIGN: A clinical retrospective study. PLACE AND DURATION OF STUDY: The ICU Emergency Department, Wuxi Second People's Hospital, Wuxi, China, from February 2015 to February 2016. METHODOLOGY: A total of 60 COPD patients with respiratory failure were selected. All patients received non-invasive positive pressure ventilation and conventional treatment. PetCO(2) values were recorded two hours before and after NPPV treatment. At the same time, blood was collected for arterial blood gas analysis. Changes in PetCO(2), PaCO(2) and the difference between PaCO(2) and PetCO(2) (Pa-etCO(2)) were also monitored to determine the correlation between PetCO(2) and PaCO(2). RESULTS: After two hours of initial NPPV treatment, among the 60 patients, the PaCO(2) and Pa-etCO(2) of 40 patients were significantly decreased (66.7%), the PaCO(2) and Pa-etCO(2) of 20 patients were not

significantly decreased (33.3%). The correlation analysis revealed that PaCO(2) and PetCO(2) were negatively correlated (correlation coefficient r = -0.537, p=0.001, p<0.001). Furthermore, there were no significant correlations between PaCO(2) and PetCO(2) in the ineffective group (correlation coefficient r = -0.253, p=0.116, p>0.05). CONCLUSION: PaCO(2) monitoring could not be replaced by PetCO(2) monitoring for patients with COPD combined with severe respiratory failure. Nevertheless, dynamic monitoring can instantly feedback the respiration state, which can guide the respiration, and improve the success rate of NPPV treatment and prognosis.

Carette, H., M. Zysman, et al. (2019). **"Prevalence and management of chronic breathlessness in COPD in a tertiary care center."** BMC Pulm Med **19**(1): 95.

BACKGROUND: Breathlessness is the prominent symptom of chronic obstructive pulmonary disease (COPD). Despite optimal therapeutic management including pharmacological and non-pharmacological interventions, many COPD patients exhibit significant breathlessness. Chronic breathlessness is defined as breathlessness that persists despite optimal treatment of the underlying disease. Because of the major disability related to chronic breathlessness, symptomatic treatments including opioids have been recommended by several authors. The prevalence of chronic breathlessness in COPD and its management in routine clinical practice have been poorly investigated. Our aim was to examine prevalence, associated characteristics and management of chronic breathlessness in patients with COPD recruited in a real-life tertiary hospital-based cohort. METHODS: A prospective study was conducted among 120 consecutive COPD patients recruited, in stable condition, at Nancy University Hospital, France. In parallel, 88 pulmonologists of the same geographical region were asked to respond to an on-line questionnaire on breathlessness management. RESULTS: Sixty four (53%) patients had severe breathlessness (modified Medical Research Council scale>/=3), despite optimal inhaled medications for 94% of them; 40% had undergone pulmonary rehabilitation within the past 2 years. The severity of breathlessness increased with increasing airflow limitation. Breathlessness was associated with increased symptoms of anxiety, depression and with osteoporosis. No relation was found with other symptoms, exacerbation rate, or cardiovascular comorbidities. Among the patients with chronic breathlessness and Hospitalized Anxiety and/or Depression score > 10, only 25% were treated with antidepressant or anxiolytic. Among the pulmonologists 46 (52%) answered to the questionnaire and expressed a high willingness to prescribe opioids forchronic breathlessness, which contrasted with the finding that none of these patients received such treatments against breathlessness. CONCLUSION: Treatment approaches to breathlessness and associated psychological distress are insufficient in COPD. This study highlights underuse of pulmonary rehabilitation and symptomatic treatment for breathlessness.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6524222/pdf/12890_2019_Article_851.pdf

Cetin, E. and L. Altinay (2019). **"Effects of cardiopulmonary bypass on pulmonary function in COPD patients undergoing beating heart coronary artery bypass surgery."** Cardiovasc J Afr **30**: 1-5.

BACKGROUND: The aim of this study was to compare the effects of cardiopulmonary bypass (CPB) on the postoperative course of patients with chronic obstructive pulmonary disease (COPD) following coronary artery bypass graft (CABG) surgery. METHODS: This retrospective study included 375 COPD patients who underwent isolated CABG surgery with either on-pump (group 1) or off-pump beating heart techniques (group 2) between April 2014 and August 2018. RESULTS: Group 1 included 42 (11.2%) and group 2 included 333 (88.8%) patients. The mean mechanical ventilatory support times of groups 1 and 2 were 10.6 +/- 36.2 and 5.1 +/- 2.61 hours, respectively (p = 0.561). The mortality rates of groups 1 and 2 were 4.76% (two patients) and 1.50% (five patients), respectively (p = 0.142). CONCLUSIONS: The on-pump beating heart CABG surgery did not affect the postoperative mechanical ventilatory support times in patients with COPD.

Cha, Y. H., Y. C. Ha, et al. (2019). **"Relationship of chronic obstructive pulmonary disease severity with early and late mortality in elderly patients with hip fracture."** InjuryINTRODUCTION: We conducted a comparative study to compare patients with and without chronic obstructive pulmonary disease (COPD) and to analyze the effect of COPD severity on mortality in elderly patients with hip fractures who were diagnosed by pulmonologists. The purposes of this study were to compare early and late mortality after hip fracture between COPD and non-COPD patients and to assess risk factors of mortality after hip fractures in elderly patients with COPD. METHODS: This study included 1294 patients (1294 hips) who were diagnosed as having unilateral femoral neck or intertrochanteric fractures and who underwent surgery at two hospitals between 2004 and 2017. The patients were categorized into a non-COPD group (853 patients) and a COPD group (441 patients; mild-to-moderate [354 patients] and severe-to-very severe COPD subgroups [87 patients]). The cumulative crude mortality rate was calculated, and 30-day, 60-day, 3-month, 6-month, and 1-year mortality rates were compared between the non-COPD and COPD groups. Logistic regression analysis was conducted to identify independent factors associated with mortality. RESULTS: The 30-day, 60-day, 3-month, 6-month, and 1-year postoperative cumulative mortality rates were 1.3%, 2.5%, 3.5%, 6.6%, and 10.7%, respectively, in the non-COPD group, and 2.9%, 5.7%, 7.7%, 11.8%, and 16.6%, respectively, in the COPD group ($p = 0.049$, $p = 0.004$, $p = 0.002$, $p = 0.002$, and $p = 0.004$, respectively). The 30-day, 60-day, 3-month, 6-month, and 1-year postoperative cumulative mortality rates in the severe-to-very severe COPD group were 4.6%, 6.9%, 11.5%, 20.7%, and 26.4%, respectively. In elderly patients with hip fracture, COPD increased the risk of mortality for 1.6 times and 1.7 times at 3 months and 1 year postoperative, respectively. In subgroup analysis, severe-to-very severe COPD was associated with 1.55-fold and 1.65-fold increased postoperative mortality risk at 6 months and 1 year respectively, as compared with mild-moderate COPD. CONCLUSIONS: In elderly patients with hip fracture, the comparison between the COPD and non-COPD patients revealed that COPD was an independent factor of mortality at a minimum of 1-year follow-up, and COPD severity in patients with hip fracture was also a risk factor of 6-month and 1-year mortality.

https://www.injuryjournal.com/article/S0020-1383(19)30300-6/fulltext

Chang, Y. Y. and Y. T. Dai (2019). **"The efficacy of a flipping education program on improving self-management in patients with chronic obstructive pulmonary disease: a randomized controlled trial."** Int J Chron Obstruct Pulmon Dis **14**: 1239-1250.

Purpose: Self-management is widely used among patients with a chronic disease to control their condition. However, the self-management programs are less distinctive for patients with chronic obstructive pulmonary disease (COPD) than those with other chronic diseases. This study examines the efficacy of a flipping education program on improving self-management in patients with COPD. Patients and methods: A single-blinded, randomized controlled trial was conducted at a medical center in northern Taiwan from January 2015 to May 2016. Sixty participants were randomized to an experimental group and a control group. The self-management program with flipped teaching, customized action plans, and scheduled telephone interviews was implemented in the experimental group for three months. Conventional patient education was implemented in the control group. Disease knowledge, self-efficacy, the patient's activation level, and the impact of COPD were assessed at baseline, 1 month, and 3 months after the intervention. SPSS 22.0 was used for data analysis. Results: The results showed that the patients who received the flipping education program of self-management had statistically significant improvements in their disease knowledge ($p<0.05$), self-efficacy ($p<0.01$), and activation levels ($p<0.01$) from baseline to the 1 month and 3 months follow-up compared to the control group. Conclusion: The findings supported that flipped teaching could be applied to patient education in adults and that a nurse case manager can feasibly use this flipping education program of self-management to motivate and support patients with COPD to acquire self-management skills, carry out their action plans, and help them achieve beneficial behaviors in their daily lives.

https://www.dovepress.com/getfile.php?fileID=50364

Chen, J., M. Cho, et al. (2019). **"Turning subtypes into disease axes to improve prediction of COPD progression."** Thorax Chronic obstructive pulmonary disease (COPD) is an umbrella definition encompassing multiple disease processes. COPD heterogeneity has been described as distinct subgroups of individuals (subtypes) or as continuous measures of COPD variability (disease axes). There is little consensus on whether subtypes or disease axes are preferred, and the relative value of disease axes and subtypes for predicting COPD progression is unknown. Using a propensity score approach to learn disease axes from pairs of subtypes, we demonstrate that these disease axes predict prospective forced expiratory volume in 1 s decline and emphysema progression more accurately than the subtype pairs from which they were derived.

https://thorax.bmj.com/content/early/2019/06/12/thoraxjnl-2018-213005

Chen, P. K., Y. H. Hsiao, et al. (2019). **"Independent factors associate with hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease requiring intensive care unit admission: Focusing on the eosinophil-to-neutrophil ratio."** PLoS One **14**(7): e0218932.

BACKGROUND: Factors associated with hospital mortality are unclear in patients with acute exacerbation of COPD (AECOPD) requiring intensive care unit (ICU) admission. We aimed to characterize these patients and identify factors associated with hospital mortality. PATIENTS AND METHODS: We used a retrospective observational case-control design and recruited patients between January 2015 and March 2017. Of 146 patients enrolled, 24 (16.4%) died during their hospital stay, while 122 survived. RESULTS: Multivariate logistic regression analyses revealed factors associated with hospital mortality: age (adjusted odds ratio [AOR] 1.12, 95% CI: 1.03-1.23), C-reactive protein (CRP) level >7.5 mg/dL at the emergency room (AOR 4.52, 95% CI: 1.27-16.04), peak eosinophil-to-neutrophil ratio (ENR)x102 on days 8-14 of treatment (AOR 0.22, 95% CI: 0.08-0.63), and in-hospital complications (AOR 4.23, 95% CI: 1.12-15.98) (all P<0.05). After receiver operating characteristic curve analyses, cutoff level for peak ENRx102 was 0.224. To examine the synergistic effects of CRP level and peak ENR, we divided patients into four groups: (G0, reference group) Peak ENRx102 >0.224 on days 8-14 and initial CRP <7.5 mg/dL; (G1) Peak ENRx102 >0.224 on days 8-14 and initial CRP >7.5 mg/dL; (G2) Peak ENRx102 <0.224 on days 8-14 and initial CRP <7.5 mg/dL; and (G3) Peak ENRx102 <0.224 on days 8-14 and initial CRP >7.5 mg/dL. For G2 and G3 patients, the AOR of mortality was significantly different from that of the reference group (G2: AOR 10.00, P = 0.020; G3: AOR 61.79, P<0.001). The relationship between 28-day mortality and the four groups was statistically significant (log-rank test, P<0.001). CONCLUSION: Older age, initial CRP >7.5 mg/dL, peak ENR on days 8-14, and in-hospital complications were associated with hospital mortality in patients with AECOPD requiring ICU admission. Patients with both biomarkers, initial CRP >7.5 mg/dL, and peak ENRx102 <0.224 on days 8-14 of treatment, had an increased risk of hospital mortality.

https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0218932&type=printable

Chen, X., T. Dong, et al. (2019). **"Electrochemical methods for detection of biomarkers of Chronic Obstructive Pulmonary Disease in serum and saliva."** Biosens Bioelectron **142**: 111453.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death nowadays, and its underdiagnosis is still a great challenge. More effective diagnosis method is in urgent need since the traditional spirometry has many limitations in the practical application. The electrochemical (EC) detection methods have their unique advantages of high accuracy, short response time and easy integration of the system. In this review, recent works on the EC methods for COPD biomarkers including interleukin 6 (IL-6), interleukin 8 (IL-8) and C-reactive protein (CRP) are summarized. Five types of EC methods are highlighted in this study, as enzyme-labelled immunosensors, nanoparticle-labelled immunosensors, capacitive or impedimetric immunosensors, magnetoimmunosensors, and field effect

transistor (FET) immunosensors. To date, EC immunosensors have been exhibiting high analytical performance with a detection limit that can achieve several pg/mL or even lower. The simplicity of EC immunosensors makes them a perfect solution for a future point-of-care device to use in settings for COPD diagnosis and follow-up. Nevertheless, more efforts need to be paid on the simultaneous detection of multiple biomarkers, a demand for the clinical diagnosis, and processes of assay simplification towards achieving one-step detection.

https://www.sciencedirect.com/science/article/pii/S0956566319305329?via%3Dihub

Contoli, M., S. Baraldo, et al. (2019). **"Airway inflammatory profile is correlated with symptoms in stable COPD: A longitudinal proof-of-concept cohort study."** RespirologyBACKGROUND AND OBJECTIVE: Symptoms negatively impact the quality of life and long-term prognosis of patients with chronic obstructive pulmonary disease (COPD). Little is known about the relationship linking airway inflammation and symptoms in stable COPD. In this study, we evaluated whether respiratory symptoms in COPD are related to sputum inflammatory cellular profile and whether symptom changes are associated with changes in airway inflammation. METHODS: A total of 40 patients with stable COPD with moderate-to-severe airflow obstruction were enrolled. Patients were visited weekly over 4 weeks. At each visit, patients underwent clinical assessments, lung function tests and sputum induction. Patients recorded daily dyspnoea, sputum and cough scores. RESULTS: The changes between two consecutive visits in the percent of sputum neutrophils and eosinophils were related to the changes in the cough ($P < 0.001$; $r = 0.63$) and dyspnoea scores ($P < 0.001$; $r = 0.58$) of the prior week. Furthermore, using regression analyses, we were able to demonstrate that changes in the cough score were specifically associated to the change in neutrophils, while changes in the dyspnoea score and use of rescue medications were associated with changes in eosinophils numbers. CONCLUSION: Our study showed an association between symptoms and the sputum inflammatory profile. In particular, changes in symptoms (cough and dyspnoea) were correlated with changes in the specific sputum inflammatory cell components of airway inflammation (neutrophils and eosinophils, respectively), providing novel information on the mechanisms of disease manifestation.

https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13607

Cornwell, W. D., C. Kim, et al. (2019). **"Inflammatory signature in lung tissues in patients with combined pulmonary fibrosis and emphysema."** Biomarkers **24**(3): 232-239.

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

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

Corsico, A. G., F. Braido, et al. (2019). **"Corrigendum to "Healthcare costs of the SATisfaction and adherence to COPD treatment (SAT) study follow-up" [Respir. Med. 153 (2019) 68-75]."** Respir Med
https://www.resmedjournal.com/article/S0954-6111(19)30197-0/pdf

De Matteis, S., D. Jarvis, et al. (2019). **"The occupations at increased risk of chronic obstructive pulmonary disease (COPD): analysis of lifetime job-histories in the population-based UK Biobank Cohort."** Eur Respir JOccupational 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 (FEV1)/forced vital capacity (FVC) <lower limit of normal (LLN). Lifetime job-histories were collected via OSCAR, 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 also 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

de Miguel-Diez, J., J. Hernandez-Vazquez, et al. (2019). **"Analysis of environmental risk factors for chronic obstructive pulmonary disease exacerbation: A case-crossover study (2004-2013)."** PLoS One **14**(5): e0217143.
PURPOSE: We aim to assess if air pollution levels and climatological factors are associated with hospital admissions for exacerbation of chronic obstructive pulmonary disease (COPD) in Spain from 2004 to 2013. METHODS: We conducted a retrospective study. Information on pollution level and climatological factors were obtained from the Spanish Meteorological Agency and hospitalizations from the Spanish hospital discharge database. A case-crossover design was used to identify factors associated with hospitalizations and in hospital mortality. Postal codes were used to assign climatic and pollutant factors to each patient. RESULTS: We detected 162,338 hospital admissions for COPD exacerbation. When seasonal effects were evaluated we observed that hospital admissions and mortality were more frequent in autumn and winter. In addition, we found significant associations of temperature, humidity, ozone (O3), carbon monoxide (CO), particulate matter up to 10 mum in size (PM10) and nitrogen dioxide (NO2) with hospital admissions. Lower temperatures at admission with COPD exacerbation versus 1, 1.5, 2 and 3 weeks prior to hospital admission for COPD exacerbation, were associated with a higher probability of dying in the hospital. Other environmental factors that were related to in-hospital mortality were NO2, O3, PM10 and CO. CONCLUSIONS: Epidemiology of hospital admissions by COPD exacerbation was negatively affected by colder climatological factors (seasonality and absolute temperature) and short-term exposure to major air pollution (NO2, O3, CO and PM10).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6532877/pdf/pone.0217143.pdf

Ding, Y., Q. Li, et al. (2019). **"TERT gene polymorphisms are associated with chronic obstructive pulmonary disease risk in the Chinese Li population."** Mol Genet Genomic Med: e773.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide and is characterized by a partially reversible airflow limitation. Currently, many studies put forward that COPD is associated with both genetic and environmental factors. It has been reported that germline mutations in telomerase are risk factors for COPD susceptibility. In this study, we validated the association between TERT polymorphisms and COPD risk with a case-control study in the Chinese Li population. METHODS: A total of 279 COPD patients and 290 control individuals were recruited. We identified five single nucleotide polymorphisms (SNPs) in TERT that were associated with COPD. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in logistic regression models after adjusting for age and gender to assess the association. RESULTS: In the genetic model analysis, we found the "C/T-T/T" genotype of rs10069690 in TERT was associated with an increased COPD risk in the dominant model (p = 0.046); the rs2853677 in TERT was significantly associated with increased COPD risk based on the codominant model ("A/G" genotype, p = 0.033), dominant model (A/G-G/G genotype, p = 0.0091), and log-additive model (p = 0.023). The rs2853676 in TERT could increase the risk of COPD in the dominant model ("C/T-T/T" genotype, p = 0.026) and in the Log-additive model (p = 0.022). CONCLUSION: Our data shed new light on the association between TERT SNPs and COPD susceptibility in the Chinese Li population.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/mgg3.773

Djamin, R. S., M. Bafadhel, et al. (2019). **"Blood eosinophil count and GOLD stage predict response to maintenance azithromycin treatment in COPD patients with frequent exacerbations."** Respir Med **154**: 27-33.

INTRODUCTION: Maintenance treatment with macrolides are useful in preventing COPD exacerbations. We investigated which characteristics of COPD patients with frequent exacerbations predicted the best response to maintenance treatment with azithromycin. METHODS: This study was part of the COLUMBUS trial, a prospective randomized, double-blind, placebo-controlled study in 92 COPD patients with frequent exacerbations. During the 1-year treatment period, follow-up data were collected for spirometry, mMRC scores, sputum cultures and blood inflammatory markers. RESULTS: In the azithromycin group a significant lower number of exacerbations per patient was observed in patients with the following characteristics: baseline blood eosinophil count >/=2.0% (x=1.26), compared to an eosinophil count<2.0% (x=2.50; p=0.02), GOLD stage 1-2 (x=1.06), versus GOLD stage 4 (x=2.62; p=0.02) and GOLD group C (x=0.45) compared to group D (x=2.18; p<0.01). Moreover, the number of hospitalizations was significantly lower in patients, with a blood eosinophil count >/=2.0% (x=0.26) compared to an eosinophil count<2.0% (x=0.90; p=0.01) and in GOLD stages 1-2 (x=1.06) compared to stage 4 (x=2.62; p=0.04). CONCLUSION: In conclusion, azithromycin maintenance treatment appears to be effective in COPD patients with frequent exacerbations, who are either classified in GOLD stage 1-2 or GOLD C and those with a blood eosinophil count of >/=2.0%.

https://www.resmedjournal.com/article/S0954-6111(19)30193-3/fulltext

Dong, W., Y. Zhu, et al. (2019). **"Association between features of COPD and risk of venous thromboembolism."** Clin Respir JINTRODUCTION: Chronic obstructive pulmonary disease (COPD) is associated with risk of venous thromboembolism (VTE) events. A detailed understanding of which clinical features of COPD increase risk of VTE events is needed. OBJECTIVES: To investigate the association between features of COPD and risk of venous thromboembolism. METHODS: A retrospective observational clinical study was conducted on 551 consecutive COPD patients visiting the Department of Respiratory and Critical Care Medicine of Tianjin Chest Hospital between February 2014 and April 2018. Finally, 151 patients were eligible for inclusion. Of these, 29 patients had COPD with VTE and 121 patients had COPD without VTE. Patient informations regarding age, gender, BMI, smoking history, smoking status (package/year), COPD-related symptoms, lung function, number of acute exacerbations

and imaging visual emphysema were gathered. RESULTS: Among the 29 VTE patients, 18 patients had PE and five had DVT, while 6 patients had simultaneous PE and DVT. There were statistically significant differences in GOLD grade, Imaging visual emphysema, and frequent acute exacerbations between the two groups. Multivariate logistic regression analysis showed that after adjustment for gender, age, BMI and smoking history, there were statistically significant for visible emphysema (OR = 3.54, 95% CI: 1.13-11.08; P = 0.03) and GOLD grade (OR = 1.77, 95% CI: 1.04-3.01; P = 0.035), but not for frequent acute exacerbations (OR = 1.65, 95% CI: 0.62-4.38; P = 0.31). CONCLUSIONS: Visual emphysema is an independent risk factor for VTE events and the risk of VTE in COPD patients increases with the degree of airway obstruction. However, there is no evidence of an association between exacerbation frequency and VTE events.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.13051

Duarte, A. G., L. Tung, et al. (2019). **"Spirometry Measurement of Peak Inspiratory Flow Identifies Suboptimal Use of Dry Powder Inhalers in Ambulatory Patients with COPD."** Chronic Obstr Pulm Dis **6**(3)Objectives: Determine the prevalence of suboptimal peak inspiratory flow rate (PIFR) and associated patient characteristics and compare PIFR measurements obtained with spirometry and In-Check DIAL((R)) device in ambulatory patients with COPD. Methods: Patients underwent PIFR measurement with In-Check DIAL((R)) device and pulmonary function testing with calibrated equipment. Group characteristics and lung function were compared for patients with suboptimal (</= 60 L/min) and optimal (> 60 L/min) PIFR. Receiver operating curve analysis determined the best maximal forced inspiratory flow (FIF max) value in identifying optimal PIFR by gender and height. Results: From July 1, 2016 to January 31, 2018, a total of 303 patients with chronic obstructive pulmonary disease (COPD) had PIFR and pulmonary function measurements. Group mean age was 65.5 +/- 11.3 years with equal gender distribution. Suboptimal PIFR was observed in 61 (20.1%) patients. A significant correlation was observed between PIFR and FIF max, inspiratory capacity and residual volume (RV) to total lung capacity (TLC) ratio. In the suboptimal PIFR group, mean FIF max measured by spirometry was significantly less compared with the optimal PIFR group; 178.5 +/- 56.9 L/min and 263.4 +/- 89.9 L/min, respectively ($p<0.0001$). Receiver operator curve analysis of FIF max to identify an optimal PIFR yielded an area under the curve of 0.79. Males < 65 inches had a suboptimal PIFR in 16.7 % of the male cohort, while females < 65 inches had a suboptimal PIFR in 27.4 % of the women. Conclusions: Suboptimal PIFR was present in 1 in 5 stable patients with COPD and was more frequent in short statured females. Spirometry determined FIF max was associated with PIFR based on gender and height.

https://journal.copdfoundation.org/Portals/0/JCOPDF/Files/Volume6-Issue3/JCOPDF-2018-0163-Duarte.pdf

Duarte-de-Araujo, A., P. Teixeira, et al. (2019). **"Characterisation of morbidity in a COPD hospital cohort."** Pulmonology **25**(4): 200-207.

OBJECTIVES: To characterise the morbidity of COPD out-patients based on symptoms, acute exacerbations, FEV1 and comorbidities, and to explore the association between different patients' characteristics such as social, demographic, clinical history or exposure. METHODS: Stable COPD outpatients over 40 years old diagnosed according to GOLD criteria were included consecutively; the exclusion criteria were only refusal to participate and inability to understand clinical questionnaires. A survey of demographic and clinical data was conducted. Symptoms were evaluated using the CAT and mMRC questionnaires. The number of COPD acute exacerbations reported in the previous year was assessed, and spirometry performed on all participants according to ATS/ERS recommendations. Different variables were collected and then related to each other. RESULTS: We studied 303 COPD outpatients, all Caucasians, 79.5% males and mostly elderly. 65.7% of participants reported having low monthly income and 87.8% a low education level. Tobacco smoking was the most common exposure identified but a substantial proportion of COPD patients were non-smokers (26%). Frequent acute exacerbations were reported by 38.0% of patients. The mean post-bronchodilator FEV1 was 53.2%. The distribution of patients according to GOLD 2017 stage and classification was respectively 9.9%, 41.9%, 35.0% and 13.2% from 1 to 4 and

23.1%, 39.6%, 2.3% and 35.0% from GOLD A to D. Only 29 patients (9.5%) presented no comorbid conditions, and the most common were hypertension, heart diseases and dyslipidaemia. CONCLUSIONS: Our data confirms COPD as a complex and heterogeneous disorder, with a significant morbidity due to the nature of symptoms, frequent comorbidities and exacerbations. A substantial proportion of COPD patients were never-smokers, mainly women, calling attention to the need for COPD recognition in these cases. COPD in women, in never-smokers and in patients with a previous diagnosis of asthma presented some specific characteristics. Some patient characteristics are associated with frequent acute exacerbations. FEV1 was strongly related both to symptoms and exacerbations.

https://pdf.sciencedirectassets.com/318509/1-s2.0-S2531043719X00045/1-s2.0-S253104371930042X/main.pdf?X-Amz-Security-Token=AgoJb3JpZ2luX2VjEAIaCXVzLWVhc3QtMSJHMEUCIBmPcQiJkn%2FcimqOX7O3fp6PHrzlnRTGSyvSQ5WmE%2BceAiEAkhRV0tt6ruXSEVXiJ%2Fudfg4Qd9bwrKEhWf%2B%2BYeW8LFkq2gMIaxACGgwwNTkwMDM1NDY4NjUiDJYdlgkzgaJ%2FA7%2BBBiq3AwcqrDiQMfPOsnCjvqp6XO%2Fgivgj0JJcsA9ORAKoTNPDpjPiZwPqa%2FVL7AGOLFfduWG5kMzIAiDG7JJX449C1Gk6H0l%2FXNmcpMhQFRKgip6PUsS5lYY2RpM%2FY9xwm8PGU17Ix4AMd1JMt%2BipX8fTvUaG3tBmm0l9QzlH7oZhihVp2dvzb9qQbhK92bAD8Ochjs4fj%2BlhKvZRKo3dsefhqrcpQ2cSqRfAjztflwMvjdZLvMdI2yRuBPZThRQZQGK1O%2BU0XgCE3xiURftsdvsV0Ea40YweDjrx18T7AHHw5hWNrAyfBPZ1CcBCY%2FoK3SAui5h3siJxc5CknulJT%2FoN8p7%2BCASCWN6XQl3Ut0TpvzM9m54LMph5N%2F8hpPUfqN78BXQv8znl7PAmRtzObVvyQeEW9I1Pg2pZmdzadTObcQup0hbIC%2BiJjaCUwdkmhHXVnSXLfjoRGyb%2FqvPn6U1v%2Fs%2BXc7FC41jdr9ePlaScW%2BKWmU3xOx3PiBev51WUB%2FlloSPM%2BHNIk49%2FxJSoyUrnKVaSXglFn5CWnkAww6hv0FKHvE7FnPtEvOJ1GdcjZ%2BvqnuWYNFBzpt4w2cnE6QU6tAH1vScOcUm9ll%2Bl%2Bz4%2F5G4Q6WBsqJsOhZniGa%2FPszvN9YOZaY3HtC49uadEOqkPReZykFN4mQJmS1ikcyBRBl1HZXsYhMdbigG%2BSm9zA%2Fwf1IV53Twfsy5PqvF9bbzEtuq0kSqd62TE%2BxBe3KL2eu8CrjTdztYgQp0TcbOvF7Aqy2c%2FPuth2b5YkR1sigu8V8Lo5548hQAiLkLuiz0sK4emFQhzaKMq2xerZZY6ga7vrx2y8Pg%3D&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Date=20190719T024123Z&X-Amz-SignedHeaders=host&X-Amz-Expires=300&X-Amz-Credential=ASIAQ3PHCVTY3Q2YSHAG%2F20190719%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Signature=1e5fdbfed8b8d086e1138c207224326d044300194f2921459203a32a599bd331&hash=8dd0a9b7c5d3e39b4c256fc0b376c3615f78f3ed8e7f0eaf6f7b7e5c9d001987&host=68042c943591013ac2b2430a89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S253104371930042X&tid=spdf-2fa87e77-2ef1-4a23-9030-95d0c7fd6374&sid=ed3efb987d8a374be97bde61814aa9d67edcgxrqa&type=client

Farre-Garros, R., J. Y. Lee, et al. (2019). **"Quadriceps miR-542-3p and -5p are elevated in COPD and reduce function by inhibiting ribosomal and protein synthesis."** J Appl Physiol (1985) **126**(6): 1514-1524.

Reduced physical performance reduces quality of life in patients with chronic obstructive pulmonary disease (COPD). Impaired physical performance is, in part, a consequence of reduced muscle mass and function, which is accompanied by mitochondrial dysfunction. We recently showed that miR-542-3p and miR-542-5p were elevated in a small cohort of COPD patients and more markedly in critical care patients. In mice, these microRNAs (miRNAs) promoted mitochondrial dysfunction suggesting that they would affect physical performance in patients with COPD, but we did not explore the association of these miRNAs with disease severity or physical performance further. We therefore quantified miR-542-3p/5p and mitochondrial rRNA expression in RNA extracted from quadriceps muscle of patients with COPD and determined their association with physical performance. As miR-542-3p inhibits ribosomal protein synthesis its ability to inhibit protein synthesis was also determined in vitro. Both miR-542-3p expression and -5p expression were elevated in patients with COPD (5-fold $P < 0.001$) and the degree of elevation associated with impaired lung function (transfer capacity of the lung for CO in % and forced expiratory volume in 1 s in %) and physical performance (6-min walk distance in %). In COPD patients, the ratio of 12S rRNA to 16S rRNA was suppressed suggesting mitochondrial ribosomal stress and mitochondrial dysfunction and miR-542-3p/5p expression was inversely associated with mitochondrial gene expression and positively associated with p53 activity. miR-542-3p suppressed RPS23 expression and maximal protein synthesis in vitro. Our data show that miR-542-3p and -5p expression is elevated in COPD patients and may suppress physical performance at least in part by inhibiting mitochondrial and cytoplasmic ribosome synthesis and suppressing protein synthesis. NEW & NOTEWORTHY miR-542-3p and -5p are elevated in the quadriceps muscle of patients with chronic obstructive pulmonary disease (COPD) in proportion to the severity of their lung disease. These microRNAs inhibit mitochondrial and

cytoplasmic protein synthesis suggesting that they contribute to impaired exercise performance in COPD.

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

Fathima, M., B. Saini, et al. (2019). **"A mixed methods analysis of community pharmacists' perspectives on delivering COPD screening service to guide future implementation."** Res Social Adm Pharm **15**(6): 662-672.

BACKGROUND: Studies have shown that COPD screening by community pharmacists is effective, but it is unknown if it can be successfully implemented in Australian pharmacies. OBJECTIVE: We aimed to investigate the pharmacist-perceived barriers and facilitators to the implementation of a community pharmacy-based COPD screening service guided by implementation science methodology. METHODS: Trained pharmacists participated in a 6 month longitudinal study designed and based on implementation science frameworks. Pharmacists completed feedback questionnaires pre-and post-study and participated in semi-structured telephone interviews about their experience of implementing the service, the training provided, their views on patient recruitment, their interactions with health professionals and patients, and their future recommendations for such a service. Interviews were recorded and transcribed verbatim, analysed thematically, and questionnaire and interview data were triangulated. RESULTS: Of 20 pharmacists providing questionnaire data, 15 pharmacists (male 53%; age 39.8+/-8.6yrs, rural 47%) participated in an interview. Questionnaire data revealed that pharmacists engaged positively with the service and reported that it was very useful for patients and for the profession. In-depth qualitative analysis revealed 6 main implementation themes: 1. Patient recruitment (pharmacists lacked patient recruitment skills), 2. Adaptation and entrepreneurship (protocol adaptation increased patient engagement), 3. Training and resource needs (face-to-face training was preferred for skill-based learning), 4. Lack of GP involvement (sub-optimal GP-pharmacist collaboration), 5. Factors related to the operation or full implementation phase (high professional satisfaction, need for remuneration) and 6. Suggestions for refining the screening service (raise public awareness about the service, provide service remuneration, use electronic methods to improve GP referral uptake). A number of effective adaptations to the service were reported by pharmacists, such as advertising, recruitment practices, patient inclusion criteria and inter-professional communication with GPs which would be beneficial to implementation. CONCLUSION: This mixed methods study identified a number of key facilitators to service implementation and challenges such as difficulty with patient recruitment, low public awareness of pharmacy-based clinical services, remuneration, and sub-optimal GP-pharmacist collaboration. Working with stakeholders to identify and resolve challenges and to optimise the fit of the service for individual settings may lead to increasingly successful implementation of pharmacy-based service models.

https://www.sciencedirect.com/science/article/abs/pii/S1551741117309518?via%3Dihub

Faverio, P., A. Stainer, et al. (2019). **"Noninvasive Ventilation Weaning in Acute Hypercapnic Respiratory Failure due to COPD Exacerbation: A Real-Life Observational Study."** Can Respir J **2019**: 3478968.

The most recent British Thoracic Society/Intensive Care Society (BTS/ICS) guidelines on the use of noninvasive ventilation (NIV) in acute hypercapnic respiratory failure (AHRF) suggest to maximize NIV use in the first 24 hours and to perform a slow tapering. However, a limited number of studies evaluated the phase of NIV weaning. The aim of this study is to describe the NIV weaning protocol used in AHRF due to acute exacerbation of chronic obstructive pulmonary disease (AE-COPD), patients' characteristics, clinical course, and outcomes in a real-life intermediate respiratory care unit (IRCU) setting. We performed a retrospective study on adult patients hospitalized at the IRCU of San Gerardo Hospital, Monza, Italy, from January 2015 to April 2017 with a diagnosis of AHRF due to COPD exacerbation. The NIV weaning protocol used in our institution consists of the interruption of one of the three daily NIV sessions at the time, starting from the morning session and finishing with the night session. The 51 patients who started weaning were divided into three groups: 20 (39%) patients (median age 80 yrs, 65% males) who

completed the protocol and were discharged home without NIV (Completed Group), 20 (39%) did not complete it because they were adapted to domiciliary ventilation (Chronic NIV Group), and 11 (22%) interrupted weaning ex abrupto mainly due to NIV intolerance (Failed Group). Completed Group patients were older, had a higher burden of comorbidities, but a lower severity of COPD compared to Chronic NIV Group. Failed Group patients experienced higher frequency of delirium after NIV discontinuation. None of the patients who completed weaning had AHRF relapse during hospitalization. While other NIV weaning methods have been previously described, our study is the first to describe a protocol that implies the interruption of a ventilation session at the time. The application of a weaning protocol may prevent AHRF relapse in the early stages of NIV interruption and in elderly frail patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6452557/pdf/CRJ2019-3478968.pdf

Fernandez-Garcia, S., C. Represas-Represas, et al. (2019). **"Social and clinical predictors associated with prolonged hospital stays for patients with severe exacerbation of chronic obstructive pulmonary disease."** Rev Clin EspOBJECTIVE: To determine whether there are social factors that affect the prolonged hospital stay (PHS) of patients with severe chronic obstructive pulmonary disease exacerbation (COPDE), as well as clinical-demographic factors. METHODOLOGY: We conducted a prospective cohort study that consecutively included patients who were admitted to a Pneumology department for COPDE. We recorded demographic, clinical (tobacco use, exacerbations and infections, dyspnoea, impact according to CAT questionnaire, pulmonary function, comorbidities, oxygen therapy and noninvasive ventilation) and social (financial status, caregiver availability and overload, dependence for basic and instrumental activities, social risk and use of social services) variables, employing questionnaires and indices such as Barthel, Lawton-Brody, Zarit, Barber and Gijon. We performed a univariate and multivariate analysis using a logistic regression model. RESULTS: The study included 253 patients, with a mean age of 68.9+/-9.8years; 77.1% of whom were men. The logistic regression model included active tobacco use, FEV1 value, CAT score >10, dyspnoea 3-4 on the MMRC, the presence of bacteria in sputum cultures, cardiovascular comorbidity, anaemia, home oxygen therapy, living alone, rural residence, caregiver overload and detecting social-family risks/problems. The variables independently associated with the possibility of PHS were a CAT score >10 (OR, 8.9; P=.04) and detecting a social-family risk/problem (OR, 2.6; P=.04). Active smoking was a predictor of shorter stays (OR, 0.15; P=.002). CONCLUSIONS: Variables related to the social sphere play a relevant role in hospital stays, as do the impact of the disease and the persistent use of tobacco by patients with severe COPD exacerbation.

https://www.sciencedirect.com/science/article/pii/S0014256519301493?via%3Dihub

Frazao, M., P. E. Silva, et al. (2019). **"Dynamic Hyperinflation Impairs Cardiac Performance During Exercise in COPD."** J Cardiopulm Rehabil Prev **39**(3): 187-192.

PURPOSE: To investigate the correlation between a plateau in minute ventilation (Equation is included in full-text article.)E during cardiopulmonary exercise tests (CPETs) and its impact on cardiac performance. METHODS: This retrospective study analyzed 2575 CPETs of patients with chronic obstructive pulmonary disease. The study randomly selected 10 patients with a plateau in the (Equation is included in full-text article.)E curve, suggesting dynamic hyperinflation, 10 patients with normal pattern for the (Equation is included in full-text article.)E curve, and 10 healthy persons. Classic CPET variables, the new ventilation hyperinflation index, and the dynamic cardiac constraint index were analyzed. RESULTS: The patients with dynamic hyperinflation presented with lower ventilation at 100% work rate ($P < .0001$), without significant differences in (Equation is included in full-text article.)E at 50% and 100% work rate. Patients with dynamic hyperinflation also presented with a lower oxygen pulse (O_2 pulse) at 100% ($P < .0001$), without significant difference in O_2 pulse at 50% and 100% work rate. The subjects with dynamic hyperinflation had a higher ventilation hyperinflation index ($P < .0001$) and dynamic cardiac constraints index ($P < .0001$). The ventilation hyperinflation index correlated with the dynamic cardiac constraints index ($r = 0.81$, $P < .0001$); oxygen pulse variation ($r = -0.63$, $P < .001$); (Equation is included in full-text

article.)E/(Equation is included in full-text article.)CO2 slope (r =-0.57, P < .01); work rate (r =-0.86, P < .0001); (Equation is included in full-text article.)O2 (r =-0.80, P < .0001), and (Equation is included in full-text article.)E (r =-0.83, P < .0001). CONCLUSION: There is a correlation between a plateau in the (Equation is included in full-text article.)E during CPET, suggesting hyperinflation, and it has an impact on cardiac performance.

Gamper, E., U. Schmidt, et al. (2019). **"Outdoor Walking Training Compared To Cycle Ergometer Training in Severe COPD: A Randomized Controlled Feasibility Trial."** Copd **16**(1): 37-44.

Exercise can improve walking capacity in persons with chronic obstructive pulmonary disease (COPD). However, most endurance training programs use cycle ergometers. The objectives of this study were: (i) to evaluate the feasibility of a randomized controlled trial (RCT) comparing outdoor walking training (OWT) to cycle ergometer training (CT) during inpatient rehabilitation in persons with severe COPD; (ii) to estimate the effect of OWT and CT on health-related quality of life, physical capacity and physical activity; and (iii) to estimate the required sample size for a RCT. A single-blind randomized controlled feasibility trial was conducted with three months' follow-up in the rehabilitation center in Walenstadtberg, Switzerland. Sixteen patients were included in the study, which had a recruitment rate of 33% (16/48). Patients were allocated to an OWT (n = 8) or CT (n = 8) group. Participants completed 75% of scheduled training and the follow-up rate was 75%. All participants in the OWT group were satisfied with the training. The OWT group had better health-related quality of life after three weeks' training compared to the CT group (p = 0.042, 95% confidence interval (95% CI) 1.06-49.94, effect size (d)=1.19). No exacerbations occurred in the OWT group, but three occurred in the CT group after three months' follow-up. There was no significant difference in the other outcomes. In conclusion, the study design and the OWT are feasible. Health-related quality of life improved in the OWT group compared to the CT group after three weeks' inpatient rehabilitation. A minimum of 46 participants is needed for a RCT. Trial registration: www.who.int/trialsearch DRKS00010977.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1586865

Gayle, A., S. Dickinson, et al. (2019). **"Incidence of type II diabetes in chronic obstructive pulmonary disease: a nested case-control study."** NPJ Prim Care Respir Med **29**(1): 28.

We investigated the incidence of type II diabetes mellitus (T2DM) among people with COPD and whether exposure to inhaled corticosteroid (ICS) and exacerbation status was associated with T2DM. This descriptive cohort study used primary care data from the Clinical Practice Research Datalink (CPRD). The patient cohort included people with a diagnosis of COPD and previous smoking history registered at a CPRD practice between January 2010 and December 2016. We determined incidence rates by age, gender and deprivation. Using a nested case-control design-where cases and controls are drawn from the cohort population-we matched 1:5 with patients by age, gender and GP practice and estimated odds of T2DM using logistic regression (adjusting for smoking status, deprivation, BMI, hypertension, coronary heart disease and heart failure). We identified 220,971 COPD patients; mean age at COPD diagnosis was 66 years (SD 12) and 54% were male. The incidence rate of T2DM in COPD patients was 1.26 per 100 patient years (95% CI: 1.24-1.28) and was higher among men (1.32 vs 1.18 among women). The adjusted odds ratio for T2DM was 1.47 (95% CI: 1.36-1.60) among frequent exacerbators (>/=2 treated exacerbations per year) compared to infrequent exacerbators and the odds ratio for patients receiving high-dose ICS (>800 mcg budesonide equivalent dose) was 1.73 (95% CI 1.65-1.82) compared to patients receiving no ICS therapy. Incidence of T2DM among COPD patients is high and exposure to ICS and frequent exacerbations are associated with a higher risk of T2DM among patients with COPD.

https://www.nature.com/articles/s41533-019-0138-6.pdf

Germovsek, E., C. Ambery, et al. (2019). **"A Novel Method for Analysing Frequent Observations from Questionnaires in Order to Model Patient-Reported Outcomes: Application to EXACT(R) Daily Diary Data from COPD Patients."** Aaps j **21**(4): 60.

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease with approximately 174 million cases worldwide. Electronic questionnaires are increasingly used for collecting patient-reported-outcome (PRO) data about disease symptoms. Our aim was to leverage PRO data, collected to record COPD disease symptoms, in a general modelling framework to enable interpretation of PRO observations in relation to disease progression and potential to predict exacerbations. The data were collected daily over a year, in a prospective, observational study. The e-questionnaire, the EXAcerbations of COPD Tool (EXACT(R)) included 14 items (i.e. questions) with 4 or 5 ordered categorical response options. An item response theory (IRT) model was used to relate the responses from each item to the underlying latent variable (which we refer to as disease severity), and on each item level, Markov models (MM) with 4 or 5 categories were applied to describe the dependence between consecutive observations. Minimal continuous time MMs were used and parameterised using ordinary differential equations. One hundred twenty-seven COPD patients were included (median age 67 years, 54% male, 39% current smokers), providing approximately 40,000 observations per EXACT(R) item. The final model suggested that, with time, patients more often reported the same scores as the previous day, i.e. the scores were more stable. The modelled COPD disease severity change over time varied markedly between subjects, but was small in the typical individual. This is the first IRT model with Markovian properties; our analysis proved them necessary for predicting symptom-defined exacerbations.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6486532/pdf/12248_2019_Article_319.pdf

Gershon, A. S., D. Thiruchelvam, et al. (2019). **"Socioeconomic status (SES) and 30-day hospital readmissions for chronic obstructive pulmonary (COPD) disease: A population-based cohort study."** PLoS One **14**(5): e0216741.

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) are more likely to be readmitted than patients with other chronic medical conditions, yet knowledge regarding such readmissions is limited. We aimed to determine factors associated with readmission within 30 days of a COPD hospitalization or death with an emphasis on examining aspects of socioeconomic status and specific comorbidities. METHODS: A population-based cohort study was conducted using health administrative data from Ontario, Canada. All hospitalizations for COPD between 2004 and 2014 were considered. The primary exposures were socioeconomic status as measured by residential instability (an ecologic variable), and comorbidities such as cardiovascular disease and cancer. Other domains of socioeconomic status were considered as secondary exposures. Logistic regression with generalized estimating equations was used to examine the effect of exposures, adjusting for other patient factors, on 30-day readmission or death. RESULTS: There were 126,013 patients contributing to 252,756 index COPD hospitalizations from 168 Ontario hospitals. Of these hospitalizations, 19.4% resulted in a readmission and 2.8% resulted in death within 30 days. After adjusting for other factors, readmissions or death were modestly more likely among people with the highest residential instability compared to the lowest (OR 1.05, 95% CI 1.01-1.09). Comorbidities such as cardiovascular disease and cancer, as well as other aspects of low socioeconomic status also increased readmission or death risk. INTERPRETATION: Socioeconomic status, measured in various ways, and many comorbidities predict 30-day readmission or death in patients hospitalized for COPD. Strategies that address these factors may help reduce readmissions and death.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6528994/pdf/pone.0216741.pdf

Ghosh, N., P. Choudhury, et al. (2019). **"Metabolomic signatures of asthma-COPD overlap (ACO) are different from asthma and COPD."** Metabolomics **15**(6): 87.

INTRODUCTION: Asthma-chronic obstructive pulmonary disease (COPD) overlap, termed as ACO, is a complex heterogeneous disease without any clear diagnostic or therapeutic guidelines. The pathophysiology of the disease, its characteristic features, and existence as a unique disease entity remains unclear. Individuals with ACO have a faster lung function decline, more frequent exacerbations, and worse quality of life than those with COPD or asthma alone. OBJECTIVES: The present study aims to determine whether ACO has a distinct metabolic profile in comparison to asthma and COPD. METHODS: Two different groups of patients were recruited as discovery (D) and validation (V) cohorts. Serum samples obtained from moderate and severe asthma patients diagnosed as per GINA guidelines [n = 34(D); n = 32(V)], moderate and severe COPD cases identified by GOLD guidelines [n = 30(D); 32(V)], ACO patients diagnosed by joint GOLD and GINA guidelines [n = 35(D); 40(V)] and healthy controls [n = 33(D)] were characterized using nuclear magnetic resonance (NMR) spectrometry. RESULTS: Multivariate and univariate analysis indicated that 12 metabolites [lipid, isoleucine, N-acetylglycoproteins (NAG), valine, glutamate, citric acid, glucose, L-leucine, lysine, asparagine, phenylalanine and histidine] were dysregulated in ACO patients when compared with both asthma and COPD. These metabolites were further validated in a fresh cohort of patients, which again exhibited a similar expression pattern. CONCLUSIONS: Our findings suggest that ACO has an enhanced energy and metabolic burden associated with it as compared to asthma and COPD. It is anticipated that our results will stimulate researchers to further explore ACO and unravel the pathophysiological complexities associated with the disease.

https://link.springer.com/article/10.1007%2Fs11306-019-1552-z

Gilmer, T. P., B. R. Celli, et al. (2019). **"Predictors of Nebulized Arformoterol Treatment: A Retrospective Analysis of Medicare Beneficiaries with Chronic Obstructive Pulmonary Disease."** Copd: 1-12.

This study examined sociodemographic and clinical characteristics, treatment patterns, and health resource utilization among Medicare beneficiaries with chronic obstructive pulmonary disease (COPD) to identify predictors of nebulized arformoterol treatment. Using Medicare administrative data from 2010 to 2014, beneficiaries with >/=2 COPD outpatient visits >/=30 d apart or >/=1 COPD-related hospitalization(s) (ICD-9-CM 491.xx, 492.xx, and 496) were identified. Inclusion criteria required >/=1 COPD medication claim(s) and continuous enrollment in Parts A, B, and D. Four cohorts were identified: (a) 11,887 arformoterol users, (b) a subsample of arformoterol users (n = 1,778) who were hospitalized and discharged 30 d before initiating arformoterol, (c) 450,178 controls who had not received arformoterol, and (d) a subsample of controls (n = 21,910) who had hospitalizations. Logistic regression analysis was used to evaluate predictors of arformoterol treatment. The majority of beneficiaries were older than 70 years of age, female, Caucasian, and 47% were dual-eligible. The strongest predictors of arformoterol treatment were oxygen therapy, systemic corticosteroid or methylxanthine use, an exacerbation, a COPD-related hospitalization, and receiving care from a pulmonologist (all p < .001). Dual-eligibility, being a racial/ethnic minority, and having severe psychiatric comorbidity or immunodeficiency lowered the odds of receiving nebulized arformoterol (all p < .001). Among beneficiaries with recent hospitalizations, exacerbations and COPD-related admissions increased the odds of receiving arformoterol (p < .001). Nebulized arformoterol treatment was more likely to be initiated in sicker patients with COPD. Ensuring access to nebulized maintenance therapy is important and particularly warranted for COPD populations with greater medical needs.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1618256

Goedemans, L., G. E. Hoogslag, et al. (2019). **"ST-Segment Elevation Myocardial Infarction in Patients With Chronic Obstructive Pulmonary Disease: Prognostic Implications of Right Ventricular Systolic Dysfunction as Assessed with Two-Dimensional Speckle-Tracking Echocardiography."** J Am Soc EchocardiogrBACKGROUND: Right ventricular (RV) systolic function in patients admitted with ST-segment elevation myocardial infarction (STEMI) with chronic obstructive pulmonary disease (COPD) and its impact on prognosis have not been characterized. The present study aims to compare the prevalence

of RV systolic dysfunction in COPD versus non-COPD patients with STEMI and evaluate the prognostic implications. METHODS: One hundred seventeen STEMI patients with COPD with transthoracic echocardiography performed within 48 hours of admission were retrospectively selected. Matched on age, gender, and infarct size (determined by cardiac biomarkers and left ventricular ejection fraction [LVEF]), 207 non-COPD patients were selected. RV dysfunction was defined based on tricuspid annular plane systolic excursion <17 mm (TAPSE), tricuspid annular systolic velocity <6 cm/s (S'), RV fractional area change <35% (FAC), and RV longitudinal free wall strain (FWSL) measured with speckle-tracking echocardiography >-20%. Patients were followed for the occurrence of all-cause mortality. RESULTS: RV assessment was feasible in 112 COPD and 199 non-COPD patients (mean age, 69 +/- 10; 74% male; mean, LVEF 47% +/- 8%). Patients with COPD had significantly lower RV FAC (38% +/- 11% vs 40% +/- 9%; P = .04), equal TAPSE and S' (17.9 +/- 3.7 vs 18.1 +/- 3.8 mm, P = .72; and 8.4 +/- 2.2 vs 8.5 +/- 2.2 cm/sec, P = .605, respectively) and more impaired RV FWSL (-21.1% +/- 6.6% vs -23.4% +/- 6.5%, P = .005), compared with patients without COPD. RV dysfunction was more prevalent in patients with COPD, particularly when assessed with RV FWSL (46% vs 32%; P = .021). During a median follow-up of 30 (interquartile range 1.5-44) months, 49 patients died (16%). Multivariate models stratified for COPD status showed that RV FWS >-20% was independently associated with 5-year all-cause mortality (hazard ratio, 2.05; 95% CI, 1.12-3.76; P = .020), after adjusting for age, diabetes, peak troponin level, and LVEF. Interestingly, RV FAC < 35%, S'< 6 cm/sec, and TAPSE < 17 mm were not independently associated with survival. CONCLUSION: In a STEMI population with relatively preserved LVEF, COPD patients had significantly worse RV FWSL compared with patients without COPD. Moreover, RV FWSL > -20% was independently associated with worse survival. In contrast, conventional parameters were not associated with survival.

https://www.onlinejase.com/article/S0894-7317(19)30727-8/fulltext

Gulbas, G., O. Turan, et al. (2019). **"Carotid intima-media thickness in chronic obstructive pulmonary disease and survival: A multicenter prospective study."** Clin Respir J **13**(6): 391-399.

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

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

Gulea, C., R. Zakeri, et al. (2019). **"Impact of chronic obstructive pulmonary disease on readmission after hospitalization for acute heart failure: A nationally representative US cohort study."** Int J Cardiol **290**: 113-118.

BACKGROUND: Patients hospitalized for heart failure (HF) are at high risk of readmission. Chronic obstructive pulmonary disease (COPD) is one of the most prevalent comorbidities in this population. However, few data and only small studies describe the impact of COPD on the risk of readmission. METHODS AND RESULTS: Hospitalizations for HF were identified in the 2012 National Readmissions Database. We compared clinical characteristics and the risk of all-cause, cardiovascular (CV) and respiratory-related readmission for patients with and without COPD. We included 225,160 patients hospitalized for HF among whom 54,953 had comorbid COPD. Patients with COPD were younger (median age 76years COPD versus 77years without COPD; p<0.001), had a higher burden of comorbidity and were more frequently male (53% versus 49%, p<0.001). Thirty-day all-cause readmission risk was two-fold greater in patients with COPD compared to those without COPD (adjusted HR 2.02, 95%CI 1.97-2.08). Most readmissions were attributed to a CV cause, though fewer patients with COPD had a CV admission (49% versus 51% without COPD). COPD was independently associated with significantly more frequent unplanned respiratory-related readmission (adjusted HR 2.90, 95%CI 2.68-3.15) as well as CV readmission risk (adjusted HR 1.92, 95%CI 1.85-1.99). CONCLUSIONS: In patients hospitalized for HF, most readmissions are due to a CV cause. However, patients with comorbid COPD are at a significantly elevated risk of respiratory in addition to CV-related readmission. These data stress the importance of a multidisciplinary management approach, including optimization of non-CV conditions, in order to reduce readmissions post index HF hospitalization.

https://www.internationaljournalofcardiology.com/article/S0167-5273(19)31403-2/fulltext

Haghighi, B., S. Choi, et al. (2019). **"Imaging-based clusters in former smokers of the COPD cohort associate with clinical characteristics: the SubPopulations and intermediate outcome measures in COPD study (SPIROMICS)."** Respir Res **20**(1): 153.

BACKGROUND: Quantitative computed tomographic (QCT) imaging-based metrics enable to quantify smoking induced disease alterations and to identify imaging-based clusters for current smokers. We aimed to derive clinically meaningful sub-groups of former smokers using dimensional reduction and clustering methods to develop a new way of COPD phenotyping. METHODS: An imaging-based cluster analysis was performed for 406 former smokers with a comprehensive set of imaging metrics including 75 imaging-based metrics. They consisted of structural and functional variables at 10 segmental and 5 lobar locations. The structural variables included lung shape, branching angle, airway-circularity, airway-wall-thickness, airway diameter; the functional variables included regional ventilation, emphysema percentage, functional small airway disease percentage, Jacobian (volume change), anisotropic deformation index (directional preference in volume change), and tissue fractions at inspiration and expiration. RESULTS: We derived four distinct imaging-based clusters as possible phenotypes with the sizes of 100, 80, 141, and 85, respectively. Cluster 1 subjects were asymptomatic and showed relatively normal airway structure and lung function except airway wall thickening and moderate emphysema. Cluster 2 subjects populated with obese females showed an increase of tissue fraction at inspiration, minimal emphysema, and the lowest progression rate of emphysema. Cluster 3 subjects populated with older males showed small airway narrowing and a decreased tissue fraction at expiration, both indicating air-trapping. Cluster 4 subjects populated with lean males were likely to be severe COPD subjects showing the highest progression rate of emphysema. CONCLUSIONS: QCT imaging-based metrics for former smokers allow for the derivation of statistically stable clusters associated with unique clinical characteristics. This approach helps better categorization of COPD sub-populations; suggesting possible quantitative structural and functional phenotypes.

https://respiratory-research.biomedcentral.com/track/pdf/10.1186/s12931-019-1121-z

Han, Y., Y. Heo, et al. (2019). **"Correlation between Physical Activity and Lung Function in Dusty Areas: Results from the Chronic Obstructive Pulmonary Disease in Dusty Areas (CODA) Cohort."** Tuberc Respir Dis (Seoul)BACKGROUND: Although physical activity is known to be beneficial to lung function, few studies have been conducted to investigate the correlation between physical activity and lung

function in dusty areas. Therefore, the purpose of this study is to investigate the correlation between physical activity and lung function in a Korean cohort including normal and COPD-diagnosed participants. METHODS: Data obtained from the COPD in dusty areas (CODA) cohort was analyzed for the following factors: lung function, symptoms, and information about physical activity. Information on physical activity was valuated using questionnaires, and participants were categorized into two groups: active and inactive. The evaluation of the mean lung function, modified Medical Research Council dyspnea grade scores, and COPD assessment test scores was done based on the participant physical activity using a general linear model after adjusting for age, sex, smoking status, pack-years, height, and weight. In addition, a stratification analysis was performed based on the smoking status and COPD. RESULTS: Physical activity had a correlation with high forced expiratory volume in 1 second (FEV(1)) among CODA cohort (p=0.03). While the active group exhibited significantly higher FEV(1) compared to one exhibited by the inactive group among past smokers (p=0.02), no such correlation existed among current smokers. There was no significant difference observed in lung function after it was stratified by COPD. CONCLUSION: This study established a positive correlation between regular physical activity in dusty areas and lung function in participants.

https://e-trd.org/Synapse/Data/PDFData/0003TRD/trd-82-e14.pdf

Hansen, G. M., J. L. Marott, et al. (2019). **"Midlife cardiorespiratory fitness and the long-term risk of chronic obstructive pulmonary disease."** ThoraxBACKGROUND: Good midlife cardiorespiratory fitness (CRF) may reduce the risk of chronic obstructive pulmonary disease (COPD). Reverse causation may play a role if follow-up time is short. We examined the association between CRF and both incident COPD and COPD mortality in employed men with up to 46 years follow-up, which allowed us to account for reverse causality. METHODS: Middle-aged men (n=4730) were recruited in 1970-1971. CRF was determined as VO2max by ergometer test. Categories of CRF (low, normal, high) were defined as +/- 1 Z-score (+/- 1 SD) above or below the age-adjusted mean. Endpoints were identified through national registers and defined as incident COPD, and death from COPD. Multi-adjusted Cox models and restricted mean survival times (RMST) were performed. RESULTS: Compared with low CRF, the estimated risk of incident COPD was 21% lower in participants with normal CRF (HR 0.79, 95% CI 0.63 to 0.99) and 31 % lower with high CRF (HR 0.69, 95% CI 0.52 to 0.91). Compared with low CRF, the risk of death from COPD was 35% lower in participants with normal CRF (HR 0.65, 95% CI 0.46 to 0.91) and 62% lower in participants with high CRF (HR 0.38, 95% CI 0.23 to 0.61). RMST showed a delay to incident COPD and death from COPD in the magnitude of 1.3-1.8 years in normal and high CRF vs low CRF. Test for reverse causation did not alter the results. CONCLUSION: In a population of healthy, middle-aged men, higher levels of CRF were associated with a lower long-term risk of incident COPD and death from COPD.

https://thorax.bmj.com/content/early/2019/05/22/thoraxjnl-2018-212821

Hlavati, M., K. Buljan, et al. (2019). **"Impaired cerebrovascular reactivity in chronic obstructive pulmonary disease."** Acta Neurol BelgImpaired cerebrovascular reactivity (CVR) is associated with stroke. Cerebrovascular diseases are common comorbidity in chronic obstructive pulmonary disease (COPD) patients. The aim of our study was to quantify CVR in the anterior and posterior cerebral circulation during voluntary breath-holding in COPD patients according to airflow limitation severity. In this cross-sectional study, we compared 90 COPD patients without previous cerebrovascular disease and 30 age- and sex-matched healthy volunteers (mean age 67 +/- 7.9, 87 males). Using transcranial Doppler ultrasound and breath-holding index (BHI), we analysed baseline mean flow velocities (MFV) and CVR of middle cerebral artery (MCA) and basilar artery (BA). Our results demonstrated that COPD patients had lower baseline MFV of both MCA and BA than controls. COPD patients had significantly lower BHImMCA and BHImBA than controls (0.8 and 0.7 versus 1.24 and 1.07, respectively; $p < 0.001$). With the severity of airflow obstruction, there were significant declines of BHImMCA and BHImBA in mild (0.94 and 0.83), moderate (0.8 and 0.7) and severe to very severe COPD (0.7 and 0.6), respectively ($p < 0.001$). For all participants, we found a significant and positive correlation between forced expiratory volume in one

second (FEV1) and BHImMCA (Rho = 0.761, p < 0.001) and between FEV1 and BHImBA (Rho = 0.409, p < 0.001). COPD patients have impaired CVR in anterior and posterior cerebral circulation. Impairment of CVR increase with the airflow limitation severity. CVR is an appropriate marker to identify vulnerable COPD subjects at high risk to develop cerebrovascular disease. Prospective studies are needed for further evaluation.

https://link.springer.com/article/10.1007%2Fs13760-019-01170-y

Ho, S. C., K. J. Chuang, et al. (2019). **"Chronic obstructive pulmonary disease patients have a higher risk of occurrence of pneumonia by air pollution."** Sci Total Environ **677**: 524-529.

Epidemiological evidence has shown that air pollution is associated with chronic obstructive pulmonary disease (COPD). The objective of this study was to investigate the effects of air pollution on patients with COPD and pneumonia. A case-control study of patients who had undergone thoracentesis for pleural effusion drainage in a hospital was recruited for this study. COPD and non-COPD patients with pneumonia respectively served as the case and control groups. Increases in particulate matter of <2.5mum in aerodynamic diameter (PM2.5) and NO2 increased the risk of pneumonia in COPD patients (adjusted odd ratio (OR)=4.136, 95% confidence interval (CI)=1.740-9.832 for PM2.5; adjusted OR=1.841, 95% CI=1.117-3.036 for NO2). COPD patients with pneumonia had higher levels of CD14 in pleural effusion than did non-COPD with pneumonia (p<0.05). An increase in CD14 of the pleural effusion increased the risk of pneumonia in COPD patients (adjusted OR=1.126, 95% CI=1.009-1.256). We further observed that an increase in Cu and a decrease in Zn in the pleural effusion increased the risk of pneumonia in COPD patients (adjusted OR=1.005, 95% CI=1.000-1.010 for Cu; adjusted OR=0.988, 95% CI=0.978-0.997 for Zn). In conclusion, our results suggest that COPD patients had a high risk of pneumonia occurring due to air pollution exposure.

https://www.sciencedirect.com/science/article/pii/S0048969719319011?via%3Dihub

Honeyford, K., D. Bell, et al. (2019). **"Unscheduled hospital contacts after inpatient discharge: A national observational study of COPD and heart failure patients in England."** PLoS One **14**(6): e0218128.

INTRODUCTION: Readmissions are a recognised challenge for providers of healthcare and incur financial penalties in a growing number of countries. However, the scale of unscheduled hospital contacts including attendances at emergency departments that do not result in admission is not well known. In addition, little is known about the route to readmission for patients recently discharged from an emergency hospital stay. METHODS: This is an observational study of national hospital administration data for England. In this retrospective cohort study, we tracked patients for 30 days after discharge from an emergency admission for heart failure (HF) or chronic obstructive pulmonary disorder (COPD). RESULTS: The majority of patients (COPD:79%; HF:75%) had no unscheduled contact with secondary health care within 30 days of discharge. Of those who did have unscheduled contact, the most common first unscheduled contact was emergency department (ED) attendance (COPD:16%; HF:18%). A further 5% of COPD patients and 4% of HF patients were admitted for an emergency inpatient stay, but not through the ED. A small percentage of patients (COPD:<1%, HF:2%) died without any known contact with secondary care. ED conversion rates at first attendance for both COPD and HF were high: 75% and 79% respectively. A quarter of patients who were not admitted during this first ED attendance attended the ED again within the 30-day follow-up period, and around half (COPD:56%; HF:63%) of these were admitted at this point. Patients who live alone, had an index admission which included an overnight stay and were comorbid had higher odds of being admitted through the ED than via other routes. CONCLUSION: While the majority of patients did not have unscheduled contact with secondary care in the 30 days after index discharge, many patients attended the ED, often multiple times, and many were admitted to hospital, not always via the ED. More frail patients were more likely to be admitted through the ED, suggesting a possible area of focus as discharge bundles are developed.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6563993/pdf/pone.0218128.pdf

Husebo, G. R., R. Nielsen, et al. (2019). **"Risk factors for lung cancer in COPD - results from the Bergen COPD cohort study."** Respir Med **152**: 81-88.

BACKGROUND: COPD patients have an increased risk of developing lung cancer, but the underlying mechanisms are poorly understood. We aimed to identify risk factors for lung cancer in patients from the Bergen COPD Cohort Study. METHODS: We compared 433 COPD patients with 279 healthy controls, all former or current smokers. All COPD patients had FEV1<80% and FEV1/FVC-ratio<0.7. Baseline predictors were sex, age, spirometry, body composition, smoking history, emphysema assessed by CT, chronic bronchitis, prior exacerbation frequency, Charlson Comorbidity Score, inhalation medication and 44 serum/plasma inflammatory biomarkers. Patients were followed up for 9 years recording incidence of lung cancer. Cox-regression models were fitted for the statistical analyses. The biomarkers were evaluated using principal component analysis. RESULTS: 28 COPD patients and 3 controls developed lung cancer, COPD patients had a significantly higher risk of developing lung cancer, (HR 5.0; 95% CI 1.5-17.1, p<0.01, adjusted values). Among COPD patients, emphysema (HR 4.4; 1.7-10.8, p<0.01) and obesity (HR 3.3; 1.3-8.5, p=0.02) were associated with a higher cancer rate. Use of inhaled steroids was associated with a lower rate (HR 0.4; 0.2-0.9, p=0.03). Smoking status, pack-years smoked or levels of systemic inflammatory markers, except for interferon gamma-induced protein 10, did not affect the lung cancer rate in patients with COPD. CONCLUSION: Patients with COPD have a higher lung cancer rate compared to healthy controls adjusted for smoking. The presence of emphysema and obesity in COPD predicted a higher lung cancer risk in COPD patients. Systemic inflammation was not associated with increased lung cancer risk.

https://www.resmedjournal.com/article/S0954-6111(19)30147-7/fulltext

Janciauskiene, S., D. S. DeLuca, et al. (2019). **"Serum Levels of Alpha1-antitrypsin and Their Relationship With COPD in the General Spanish Population."** Arch BronconeumolBACKGROUND: Low plasma level of alpha1-antitrypsin (AAT) is an established risk factor for early-onset chronic obstructive lung disease (COPD). However, less attention is given to the levels of AAT in the general population. METHODS: This is a part of a multicentre, population-based study conducted at 11 sites throughout Spain. Plasma levels of AAT were available for 837 persons with a mean (SD) age of 58.05 (11.3) years: 328-smokers, 272-ex-smokers and 237 non-smokers. Out of 837, 303 (36.2%) had a diagnosis of COPD, 222 (26.5%) had respiratory symptoms but no COPD, and 312 (37.3%) were healthy controls. RESULTS: In the whole cohort, the mean level of plasma AAT was 1.51 (0.47)g/L. Levels were higher in COPD patients [1.55 (0.45)g/L] and individuals with respiratory symptoms [1.57 (0.47)g/L] than in controls [1.43 (0.47)g/L], p<0.001, a finding which persisted after correction for age and CRP. Plasma AAT levels were negatively associated with FEV1/FVC ratio, after adjustment for age, sex, smoking status, CRP, TNFalpha, fibrinogen and albumin. The risk for COPD was significantly associated with higher AAT levels in univariate and multivariate models, with odds ratios of 1.8 and 1.5, respectively. In the univariate and multivariate models smoking status, gender, and CRP levels were also associated with COPD probability, demonstrating that they act independently. CONCLUSION: Increased circulating levels of AAT, similarly to CRP and other markers of systemic inflammation, is an important feature of COPD. Our results highlight a complex interrelationship between levels of AAT and health of respiratory system.

https://www.sciencedirect.com/science/article/pii/S0300289619301127?via%3Dihub

Ji Kwak, M., V. Bhise, et al. (2019). **"National trend of utilization, clinical and economic outcomes of transcatheter aortic valve replacement among patients with chronic obstructive pulmonary disease."** Curr Med Res Opin **35**(8): 1321-1329.

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

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

Jin, H., C. Heo, et al. (2019). **"Deep learning-enabled accurate normalization of reconstruction kernel effects on emphysema quantification in low-dose CT."** Phys Med Biol **64**(13): 135010.

Lung densitometry is being frequently adopted in CT-based emphysema quantification, yet known to be affected by the choice of reconstruction kernel. This study presents a two-step deep learning architecture that enables accurate normalization of reconstruction kernel effects on emphysema quantification in low-dose CT. Deep learning is used to convert a CT image of a sharp kernel to that of a standard kernel with restoration of truncation artifacts and smoothing-free pixel size normalization. We selected 353 scans reconstructed by both standard and sharp kernels from four different CT scanners from the United States National Lung Screening Trial program database. A truncation artifact correction model was constructed with a combination of histogram extrapolation and a deep learning model trained with truncated and non-truncated image sets. Then, we performed frequency domain zero-padding to normalize reconstruction field of view effects while preventing image smoothing effects. The kernel normalization model has a U-Net based architecture trained for each CT scanner dataset. Three lung density measurements including relative lung area under 950 HU (RA950), lower 15th percentile threshold (perc15), and mean lung density were obtained in the datasets from standard, sharp, and normalized kernels. The effect of kernel normalization was evaluated with pair-wise differences in lung density metrics. The mean of pair-wise differences in RA950 between standard and sharp kernel reconstructions was reduced from 10.75% to -0.07% using kernel normalization. The difference for perc15 decreased from -31.03 HU to -0.30 HU after kernel normalization. Our study demonstrated the feasibility of applying deep learning techniques for normalizing CT kernel effects, thereby reducing the kernel-induced variability in lung density measurements. The deep learning model could increase the accuracy of emphysema quantification, thereby allowing reliable surveillance of emphysema in lung cancer screening even when follow-up CT scans are acquired with different reconstruction kernels.

https://iopscience.iop.org/article/10.1088/1361-6560/ab28a1

Kalinov, R. I., B. I. Marinov, et al. (2019). **"Desaturation during Physical Exercise in COPD Patients - a Stable-over-time Phenomenon."** Folia Med (Plovdiv) **61**(2): 204-212.

INTRODUCTION: Exercise-induced desaturation is a common finding in patients with moderate and severe COPD. It is an important marker in the course of disease that has a prognostic value for mortality risk. AIM: To monitor over time COPD patients with and without desaturation during 6-minute walking test (6MWT) and to assess the stability of that phenomenon. MATERIALS AND METHODS: A 6MWT was administered

to 70 patients with COPD which ranged in severity from stage 2A to stage 4D (GOLD 2011); the patients had a mean age of 64.5+/-10.1, mean pack-years - 38.8+/-21, FEV1% = 46.4%+/-15.7%, FVC% = 73.7%+/-1.3%, MRC = 2.31+/-0.84, CAT = 20.8+/-6.6. Oxygen saturation was monitored during the test; indications for desaturation were a decrease of SpO2 by >/=4% and a fall in SpO2 to </=88% for at least 3 min. The patients were followed-up for mean 40.9+/-22.3 months and tests were repeated. RESULTS: Patients were divided into two groups based on the decrease in SpO2: Group A included patients with desaturation (n=35) and Group B - patients with no desaturation (n=35). In 66 of the patients the desaturation profile was stable over time. Only two patients, who did not desaturated at baseline, experienced desaturation in the follow-up 6MWT and another two patients, who desaturated at baseline, did not have it later in the follow-up. CONCLUSION: Desaturation is a phenomenon that is persistent over time. Based on the results, it could be concluded that exercise-induced desaturation is a major marker of a particular COPD phenotype.

https://www.degruyter.com/downloadpdf/j/folmed.2018.61.issue-2/folmed-2018-0079/folmed-2018-0079.pdf

Kang, H. R., S. H. Hong, et al. (2019). **"Differences in the risk of mood disorders in patients with asthma-COPD overlap and in patients with COPD alone: a nationwide population-based retrospective cohort study in Korea."** Respir Res **20**(1): 80.

BACKGROUND: Although feelings of anxiety and depression are common in patients with chronic obstructive pulmonary disease (COPD), little is known about the estimates of their incidence in patients with asthma-COPD overlap (ACO), which has been described and acknowledged as a distinct clinical entity. We aimed to estimate the risk of depression and anxiety among patients with ACO and compare it with the risk among those with COPD alone in the general population. METHODS: We conducted a nationwide population-based retrospective cohort study using the Korean National Sample Cohort database between 1 January, 2002, and 31 December, 2013. Patients who were diagnosed with COPD (International Classification of Diseases, 10th revision [ICD-10] codes J42-J44) at least twice and prescribed COPD medications at least once between 2003 and 2011 were classified into two categories: patients who were diagnosed with asthma (ICD-10 codes J45-J46) more than twice and at least once prescribed asthma medications comprised the ACO group, and the remaining COPD patients comprised the COPD alone group. Patients who had been diagnosed with depression or anxiety within a year before the index date were excluded. We defined the outcome as time to first diagnosis with depression and anxiety. Matched Cox regression models were used to compare the risk of depression and anxiety among patients with ACO and patients with COPD alone after propensity score matching with a 1:1 ratio. RESULTS: After propensity score estimation and matching in a 1:1 ratio, the cohort used in the analysis included 15,644 patients. The risk of depression during the entire study period was higher for patients with ACO than for patients with COPD alone (adjusted hazard ratio, 1.10; 95% confidence interval, 1.03-1.18; P value = 0.0039), with an elevated risk in patients aged 40-64 years (1.21; 1.10-1.34; 0.0001) and in women (1.18; 1.07-1.29; 0.0005). The risk of anxiety was higher for patients with ACO than for patients with COPD alone (1.06; 1.01-1.12; 0.0272), with a higher risk in patients aged 40-64 years (1.08; 1.00-1.17; 0.0392); however, the risk was not significant when stratified by sex. CONCLUSIONS: This population-based study revealed a higher incidence of depression and anxiety in patients with ACO than in patients with COPD alone.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6492426/pdf/12931_2019_Article_1039.pdf

Kendzerska, T., S. D. Aaron, et al. (2019). **"Effectiveness and Safety of Inhaled Corticosteroids in Older Individuals with COPD and/or Asthma: A Population Study."** Ann Am Thorac SocRATIONALE: 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 areas, specifically for asthma in older adults, for people with concurrent asthma and COPD and for some people with COPD given their association 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 aged 66 years 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. Primary effectiveness and safety outcomes were, respectively, hospitalizations for obstructive lung disease (OLD) and hospitalizations for pneumonia. Propensity scores were used to adjust for confounders. RESULTS: There were 87,690 individuals with asthma (27% with concurrent COPD) and 150,593 with COPD (25% with concurrent asthma). In terms of effectiveness, controlling for confounders, ICS was associated with fewer OLD hospitalizations (HR 0.84, 0.79-0.88) in those with asthma alone with concurrent COPD attenuating the benefit; a similar association was seen in those with COPD and concurrent asthma (HR 0.88, 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 marginal increased risk of pneumonia hospitalizations in people with COPD and no asthma (HR 1.03, 1.00-1.06), but not in the other groups. CONCLUSIONS: ICS was associated with fewer obstructive lung disease hospitalizations in older adults with asthma and concurrent asthma and COPD but had little impact on obstructive lung disease and pneumonia hospitalizations in those with COPD alone.

Kim, V., H. Zhao, et al. (2019). **"The St. George's Respiratory Questionnaire Definition of Chronic Bronchitis May Be a Better Predictor of COPD Exacerbations Compared With the Classic Definition."** Chest BACKGROUND: Chronic bronchitis (CB) increases risk of COPD exacerbations. We have shown that the St. George's Respiratory Questionnaire (SGRQ) CB definition identifies patients with a similar clinical phenotype as classically defined CB. Whether the SGRQ CB definition is a predictor of future COPD exacerbations is unknown. METHODS: We analyzed 7,557 smokers with normal spirometry and Global Initiative for Chronic Obstructive Lung Disease stage 1-4 COPD in the Genetic Epidemiology of COPD study with longitudinal follow-up data on exacerbations. Subjects were divided into classic CB(+) or classic CB(-), using the classic definition. In addition, subjects were divided into SGRQ CB(+) or SGRQ CB(-). Exacerbation frequency and severe exacerbation frequency were determined in each group. Multivariable linear regressions were performed for exacerbation frequency with either classic CB or SGRQ CB and relevant covariates. RESULTS: There were 1,434 classic CB(+) subjects and 2,290 SGRQ CB(+) subjects. The classic CB(+) group had a greater exacerbation frequency compared with the classic CB(-) group (0.69 +/- 1.26 vs 0.36 +/- 0.90 exacerbations per patient per year; P < .0001) and a greater severe exacerbation frequency (0.26 +/- 0.74 vs 0.13 +/- 0.46 severe exacerbations per patient per year; P < .0001). There were similar differences between the SGRQ CB(+) and SGRQ CB(-) groups. In multivariable analysis, both SGRQ CB and classic CB were independent predictors of exacerbation frequency, but SGRQ CB had a higher regression coefficient. In addition, SGRQ CB was an independent predictor of severe exacerbation frequency whereas classic CB was not. CONCLUSIONS: The SGRQ CB definition identified more subjects at risk for future exacerbations than the classic CB definition. SGRQ CB was at least a similar if not better predictor of future exacerbations than classic CB.

https://journal.chestnet.org/article/S0012-3692(19)30881-5/fulltext

Koreny, M., H. Demeyer, et al. (2019). **"Determinants of study completion and response to a 12-month behavioral physical activity intervention in chronic obstructive pulmonary disease: A cohort study."** PLoS One **14**(5): e0217157.

OBJECTIVES: Physical activity is key to improve the prognosis of chronic obstructive pulmonary disease (COPD). To help to tailor future interventions we aimed to identify the baseline characteristics of COPD patients which predict 12-month completion and response to a behavioral physical activity intervention. METHODS: This is a 12-month cohort study of the intervention arm of the Urban Training randomized controlled trial (NCT01897298), an intervention proven to be efficacious to increase physical activity. We

considered baseline sociodemographic, interpersonal, environmental, clinical and psychological characteristics as potential determinants of completion and response. We defined completion as attending the 12-month study visit. Among completers, we defined response as increasing physical activity >/=1100 steps/day from baseline to 12 months, measured by accelerometer. We estimated the factors independently for completion and response using multivariable logistic regression models. RESULTS: Of a total of 202 patients (m (SD) 69 (9) years, 84% male), 132 (65%) completed the study. Among those, 37 (28%) qualified as responders. Higher numbers of baseline steps/day (OR [95% CI] 1.11 [1.02-1.21] per increase of 1000 steps, p<0.05) and living with a partner (2.77 [1.41-5.48], p<0.01) were related to a higher probability of completion while more neighborhood vulnerability (0.70 [0.57-0.86] per increase of 0.1 units in urban vulnerability index, p<0.01) was related to a lower probability. Among the completers, working (3.14 [1.05-9.33], p<0.05) and having an endocrino-metabolic disease (4.36 [1.49-12.80], p<0.01) were related to a higher probability of response while unwillingness to follow the intervention (0.21 [0.05-0.98], p<0.05) was related to a lower probability. CONCLUSIONS: This study found that 12-month completion of a behavioral physical activity intervention was generally determined by previous physical activity habits as well as interpersonal and environmental physical activity facilitators while response was related to diverse factors thought to modify the individual motivation to change to an active lifestyle.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6527234/pdf/pone.0217157.pdf

Krachunov, I., N. Kyuchukov, et al. (2018). **"Stability of Frequent Exacerbator Phenotype in Patients with Chronic Obstructive Pulmonary Disease."** Folia Med (Plovdiv) **60**(4): 536-545.

BACKGROUND: At present, there is little information in Bulgaria regarding the rate and stability of frequent-exacerbation phenotype in COPD patients. AIM: To study the rate and stability of frequent-exacerbation phenotype in COPD patients. MATERIALS AND METHODS: We followed up 465 COPD patients for exacerbations over a 3-year period. Exacerbations were defined as events that resulted in treatment with antibiotics and/or corticosteroids (moderate), or that led to hospitalization (severe). RESULT: Approximately 10% of the patients had two or more exacerbations per year (frequent-exacerbation phenotype), and this structure stayed stable over the study period. The exacerbation rate in the first year of follow up was 0.33 per stage I COPD patients (according to GOLD stages), 0.49 per stage II COPD patients; 0.69 - for stage III, and 1.06 for stage IV COPD patients. The frequent-exacerbation rate increased from stage I to stage IV by 4.35%, 9.17%, 10.79%, and 20.97%, respectively. A history of previous year exacerbations increased the risk of new exacerbations: with a history of one exacerbation - OR 2.1820 (95% CI: 1.4018 to 3.3965, p = 0.0005), and with a history of two exacerbations - OR 4.6460 (95% CI: 2.3286 to 9.2696; p < 0.0001). The frequent-exacerbation phenotype appeared to be unstable over the study period - up to 33% from those patients stayed in the phenotype for the next year. CONCLUSIONS: The exacerbation frequency and the rate of frequent-exacerbation phenotype increases with COPD progression. History of exacerbations in the previous year is a significant risk factor for exacerbations of COPD. The frequent-exacerbation phenotype appeared to be unstable over the study period. The pheno-type of non-exacerbators was more likely to remain stable over time.

https://content.sciendo.com/downloadpdf/journals/folmed/60/4/article-p536.pdf

Kraskovsky, V., J. Schneider, et al. (2019). **"Longer Duration of Palliative Care in Patients With COPD Is Associated With Death Outside the Hospital."** J Palliat Care: 825859719851486.

BACKGROUND: Patients with advanced chronic obstructive pulmonary disease (COPD) have a significant symptom burden despite maximal medical therapy, yet few are referred for concomitant palliative care. OBJECTIVE: To evaluate the utilization and impact of palliative care on the location of death and to identify clinical variables associated with palliative care contact. DESIGN: Retrospective chart review from 2010 to 2016 at the VA Western New York Healthcare System using ICD-9/10 diagnosis of COPD. Palliative care contact was identified by Z51.5 or stop code 353. RESULTS: Only 0.5% to 2% of living patients received palliative care, increasing abruptly at death (6%). Lower diffusion capacity for carbon

monoxide (DLCO) (greater emphysema) was associated with palliative care contact, independent of comorbid disease burden or age. Initial outpatient contact was associated with a longer duration of palliative care (P = .003) and death in a home-like setting. Outpatient palliative care was associated with more severe airflow obstruction (forced expiratory volume in 1 second, percent predicted [FEV1%]), whereas greater disease exacerbation frequency was associated with inpatient contact. COPD patients not referred to palliative care had a greater comorbid disease burden, similar FEV1%, fewer disease exacerbations, and a greater DLCO. CONCLUSION: Few patients with COPD received palliative care, similar to national trends. Initial outpatient palliative contact had the longest duration of care and death in the preferred home environment. The extent of emphysema (DLCO reduction) and more frequent disease exacerbations identified in patients were more likely to receive palliative care. Our study begins to define the benefits of palliative care in advanced COPD and confirms underutilization in the years before death, where a prolonged impact on the quality of life may be realized.

Kwan, H. Y., M. Maddocks, et al. (2019). **"The prognostic significance of weight loss in chronic obstructive pulmonary disease-related cachexia: a prospective cohort study."** J Cachexia Sarcopenia MuscleBACKGROUND: Cachexia is an important extra-pulmonary manifestation of chronic obstructive pulmonary disease (COPD) presenting as unintentional weight loss and altered body composition. Previous studies have focused on the relative importance of body composition compared with body mass rather than the relative importance of dynamic compared with static measures. We aimed to determine the prevalence of cachexia and pre-cachexia phenotypes in COPD and examine the associations between cachexia and its component features with all-cause mortality. METHODS: We enrolled 1755 consecutive outpatients with stable COPD from two London centres between 2012 and 2017, stratified according to European Respiratory Society Task Force defined cachexia [unintentional weight loss >5% and low fat-free mass index (FFMI)], pre-cachexia (weight loss >5% but preserved FFMI), or no cachexia. The primary outcome was all-cause mortality. We calculated hazard ratios (HRs) using Cox proportional hazards regression for cachexia classifications (cachexia, pre-cachexia, and no cachexia) and component features (weight loss and FFMI) and mortality, adjusting for age, sex, body mass index, and disease-specific prognostic markers. RESULTS: The prevalence of cachexia was 4.6% [95% confidence interval (CI): 3.6-5.6] and pre-cachexia 1.6% (95% CI: 1.0-2.2). Prevalence was similar across sexes but increased with worsening Global Initiative for Chronic Obstructive Pulmonary Disease spirometric stage and Medical Research Council dyspnoea score (all P < 0.001). There were 313 (17.8%) deaths over a median (interquartile range) follow-up duration 1089 (547-1704) days. Both cachexia [HR 1.98 (95% CI: 1.31-2.99), P = 0.002] and pre-cachexia [HR 2.79 (95% CI: 1.48-5.29), P = 0.001] were associated with increased mortality. In multivariable analysis, the unintentional weight loss feature of cachexia was independently associated with mortality [HR 2.16 (95% CI: 1.31-3.08), P < 0.001], whereas low FFMI was not [HR 0.88 (95% CI: 0.64-1.20), P = 0.402]. Sensitivity analyses using body mass index-specific, age-specific, and gender-specific low FFMI values found consistent findings. CONCLUSIONS: Despite the low prevalence of cachexia and pre-cachexia, both confer increased mortality risk in COPD, driven by the unintentional weight loss component. Our data suggest that low FFMI without concurrent weight loss may not confer the poor prognosis as previously reported for this group. Weight loss should be regularly monitored in practice and may represent an important target in COPD management. We propose the incorporation of weight monitoring into national and international COPD guidance.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/jcsm.12463

Kyomoto, Y., K. Asai, et al. (2019). **"Handgrip strength measurement in patients with chronic obstructive pulmonary disease: Possible predictor of exercise capacity."** Respir InvestigBACKGROUND: Impaired exercise capacity is one of the most important prognostic factors for patients with chronic obstructive pulmonary disease (COPD). The 6-min walk test (6MWT) is a widely used method for assessing exercise capacity in patients with COPD. However, the 6MWT requires considerable effort from patients.

Therefore, a less physically demanding, but also noninvasive, method is warranted. The objective of this study was to determine the predictors of the 6MWT distance (6MWD) in patients with COPD. METHODS: This retrospective observational study enrolled 133 Japanese patients with COPD. All patients underwent the 6MWT, COPD assessment test (CAT), spirometry, respiratory muscle strength evaluation, body composition assessment, and handgrip strength (HGS) measurement. We examined the associations between the 6MWD and evaluated parameters. RESULTS: From single regression analysis, the 6MWD was significantly correlated with age, CAT score, several spirometric measurements (e.g., percentages of forced vital capacity, forced expiratory volume in 1 s, and carbon monoxide diffusing capacity of the lungs [%DLCO]), respiratory muscle strength parameters (e.g., percentages of maximal expiratory and inspiratory pressures), skeletal muscle mass index, and HGS. In multiple regression analysis, age, CAT score, %DLCO, and HGS were independent predictors of the 6MWD. The %DLCO and HGS were strongly correlated as predictors of the 6MWD ($p < 0.001$). CONCLUSIONS: We found that HGS was significantly correlated with the 6MWD compared with spirometric measurements or respiratory muscle strength parameters in Japanese patients with COPD, suggesting that HGS could be a simple and noninvasive predictor of the 6MWD in patients with COPD.

https://www.sciencedirect.com/science/article/abs/pii/S2212534518303022?via%3Dihub

Larson, T. (2019). **"Economic impact and chronic obstructive pulmonary disease outcomes of a comprehensive inhaler to nebulization therapy protocol implementation in a large multi-state healthcare system."** Curr Med Res Opin: 1-13.

Objective: There are currently 39 FDA-approved metered-dose (MDI) or dry-powder inhalers (DPI) on the US market. Most are high cost with significantly more drug in the device than needed for a typical average length of stay in acute care hospitals, which leads to significant waste. The objective was to assess the financial impact and chronic obstructive pulmonary disease (COPD) outcomes of a comprehensive inhaler to nebulization protocol implemented in a large multi-state US health system. Methods: The retrospective study evaluated respiratory drug costs at 28 hospitals in the health system after a phased implementation of the automatic inhaler to nebulization protocol. Purchasing data was collected for all respiratory medications impacted by the protocol for the twelve months preceding as well as the two subsequent twelve-month periods following implementation at each facility. COPD length of stay (LOS) and 30 day readmissions were also reviewed. An attempt was made to evaluate the impact on respiratory therapy (RT) department workload. Results: Compared to pre-implementation, system-wide drug expenditures declined $1,561,011 (38.5%) and $1,646,411 (40.6%) in post-implementation year 1 (PY1) and post-implementation year 2 (PY2), respectively. COPD LOS and 30 day readmissions were not adversely affected and remained relatively stable in comparative periods. Objective impact on RT productivity and labor statistics was not ascertained due to complicated variables and multiple service lines. Conclusions: In an era of increased drug costs incurred by hospitals, a comprehensive inhaler to nebulization protocol significantly decreased costs without incurring any negative observed trends in COPD LOS or readmissions.

https://www.tandfonline.com/doi/pdf/10.1080/03007995.2019.1628562?needAccess=true

Larsson, K., C. Janson, et al. (2019). **"Impact of COPD diagnosis timing on clinical and economic outcomes: the ARCTIC observational cohort study."** Int J Chron Obstruct Pulmon Dis **14**: 995-1008.

Purpose: Assess the clinical and economic consequences associated with an early versus late diagnosis in patients with COPD. Patients and methods: In a retrospective, observational cohort study, electronic medical record data (2000-2014) were collected from Swedish primary care patients with COPD. COPD indicators (pneumonia, other respiratory diseases, oral corticosteroids, antibiotics for respiratory infections, prescribed drugs for respiratory symptoms, lung function measurement) registered prior to diagnosis were applied to categorize patients into those receiving early (2 or less indicators) or late diagnosis (3 or more indicators registered >90 days preceding a COPD diagnosis). Outcome measures included annual rate of and time to first exacerbation, mortality risk, prevalence of comorbidities and health care

utilization. Results: More patients with late diagnosis (n=8827) than with early diagnosis (n=3870) had a recent comorbid diagnosis of asthma (22.0% vs 3.9%; P<0.0001). Compared with early diagnosis, patients with late diagnosis had a higher exacerbation rate (hazard ratio [HR] 1.89, 95% confidence interval [CI]: 1.83-1.96; P<0.0001) and shorter time to first exacerbation (HR 1.61, 95% CI: 1.54-1.69; P<0.0001). Mortality was not different between groups overall but higher for late versus early diagnosis, after excluding patients with past asthma diagnosis (HR 1.10, 95% CI: 1.02-1.18; P=0.0095). Late diagnosis was also associated with higher direct costs than early diagnosis. Conclusion: Late COPD diagnosis is associated with higher exacerbation rate and increased comorbidities and costs compared with early diagnosis. The study highlights the need for accurate diagnosis of COPD in primary care in order to reduce exacerbations and the economic burden of COPD.

https://www.dovepress.com/getfile.php?fileID=49810

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 MedRATIONALE: Clinical variables associated with shortened survival in advanced-stage cystic fibrosis (CF) patients are not included in the lung allocation score (LAS). OBJECTIVE: Identify variables associated with waitlist and posttransplant mortality for CF lung transplant candidates using a novel database; analyze the impact of including new CF-specific variables in the LAS. METHODS: A deterministic matching algorithm identified patients from the Scientific Registry of Transplant Recipients and the Cystic Fibrosis Foundation Patient Registry. LAS waitlist and posttransplant survival models were recalculated using CF-specific variables. This multi-center, retrospective, population-based study of lung transplant waitlist candidates aged >/= 12 years, January 1, 2011-December 31, 2014, included 9043 patients on the lung transplant waiting list and 6110 lung transplant recipients, 2011-2014, 1020 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 2.8, 95% confidence interval 1.2-6.6), 29-42 days hospitalized (2.8, 1.3-5.9), massive hemoptysis (2.1, 1.1-3.9), and relative drop in FEV1 >/= 30% over 12 months (1.7, 1.0-2.8) increased waitlist mortality risk; pulmonary exacerbation time 15-28 days (1.8, 1.1-2.9) increased posttransplant mortality risk. A relative drop in FEV1 of >/= 10% in chronic obstructive pulmonary disease (COPD) candidates was associated with increased waitlist mortality risk (2.6, 1.2-5.4). Variability in LAS score and rank increased in CF patients. Priority for transplant increased for COPD candidates. Access did not change for other diagnosis groups. CONCLUSIONS: Adding CF-specific variables improved discrimination among waitlisted CF candidates, and benefitted COPD candidates.

Leitao Filho, F. S., N. M. Alotaibi, et al. (2019). **"Sputum Microbiome Is Associated with 1-Year Mortality after Chronic Obstructive Pulmonary Disease Hospitalizations."** Am J Respir Crit Care Med **199**(10): 1205-1213.

Rationale: Lung dysbiosis promotes airway inflammation and decreased local immunity, potentially playing a role in the pathogenesis of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Objectives: We sought to determine the relationship between sputum microbiome at the time of AECOPD hospitalization and 1-year mortality in a COPD cohort. Methods: We used sputum samples from 102 patients hospitalized because of AECOPD. All subjects were followed for 1 year after discharge. The microbiome profile was assessed through sequencing of 16S rRNA gene. Microbiome analyses were performed according to 1-year mortality status. To investigate the effect of alpha-diversity measures and taxon features on time to death, we applied Cox proportional hazards regression models and obtained hazard ratios (HRs) associated with these variables. Measurements and Main Results: We observed significantly lower values of alpha-diversity (richness, Shannon index, evenness, and Faith's Phylogenetic Diversity) among nonsurvivors (n = 19, 18.6%) than survivors (n = 83, 81.4%). beta-Diversity analysis also demonstrated significant differences between both groups (adjusted permutational multivariate ANOVA,

P = 0.010). The survivors had a higher relative abundance of Veillonella; in contrast, nonsurvivors had a higher abundance of Staphylococcus. The adjusted HRs for 1-year mortality increased significantly with decreasing alpha-diversity. We also observed lower survival among patients in whom sputum samples were negative for Veillonella (HR, 13.5; 95% confidence interval, 4.2-43.9; P < 0.001) or positive for Staphylococcus (HR, 7.3; 95% confidence interval, 1.6-33.2; P = 0.01). Conclusions: The microbiome profile of sputum in AECOPD is associated with 1-year mortality and may be used to identify subjects with a poor prognosis at the time of hospitalization.

Lewis, R. J., A. G. Mandler, et al. (2019). **"Delayed complication of tracheocutaneous fistula closure with severe compromising subcutaneous emphysema."** BMJ Case Rep **12**(6)We report a significant complication after tracheocutaneous fistula (TCF) excision with closure by secondary intention in a 4-year-old boy who had been tracheostomy dependent since infancy. He had a persistent 3 mm TCF one year after decannulation. On postoperative day 2 the patient developed profound subcutaneous emphysema and pneumomediastinum. He was extubated after 2 days and discharged from the hospital on postoperative day 7. At follow up he had complete resolution of subcutaneous emphysema and complete closure of the TCF. The main methods of TCF closure and management of subcutaneous emphysema are discussed along with the lessons learned from this case.

https://casereports.bmj.com/content/12/6/e229526

Li, J., C. Qin, et al. (2019). **"Solid Fuel Use and Incident COPD in Chinese Adults: Findings from the China Kadoorie Biobank."** Environ Health Perspect **127**(5): 57008.

BACKGROUND: Solid fuels are widely used in China. Household air pollution from the burning of solid fuels may increase the risk of chronic obstructive pulmonary disease (COPD), but prospective evidence is limited. OBJECTIVES: We examined the association of solid fuel use for cooking and heating with the risk of COPD in a prospective cohort study. METHODS: Participants were from the China Kadoorie Biobank. Current and previous fuels used for household cooking and heating were self-reported at baseline in 2004-2008. In the present study, "solid fuels" refers to coal and wood, whereas "cleaner fuels" refers to energy sources that presumably produce lower levels of indoor pollution, including electricity, gas, and central heating. A total of 475,827 adults 30-79 y of age without prevalent COPD were followed through the end of 2015. We used adjusted Cox regression models to estimate hazard ratios for COPD. RESULTS: Over 9.1 y of follow-up, 9,835 incident COPD cases were reported. Compared with the use of cleaner fuels for cooking, using coal and wood for cooking was positively associated with COPD, with fully adjusted HRs of 1.06 (95% CI: 0.98, 1.15) and 1.14 (95% CI: 1.06, 1.23), respectively. Adjusted HRs for heating with coal and wood were 1.16 (95% CI: 1.04, 1.29) and 1.21 (95% CI: 1.09, 1.35), respectively. The positive association between cooking with solid fuel and COPD appeared to be limited to women and never- (vs. ever-) smokers. COPD risk increased with a higher number of years of solid fuel use for heating and wood use for cooking. CONCLUSIONS: The use of solid fuel for cooking and heating was associated with the increased risk of COPD in this prospective cohort study. Studies with more accurate exposure assessment are needed to confirm the association. https://doi.org/10.1289/EHP2856.

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

BACKGROUND: To investigate the relationship between 7 polymorphisms of the serine protease inhibitor-2 (SERPINE2) gene and the risk of chronic obstructive pulmonary disease (COPD) in a Uygur population by

a case-control study. METHODS: A total of 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 7 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 than those with the rs16865421-A allele (OR=0.68, 95% CI: 0.47-0.98, 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, S., G. Wang, et al. (2019). **"The REACH Trial: A Randomized Controlled Trial Assessing the Safety and Effectiveness of the Spiration(R) Valve System in the Treatment of Severe Emphysema."** Respiration **97**(5): 416-427.

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

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

Liao, K. M., L. T. Kuo, et al. (2019). **"Increased risk of peripheral arterial occlusive diseases in patients with chronic obstructive pulmonary disease: a nationwide study in Taiwan."** Int J Chron Obstruct Pulmon Dis **14**: 1455-1464.

Objective: Chronic obstructive pulmonary disease (COPD) is associated with atherosclerosis. Previous studies including limited sample sizes have shown the prevalence of peripheral arterial occlusive disease (PAOD) among COPD patients. We sought to investigate the incidence of PAOD among COPD patients in Taiwan using a national database. Methods: COPD patients were collected from the National Health Insurance Research Database of Taiwan from 1996 to 2010. The COPD cohort was propensity score matched according to age, sex, and comorbidities of atrial fibrillation, hypertension, diabetes, hyperlipidemia, cerebrovascular accidents, and chronic liver disease to patients without COPD (the control cohort). We evaluated the incidence of PAOD in COPD patients and the risk of PAOD associated with atrial fibrillation, hypertension, diabetes, hyperlipidemia, cerebrovascular accidents, and chronic liver disease. Results: The study included 51,869 COPD patients and 51,869 control patients without COPD. The incidence of PAOD was 1.23-fold higher (95% confidence interval [CI] =1.17-1.29) in the COPD group

than in the non-COPD group. Moreover, COPD and atrial fibrillation alone (adjusted hazard ratio (aHR) 2.99; P=0.001), hypertension alone (aHR, 2.05; P<0.001), diabetes alone (aHR, 2.62; P<0.001) and cerebrovascular accidents alone (aHR 2.05; P<0.001), increased the risk of developing PAOD. The significant aHRs increased (from 3.7 to 4.9) when the number of comorbidities increased (from >/=1 to >/=3 comorbidities). Conclusion: COPD patients have a higher incidence and an independently higher risk of PAOD than patients without COPD. The risk of PAOD is markedly elevated in COPD patients with more comorbidities.

https://www.dovepress.com/getfile.php?fileID=50955

Lim, J. U., C. D. Yeo, et al. (2019). **"Comparison of clinical characteristics and overall survival between spirometrically diagnosed chronic obstructive pulmonary disease (COPD) and non-COPD never-smoking stage I-IV non-small cell lung cancer patients."** Int J Chron Obstruct Pulmon Dis **14**: 929-938.

Objectives: A significant proportion of non-small cell lung cancer (NSCLC) patients are never-smokers. However, the clinical impact of spirometrically diagnosed chronic obstructive pulmonary disease (COPD) on the prognosis of never-smoking NSCLC has not been evaluated in the context of treatment modalities and other cancer-related factors. In the present study, we evaluated the clinical impact of COPD in non-smoking NSCLC patients, and correlations between COPD and other previously unevaluated clinical variables. Materials and methods: Lung cancer patients (stages I to IV) diagnosed with NSCLC between January 2008 and December 2015 at six university hospitals were enrolled in the study cohort and retrospectively evaluated. Clinical parameters were compared between spirometrically diagnosed COPD and non-COPD groups. Correlations between COPD status and other variables were evaluated. In order to reduce the effect of potential confounders and selection bias, we performed adjustment for differences in baseline parameters by using propensity score matching (PSM). After PSM, clinical variables were evaluated for their effects on overall survival (OS). Results: Of the 345 patients enrolled in the study, 277 were categorized as non-COPD and 68 as COPD. Old age, male gender, and wild-type EGFR were significantly correlated with COPD. By univariate analysis of 218 patients in a propensity score matched cohort, not receiving active anticancer treatment, advanced stage, and COPD were significantly associated with shorter OS. Multivariate analysis showed that not receiving active anticancer treatment, advanced cancer stage, and COPD (P=0.044, HR: 1.526, 95% CI: 1.012-2.300) were significant predictors of shorter OS. Conclusion: In the present study, never-smoker NSCLC patients with COPD had shorter OS times, compared to non-COPD never-smoker NSCLC patients.

https://www.dovepress.com/getfile.php?fileID=49532

Lindskrog, S., K. B. Christensen, et al. (2019). **"Relationship Between Patient-Reported Outcome Measures and the Severity of Chronic Obstructive Pulmonary Disease in the Context of an Innovative Digitally Supported 24-Hour Service: Longitudinal Study."** J Med Internet Res **21**(6): e10924.

BACKGROUND: Individuals with chronic obstructive pulmonary disease (COPD) live with the burden of a progressive life-threatening condition that is often accompanied by anxiety and depression. The severity of the condition is usually considered from a clinical perspective and characterized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of severity (1-4) and a risk assessment (A through D) that focuses on the patient's symptoms and number of exacerbations, but information about perceived health or ability to manage the condition are rarely included. OBJECTIVE: We evaluated 3 patient-reported outcome measurements (PROMs) to examine how these can be used to report on individuals with COPD who were supported by a digitally assisted intervention that aims to increase the patient's management of their condition to improve their well-being. METHODS: A total of 93 individuals with COPD were enrolled. At baseline and after 6 and 12 months, we measured self-reported self-management (Health Education Impact Questionnaire, heiQ) and health literacy (Health Literacy Questionnaire, HLQ), and physical and mental health (Short Form-36, SF-36) PROMs were collected. The scores of the 19 PROM dimensions were related to COPD severity, that is, GOLD risk

assessment, pulmonary function at entry, and number of exacerbations of a period up to 12 months. The initial PROM scores were also compared with pulmonary function, exacerbations, and GOLD risk assessment to predict the number of contacts within the first 90 days. RESULTS: At baseline, 2 dimensions from heiQ and SF-36 Physical health differed significantly between GOLD risk factor groups, indicating more distress and poorer attitudes and health status with increasing severity (GOLD risk assessment). Pulmonary function (FEV1) was negatively associated with the severity of the condition. After 6 months, we observed an increase in heiQ6 (skill and technique acquisition) and a reduction in emotional distress. The latter effect persisted after 12 months, where heiQ4 (self-monitoring and insight) also increased. HLQ3 (actively managing my health) decreased after 6 and 12 months. The number of exacerbations and the GOLD risk factor assessment predicted the number of contacts during the first 90 days. Furthermore, 2 of the PROMS heiQ6 (skill and technique acquisition) and HLQ8 (ability to find good health information) evaluated at baseline were associated with the number of contacts within the first 90 after enrollment. The pulmonary function was not associated with the number of contacts. CONCLUSIONS: Our data suggest that selected dimensions from HLQ, heiQ, and SF-36 can be used as PROMs in relation to COPD to provide researchers and clinicians with greater insight into how this condition affects individuals' ability to understand and manage their condition and perception of their physical and mental health. The PROMs add to the information obtained with the clinical characteristics including the GOLD risk factor assessment. INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): RR2-10.2196/resprot.6506.

Lutz, S. M., B. Frederiksen, et al. (2019). **"Common and Rare Variants Genetic Association Analysis of Cigarettes per Day Among Ever-Smokers in Chronic Obstructive Pulmonary Disease Cases and Controls."** Nicotine Tob Res **21**(6): 714-722.

INTRODUCTION: Cigarette smoking is a major environmental risk factor for many diseases, including chronic obstructive pulmonary disease (COPD). There are shared genetic influences on cigarette smoking and COPD. Genetic risk factors for cigarette smoking in cohorts enriched for COPD are largely unknown. METHODS: We performed genome-wide association analyses for average cigarettes per day (CPD) across the Genetic Epidemiology of COPD (COPDGene) non-Hispanic white (NHW) (n = 6659) and African American (AA) (n = 3260), GenKOLS (the Genetics of Chronic Obstructive Lung Disease) (n = 1671), and ECLIPSE (the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) (n = 1942) cohorts. In addition, we performed exome array association analyses across the COPDGene NHW and AA cohorts. We considered analyses across the entire cohort and stratified by COPD case-control status. RESULTS: We identified genome-wide significant associations for CPD on chromosome 15q25 across all cohorts (lowest p = 1.78 x 10-15), except in the COPDGene AA cohort alone. Previously reported associations on chromosome 19 had suggestive and directionally consistent associations (RAB4, p = 1.95 x 10-6; CYP2A7, p = 7.50 x 10-5; CYP2B6, p = 4.04 x 10-4). When we stratified by COPD case-control status, single nucleotide polymorphisms on chromosome 15q25 were nominally associated with both NHW COPD cases (beta = 0.11, p = 5.58 x 10-4) and controls (beta = 0.12, p = 3.86 x 10-5) For the gene-based exome array association analysis of rare variants, there were no exome-wide significant associations. For these previously replicated associations, the most significant results were among COPDGene NHW subjects for CYP2A7 (p = 5.2 x 10-4). CONCLUSIONS: In a large genome-wide association study of both common variants and a gene-based association of rare coding variants in ever-smokers, we found genome-wide significant associations on chromosome 15q25 with CPD for common variants, but not for rare coding variants. These results were directionally consistent among COPD cases and controls. IMPLICATIONS: We examined both common and rare coding variants associated with CPD in a large population of heavy smokers with and without COPD of NHW and AA descent. We replicated genome-wide significant associations on chromosome 15q25 with CPD for common variants among NHW subjects, but not for rare variants. We demonstrated for the first time that common variants on chromosome 15q25 associated with CPD are similar among COPD cases and controls. Previously reported associations on chromosome 19 showed suggestive and directionally consistent associations among common variants (RAB4, CYP2A7, and CYP2B6) and for rare variants (CYP2A7) among COPDGene NHW subjects. Although the genetic effect sizes for these single nucleotide

polymorphisms on chromosome 15q25 are modest, we show that this creates a substantial smoking burden over the lifetime of a smoker.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6528143/pdf/nty095.pdf

MacDonald, M. I., C. R. Osadnik, et al. (2019). **"Low and High Blood Eosinophil Counts as Biomarkers in Hospitalized Acute Exacerbations of COPD."** Chest **156**(1): 92-100.

BACKGROUND: Characterizing acute exacerbations of COPD (AECOPD) and individualizing therapy is challenging. Key exacerbation therapies include antibiotics and systemic corticosteroids. Blood eosinophils, when either low or high, may offer a simple, inexpensive distinction to predict beneficial responses to these therapies. METHODS: We conducted derivation (n = 242) and validation (n = 99) cohort studies of patients hospitalized for AECOPD. Patients who received oral corticosteroids before ED presentation were excluded. The derivation cohort was identified by individual case file review. The validation cohort was prospectively recruited during hospital admission. Exacerbations were grouped according to blood eosinophil count as low (<50/muL), normal (50-150/muL), or high (>150/muL). Exacerbations were classified as being associated with infection if either virus testing was positive or C-reactive protein was >/=20 mg/L. Associations of eosinophil groups with infection, hospital length of stay, and 12-month survival were compared using appropriate statistical methods. RESULTS: There were no significant differences in baseline characteristics between patients with low, normal, or high blood eosinophils in either cohort. Eosinophil counts <50/muL were more strongly associated with infection (91% vs 51.9%, P = .001), distinguished patients with longer median hospital stays (7 vs 4 days, P < .001), and were associated with lower 12-month survival (82.4% vs 90.7%, P = .028; pooled data of both cohorts) than eosinophil counts >150/muL. CONCLUSIONS: Low and high blood eosinophil counts in hospitalized patients with AECOPD provide a practical clinical distinction that can potentially be used to inform management strategies. Prospective studies are needed to evaluate if this strategy can guide discriminate use of antibiotics and/or corticosteroids.

https://journal.chestnet.org/article/S0012-3692(19)30822-0/fulltext

Maignan, M., J. M. Chauny, et al. (2019). **"Pain during exacerbation of chronic obstructive pulmonary disease: A prospective cohort study."** PLoS One **14**(5): e0217370.

BACKGROUND AND OBJECTIVE: Pain, a symptom often present in patients with Chronic Obstructive Pulmonary Disease (COPD), alters quality of life. COPD exacerbation augments several mechanisms that may cause pain (dyspnea, hyperinflation and inflammation) and therefore we hypothesized that pain might be increased during exacerbation. METHODS: A prospective cohort study was conducted in patients admitted for acute exacerbations of COPD (AECOPD) in two emergency departments in France and Canada. Patients with cancer-related pain or recent trauma were not included. The Short Form McGill Pain Questionnaire (SF-MPQ) and the Brief Pain Inventory (BPI) scale were used to evaluate pain intensity and location. Patients also completed the Borg Dyspnea Scale and Hospital Anxiety and Depression Scale. The questionnaires were completed again during an outpatient assessment in the stable phase. The primary outcome was difference in pain intensity (SF-MPQ) between the exacerbation and stable phases. RESULTS: Fifty patients were included. During exacerbation, 46 patients (92%) reported pain compared to 29 (58%) in the stable phase (p<0.001). Pain intensity was higher during exacerbation (SF-MPQ 29.7 [13.6-38.2] vs. 1.4 [0.0-11.2]; p<0.001). Pain was predominantly located in the chest during exacerbation and in the limbs during the stable phase. Pain intensity during exacerbation correlated with anxiety score. CONCLUSION: The frequency and intensity of pain were higher during AECOPD, with a specific distribution. Pain should therefore be routinely assessed and treated in patients with AECOPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6534306/pdf/pone.0217370.pdf

Maselli, D. J., S. P. Bhatt, et al. (2019). **"Clinical Epidemiology of COPD: Insights From 10 Years of the COPDGene Study."** ChestThe Genetic Epidemiology of COPD (COPDGene) study is a noninterventional, multicenter, longitudinal analysis of > 10,000 subjects, including smokers with a >/= 10 pack-year history with and without COPD and healthy never smokers. The goal was to characterize disease-related phenotypes and explore associations with susceptibility genes. The subjects were extensively phenotyped with the use of comprehensive symptom and comorbidity questionnaires, spirometry, CT scans of the chest, and genetic and biomarker profiling. The objective of this review was to summarize the major advances in the clinical epidemiology of COPD from the first 10 years of the COPDGene study. We highlight the influence of age, sex, and race on the natural history of COPD, and the impact of comorbid conditions, chronic bronchitis, exacerbations, and asthma/COPD overlap.

https://journal.chestnet.org/article/S0012-3692(19)31128-6/fulltext

McGuire, K., J. A. Avina-Zubieta, et al. (2019). **"Risk of Incident Chronic Obstructive Pulmonary Disease in Rheumatoid Arthritis: A Population-Based Cohort Study."** Arthritis Care Res (Hoboken) **71**(5): 602-610.

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

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

Mihaltan, F., Y. Adir, et al. (2019). **"Importance of the relationship between symptoms and self-reported physical activity level in stable COPD based on the results from the SPACE study."** Respir Res **20**(1): 89.

BACKGROUND: The burden of symptoms and risk of exacerbations are the main drivers of the overall assessment of the Chronic Obstructive Pulmonary Disease (COPD) and the adequate treatment approaches per current Global Initiative for Chronic Obstructive Lung Disease (GOLD). Physical activity has emerged as both functional outcome and non-pharmacological intervention in COPD patients, despite the lack of standardized measures or guidelines in clinical practice. This study aimed to explore in more depth the 24-h respiratory symptoms, the physical activity level (PAL) and the relationship between these two determinants in stable COPD patients. METHODS: This was a multinational, multicenter, observational, cross-sectional study conducted in ten European countries and Israel. Dedicated questionnaires for each part of the day (morning, daytime, night) were used to assess respiratory symptoms. PAL was evaluated

with self- and interview-reported tools [EVS (exercise as vital sign) and YPAS (Yale Physical Activity Survey)], and physician's judgement. Patients were stratified in ABCD groups by 2013 and 2017 GOLD editions using the questionnaires currently recommended: modified Medical Research Council dyspnea scale and COPD Assessment Test. RESULTS: The study enrolled 2190 patients (mean age: 66.9 years; male: 70.0%; mean % predicted FEV1: 52.6; GOLD groups II-III: 84.5%; any COPD treatment: 98.9%). Most patients (> 90%) reported symptoms in any part of the 24-h day, irrespective of COPD severity. PAL evaluations showed discordant results between patients and physicians: 32.9% of patients considered themselves completely inactive, while physicians judged 11.9% patients as inactive. By YPAS, the overall study population spent an average of 21.0 h/week performing physical activity, and 68.4% of patients were identified as sedentary. In any GOLD ABCD group, the percentage of inactive patients was high. Our study found negative, weak correlations between respiratory symptoms and self-reported PAL ($p < 0.001$). CONCLUSIONS: Despite regular treatment, the majority of stable COPD patients with moderate to severe disease experienced daily variable symptoms. Physical activity level was low in this COPD cohort, and yet overestimated by physicians. With evidence indicating the negative consequences of inactivity, its adequate screening, a more active promotion and regular assessment of physical activity are urgently needed in COPD patients for better outcomes. TRIAL REGISTRATION: NCT03031769 , retrospectively registered, 23 Jan 2017.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6518503/pdf/12931_2019_Article_1053.pdf

Morais, N., J. Cruz, et al. (2019). **"The Kinematic Chain of Arm Elevation Is Impaired in Patients with Chronic Obstructive Pulmonary Disease."** Copd: 1-6.

Patients with chronic obstructive pulmonary disease (COPD) often complain about difficulties in performing activities with their arms above shoulders height. These difficulties have been associated with increased cardiorespiratory demand and altered lung mechanics; however, musculoskeletal-related mechanisms may also contribute to constrain the mechanics of the upper body quadrant, increasing the effort to perform the activities. This exploratory research aimed to assess potential changes in the kinematic chain of arm elevation in patients with COPD. A secondary analysis from a cross-sectional exploratory case-control and prediction study was conducted in 15 patients with COPD (2 females) and 15 controls (8 females) matched for age and body mass index. The sagittal alignment and active range of motion (ROM) of the head, thoracic spine and shoulder complex were measured, using a computer software, in digital lateral photographs obtained in three different testing positions: arms at rest, arms at 90 degrees of shoulder flexion and full arm elevation. From rest to full arm elevation, both groups moved from a more flexed to a less flexed or more upright thoracic spine position (approximately 7 degrees , $p < 0.001$, $0.419 < etap2 < 0.767$). However, the COPD group showed significantly less shoulder flexion (approximately 12 degrees , $p = 0.007$, $d = 1.05$) and thoracic spine extension (approximately 6 degrees , $p = 0.015$, $etap2 = 0.139$) ROM than the control group in the full arm elevation position. These findings suggest that this population may show changes in the kinematic chain of arm elevation that possibly contribute to arm movement-related complains and limited performance in their daily living.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1632281

Mullerova, H., W. H. Meeraus, et al. (2019). **"Clinical burden of illness among patients with severe eosinophilic COPD."** Int J Chron Obstruct Pulmon Dis **14**: 741-755.

Background: There are currently limited real-world data on the clinical burden of illness in patients with COPD who continue to exacerbate despite receiving triple therapy. The aim of this study was to compare the burden of COPD in patients with and without a phenotype characterized by a high blood eosinophil count and high risk of exacerbations while receiving triple therapy. Methods: This retrospective cohort study (GSK ID: 207323/PRJ2647) used UK Clinical Practice Research Datalink records linked with Hospital Episode Statistics. Eligible patients had a COPD medical diagnosis code recorded between January 1, 2004 and December 31, 2014, and a blood eosinophil count recorded on/after that date. Patients were followed from index date (first qualifying blood eosinophil count) until December 31, 2015. The study

phenotype was defined as >/=2 moderate/>/=1 severe acute exacerbation of COPD (AECOPD) in the year prior to the index date, current use of multiple-inhaler triple therapy (MITT), and blood eosinophil count >/=150 cells/microL on the index date. Outcomes measured during follow-up included moderate/severe AECOPDs, severe AECOPDs, all-cause mortality, primary care (GP) clinical consultations, and non-AECOPD-related unscheduled hospitalizations. Results: Of 46,814 patients eligible for inclusion, 2512 (5.4%) met the definition of the study phenotype. Adjusted rate ratios (95% CI) of moderate/severe AECOPDs and all-cause mortality in patients with the study phenotype versus those without were 2.32 (2.22, 2.43) and 1.26 (1.16, 1.37), respectively. For GP visits and non-AECOPD-related unscheduled hospitalizations, adjusted rate ratios (95% CI), in patients with the study phenotype versus those without, were 1.09 (1.05, 1.12) and 1.31 (1.18, 1.46), respectively. Conclusion: Patients with COPD and raised blood eosinophil counts who continue to exacerbate despite MITT represent a distinct subgroup who experience substantial clinical burden and account for high healthcare expenditure. There is a need for more effective management and therapeutic options for these patients.

https://www.dovepress.com/getfile.php?fileID=48801

Nolan, C. M., D. Kaliaraju, et al. (2019). **"Home versus outpatient pulmonary rehabilitation in COPD: a propensity-matched cohort study."** ThoraxHome-based exercise has been proposed as an equivalent treatment strategy to supervised outpatient pulmonary rehabilitation (PR), but it is not known whether its implementation into clinical practice produces similar benefits to those observed in trials. We compared the real-world responses of 154 patients with COPD undergoing home-based exercise with a matched group attending supervised PR. We observed smaller improvements in exercise capacity with home-based exercise compared with PR, but similar improvements in quality of life. We propose that supervised PR remains the standard of care, with home-based exercise a less effective alternative for those unable to attend PR.

https://thorax.bmj.com/content/early/2019/07/05/thoraxjnl-2018-212765

O'Brien, M. E., D. Chandra, et al. (2019). **"Loss of skin elasticity is associated with pulmonary emphysema, biomarkers of inflammation, and matrix metalloproteinase activity in smokers."** Respir Res **20**(1): 128.

BACKGROUND: Elastin breakdown and the resultant loss of lung elastic recoil is a hallmark of pulmonary emphysema in susceptible individuals as a consequence of tobacco smoke exposure. Systemic alterations to the synthesis and degradation of elastin may be important to our understanding of disease phenotypes in chronic obstructive pulmonary disease. We investigated the association of skin elasticity with pulmonary emphysema, obstructive lung disease, and blood biomarkers of inflammation and tissue protease activity in tobacco-exposed individuals. METHODS: Two hundred and thirty-six Caucasian individuals were recruited into a sub-study of the University of Pittsburgh Specialized Center for Clinically Orientated Research in chronic obstructive pulmonary disease, a prospective cohort study of current and former smokers. The skin viscoelastic modulus (VE), a determinant of skin elasticity, was recorded from the volar forearm and facial wrinkling severity was determined using the Daniell scoring system. RESULTS: In a multiple regression analysis, reduced VE was significantly associated with cross-sectional measurement of airflow obstruction (FEV1/FVC) and emphysema quantified from computed tomography (CT) images, beta = 0.26, p = 0.001 and beta = 0.24, p = 0.001 respectively. In emphysema-susceptible individuals, elasticity-determined skin age was increased (median 4.6 years) compared to the chronological age of subjects without emphysema. Plasma biomarkers of inflammation (TNFR1, TNFR2, CRP, PTX3, and SAA) and matrix metalloproteinase activity (MMP1, TIMP1, TIMP2, and TIMP4) were inversely associated with skin elasticity. CONCLUSIONS: We report that an objective non-invasive determinant of skin elasticity is independently associated with measures of lung function, pulmonary emphysema, and biomarkers of inflammation and tissue proteolysis in tobacco-exposed individuals. Loss of skin elasticity is a novel observation that may link the common pathological processes that drive tissue elastolysis in the extracellular matrix of the skin and lung in emphysema-susceptible individuals.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6591816/pdf/12931_2019_Article_1098.pdf

Oshagbemi, O. A., F. M. E. Franssen, et al. (2019). **"Blood Eosinophil Counts, Withdrawal of Inhaled Corticosteroids and Risk of COPD Exacerbations and Mortality in the Clinical Practice Research Datalink (CPRD)."** Copd: 1-8.

Although recently introduced in the pharmacological treatment algorithm of chronic obstructive pulmonary disease (COPD), there is a need for more data supporting the use of blood eosinophil counts as a biomarker to guide inhaled corticosteroids (ICS) therapy. The aim of this study was to evaluate the risk of moderate and/or severe exacerbations and all-cause mortality in a large primary care population after withdrawal of ICS compared to continued users stratified by elevated blood eosinophil counts. In this population based cohort study, we used data from the Clinical Practice Research Datalink (CPRD) in the United Kingdom. We included subjects' aged 40 years or more who had a diagnosis of COPD. We excluded subjects with a history of asthma, pulmonary fibrosis, cardiac arrhythmia and bronchiectasis, COPD exacerbations occurring within 6 weeks prior to index date, or with a myocardial infarction within 3 months prior to index date. Continuous users were subjects who received their most recent ICS prescription within 3 months before the start of an interval. ICS withdrawals were those who discontinued ICS for more than 3 months. We evaluated the risk of moderate and/or severe exacerbations and all-cause mortality among subjects with various blood eosinophil thresholds who withdrew from ICS compared to continuous ICS users with elevated blood eosinophil levels using Cox regression analysis adjusted for potential confounders. We identified 48,157 subjects diagnosed with COPD between 1 January 2005 to 31 January 2014. Withdrawal of ICS was not associated with an increased risk of moderate-to-severe exacerbations among subjects with absolute blood eosinophil counts >/=0.34 x 10(9) cells/L [adjusted hazard ratio (adj. HR) 0.72; 95% confidence interval (CI) 0.63-0.81] or relative counts >/= 4.0% (adj. HR 0.72; 95% CI: 0.66-0.78). Similarly, withdrawal of ICS was not associated with an increased risk of severe exacerbations among subjects with absolute blood eosinophil >/=0.34 x 10(9) cells/L (adj. HR 0.82; 95% CI: 0.61-1.10) or relative blood eosinophil counts >/=4.0% (adj. HR 0.80; 95% CI: 0.61-1.04). No increased risk of all-cause mortality was observed among subjects who withdrew from ICS irrespective of elevated absolute or relative blood eosinophil counts. In a real-world primary care population, we did not observe an increased risk of moderate and/or severe COPD exacerbations or all-cause mortality among subjects with eosinophilia who withdrew their use of ICS.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2019.1608172?needAccess=true

Pahus, L., P. R. Burgel, et al. (2019). **"Randomized controlled trials of pharmacological treatments to prevent COPD exacerbations: applicability to real-life patients."** BMC Pulm Med **19**(1): 127.

BACKGROUND: In patients with chronic obstructive pulmonary disease, all efforts should be made to prevent exacerbations because each event modifies the trajectory of the disease. Treatment recommendations are mostly built on results from randomized controlled trials (RCTs) whose methodology ensure internal validity. However, their relevance may be compromised by the lack of generalizability, due to poor representability of study populations compared to real-life patients. In order to delimit to whom the results of studies on current and future treatments apply, we sought to identify and characterize the fraction of COPD population that would be eligible for inclusion into RCTs aiming at decreasing exacerbation risk. METHODS: We used the Initiatives-BPCO database, a French cohort of 1309 real-life COPD patients monitored in academic centers. We identified industry-sponsored phase III and IV trials that enrolled more than 500 patients, lasted at least one year and used exacerbations related endpoints. Eligibility criteria were extracted from each trial and applied to the patients. RESULTS: The eligibility criteria of 16 RCTs were applied to the 1309 patients. The most discriminating eligibility criteria were FEV1, minimum exacerbation rate in the previous year and smoking history, responsible for the exclusion of 39.9, 36.7 and 16.8% of patients, respectively. Altogether, 2.3 to 46.7% of our patients would have satisfied all eligibility criteria. CONCLUSION: These analyses confirm that an important gap exists

between real-life patients and clinical trials populations in COPD, which limits the relevance of results and therefore should be considered when grading levels of evidence and designing future studies.

https://bmcpulmmed.biomedcentral.com/track/pdf/10.1186/s12890-019-0882-y

Paly, V. F., I. Naya, et al. (2019). **"Long-term cost and utility consequences of short-term clinically important deterioration in patients with chronic obstructive pulmonary disease: results from the TORCH study."** Int J Chron Obstruct Pulmon Dis **14**: 939-951.

Purpose: Clinically important deterioration (CID) in chronic obstructive pulmonary disease (COPD) is a novel composite endpoint that assesses disease stability. The association between short-term CID and future economic and quality of life (QoL) outcomes has not been previously assessed. This analysis considers 3-year data from the TOwards a Revolution in COPD Health (TORCH) study, to examine this question. Patients and methods: This post hoc analysis of TORCH (NCT00268216) compared costs and utilities at 3 years among patients without CID (CID-) and with CID (CID+) at 24 weeks. A positive CID status was defined as either: a deterioration in forced expiratory volume in 1 second (FEV1) of >/=100 mL from baseline; or a >/=4-unit increase from baseline in St George's Respiratory Questionnaire (SGRQ) total score; or the incidence of a moderate/severe exacerbation. Patients from all treatment arms were included. Utility change was based on the EQ-5D utility index. Costs were based on healthcare resource utilization from 24 weeks to end of follow-up combined with unit costs for the UK (2016 GBP), and reported as per patient per year (PPPY). Adjusted estimates were generated controlling for baseline characteristics, treatment assignment, and number of CID criteria met. Results: Overall, 3,769 patients completed the study and were included in the analysis (stable CID- patients, n=1,832; unstable CID+ patients, n=1,937). At the end of follow-up, CID- patients had higher mean (95% confidence interval [CI]) utility scores than CID+ patients (0.752 [0.738, 0.765] vs 0.697 [0.685, 0.71]; difference +0.054; P<0.001), and lower costs PPPY (pound538 vs pound916; difference: pound378 [95% CI: pound244, pound521]; P<0.001). The cost differential was primarily driven by the difference in general hospital ward days (P=0.003). Conclusion: This study demonstrated that achieving early stability in COPD by preventing short-term CID is associated with better preservation of future QoL alongside reduced healthcare service costs.

https://www.dovepress.com/getfile.php?fileID=49559

Park, H. J., J. H. Cho, et al. (2019). **"The effect of low body mass index on the development of chronic obstructive pulmonary disease and mortality."** J Intern MedBACKGROUND: Sarcopenia may worsen disease progression and lead to poor outcomes in chronic obstructive pulmonary disease (COPD). OBJECTIVES: We aimed to determine the effect of BMI on the development of COPD and mortality. METHODS: We enrolled 437 584 participants with COPD registered in the physical health check-up cohort database of the Korean National Health Interview Survey from 2002 to 2003, based on the ICD-10 code and prescribed medication. BMI (kg m(-2)) classified them to five groups (low BMI < 18.5, normal BMI 18.5-23, overweight 23-25, obesity 25-30, severe obesity >/=30) at baseline. RESULTS: Participants in the low BMI group had a significantly higher rate of COPD development for 13 years (7.6%) than those in other groups (3.4-4.1%, P < 0.0001). Amongst never or light smokers, COPD development in the low BMI group (5.6-6.7%) was significantly higher than that in other groups (2.8-4.7%). Similarly, amongst participants with a smoking history of >/=30 years, COPD development in the low BMI group (20.1%) was higher than those in other groups (8.4-12.4%). On multivariable analysis, normal or higher than normal body weight was significantly protective against the development of COPD (hazard ratio [HR], 0.609-0.739,) compared to low BMI. COPD-free-survival (HR, 0.491-0.622) and overall survival (HR, 0.440-0.585) were also better in them compared to those with low BMI (all P < 0.0001). CONCLUSIONS: Low BMI is an important risk factor for COPD development and mortality. Maintaining adequate body weight may reduce the risk for COPD development and mortality.

https://onlinelibrary.wiley.com/doi/abs/10.1111/joim.12949

Park, J., B. D. Hobbs, et al. (2019). **"Subtyping COPD using visual and quantitative CT features."** ChestBACKGROUND: Multiple studies have identified COPD subtypes using visual or quantitative evaluation of CT images. However, there has been no systematic assessment of a combined visual and quantitative CT classification. We integrated visually defined patterns of emphysema with quantitative imaging features and spirometry data to produce a set of ten non-overlapping CT subtypes, and we assessed differences between subtypes in demographic features, physiology, longitudinal disease progression, and mortality. METHODS: We evaluated 9,080 current and former smokers in the COPDGene study with available volumetric inspiratory and expiratory CT images obtained using a standardized imaging protocol. We defined ten discrete, non-overlapping CT subtypes: no CT abnormality, paraseptal emphysema, 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 five-year longitudinal characteristics, as well as mortality, were compared across these CT subtypes. RESULTS: The overall mortality differed significantly between groups (P<0.01) and was highest in the three moderate-to-severe CLE groups. Subjects having quantitative but no visual emphysema and subjects with visual but not quantitative emphysema represent unique groups with mild COPD, at risk for progression, and with likely different underlying mechanisms. Paraseptal and moderate-to-severe CLE subjects showed substantial progression of emphysema over five years compared to individuals with no CT abnormality (P<0.05). CONCLUSIONS: The combination of visual and quantitative CT features reflects different underlying pathological processes in the heterogeneous COPD syndrome and provides a useful approach to reclassify persons with COPD.

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

Patout, M., L. Meira, et al. (2019). **"Neural respiratory drive predicts long-term outcome following admission for exacerbation of COPD: a post hoc analysis."** ThoraxNeural respiratory drive (NRD), as reflected by change in parasternal muscle electromyogram (EMGpara), predicts clinical deterioration and safe discharge in patients admitted to hospital with an acute exacerbation of COPD (AECOPD). The clinical utility of NRD to predict the long-term outcome of patients following hospital admission with an AECOPD is unknown. We undertook a post hoc analysis of a previously published prospective observational cohort study measuring NRD in 120 patients with AECOPD. Sixty-nine (57.5%) patients died during follow-up (median 3.6 years). Respiratory failure was the most common cause of death (n=29; 42%). In multivariate analysis, factors independently associated with an increased mortality included NRD (HR 2.14, 95% CI 1.29 to 3.54, p=0.003), age (HR 2.03, 95% CI 1.23 to 3.34, p=0.006), PaCO2 at admission (HR 1.83, 95% CI 1.06 to 3.06, p=0.022) and long-term oxygen use (HR 2.98, 95% CI 1.47 to 6.03, p=0.002). NRD at hospital discharge could be measured in order to assess efficacy of interventions targeted to optimise COPD and reduce mortality following an AECOPD.Original clinicaltrial.gov number:NCT01361451.

https://thorax.bmj.com/content/early/2019/04/26/thoraxjnl-2018-212074

Perez, T., G. Deslee, et al. (2019). **"Predictors in routine practice of 6-min walking distance and oxygen desaturation in patients with COPD: impact of comorbidities."** Int J Chron Obstruct Pulmon Dis **14**: 1399-1410.

Background: The 6-min walk test (6MWT) allows exercise tolerance to be assessed, and it has a significant prognostic value in COPD. The goal of this study was to analyse the determinants (obtained in routine practice) of a low 6-min walking distance (6MWD) and exercise-induced desaturation (EID) in COPD, including comorbidities. Methods: Patients were recruited from the real-life French COPD cohort

"Initiatives BPCO". A low 6MWD was defined as <350 m. EID was defined by a minimum pulse oxygen saturation (SpO2)<90% and delta SpO2>/=4% from baseline. Multivariate logistic regression analyses assessed the influence on 6MWD and EID of age, sex, obesity (body mass index, BMI >30 kg/m(2)), low BMI (BMI <18.5 kg/m(2)), modified Medical Research Council (mMRC) dyspnea scale, FEV1% pred, FVC % pred, hyperinflation and comorbidities including cardiovascular diseases. Results: Among 440 patients with available 6MWT data, a 6MWD <350 m was found in 146 patients (33%), which was positively associated in multivariate analyses with age and mMRC and negatively with resting SpO2 and FVC % pred (rescaled r(2)=0.34), whereas no comorbidity was associated with a low 6WMD. EID was found in 155 patients (35%). This was positively associated with hypertension and negatively with age, obesity, FEV1% pred and resting SpO2 (rescaled r(2)=0.37). Conclusion: 6MWD and EID exhibit different determinants in COPD with a minor impact of comorbidities limited to hypertension in EID and to obesity, which was unexpectedly associated with less EID. Other variables including age, routine resting lung function and SpO2 were weakly associated with 6MWD and EID. Altogether, these results suggest that 6MWT performance remains difficult to predict with routine clinical/functional parameters.

https://www.dovepress.com/getfile.php?fileID=50887

Pichl, A., N. Sommer, et al. (2019). **"Riociguat for treatment of pulmonary hypertension in COPD: a translational study."** Eur Respir J **53**(6)Chronic obstructive pulmonary disease (COPD), which comprises the phenotypes of chronic bronchitis and emphysema, is often associated with pulmonary hypertension (PH). However, currently, no approved therapy exists for PH-COPD. Signalling of the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) axis plays an important role in PH and COPD.We investigated the treatment effect of riociguat, which promotes the NO-cGMP pathway, in the mouse model of smoke-induced PH and emphysema in a curative approach, and retrospectively analysed the effect of riociguat treatment on PH in single patients with PH-COPD.In mice with established PH and emphysema (after 8 months of cigarette smoke exposure), riociguat treatment for another 3 months fully reversed PH. Moreover, histological hallmarks of emphysema were decreased. Microarray analysis revealed involvement of different signalling pathways, e.g. related to matrix metalloproteinases (MMPs). MMP activity was decreased in vivo by riociguat. In PH-COPD patients treated with riociguat (n=7), the pulmonary vascular resistance, airway resistance and circulating MMP levels decreased, while oxygenation at rest was not significantly changed.Riociguat may be beneficial for treatment of PH-COPD. Further long-term prospective studies are necessary to investigate the tolerability, efficacy on functional parameters and effect specifically on pulmonary emphysema in COPD patients.

https://erj.ersjournals.com/content/53/6/1802445

Pragman, A. A., K. A. Knutson, et al. (2019). **"Chronic obstructive pulmonary disease upper airway microbiota alpha diversity is associated with exacerbation phenotype: a case-control observational study."** Respir Res **20**(1): 114.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) frequent exacerbators (FE) suffer increased morbidity and mortality compared to infrequent exacerbators (IE). The association between the oral and sputum microbiota and exacerbation phenotype is not well defined. The objective of this study was to determine key features that differentiate the oral and sputum microbiota of FEs from the microbiota of IEs during periods of clinical stability. METHODS: We recruited 11 FE and 11 IE who had not used antibiotics or systemic corticosteroids in the last 1 month. Subjects provided oral wash and sputum samples, which underwent 16S V4 MiSeq sequencing and qPCR of 16S rRNA. Data were analyzed using Dada2 and R. RESULTS: FE and IE were similar in terms of age, FEV1 percent predicted (FEV1pp), pack-years of tobacco exposure, and St. George's Respiratory Questionnaire score. 16S copy numbers were significantly greater in sputum vs. oral wash ($p = 0.01$), but phenotype was not associated with copy number. Shannon diversity was significantly greater in oral samples compared to sputum ($p = 0.001$), and IE samples were more diverse than FE samples ($p < 0.001$). Sputum samples from FE had more Haemophilus and Moraxella compared to IE sputum samples, due to dominance of these COPD-

associated taxa in three FE sputum samples. Amplicon sequencing variant (ASV)-level analysis of sputum samples revealed one ASV (Actinomyces) was significantly more abundant in IE vs. FE sputum (padj = 0.048, Wilcoxon rank-sum test), and this persisted after controlling for FEV1pp. Principal coordinate analysis using Bray-Curtis distance with PERMANOVA analyses demonstrated clustering by anatomic site, phenotype, inhaled corticosteroid use, current tobacco use, COPD severity, and last professional dental cleaning. CONCLUSIONS: FE have less diverse oral and sputum microbiota than IE. Actinomyces was significantly more abundant in IE sputum than FE sputum. The oral and sputum microbiota of COPD subjects cluster based on multiple clinical factors, including exacerbation phenotype. Even during periods of clinical stability, the frequent exacerbator phenotype is associated with decreased alpha diversity, beta-diversity clustering, and changes in taxonomic abundance.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6555967/pdf/12931_2019_Article_1080.pdf

Praveen, C. K., M. Manu, et al. (2019). **"Power of BODE Index in Predicting Future Exacerbations of COPD: A Prospective Observational Study in Indian Population."** J Assoc Physicians India **67**(4): 14-16.

Background: BODE index is a multidimensional measure of survival in chronic obstructive pulmonary disease (COPD). It is composed of body mass index (B), the degree of airflow obstruction (O), dyspnoea (D), and exercise capacity (E). Studies have shown that BODE index can predict future exacerbations, but similar data in Indian population is unavailable. This study was aimed at evaluating the power of BODE index to predict the frequency of exacerbations of COPD in Indian cohort. Methods: We conducted a prospective observational cohort study that included stable COPD subjects aged above 40 years. We assessed the BODE index at baseline and recorded the number of exacerbations at the end of 12 months. Spearman's Rho and Poisson regression model were used to correlate the BODE index with the frequency of exacerbations. Results: We analysed 78 COPD patients. A significant correlation was seen between BODE index at baseline and number of exacerbations at 12 months (Spearman's Rho 0.738). A unit change in BODE index at baseline would have 1.25 times higher number of exacerbations at 12 months (95% CI: 1.17-1.33). Conclusions: BODE index has significant power to predict the frequency of future exacerbations in Indian COPD patients.

Ragaselvi, S., A. K. Janmeja, et al. (2019). **"Predictors of response to pulmonary rehabilitation in stable chronic obstructive pulmonary disease patients: A prospective cohort study."** J Postgrad Med **65**(2): 101-106.

Context: Pulmonary rehabilitation (PR) has become a standard of care in the management of chronic obstructive pulmonary disease (COPD). However, a significant proportion of the patients do not show benefit after the PR program. Aims: The study was planned to find different patient- and/or disease-related factors that may predict response to PR in stable COPD. Subjects and Methods: A total of 102 stable COPD patients were prospectively enrolled. Baseline evaluation and investigations, including spirometry, arterial blood gas analysis, and bone mineral density assessment, were done. Thereafter, all patients underwent an 8-week comprehensive outpatient PR program that consisted of exercise training, education, nutritional, and psychological counseling. The response to PR was dichotomously (yes/no) defined by the combined improvement in exercise tolerance (6-min walk distance [6MWD] +54 m) and quality of life (St. George's Respiratory Questionnaire [SGRQ] score - 4 points) measured before and after the program. Thereafter, different predefined factors were analyzed for their possible association with the PR response. Results: A total of 80 patients (78.4%) completed the PR program and were subjected for analysis. Out of them, 42 (52.5%) showed improvement in both 6MWD and SGRQ score (46 in 6MWD and 54 in SGRQ score). After application of multivariate logistic regression analysis, forced expiratory volume in 1 s <50% predicted (odds ratio [OR]: 2.9; 95% confidence interval [CI]: 1.1-8.3; P = 0.04) and osteoporosis (OR: 0.26; 95% CI: 0.13-0.53; P < 0.001) were found as independent factors predicting PR efficacy. Conclusions: Poor baseline lung function predicts a short-term improvement in exercise capacity and quality of life in COPD patients, whereas osteoporosis is a negative predictor of PR

response. Active search for these factors may help in better patient selection, thus leading to improved outcome after PR.

http://www.jpgmonline.com/article.asp?issn=0022-3859;year=2019;volume=65;issue=2;spage=101;epage=106;aulast=Ragaselvi

Raymakers, A. J. N., M. Sadatsafavi, et al. (2019). **"Inhaled corticosteroids and the risk of lung cancer in COPD: a population-based cohort study."** Eur Respir J **53**(6)Inhaled corticosteroids (ICSs) are often prescribed in patients with chronic obstructive pulmonary disease (COPD). Their impact on the risk of lung cancer, a leading cause of mortality in COPD patients, remains uncertain.Population-based linked administrative data between the years 1997 and 2007 from the province of British Columbia, Canada, were used to evaluate the association between lung cancer risk and ICS use in COPD patients. COPD was defined on the basis of receipt of three COPD-related prescriptions in subjects >/=50 years of age. Exposure to ICS was incorporated into multivariable Cox regression models using several time-dependent methods ("ever" exposure, cumulative duration of use, cumulative dose, weighted cumulative duration of use and weighted cumulative dose).There were 39 676 patients who met the inclusion criteria. The mean+/-sd age of the cohort was 70.7+/-11.1 years and 53% were female. There were 994 (2.5%) cases of lung cancer during follow-up. In the reference case analysis (time-dependent "ever" exposure), ICS exposure was associated with a 30% reduced risk of lung cancer (HR 0.70 (95% CI 0.61-0.80)). ICS exposure was associated with a decrease in the risk of lung cancer diagnosis over all five methods of quantifying exposure.This population-based study suggests that ICS use reduces the risk of lung cancer in COPD patients.

https://erj.ersjournals.com/content/53/6/1801257

Russell, R., S. Beer, et al. (2019). **"The acute wheezy adult with airways disease in the emergency department: a retrospective case-note review of exacerbations of COPD."** Int J Chron Obstruct Pulmon Dis **14**: 971-977.

Introduction: There has been an increase in interest in the peripheral blood eosinophil count as a biomarker in COPD. Few studies have examined the eosinophil count in patients attending the emergency department (ED) with acute exacerbations of COPD (AECOPD). We investigated the relationship between the blood eosinophil and other variables collected routinely at ED presentation and outcomes. Methods: Retrospective case note review of patients attending the ED with an AECOPD over 18 months. Demographic, clinical and pharmacological data were analyzed at the time of presentation, and clinical outcomes relating to hospital admission, length of hospital stay and mortality were investigated. Results: There were 743 AECOPD index events in 537 patients. Over half (57%) of all attendees were admitted to hospital. They were older, reported an increased number of exacerbations and higher levels of total leukocytes and neutrophils. Length of stay was shorter in patients with a blood eosinophil count >/=2% compared to <2% (median (IQR) 3 days (1-7) vs 4 days (2-8) respectively, p<0.05). Length of stay correlated with peripheral blood neutrophils (r=0.12, p=0.021), peripheral blood absolute and relative eosinophils (r=-0.12, p=0.024 and r=-0.11, p=0.035, respectively) and CRP (r=0.16, p=0.027). Non-eosinophilic AECOPD were associated with an increased risk of mortality during an exacerbation (chi (2) 5.9, OR 3.08, 95% CI 1.19-7.96, p=0.015). Conclusion: In exacerbations of COPD presenting to ED, a higher blood eosinophil count is associated with a shorter length of stay and reduced mortality.

https://www.dovepress.com/getfile.php?fileID=49653

Sertpoyraz, F. M. and S. Deniz (2019). **"Bone mineral density and vitamin D levels in patients with group a COPD."** Aging Male: 1-6.

INTRODUCTION: Chronic Obstructive Pulmonary Disease (COPD) is a chronic, inflammatory airway disease associated with osteoporosis. Reduced bone mineral density (BMD) and impaired bone quality were shown to cause increased bone fragility and fractures in COPD patients. The aim of this study was to evaluate vitamin D levels and BMDs in Group A COPD patients. METHODS: This case-control study involved 33 males aged 50 or above diagnosed with Group A COPD and 44 age-matched healthy males. Participants' serum vitamin D and other indicators were evaluated as well as lumbar and hip BMD of COPD patients. RESULTS: Vitamin D levels were significantly lower in COPD patients (15.13 +/- 6.02 ng/L) than controls (21.89 +/- 4.49 ng/L). Two patients had a history of thoracic vertebral fracture. Lumbar (L1-L4) T scores were normal in 16 patients (48.5%) and indicated osteopenia in 15 (45.5%) and osteoporosis in 2 (6%). Hip femur total T scores were normal in 19 patients (57.6%) and indicated osteopenia in 14 (42.4%). CONCLUSION: Vitamin D deficiency/insufficiency is prevalent in COPD patients, and BMD decreases in the early period of the disease. Vitamin D and BMD should be evaluated in the early stages to prevent osteoporosis and its complications in COPD patients.

https://www.tandfonline.com/doi/full/10.1080/13685538.2019.1612869

Sharanya, A., M. Ciano, et al. (2019). **"Sex differences in COPD-related quadriceps muscle dysfunction and fibre abnormalities."** Chron Respir Dis **16**: 1479973119843650.

In chronic obstructive pulmonary disease (COPD), lower limb dysfunction is associated with reduced exercise capacity, increased hospitalizations and mortality. We investigated sex differences in the prevalence of quadriceps dysfunction and fibre abnormalities in a large COPD cohort, controlling for the normal sex differences in health. We compared existing data from 76 male and 38 female COPD patients where each variable was expressed as a function of gender-specific normal values (obtained from 16 male and 14 female controls). Female COPD patients had lower quadriceps muscle strength and peak workload on a maximal incremental cycle ergometry protocol compared to male patients. Female patients had a smaller type II fibre cross-sectional area (CSA) compared to male patients, suggesting a greater female preponderance to fibre atrophy, although this result was largely driven by a few male patients with a large type II fibre CSA. Female patients had significantly higher concentrations of a number of plasma pro-inflammatory cytokines including tumour necrosis factor alpha and interleukin 8 (IL8), but not lower levels of physical activity or arterial oxygenation, compared to males. Our data confirm results from a previous small study and suggest that female COPD patients have a greater prevalence of muscle wasting and weakness. Larger studies investigating sex differences in COPD-related muscle atrophy and weakness are needed, as the results will have implications for monitoring in clinical practice and for design of clinical trials evaluating novel muscle anabolic agents.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6537500/pdf/10.1177_1479973119843650.pdf

Sheikh, M. A. (2019). **"Confounding, Mediation, or Independent Effect? Childhood Psychological Abuse, Mental Health, Mood/Psychological State, COPD, and Migraine."** J Interpers Violence: 886260519844773.

In some settings, it may be difficult to differentiate between a confounder and a mediator. For instance, the observed association of self-reported childhood psychological abuse (CPA) with onset of chronic obstructive pulmonary disease (COPD) and migraine may be confounded by current mood/psychological state (e.g., the subjective evaluation of one's own affective state), as well as mediated by an individual's psychopathological symptoms. In this study, we propose the "independence hypothesis," which could prove meaningful to explore in data that lack prospective or objective indices of CPA. We used cross-sectional data from wave VI (2007-2008) of the Tromso Study, Norway (N = 12,981). The associations between CPA and COPD and migraine were assessed with Poisson regression models. CPA was associated with a 46% increased risk of COPD (relative risk [RR] = 1.46, 95% confidence interval [CI]: [1.02, 1.90]) and a 28% increased risk of migraine in adulthood (RR = 1.28, 95% CI: [1.04, 1.53]), independent of age, sex, parental history of psychiatric problems/asthma/dementia, smoking, respondent's mood/psychological state, and mental health. These findings suggest that the association

between retrospectively reported CPA and COPD and migraine is not driven entirely by respondent's mood/psychological state and mental health. Assessing the independent effect of self-reported CPA on COPD and migraine in retrospective studies may prove more meaningful than exploring the mediating role of mental health. Here, we provide the analytical rationale for assessing the independent effect in settings where it is difficult to differentiate between a confounder and a mediator. Moreover, we provide a theoretical rationale for assessing the independent effect of retrospectively reported childhood adversity on health and well-being.

Shorofsky, M., J. Bourbeau, et al. (2019). **"Impaired Sleep Quality in COPD Is Associated With Exacerbations: The CanCOLD Cohort Study."** ChestBACKGROUND: COPD increases susceptibility to sleep disturbances, which may in turn predispose to increased respiratory symptoms. The objective of this study was to evaluate, in a population-based sample, the relationship between subjective sleep quality and risk of COPD exacerbations. METHODS: Data were obtained from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study. Participants with COPD who had completed 18 months of follow-up were included. Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) and a three-factor analysis. Symptom-based (dyspnea or sputum change > 48 h) and event-based (symptoms plus medication or unscheduled health services use) exacerbations were assessed. Association of PSQI with exacerbation rate was assessed by using negative binomial regression. Exacerbation-free survival was also assessed. RESULTS: A total of 480 participants with COPD were studied, including 185 with one or more exacerbations during follow-up and 203 with poor baseline sleep quality (PSQI score > 5). Participants with subsequent symptom-based exacerbations had higher median baseline PSQI scores than those without (6.0 [interquartile range, 3.0-8.0] vs 5.0 [interquartile range, 2.0-7.0]; P = .01), and they were more likely to have baseline PSQI scores > 5 (50.3% vs 37.3%; P = .01). Higher PSQI scores were associated with increased symptom-based exacerbation risk (adjusted rate ratio, 1.09; 95% CI, 1.01-1.18; P = .02) and event-based exacerbation risk (adjusted rate ratio, 1.10; 95% CI, 1.00-1.21; P = .048). The association occurred mainly in those with undiagnosed COPD. Strongest associations were with Factor 3 (sleep disturbances and daytime dysfunction). Time to symptom-based exacerbation was shorter in participants with poor sleep quality (adjusted hazard ratio, 1.49; 95% CI, 1.09-2.03). CONCLUSIONS: Higher baseline PSQI scores were associated with increased risk of COPD exacerbation over 18 months' prospective follow-up.

https://journal.chestnet.org/article/S0012-3692(19)31121-3/fulltext

Siika, A., M. Lindquist Liljeqvist, et al. (2019). **"A large proportion of patients with small ruptured abdominal aortic aneurysms are women and have chronic obstructive pulmonary disease."** PLoS One **14**(5): e0216558.

OBJECTIVE: In a population-based cohort of ruptured abdominal aortic aneurysms (rAAAs), our aim was to investigate clinical, morphological and biomechanical features in patients with small rAAAs. METHODS: All patients admitted to an emergency department in Stockholm and Gotland, a region with a population of 2.1 million, between 2009-2013 with a CT-verified rupture (n = 192) were included, and morphological measurements were performed. Patients with small rAAAs, maximal diameter (Dmax) </= 60 mm were selected (n = 27), and matched 2:1 by Dmax, sex and age to intact AAA (iAAAs). For these patients, morphology including volume and finite element analysis-derived biomechanics were assessed. RESULTS: The mean Dmax for all rAAAs was 80.8 mm (SD = 18.9 mm), women had smaller Dmax at rupture (73.4 +/- 18.4 mm vs 83.1 +/- 18.5 mm, p = 0.003), and smaller neck and iliac diameters compared to men. Aortic size index (ASI) was similar between men and women (4.1 +/- 3.1 cm/m2 vs 3.8 +/- 1.0 cm/m2). Fourteen percent of all patients ruptured at Dmax </= 60 mm, and a higher proportion of women compared to men ruptured at Dmax </= 60 mm: 27% (12/45) vs. 10% (15/147), p = 0.005. Also, a higher proportion of patients with a chronic obstructive pulmonary disease ruptured at Dmax </= 60 mm (34.6% vs 14.6%, p = 0.026). Supra-renal aortic size index (14.0, IQR 13.3-15.3 vs 12.8, IQR =

11.4-14.0) and peak wall rupture index (PWRI, 0.35 +/- 0.08 vs 0.43 +/- 0.11, p = 0.016) were higher for small rAAAs compared to matched iAAAs. Aortic size index, peak wall stress and aneurysm volume did not differ. CONCLUSION: More than one tenth of ruptures occur at smaller diameters, women continuously suffer an even higher risk of presenting with smaller diameters, and this must be considered in surveillance programs. The increased supra-renal aortic size index and PWRI are potential markers for rupture risk, and patients under surveillance with these markers may benefit from increased attention, and potentially from timely repair.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6538142/pdf/pone.0216558.pdf

Stolz, D., K. Kostikas, et al. (2019). **"Differences in COPD Exacerbation Risk Between Women and Men: Analysis From the UK Clinical Practice Research Datalink Data."** ChestBACKGROUND: Historically, COPD has been considered to affect mostly older men with a history of smoking; however, in recent times, its prevalence and mortality rates have steadily increased among women. OBJECTIVES: The goal of this study was to systematically assess differences in COPD expression between women and men in UK primary care clinics who were newly diagnosed with COPD. METHODS: This retrospective cohort study compared women and men with an incident diagnosis of COPD by using electronic medical records data from the Clinical Practice Research Datalink and linked Hospital Episode Statistics data. The overall study period was between January 1, 2006, and February 28, 2016; patients with an incident diagnosis of COPD between January 1, 2010, and February 28, 2015, were analyzed. RESULTS: A cohort of 22,429 patients were identified as incident patients and included in the study; 48% of patients with COPD were women. The risk of first moderate or severe exacerbation was 17% greater in women than in men (hazard ratio, 1.17; 95% CI, 1.12-1.23), with a median time to first exacerbation of 504 days for women and 637 days for men. These differences were more prominent in the younger age group (>/= 40 years to < 65 years), as well as in Global Initiative for Chronic Obstructive Lung Disease 2016 groups B, C, and D and in individuals with moderate to severe airflow obstruction. The annual rate of moderate or severe exacerbations was higher in women compared with men in the first, second, and third year of follow-up. CONCLUSIONS: These results highlight the unmet need for appropriate identification and management of women with COPD in clinical practice.

https://journal.chestnet.org/article/S0012-3692(19)31055-4/fulltext

Strange, C., V. Walker, et al. (2019). **"Patient-reported outcomes of dual bronchodilator fixed-dose combination versus bronchodilator monotherapy in individuals with COPD."** Int J Chron Obstruct Pulmon Dis **14**: 1377-1388.

Background: This study compared real-world patient-reported outcomes (PROs) measured by the Clinical COPD Questionnaire (CCQ), the London Chest Activities of Daily Living (LCADL) scale, and the Work Productivity and Activity Impairment (WPAI) questionnaire between individuals with COPD initiating LAMA/LABA fixed-dose combination (FDC) dual therapy versus either long-acting muscarinic antagonist (LAMA) or long-acting beta2-agonist (LABA) monotherapy. Methods: Individuals with COPD aged >/=40 years initiating a LAMA/LABA FDC dual therapy or a LAMA or LABA monotherapy (index date = first prescription date) between January 1, 2016 and December 31, 2016 were identified from a large US administrative claims database. Individuals were excluded if they were prescribed an inhaled corticosteroid (ICS) or ICS/LABA two months prior to the index date or were diagnosed with cystic fibrosis, idiopathic pulmonary fibrosis, or asthma. The cohorts were propensity score matched (PSM) 1:1 for COPD severity using baseline measures. Each participant completed a survey. Results: Surveys were completed by 399 participants in the dual therapy cohort, and 718 participants in the monotherapy cohort. Following PSM, 379 participants remained in each cohort for analysis (monotherapy: 369 LAMA and 10 LABA). The dual therapy cohort reported fewer COPD-related symptoms (CCQ symptom score 2.75 vs 2.97, respectively, P=0.023), and, fewer limitations in leisure activities (LCADL leisure score 4.78 vs 5.17, respectively, P=0.021) versus the monotherapy cohort. No significant differences were found in the WPAI. A greater percentage of participants in the dual therapy cohort stayed on index therapy (63.1%)

when compared with the monotherapy cohort (30.3%, P<0.0001). Conclusions: Only 30% of the participants prescribed monotherapy, usually with a LAMA, remained on index therapy alone at the time of survey administration. In the dual therapy cohort, 63% of the participants remained on the index medication and had fewer COPD-related symptoms and fewer limitations in leisure activities compared with participants in the monotherapy cohort.

https://www.dovepress.com/getfile.php?fileID=50774

Su, K. C., H. K. Ko, et al. (2019). **"An accurate prediction model to identify undiagnosed at-risk patients with COPD: a cross-sectional case-finding study."** NPJ Prim Care Respir Med **29**(1): 22.

Underuse or unavailability of spirometry is one of the most important factors causing underdiagnosis of COPD. We reported the development of a COPD prediction model to identify at-risk, undiagnosed COPD patients when spirometry was unavailable. This cross-sectional study enrolled subjects aged >/=40 years with respiratory symptoms and a smoking history (>/=20 pack-years) in a medical center in two separate periods (development and validation cohorts). All subjects completed COPD assessment test (CAT), peak expiratory flow rate (PEFR) measurement, and confirmatory spirometry. A binary logistic model with calibration (Hosmer-Lemeshow test) and discrimination (area under receiver operating characteristic curve [AUROC]) was implemented. Three hundred and one subjects (development cohort) completed the study, including non-COPD (154, 51.2%) and COPD cases (147; stage I, 27.2%; II, 55.8%; III-IV, 17%). Compared with non-COPD and GOLD I cases, GOLD II-IV patients exhibited significantly higher CAT scores and lower lung function, and were considered clinically significant for COPD. Four independent variables (age, smoking pack-years, CAT score, and percent predicted PEFR) were incorporated developing the prediction model, which estimated the COPD probability (PCOPD). This model demonstrated favorable discrimination (AUROC: 0.866/0.828; 95% CI 0.825-0.906/0.751-0.904) and calibration (Hosmer-Lemeshow P = 0.332/0.668) for the development and validation cohorts, respectively. Bootstrap validation with 1000 replicates yielded an AUROC of 0.866 (95% CI 0.821-0.905). A PCOPD of >/=0.65 identified COPD patients with high specificity (90%) and a large proportion (91.4%) of patients with clinically significant COPD (development cohort). Our prediction model can help physicians effectively identify at-risk, undiagnosed COPD patients for further diagnostic evaluation and timely treatment when spirometry is unavailable.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6538645/pdf/41533_2019_Article_135.pdf

Su, V. Y., Y. H. Yang, et al. (2019). **"Real-world effectiveness of medications on survival in patients with COPD-heart failure overlap."** Aging (Albany NY) **11**(11): 3650-3667.

The appropriate treatment for patients with coexistent chronic obstructive pulmonary disease (COPD) and heart failure (HF) remains unclear. Data from the Taiwan National Health Insurance Research Database was used for this retrospective cohort study. Patients diagnosed with both diseases between 1997 and 2012 were enrolled as the COPD-heart failure overlap cohort. Patients were categorized as non-users and users of specific COPD and HF medications. Medication prescriptions in each 3-month and 1-year period served as time-dependent covariates. The primary endpoint was cumulative survival. The validation study confirmed the accuracy of definitions of COPD (94.0% sensitivity) and HF (96.3% sensitivity).The study included 275,436 patients with COPD-heart failure overlap, with a mean follow-up period of 9.32 years. The COPD-heart failure overlap cohort had more medical service use and higher mortality than did the COPD alone cohort. Use of inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) combinations, long-acting muscarinic antagonist (LAMA), angiotensin receptor blockers (ARBs), beta blockers, aldosterone antagonists, and statins reduced mortality risk compared with non-use. Sensitivity and subgroup analyses confirmed the consistency and robustness of results.ICS/LABA combinations, LAMA, ARBs, beta blockers, aldosterone antagonists, and statins use was associated with a lower mortality risk in patients with COPD-heart failure overlap.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6594806/pdf/aging-11-102004.pdf

Sun, H. B., X. S. Jing, et al. (2019). **"Preliminary Study on 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 NeurosurgOBJECTIVES: To assess outcomes for obese patients with chronic obstructive pulmonary disease (COPD) suffering from osteoporotic vertebral compression fracture(OVCF) treated by percutaneous vertebroplasty(PVP) in improved prone position and right lateral position. PATIENTS AND METHODS: Between January 2015 and May 2016, a total of 60 patients were enrolled in this randomized controlled study. Group A was in improved prone position via bilateral transpedicular technique; Group B was in right lateral position via left transverse process-pedicle approach. Clinical and radiological outcomes were assessed between two groups during the 12 months follow-up period. RESULTS: All operations were successfully completed without any serious sequelae. The operation time, fluoroscopic times, scores of respiratory condition during operation, intravertebral cement volume and incidence for cement leakage in group A were significantly more than that in group B, and had significantly difference between two groups ($P < 0.01$). During follow-up period, all patients in both groups had significantly improvement in pain relief. But satisfactory functional improvement would be obtained at 3 months postoperatively. CONCLUSION: Obese patients with COPD suffering from painful OVCF, treated both by PVP in improved prone position by bilateral technique and right lateral position by the unilateral technique, were relatively safe and effective. However, unilateral PVP in right lateral position received less operation time, limited fluoroscopic times, and minimal cement leakage.

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

Sun, J., Y. Li, et al. (2019). **"High flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease with acute-moderate hypercapnic respiratory failure: an observational cohort study."** Int J Chron Obstruct Pulmon Dis **14**: 1229-1237.

Background: High-flow nasal cannula (HFNC) oxygen therapy in acute hypoxic respiratory failure is becoming increasingly popular. However, evidence to support the use of HFNC in acute respiratory failure (ARF) with hypercapnia is limited. Methods: Chronic obstructive pulmonary disease (COPD) patients with moderate hypercapnic ARF (arterial blood gas pH 7.25-7.35, $PaCO_2$>50 mmHg) who received HFNC or non-invasive ventilation (NIV) in the intensive care uint from April 2016 to March 2018 were analyzed retrospectively. The endpoint was treatment failure, defined as either invasive ventilation, or a switch to the other study treatment (NIV for patients in the NFNC group, and vice-versa), and 28-day mortality. Results: Eighty-two COPD patients (39 in the HFNC group and 43 in the NIV group) were enrolled in this study. The mean age was 71.8+/-8.2 and 54 patients (65.9%) were male. The treatment failed in 11 out of 39 patients with HFNC (28.2%) and in 17 of 43 patients with NIV (39.5%) ($P=0.268$). No significant differences were found for 28-day mortality (15.4% in the HFNC group and 14% in the NIV group, $P=0.824$). During the first 24 hrs of treatment, the number of nursing airway care interventions in the HFNC group was significantly less than in the NIV group, while the duration of device application was significantly longer in the HFNC group (all $P<0.05$). Skin breakdown was significantly more common in the NIV group (20.9% vs 5.1%, $P<0.05$). Conclusion: Among COPD patients with moderate hypercarbic ARF, the use of HFNC compared with NIV did not result in increased rates of treatment failure, while there were fewer nursing interventions and skin breakdown episodes reported in the HFNC group.

https://www.dovepress.com/getfile.php?fileID=50341

Szmidt, M. K., J. Kaluza, et al. (2019). **"Long-term dietary fiber intake and risk of chronic obstructive pulmonary disease: a prospective cohort study of women."** Eur J NutrPURPOSE: Until now, only two prospective cohort studies have investigated dietary fiber intake in relation to risk of chronic obstructive

pulmonary disease (COPD), but neither examined long-term fiber intake. Both studies reported that total fiber intake was associated with decreased COPD risk; however, results for specific fiber sources were inconsistent. Thus, we prospectively evaluated the association between baseline and long-term intake of dietary fiber and COPD risk in a population-based prospective cohort of 35,339 Swedish women. METHODS: Dietary fiber intake was assessed in 1987 and 1997 with a food frequency questionnaire. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). RESULTS: During follow-up (2002-2014), 1557 COPD cases were identified via linkage to the Swedish National Patient Register. Long-term high dietary fiber intake (>/= 26.5 vs. < 17.6 g/day) was associated with a 30% (95% CI 17-41%) lower risk of COPD. For specific fiber sources, cereal (>/= 16.3 vs. < 9.4 g/day; HR 0.67, 95% CI 0.55-0.81) and fruit fiber (>/= 7.6 vs. < 2.6 g/day; HR 0.65, 95% CI 0.5-0.81), but not vegetable fiber intake (>/= 5.4 vs. < 2.2 g/day; HR 1.03, 95% CI 0.81-1.28) were associated with lower COPD risk. Current and ex-smokers with low long-term total fiber intake (< 17.6 g/day) compared to never smokers with high intake (>/= 26.5 g/day) had a 33-fold (95% CI 23.6-46.6) and tenfold (95% CI 7.0-16.3), respectively, higher risk of COPD. CONCLUSIONS: Our findings indicate that high fiber intake is a modifiable lifestyle factor which may decrease COPD risk primarily in current and ex-smokers.

https://link.springer.com/content/pdf/10.1007%2Fs00394-019-02038-w.pdf

Tachibana, Y., H. Taniguchi, et al. (2019). **"Pulmonary interstitial emphysema is a risk factor for poor prognosis and a cause of air leaks."** Respir InvestigBACKGROUND: Pulmonary interstitial emphysema is a rare, abnormal condition in which air pressure from the alveolar airspace tears the adjacent interstitial tissues of the lung and causes the formation of cystic spaces. Pulmonary interstitial emphysema is a known indication for mechanical ventilation in premature infants with neonatal respiratory distress syndrome, and it can be observed in various types of interstitial lung disease. Nevertheless, its pathogenesis and clinical impact remain unknown. METHODS: We reviewed data from 433 cases of interstitial lung disease from an external consultation archive. Multidisciplinary diagnosis along with clinical and follow-up data, including events of air leaks such as pneumothorax and mediastinal emphysema, were obtained and compared to those of 150 control cases of interstitial lung disease without pulmonary interstitial emphysema. RESULTS: We found 22 (5.1%) cases of interstitial lung disease with pulmonary interstitial emphysema. The diagnoses included idiopathic pulmonary fibrosis (5/22 [22.7%]), pleuroparenchymal fibroelastosis (4/22 [18.2%]), chronic hypersensitivity pneumonia (4/22 [18.2%]), and others (9/22 [40.9%]). Cases involving pulmonary interstitial emphysema demonstrated a significantly higher frequency of air leaks than did those without pulmonary interstitial emphysema (12/22 [54.5%] versus 23/150 [15.3%]; P < 0.001; odds ratio, 6.63) and were associated with worse prognosis (P = 0.009 [log-rank]) and a lower median percent forced vital capacity (73.2% versus 84.0%; P < 0.001). CONCLUSIONS: We found that pulmonary interstitial emphysema is an independent factor for poor prognosis, which also shows a trend to cause air leaks, including pneumothorax and mediastinal emphysema.

https://www.sciencedirect.com/science/article/abs/pii/S2212534518301588?via%3Dihub

Tickoo, M., R. Ruthazer, et al. (2019). **"The effect of respiratory viral assay panel on antibiotic prescription patterns at discharge in adults admitted with mild to moderate acute exacerbation of COPD: a retrospective before- after study."** BMC Pulm Med **19**(1): 118.

BACKGROUND: Despite well-defined criteria for use of antibiotics in patients presenting with mild to moderate Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), their overuse is widespread. We hypothesized that following implementation of a molecular multiplex respiratory viral panel (RVP), AECOPD patients with viral infections would be more easily identified, limiting antibiotic use in this population. The primary objective of our study was to investigate if availability of the RVP decreased antibiotic prescription at discharge among patients with AECOPD. METHODS: This is a single center, retrospective, before (pre-RVP) - after (post-RVP) study of patients admitted to a tertiary medical center

from January 2013 to March 2016. The primary outcome was antibiotic prescription at discharge. Groups were compared using univariable and multivariable logistic-regression. RESULTS: A total of 232 patient-episodes were identified, 133 following RVP introduction. Mean age was 68.1 (pre-RVP) and 68.3 (post-RVP) years respectively (p = 0.88). Patients in pre-RVP group were similar to the post-RVP group with respect to gender (p = 0.54), proportion of patients with BMI < 21(p = 0.23), positive smoking status (p = 0.19) and diagnoses of obstructive sleep apnea (OSA, p = 0.16). We found a significant reduction in antibiotic prescription rate at discharge in patients admitted with AECOPD after introduction of the respiratory viral assay (pre-RVP 77.8% vs. post-RVP 63.2%, p = 0.01). In adjusted analyses, patients in the pre-RVP group [OR 2.11 (CI: 1.13-3.96), p = 0.019] with positive gram stain in sputum [OR 4.02 (CI: 1.61-10.06), p = 0.003] had the highest odds of antibiotic prescription at discharge. CONCLUSIONS: In patients presenting with mild to moderate Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), utilization of a comprehensive respiratory viral panel can significantly decrease the rate of antibiotic prescription at discharge.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6604457/pdf/12890_2019_Article_872.pdf

Trethewey, S. P., R. G. Edgar, et al. (2019). **"Late presentation of acute hypercapnic respiratory failure carries a high mortality risk in COPD patients treated with ward-based NIV."** Respir Med **151**: 128-132.

INTRODUCTION: Non-invasive ventilation (NIV) is recommended for treatment of acute hypercapnic respiratory failure (AHRF) refractory to medical management in patients with COPD. This study investigated the relationship between time from hospital presentation to diagnosis of AHRF and in-hospital mortality. METHODS: Retrospective analysis of hospitalised COPD patients treated with a first episode of ward-based NIV for AHRF at a large UK teaching hospital between 2004 and 2017. Data collected prospectively as part of NIV service evaluation. Multivariable logistic regression performed to identify predictors of in-hospital mortality. RESULTS: In total, 547 unique patients were studied comprising 245 males (44.8%), median age 70.6 years, median FEV1% predicted 34%. Overall in-hospital mortality was 19% (n=104); median survival was 1.7 years. In univariate analysis, a longer time between hospital presentation to diagnosis of AHRF was associated with in-hospital mortality (median [IQR]: 8.7 [0.7-75.8] hours vs. 1.9 [0.3-13.6] hours, p<0.0001). In multivariable logistic regression, significant predictors of in-hospital mortality were AHRF >24h after hospital presentation (odds ratio [95% CI]: 2.29 [1.33-3.95], p=0.003), pneumonia on admission (1.81 [1.07-3.08], p=0.027), increased age (1.10 [1.07-1.14], p<0.001) and NIV as ceiling of treatment (5.86 [2.87-11.94], p<0.001). CONCLUSIONS: Hospitalised COPD patients with late presentation of AHRF, requiring acute ward-based NIV, may have increased in-hospital mortality. These patients may benefit from closer monitoring and earlier specialist respiratory review.

https://www.resmedjournal.com/article/S0954-6111(19)30134-9/fulltext

Trudzinski, F. C., M. Alqudrah, et al. (2019). **"Consequences of chronic kidney disease in chronic obstructive pulmonary disease."** Respir Res **20**(1): 151.

BACKGROUND: The combination of chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) is associated with a higher prevalence of comorbidities and increased mortality. The impact of kidney function on patient-centered outcomes in COPD has not been evaluated. METHODS: Patients from the German COPD and Systemic Consequences - Comorbidities Network (COSYCONET) cohort COPD were analysed. CKD was diagnosed if the estimated glomerular filtration rate (eGFR) measurements were < 60 mL/min/1.73m(2) at study inclusion and six month later. The effect of CKD, on comorbidities, symptoms [modified British Medical Research Council dyspnoea scale], physical capacity [six-minute walk test, and timed up and go] and St George's Respiratory Questionnaire were analysed. Restricted cubic spline models were used to evaluate a nonlinear relationship between eGFR with patient-centered outcomes, cox survival analysis was applied to evaluate mortality. RESULTS: 2274 patients were analysed, with CKD diagnosed in 161 (7.1%). Spline models adjusted for age, gender, BMI, FEV1 and cardiovascular comorbidities revealed independent associations between eGFR with modified British Medical Research Council dyspnoea scale, St George's Respiratory Questionnaire, (p < 0.001 and

p = 0.011), six-minute walk test (p = 0.015) and timed up and go (p < 0.001). CKD was associated with increased mortality, independently from for other cardiovascular comorbidities (hazard ratio 2.3; p < 0.001). CONCLUSION: These data show that CKD is a relevant comorbidity in COPD patients which impacts on patient-centered outcomes and mortality. TRIAL REGISTRATION: NCT01245933.

https://respiratory-research.biomedcentral.com/track/pdf/10.1186/s12931-019-1107-x

Trudzinski, F. C., K. Kahnert, et al. (2019). **"Combined effects of lung function, blood gases and kidney function on the exacerbation risk in stable COPD: Results from the COSYCONET cohort."** Respir Med **154**: 18-26.

RATIONALE: Alterations of acid-base metabolism are an important outcome predictor in acute exacerbations of COPD, whereas sufficient metabolic compensation and adequate renal function are associated with decreased mortality. In stable COPD there is, however, only limited information on the combined role of acid-base balance, blood gases, renal and respiratory function on exacerbation risk grading. METHODS: We used baseline data of the COPD cohort COSYCONET, applying linear and logistic regression analyses, the results of which were implemented into a comprehensive structural equation model. As most informative parameters it comprised the estimated glomerular filtration rate (eGFR), lung function defined via forced expiratory volume in 1s (FEV1), intrathoracic gas volume (ITGV) and (diffusing capacity for carbon monoxide (DLCO), moreover arterial oxygen content (CaO2), partial pressure of oxygen (PaCO2), base exess (BE) and exacerbation risk according to GOLD criteria. All measures were adjusted for age, gender, body-mass index, the current smoking status and pack years. RESULTS: 1506 patients with stable COPD (GOLD grade 1-4; mean age 64.5+/-8.1y; mean FEV1 54+/-18 %predicted, mean eGFR 82.3+/-16.9mL/min/1.73m(2)) were included. BE was linked to eGFR, lung function and PaCO2 and played a role as indirect predictor of exacerbation risk via these measures; moreover, eGFR was directly linked to exacerbation risk. These associations remained significant after taking into account medication (diuretics, oral and inhaled corticosteroids), whereby corticosteroids had effects on exacerbation risk and lung function, diuretics on eGFR, BE and lung function. CONCLUSION: Even in stable COPD acid-base metabolism plays a key integrative role in COPD risk assessment despite rather small deviations from normality. It partially mediates the effects of impairments in kidney function, which are also directly linked to exacerbation risk.

https://www.resmedjournal.com/article/S0954-6111(19)30195-7/fulltext

Valipour, A., P. L. Shah, et al. (2019). **"Safety and Dose Study of Targeted Lung Denervation in Moderate/Severe COPD Patients."** Respiration: 1-11.

RATIONALE: Targeted lung denervation (TLD) is a novel bronchoscopic treatment for the disruption of parasympathetic innervation of the lungs. OBJECTIVES: To assess safety, feasibility, and dosing of TLD in patients with moderate to severe COPD using a novel device design. METHODS: Thirty patients with COPD (forced expiratory volume in 1 s 30-60%) were 1:1 randomized in a double-blinded fashion to receive TLD with either 29 or 32 W. Primary endpoint was the rate of TLD-associated adverse airway effects that required treatment through 3 months. Assessments of lung function, quality of life, dyspnea, and exercise capacity were performed at baseline and 1-year follow-up. An additional 16 patients were enrolled in an open-label confirmation phase study to confirm safety improvements after procedural enhancements following gastrointestinal adverse events during the randomized part of the trial. RESULTS: Procedural success, defined as device success without an in-hospital serious adverse event, was 96.7% (29/30). The rate of TLD-associated adverse airway effects requiring intervention was 3/15 in the 32 W versus 1/15 in the 29 W group, p = 0.6. Five patients early in the randomized phase experienced serious gastric events. The study was stopped and procedural changes made that reduced both gastrointestinal and airway events in the subsequent phase of the randomized trial and follow-up confirmation study. Improvements in lung function and quality of life were observed compared to baseline values for both doses but were not statistically different. CONCLUSIONS: The results

demonstrate acceptable safety and feasibility of TLD in patients with COPD, with improvements in adverse event rates after procedural enhancements.

https://www.karger.com/Article/Pdf/500463

Van de Moortele, T., U. Goerke, et al. (2019). **"Airway morphology and inspiratory flow features in the early stages of Chronic Obstructive Pulmonary Disease."** Clin Biomech (Bristol, Avon) **66**: 60-65.

BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of death worldwide. Inhaled pollutants are the prime risk factor, but the pathogenesis and progression of the diseased is poorly understood. Most studies on the disease onset and trajectory have focused on genetic and molecular biomarkers. Here we investigate the role of the airway anatomy and the consequent respiratory fluid mechanics on the development of COPD. METHODS: We segmented CT scans from a five-year longitudinal study in three groups of smokers (18 subjects each) having: (i) minimal/mild obstruction at baseline with declining lung function at year five; (ii) minimal/mild obstruction at baseline with stable function, and (iii) normal and stable lung function over the five year period. We reconstructed the bronchial trees up to the 7th generation, and for one subject in each group we performed MRI velocimetry in 3D printed models. FINDINGS: The subjects with airflow obstruction at baseline have smaller airway diameters, smaller child-to-parent diameter ratios, larger length-to-diameter ratios, and smaller fractal dimensions. The differences are more significant for subjects that develop severe decline in pulmonary function. The secondary flows that characterize lateral dispersion along the airways are found to be less intense in the subjects with airflow obstruction. INTERPRETATION: These results indicate that morphology of the conducting airways and inspiratory flow features are correlated with the status and progression of COPD already at an early stage of the disease. This suggests that imaging-based biomarkers may allow a pre-symptomatic diagnosis of disease progression.

https://www.clinbiomech.com/article/S0268-0033(17)30286-3/fulltext

van der Plas, A. G. M., M. G. Oosterveld-Vlug, et al. (2019). **"Continuity of GP care after the last hospitalization for patients who died from cancer, chronic obstructive pulmonary disease or heart failure: a retrospective cohort study using administrative data."** Fam Pract **36**(3): 304-309.

BACKGROUND: Discharge from hospital to home can be a stressful experience for patients and carers. Contact with the GP is important to ensure continuity of care. OBJECTIVES: To investigate timing of contact with the GP and locum after the last hospitalization in the last year of life and to investigate patient and care characteristics related to contact with the GP within 2 days after discharge. METHODS: Health insurance data were combined with data from Statistics Netherlands on patients who mainly received care at home in the last 4 months of life. Patients who died from cancer (n = 3014), chronic obstructive pulmonary disease (COPD, n = 195) or heart failure (n = 171) were compared. RESULTS: First contact after hospital discharge was within 2 days for 51.7% of patients and within a week for 77.8% of patients. Patients who died from COPD or heart failure had contact less often than patients with cancer. Characteristics related to having contact within 2 days after discharge were older age, cause of death cancer, home death, timing of last hospitalization closer to death and contact with a locum in the week after discharge. CONCLUSION: Results may indicate that the GP is likely to visit patients with more care needs sooner. This would be in accordance with the finding that contact with the GP was more likely after a hospitalization closer to death and that contact within 2 days was related to contact with a locum within a week after discharge. Proactive care is necessary. This is a joint responsibility of GPs and medical specialists.

https://academic.oup.com/fampra/article-abstract/36/3/304/5047161?redirectedFrom=fulltext

van Dort, M. J., J. H. M. Driessen, et al. (2019). **"Vertebral bone attenuation in Hounsfield Units and prevalent vertebral fractures are associated with the short-term risk of vertebral fractures in current and ex-smokers with and without COPD: a 3-year chest CT follow-up study."** Osteoporos IntCT scans performed to evaluate chronic obstructive pulmonary disease (COPD) also enable evaluation of bone attenuation (BA; a measure of bone density) and vertebral fractures (VFs). In 1239 current/former smokers with (n = 999) and without (n = 240) COPD, the combination of BA and prevalent VFs was associated with the incident VF risk. INTRODUCTION: Chest CT scans are increasingly used to evaluate pulmonary diseases, including COPD. COPD patients have increased risk of osteoporosis and VFs. BA on CT scans is correlated with bone mineral density and prevalent VFs. The aim of this study was to evaluate the association between BA and prevalent VFs on chest CT scans, and the risk of incident VFs in current and former smokers with and without COPD. METHODS: In participants of the ECLIPSE study with baseline and 1-year and 3-year follow-up CT scans, we evaluated BA in vertebrae T4-T12 and prevalent and incident VFs. RESULTS: A total of 1239 subjects were included (mean age 61.3 +/- 8.0, 61.1% men, 999 (80.6%) COPD patients). The mean BA was 155.6 +/- 47.5 Hounsfield Units (HU); 253 (20.5%) had a prevalent VF and 296 (23.9%) sustained an incident VF within 3 years. BA and prevalent VFs were associated with incident VFs within 1 (per - 1SD HR = 1.38 [1.08-1.76] and HR = 3.97 [2.65-5.93] resp.) and 3 years (per - 1SD HR = 1.25 [1.08-1.45] and HR = 3.10 [2.41-3.99] resp.), while age, sex, body mass index (BMI), smoking status and history, or presence of COPD was not. In subjects without prevalent VFs and BA, and for 1-year incidence, BMI values were associated with incident fractures (1 year, BA per - 1SD HR = 1.52 [1.05-2.19], BMI per SD HR = 1.54 [1.13-2.11]; 3 years, per - 1SD HR = 1.37 [1.12-1.68]). CONCLUSIONS: On CT scans performed for pulmonary evaluation in (former) smokers with and without COPD, the combination of BA and prevalent VFs was strongly associated with the short-term risk of incident VFs.

https://link.springer.com/content/pdf/10.1007%2Fs00198-019-04977-w.pdf

Vetrano, D. L., A. Zucchelli, et al. (2019). **"Triple inhaled therapy in COPD patients: determinants of prescription in primary care."** Respir Med **154**: 12-17.

OBJECTIVE: To assess the incidence and determinants of the triple inhaled therapy in chronic obstructive pulmonary disease (COPD) primary care patients. METHODS: Data derived from the Health Search Database (HSD) gathering information on 700 Italian general practitioners. A cohort of COPD patients, prescribed for the first time with inhaled treatments, was followed-up between January 2002 and December 2014. The outcome was the first incident prescription of a triple inhaled therapy, namely the combination of inhaled corticosteroids (ICS), long-acting beta agonists (LABA), and long-acting muscarinic antagonists (LAMA). Cox regressions were used to test the association (hazard ratios, HR) between candidate determinants and the outcome. RESULTS: Out of 17589 patients (mean age 71.1+/-11.3 years; 37.4% females), 3693 (21%) were prescribed with a triple inhaled therapy during follow-up. Older age (HR=1.79 to 2.61), current and former smoking habit (HR=1.72 and 1.66), higher GOLD stage (HR=1.45 to 2.79), the number of moderate and severe COPD exacerbations (HR=1.10 to 2.63), and heart failure (HR=1.17) resulted statistically significantly associated with an increased incident prescription of the triple inhaled therapy. Female sex (HR=0.80) and some comorbidities (HR=0.21 to 0.87) resulted negatively associated with the outcome. Furthermore, patients initially treated with LAMA (HR=1.5) and LABA/ICS (HR=1.23) were more likely to escalate to the triple therapy, than those on LABA. Conversely, patients initially treated with ICS presented a negative hazard (HR=0.72). CONCLUSIONS: The knowledge of demographic and clinical determinants of the escalation to the triple inhaled therapy in real-world COPD patients may help clinicians to better personalize respiratory pharmacological treatments of their patients, and inform international societies that issue clinical guidelines.

https://www.resmedjournal.com/article/S0954-6111(19)30181-7/fulltext

Wang, Y., M. A. Bahar, et al. (2019). **"Improving antibacterial prescribing safety in the management of COPD exacerbations: systematic review of observational and clinical studies on potential drug**

interactions associated with frequently prescribed antibacterials among COPD patients." J Antimicrob ChemotherBACKGROUND: Guidelines advise the use of antibacterials (ABs) in the management of COPD exacerbations. COPD patients often have multiple comorbidities, such as diabetes mellitus and cardiac diseases, leading to polypharmacy. Consequently, drug-drug interactions (DDIs) may frequently occur, and may cause serious adverse events and treatment failure. OBJECTIVES: (i) To review DDIs related to frequently prescribed ABs among COPD patients from observational and clinical studies. (ii) To improve AB prescribing safety in clinical practice by structuring DDIs according to comorbidities of COPD. METHODS: We conducted a systematic review by searching PubMed and Embase up to 8 February 2018 for clinical trials, cohort and case-control studies reporting DDIs of ABs used for COPD. Study design, subjects, sample size, pharmacological mechanism of DDI and effect of interaction were extracted. We evaluated levels of DDIs and quality of evidence according to established criteria and structured the data by possible comorbidities. RESULTS: In all, 318 articles were eligible for review, describing a wide range of drugs used for comorbidities and their potential DDIs with ABs. DDIs between ABs and co-administered drugs could be subdivided into: (i) co-administered drugs altering the pharmacokinetics of ABs; and (ii) ABs interfering with the pharmacokinetics of co-administered drugs. The DDIs could lead to therapeutic failures or toxicities. CONCLUSIONS: DDIs related to ABs with clinical significance may involve a wide range of indicated drugs to treat comorbidities in COPD. The evidence presented can support (computer-supported) decision-making by health practitioners when prescribing ABs during COPD exacerbations in the case of co-medication.

https://academic.oup.com/jac/advance-article-abstract/doi/10.1093/jac/dkz221/5498602?redirectedFrom=fulltext

Wang, Z., B. Maschera, et al. (2019). **"Airway host-microbiome interactions in chronic obstructive pulmonary disease."** Respir Res **20**(1): 113.

BACKGROUND: Little is known about the interactions between the lung microbiome and host response in chronic obstructive pulmonary disease (COPD). METHODS: We performed a longitudinal 16S ribosomal RNA gene-based microbiome survey on 101 sputum samples from 16 healthy subjects and 43 COPD patients, along with characterization of host sputum transcriptome and proteome in COPD patients. RESULTS: Dysbiosis of sputum microbiome was observed with significantly increased relative abundance of Moraxella in COPD versus healthy subjects and during COPD exacerbations, and Haemophilus in COPD ex-smokers versus current smokers. Multivariate modeling on sputum microbiome, host transcriptome and proteome profiles revealed that significant associations between Moraxella and Haemophilus, host interferon and pro-inflammatory signaling pathways and neutrophilic inflammation predominated among airway host-microbiome interactions in COPD. While neutrophilia was positively correlated with Haemophilus, interferon signaling was more strongly linked to Moraxella. Moreover, while Haemophilus was significantly associated with host factors both in stable state and during exacerbations, Moraxella-associated host responses were primarily related to exacerbations. CONCLUSIONS: Our study highlights a significant airway host-microbiome interplay associated with COPD inflammation and exacerbations. These findings indicate that Haemophilus and Moraxella influence different components of host immune response in COPD, and that novel therapeutic strategies should consider targeting these bacteria and their associated host pathways in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6555748/pdf/12931_2019_Article_1085.pdf

Wen, H., C. Xie, et al. (2019). **"Difference in Long-Term Trends in COPD Mortality between China and the U.S., 1992(-)2017: An Age(-)Period(-)Cohort Analysis."** Int J Environ Res Public Health **16**(9)Complications due to chronic obstructive pulmonary disease (COPD) is a leading cause of death in China and the United States (U.S.). This study aimed to investigate the long-term trends in COPD mortality in China and the U.S. using data from the Global Burden of Disease Study 2017 (GBD 2017) and explore the age, period, and cohort effects independently by sex under the age-period-cohort (APC) framework. Taking the age group 40-44 years old, the period 1992-1996, and the birth cohort 1913-1917 as reference groups, we found that the age relative risks (RRs) of COPD mortality increased

exponentially in both China and the U.S., the period RRs increased in the U.S. but decreased in China; and the cohort RRs showed an overall downward trend in both China and the U.S. with the year of birth. From 1992 to 2017, the increased RRs of COPD mortality in the U.S. was mainly attributable to the increased prevalence of smoking before 1965, while the decreased RRs of COPD mortality in China was mainly attributable to reduced air pollution as well as improvements in medical technology and more accessible health services. Reducing tobacco consumption may be the most effective and feasible way to prevent COPD in China. However, we also need to pay more attention to COPD in nonsmokers in the future.

https://res.mdpi.com/ijerph/ijerph-16-01529/article_deploy/ijerph-16-01529.pdf?filename=&attachment=1

Whittaker, H. R., H. Mullerova, et al. (2019). **"Inhaled corticosteroids, blood eosinophils, and FEV1 decline in patients with COPD in a large UK primary health care setting."** Int J Chron Obstruct Pulmon Dis **14**: 1063-1073.

Background: Inhaled corticosteroid (ICS)-containing medications slow rate of decline of FEV1. Blood eosinophil (EOS) levels are associated with the degree of exacerbation reduction with ICS. Purpose: We investigated whether FEV1 decline differs between patients with and without ICS, stratified by blood EOS level. Patients and methods: The UK Clinical Practice Research Datalink (primary care records) and Hospital Episode Statistics (hospital records) were used to identify COPD patients aged 35 years or older, who were current or ex-smokers with >/=2 FEV1 measurements >/=6 months apart. Prevalent ICS use and the nearest EOS count to start of follow-up were identified. Patients were classified at baseline as higher stratum EOS (>/=150 cell/microL) on ICS; higher stratum EOS not on ICS; lower stratum EOS (<150 cells/microL) on ICS; and lower stratum EOS not on ICS. In addition, an incident ICS cohort was used to investigate the rate of FEV1 change by EOS and incident ICS use. Mixed-effects linear regression was used to compare rates of FEV1 change in mL/year. Results: A total of 26,675 COPD patients met our inclusion criteria (median age 69, 46% female). The median duration of follow up was 4.2 years. The rate of FEV1 change in prevalent ICS users was slower than non-ICS users (-12.6 mL/year vs -21.1 mL/year; P =0.001). The rate of FEV1 change was not significantly different when stratified by EOS level. The rate of FEV1 change in incident ICS users increased (+4.2 mL/year) vs -21.2 mL/year loss in non-ICS users; P<0.001. In patients with high EOS, incident ICS patients showed an increase in FEV1 (+12 mL/year) compared to non-ICS users whose FEV1 decreased (-20.8 mL/year); P<0.001. No statistical difference was seen in low EOS patients. Incident ICS use is associated with an improvement in FEV1 change, however, over time this association is lost. Conclusion: Regardless of blood EOS level, prevalent ICS use is associated with slower rates of FEV1 decline in COPD.

https://www.dovepress.com/getfile.php?fileID=50065

Winther, H. B., M. Gutberlet, et al. (2019). **"Deep semantic lung segmentation for tracking potential pulmonary perfusion biomarkers in chronic obstructive pulmonary disease (COPD): The multi-ethnic study of atherosclerosis COPD study."** J Magn Reson ImagingBACKGROUND: Chronic obstructive pulmonary disease (COPD) is associated with high morbidity and mortality. Identification of imaging biomarkers for phenotyping is necessary for future treatment and therapy monitoring. However, translation of visual analytic pipelines into clinics or their use in large-scale studies is significantly slowed by time-consuming postprocessing steps. PURPOSE: To implement an automated tool chain for regional quantification of pulmonary microvascular blood flow in order to reduce analysis time and user variability. STUDY TYPE: Prospective. POPULATION: In all, 90 MRI scans of 63 patients, of which 31 had a COPD with a mean Global Initiative for Chronic Obstructive Lung Disease status of 1.9 +/- 0.64 (mu +/- sigma). FIELD STRENGTH/SEQUENCE: 5T dynamic gadolinium-enhanced MRI measurement using 4D dynamic contrast material-enhanced (DCE) time-resolved angiography acquired in a single breath-hold in inspiration. ASSESSMENT: We built a 3D convolutional neural network for semantic segmentation using 29 manually segmented perfusion maps. All five lobes of the lung are denoted, including the middle lobe. Evaluation was performed on 61 independent cases from two sites of the Multi-Ethnic

Study of Arteriosclerosis (MESA)-COPD study. We publish our implementation of a model-free deconvolution filter according to Sourbron et al for 4D DCE MRI scans as open source. STATISTICAL TEST: Cross-validation 29/61 (# training / # testing), intraclass correlation coefficient (ICC), Spearman rho, Pearson r, Sorensen-Dice coefficient, and overlap. RESULTS: Segmentations and derived clinical parameters were processed in ~90 seconds per case on a Xeon E5-2637v4 workstation with Tesla P40 GPUs. Clinical parameters and predicted segmentations exhibit high concordance with the ground truth regarding median perfusion for all lobes with an ICC of 0.99 and a Sorensen-Dice coefficient of 93.4 +/- 2.8 (mu +/- sigma). DATA CONCLUSION: We present a robust end-to-end pipeline that allows for the extraction of perfusion-based biomarkers for all lung lobes in 4D DCE MRI scans by combining model-free deconvolution with deep learning. LEVEL OF EVIDENCE: 3 Technical Efficacy: Stage 2 J. Magn. Reson. Imaging 2019.

https://onlinelibrary.wiley.com/doi/abs/10.1002/jmri.26853

Wong, E. K. C., P. C. S. Lee, et al. (2019). **"Role of venous blood gases in hypercapnic respiratory failure chronic obstructive pulmonary disease patients presenting to the emergency department."** Intern Med J **49**(7): 834-837.

BACKGROUND: Many patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have type 2 respiratory failure (T2RF). Often arterial blood gases are not performed and correlation with venous blood gases (VBG) is controversial. The venous pH and bicarbonate (HCO_3^-) are useful, but VBG pCO_2 ($PvCO_2$) is considered too unpredictable. AIM: To examine the utility of VBG in this cohort of patients. METHODS: A prospective study of AECOPD patients with T2RF presenting to the emergency department was performed. Patients being considered for non-invasive ventilation and who required an arterial blood gas were invited to participate. A subsequent VBG was also taken, and Bland-Altman plots were used for analysis. RESULTS: Sixty-three patients were included in this study. The limits of agreement for pH and HCO_3^- were narrow. Wider limits of agreement with a systematic bias of 7.7 mmHg were noted with pCO_2 . CONCLUSIONS: The utility of VBG pH and HCO_3^- was again demonstrated. VBG pCO_2 in this cohort of patients may have a role in the assessment of patients with AECOPD. Further study is needed on the possible role of VBG in the management of such patients with T2RF particularly those using non-invasive ventilation.

https://onlinelibrary.wiley.com/doi/abs/10.1111/imj.14186

Xie, J., F. Li, et al. (2019). **"Prevalence of pulmonary embolism in patients with obstructive sleep apnea and chronic obstructive pulmonary disease: The overlap syndrome."** Heart Lung **48**(3): 261-265.

OBJECTIVE: Growing evidence indicates that both obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) may be closely associated with the prevalence of pulmonary embolism (PE). However, the relationship of overlap syndrome (OS) (coexistence of OSA and COPD) with PE is unclear. The purpose of this study was to investigate whether OS were associated with increased PE prevalence. METHODS: We performed a retrospective chart review of patients who underwent sleep study at Beijing An Zhen Hospital from 2011 to 2014. The association of OS with PE prevalence was estimated by using logistic regression models. RESULTS: In contrast to control patients (neither OSA nor COPD), those subjects with OS had higher odds of PE (OR9.61; 95%CI 4.02-21.31, $p<0.001$) with significance persisting after adjusting for covariates (OR 5.66; 95%CI 1.80-16.18, $p=0.004$). Meanwhile, patients with OS compared with those with isolated OSA also had significantly higher odds of PE in univariate (OR 4.79; 95%CI 2.04-10.33, $p=0.0007$) and adjusted models (OR 3.89; 95%CI 1.27-10.68, $p=0.019$). In subgroup analysis, patients with OS had higher odds of PE than control group among male subjects (OR 8.12, 95%CI1.86-31.87, $p=0.007$) and patients>/=58years (OR 5.50, 95%CI 1.51-18.14, $p=0.012$) in multivariable models. Percentage of total sleep time with saturation lower than 90% (T90)>/=2.6% was significantly associated with prevalence of PE (OR 4.72, 95%CI1.34-19.83, $p=0.015$) in subgroup of patients older than 58. CONCLUSIONS: OS is independently associated with PE prevalence. Longitudinal studies are needed to better understand the relationship with incident PE.

https://www.heartandlung.org/article/S0147-9563(18)30275-9/fulltext

Yang, L., Y. Zhu, et al. (2019). **"A Low Lean-to-Fat Ratio Reduces the Risk of Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Patients with a Normal or Low Body Mass Index."** Med Sci Monit **25**: 5229-5236.

BACKGROUND Increased risk of acute exacerbation of chronic obstructive pulmonary disease (COPD) has been reported in patients who are overweight and obese. However, the effects of body fat in patients with normal or low body mass index (BMI) and COPD remain unknown. This study aimed to examine the association between acute exacerbations of COPD and the lean-to-fat (LTF) ratio in patients with a normal or low BMI. MATERIAL AND METHODS Patients with COPD (n=68) underwent assessment of body composition, in whom 43 cases had a normal BMI (18.5 to 25 kg/m(2)) and 14 cases were underweight (<18.5 kg/m(2)). Patients with COPD were treated according to current clinical guidelines and underwent regular follow-up for one year. Acute exacerbations of COPD were recorded. RESULTS BMI, the fat-free mass index (FFMI), skeletal muscle mass index (SMMI), and LTF ratio had no significant effect of the risk of acute exacerbations of COPD in the whole study cohort, but a low LTF ratio was significantly associated with reduced risk of acute exacerbations of COPD in the subgroup with a BMI<25 kg/m(2) (OR=4.528; P<0.05). The Fat Mass Index (FMI) had a protective effect in the whole cohort (OR=0.292; P=0.024) and in the subgroup with BMI <25 kg/m(2) (OR=0.253, P=0.049). The cumulative incidence of acute exacerbations of COPD was significantly increased in the patients with a high LTF ratio in the whole cohort (P=0.047) and in the subgroup with BMI <25 kg/m(2) (P=0.014). CONCLUSIONS In patients with BMI <25 kg/m(2), the LTF ratio was positively correlated with the risk of occurrence of acute exacerbations of COPD.

https://www.medscimonit.com/abstract/index/idArt/914783

Yeh, J. J., S. H. Syue, et al. (2019). **"Effects of statins on anxiety and depression in patients with asthma-chronic obstructive pulmonary disease overlap syndrome."** J Affect Disord **253**: 277-284.

BACKGROUND: The effects of statins on anxiety and depression in patients with asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) have not been reported. This population-based study investigated these effects. METHODS: Taiwan's National Health Insurance Research Database between 2000 and 2010. We enrolled two ACOS cohorts, one of statin users (n=1252) and one of nonstatin users matched by age, sex, and index date (n=7887). The cumulative incidence of anxiety and depression was analyzed using time-dependent Cox proportional regression analysis. RESULTS: After adjustment for multiple confounding factors, including age, sex, comorbidities, and medications-statins, inhaled corticosteroids (ICSs), and oral steroids (OSs)-the ACOS cohort with statin use had significantly lower risks of anxiety and depression (anxiety: adjusted hazard ratio [aHR] = 0.34, 95% confidence interval [CI] = 0.28-0.42; depression: aHR = 0.36, 95% CI = 0.25-0.53). The aHRs (95% CIs) for statin use with ICSs or OSs were 0.32 (0.13-0.78) and 0.37 (0.24-0.57), respectively. CONCLUSION: The ACOS cohort with statin use had lower risks of anxiety and depression, regardless of age, sex, commodities, or ICSs and OSs. The incidences of anxiety and depression were relatively low among users of statins with ICSs or OSs in the ACOS cohort.

https://www.sciencedirect.com/science/article/abs/pii/S0165032719304495?via%3Dihub

Zakowska, I., K. Kosiek, et al. (2019). **"Community determinants of COPD exacerbations in elderly patients in Poland: protocol for a retrospective Big Data observational cohort study."** BMJ Open **9**(6): e030524.

INTRODUCTION: Analyses of large sets of electronic health-related data (Big Data), including local community indicators, may improve knowledge of the outcomes of chronic diseases among patients and healthcare

systems. Our study will estimate the prevalence of chronic obstructive pulmonary disease (COPD) and its exacerbations in elderly patients in the Lodz region, Poland; it will also evaluate local community factors potentially associated with disease exacerbations and rank local communities according to health and local community indicators. METHODS: and analysis : Local community factors, including medical/health, socioeconomic and environmental values potentially associated with COPD exacerbations will be identified. A retrospective analysis of a cohort of about half a million people 65 years old and older, living in local communities of the Lodz region in 2016 will be performed. Relevant data will be extracted from databases, including those of the National Health Fund, Tax Office and National Statistics Centre. This cross-sectional study will include data for a 1 year period, from 1 January until 31 December 2016. The data will first be checked for quality, cleaned and analysed using data mining techniques, and then multilevel logistic regression will be used to discover the community determinants of COPD exacerbations. ETHICS AND DISSEMINATION: The study protocol has been approved by the Bioethical Committee of Medical University of Lodz (RNN/248/18/KE, 10 July 2018). Our findings will be published in peer-reviewed journals and reports.

https://bmjopen.bmj.com/content/bmjopen/9/6/e030524.full.pdf

Zhang, J., W. Yao, et al. (2019). **"Comparative analysis of medical expenditure with nebulized budesonide versus systemic corticosteroids in hospitalized patients with acute exacerbations of chronic obstructive pulmonary disease in China."** Int J Chron Obstruct Pulmon Dis **14**: 1195-1207.

Purpose: Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and is a leading cause of disability in China. Acute exacerbations of COPD (AECOPD) are a leading cause of hospitalizations, and account for a substantial proportion of medical expenditure. Corticosteroids are commonly used to manage AECOPD in hospitalized patients, so our objective was to analyze the total medical expenditure associated with nebulized budesonide (nBUD) vs. systemic corticosteroids (SCS) in this population. Patients and methods: A post-hoc analysis was carried out in 1,577 and 973 patients diagnosed with COPD who had received "any" nBUD or SCS regimen for AECOPD during hospitalization, respectively. Regimens included monotherapy, sequential therapy, and sequential-combination therapy. Comparative total medical expenditure was analyzed using a generalized linear model controlling for age, gender, comorbidities, smoking history, and respiratory failure or pneumonia on admission. Results: The total medical expenditure per capita with any nBUD or SCS regimen was CN yen11,814 (US$1,922) and CN yen12,153 (US$1,977), respectively. Any nBUD regimen was associated with a significant saving of 5.1% in expenditure compared with any SCS regimen (P=0.0341). Comorbidities, Type II respiratory failure, or pneumonia were patient factors associated with higher total medical expenditure (P<0.0001). In a subgroup analysis of the patients who received monotherapy, total medical expenditure was CN yen10,900 (US$1,773) for nBUD and CN yen11,581 (US$1,884) for SCS; nBUD was associated with a significant saving of 8.7% in expenditure compared with SCS (P=0.0013). Similarly, in patients with respiratory failure, treatment with any nBUD regimen was associated with a 10.6% saving in expenditure over any SCS regimen (P=0.0239); however, the same comparison was not significant in patients without respiratory failure (3.4%; P=0.2299). Conclusion: AECOPD is a leading cause of hospitalization in China, which places substantial burden on the healthcare system. This post-hoc analysis suggests that nBUD regimens are associated with lower medical expenditure than SCS regimens in hospitalized patients with AECOPD, and may reduce the financial burden of COPD. However, prospective studies evaluating the effectiveness of nBUD therapies are warranted.

https://www.dovepress.com/getfile.php?fileID=50209

Zilberman-Itskovich, S., E. Rahamim, et al. (2019). **"Long QT and death in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease is not related to electrolyte disorders."** Int J Chron Obstruct Pulmon Dis **14**: 1053-1061.

Objectives: COPD is the fourth-leading cause of mortality worldwide. Prolonged QTc has been found to be a long-term negative prognostic factor in ambulatory COPD patients. The aim of this study was to

evaluate the extent of prolonged-QTc syndrome in COPD patients upon admission to an internal medicine department, its relationship to hypomagnesemia, hypokalemia, and hypocalcemia, and the effect of COPD treatment on mortality during hospital stay. Methods: This prospective cohort study evaluated COPD patients hospitalized in an internal medicine department. The study evaluated QTc, electrolyte levels, and known risk factors during hospitalization of COPD patients. Results: A total of 67 patients were recruited. The median QTc interval was 0.441 seconds and 0.434 seconds on days 0 and 3, respectively. Prolonged QTc was noted in 35.8% of patients on admission and 37.3% on day 3 of hospitalization. The median QTc in the prolonged-QTc group on admission was 0.471 seconds and in the normal-QTc group 0.430 seconds. There was no significant difference in age, sex, electrolyte levels, renal function tests, or blood gases on admission between the two groups. Mortality during the hospital stay was significantly higher in the prolonged-QTc group (3 deaths, 12%) than in the normal QTc group (no deaths) (P=0.04). A subanalysis was performed, removing known causes for prolonged QTc. We found no differences in age, electrolytes, or renal functions. There was a small but significant difference in bicarbonate levels. Conclusion: Our findings demonstrated that there was no correlation between QTc prolongation in hospitalized COPD patients and electrolyte levels, comorbidities, or relevant medications. A higher rate of mortality was noted in patients with prolonged QTc in comparison to normal QTc. As such, it is suggested that prolonged QTc could serve as a negative prognostic factor for mortality during hospitalization in COPD patients.