

**COPD/Emphysema PubMed search results covering the period**  
**23/10/2018 to 18/01/19**

**Cohort and case-control studies**

**Search strategy:** ("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR "emphysema"[MeSH Major Topic]) AND ("Cohort Studies"[MeSH Terms] OR "Case-Control Studies"[MeSH Terms]) AND English[lang] AND ("2018/10/23"[CDAT] : "3000"[CDAT])

AboEl-Magd, G. H. and M. M. Mabrouk (2018). "**Soluble urokinase-type plasminogen activator receptor as a measure of treatment response in acute exacerbation of COPD.**" *J Bras Pneumol* **44**(1): 36-41.

**OBJECTIVE:** To evaluate the value of soluble urokinase-type plasminogen activator receptor (suPAR) in the diagnosis of acute exacerbation of COPD (AECOPD) and in monitoring treatment response, analyzing the relationship between suPAR and fibrinogen in AECOPD. AECOPD leads to increased airway inflammation, contributing to an exaggerated release of inflammatory mediators. **METHODS:** We recruited 45 patients with AECOPD and 20 healthy control subjects. Medical histories were taken, and all subjects underwent clinical examination, chest X-ray, pulmonary function tests, and blood gas analysis. On day 1 (treatment initiation for the AECOPD patients) and day 14 (end of treatment), blood samples were collected for the determination of serum suPAR and plasma fibrinogen. **RESULTS:** Serum levels of suPAR were significantly higher in the AECOPD group than in the control group. In the AECOPD patients, there was a significant post-treatment decrease in the mean serum suPAR level. The sensitivity, specificity, and accuracy of suPAR were 95.6%, 80.0%, and 93.0%, respectively. The Global Initiative for Chronic Obstructive Lung Disease stage (i.e., COPD severity) correlated positively and significantly with serum levels of suPAR and plasma levels of fibrinogen. **CONCLUSIONS:** Monitoring the serum suPAR level can be helpful in the evaluation of the COPD treatment response and might be a valuable biomarker for determining the prognosis of AECOPD. Because serum suPAR correlated with plasma fibrinogen, both markers could be predictive of AECOPD.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6104538/pdf/1806-3713-jbpneu-44-01-00036.pdf>

Akita, T., T. Shirai, et al. (2017). "**Long-term change in reactance by forced oscillation technique correlates with FEV1 decline in moderate COPD patients.**" *Eur Respir J* **49**(4)

<https://erj.ersjournals.com/content/erj/49/4/1601534.full.pdf>

Aliagas, E., M. Munoz-Esquerre, et al. (2018). "**Is the purinergic pathway involved in the pathology of COPD? Decreased lung CD39 expression at initial stages of COPD.**" *Respir Res* **19**(1): 103.

**BACKGROUND:** Extracellular adenosine triphosphate (ATP) is up-regulated in the airways of patients with chronic obstructive pulmonary disease (COPD), resulting in increased inflammation, bronchoconstriction, and cough. Although extracellular ATP levels are tightly controlled by nucleoside triphosphate diphosphohydrolase-1 (NTPDase1; also known as CD39) in the lungs, the role of CD39 in the pathology of COPD is unknown. We hypothesized that alterations in the expression and activity of CD39 could be part of the mechanisms for initiating and perpetuating the disease. **METHODS:** We analyzed CD39 gene and protein expression as well as ATPase enzyme activity in lung tissue samples of patients with COPD (n = 17), non-obstructed smokers (NOS) (n = 16), and never smokers (NS) (n = 13). Morphometry studies were performed to analyze pulmonary vascular remodeling. **RESULTS:** There was significantly decreased CD39 gene expression in the lungs of the COPD group (1.17 [0.85-1.81]) compared with the NOS group (1.88 [1.35-4.41]) and NS group (3.32 [1.23-5.39]) (p = 0.037). This attenuation correlated with higher systemic inflammation and intimal thickening of muscular pulmonary arteries in the COPD group. Lung CD39 protein levels were also lower in the COPD group (0.34 [0.22-0.92]) compared with the NOS group (0.67 [0.32-1.06]) and NS group (0.95 [0.4-1.1]) (p = 0.133). Immunohistochemistry showed that CD39 was downregulated in lung parenchyma, epithelial bronchial cells, and the endothelial cells of pulmonary

muscular arteries in the COPD group. ATPase activity in human pulmonary structures was reduced in the lungs of patients with COPD. CONCLUSION: An attenuation of CD39 expression and activity is presented in lung tissue of stable COPD patients, which could lead to pulmonary ATP accumulation, favoring the development of pulmonary inflammation and emphysema. This may be a mechanism underlying the development of COPD.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5972409/pdf/12931\\_2018\\_Article\\_793.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5972409/pdf/12931_2018_Article_793.pdf)

Alyami, M. M., S. C. Jenkins, et al. (2018). "**Walking-based activity and sedentary behavior in Saudi males with chronic obstructive pulmonary disease.**" *Saudi Med J* **39**(5): 506-513.

OBJECTIVES: To compare walking-based activity and sedentary behavior between males with chronic obstructive pulmonary disease (COPD) and healthy controls and to examine the association between dyspnea with time spent in walking-based activity and sedentary behavior in males with COPD. METHODS: This cross-sectional study of 30 males with COPD (age 62.0+/-5.0 years; forced expiratory volume in one second [FEV1] 46+/-15% predicted) and 29 healthy controls (age 63.0+/-4.3 years; FEV1 91+/-5% predicted) was conducted at the outpatient pulmonary clinics at King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia between February 2013 and March 2014. Walking-based activity and sedentary behavior were evaluated using an activity monitor. RESULTS: Participants with COPD spent less time engaged in walking-based activity (22+/-8% versus 37+/-7% of waking hours; p less than 0.001) and more time engaged in sedentary behavior (78+/-8% versus 63+/-6% of waking hours; p less than 0.001) than healthy controls. In males with COPD, moderate to strong associations were found between the scores of the quality and emotional response components of the Dyspnea-12 (D-12) questionnaire and time spent engaged in walking-based activity and sedentary behavior (r: >|=0.46, all p less than 0.01). CONCLUSION: Males with COPD were less active and more sedentary than healthy controls. The D-12 components were associated with walking-based activity and sedentary behavior in males with COPD.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6118185/pdf/SaudiMedJ-39-506.pdf>

Amini, M., J. M. Vonk, et al. (2018). "**Blood Eosinophil Count and Metabolic, Cardiac and Pulmonary Outcomes: A Mendelian Randomization Study.**" *Twin Res Hum Genet* **21**(2): 89-100.

Blood eosinophil count is associated with a variety of common complex outcomes in epidemiological observation. The aim of this study was to explore the causal association between determined blood eosinophil count and 20 common complex outcomes (10 metabolic, 6 cardiac, and 4 pulmonary). Through Mendelian randomization, we investigated genetic evidence for the genetically determined eosinophil in association with each outcomes using individual-level LifeLines cohort data (n = 13,301), where a weighted eosinophil genetic risk score comprising five eosinophil associated variants was created. We further examined the associations of the genetically determined eosinophil with those outcomes using summary statistics obtained from genome-wide association study consortia (6 consortia and 14 outcomes). Blood eosinophil count, by a 1-SD genetically increased, was not statistically associated with common complex outcomes in the LifeLines. Using the summary statistics, we showed that a higher genetically determined eosinophil count had a significant association with lower odds of obesity (odds ratio (OR) 0.81, 95% confidence interval (CI) [0.74, 0.89]) but not with the other traits and diseases. To conclude, an elevated eosinophil count is unlikely to be causally associated to higher risk of metabolic, cardiac, and pulmonary outcomes. Further studies with a stronger genetic risk score for eosinophil count may support these results.

<https://www.cambridge.org/core/services/aop-cambridge-core/content/view/7E82A13BC2D1D9E9A9AC28334B1F65DD/S1832427418000063a.pdf/div-class-title-blood-eosinophil-count-and-metabolic-cardiac-and-pulmonary-outcomes-a-mendelian-randomization-div.pdf>

Andujar, P., D. Courbon, et al. (2018). **"Smoking, telomere length and lung function decline: a longitudinal population-based study."** *Thorax* **73**(3): 283-285.

Telomere shortening is associated with COPD and impaired lung function in cross-sectional studies, but there is no longitudinal study. We used data from 448 participants recruited as part of the French follow-up of the European Community Respiratory Health Survey. We found no relationship between telomere length at baseline and FEV1 decline after 11 years of follow-up. However, heavy smoking was associated with an accelerated FEV1 decline in individuals with short telomeres, but not in subjects with longer telomeres (p for interaction p=0.08). Our findings suggest that short telomere length in peripheral leucocytes might be a marker for increased susceptibility to the effect of smoking.

<https://thorax.bmj.com/content/73/3/283.long>

Aras, Y. G., Y. Aydemir, et al. (2018). **"Evaluation of central and peripheral neuropathy in patients with chronic obstructive pulmonary disease."** *Int J Chron Obstruct Pulmon Dis* **13**: 1857-1862.

Background: The aim of the study was to investigate the frequency and characteristics of peripheral nervous system (PNS) and central nervous system (CNS) involvement in COPD. Methods: The study included 41 COPD patients and 41 healthy volunteers. Electrophysiological studies were carried out: electromyography (EMG) and visual evoked potentials (VEPs). The median nerve, ulnar nerve, common peroneal nerve, and tibial nerve were evaluated for latency, amplitude, and conduction velocity. Results: The mean age of patients with COPD was 61.8 years and disease duration 10.3 years. There was no difference between patient and control groups in terms of age, BMI, smoking status, or biochemical parameters. Upon VEP examination, latencies were significantly prolonged and amplitudes shortened in the patient group compared to the control group. In EMG measurements, conduction velocity and amplitudes in all nerves were low in the patient group. Similarly, latencies in all nerves were higher in patients with COPD. Conclusion: Central and peripheral nervous system involvement could develop in patients with moderate-severe COPD, and these patients should be monitored for neuropathic changes in combination with neurological examination.

<https://www.dovepress.com/getfile.php?fileID=42512>

Asker, S., M. Asker, et al. (2018). **"Serum levels of trace minerals and heavy metals in severe COPD patients with and without pulmonary hypertension."** *Int J Chron Obstruct Pulmon Dis* **13**: 1803-1808.

Aim: The aim of the current study was to assess the serum levels of trace minerals/heavy metals in COPD patients with and without pulmonary hypertension (PH) and to investigate their correlations to demographic, clinical, and biochemical variables. Materials and methods: This cross-sectional study was performed in Van Yuzuncu Yil University Medical Faculty between April 2013 and July 2013. Cases were allocated into three groups: Group 1 consisted of severe COPD patients; Group 2 was made up of COPD patients with PH; and healthy controls constituted Group 3. Demographic, radiological, and biochemical variables, as well as the serum levels of trace minerals and heavy metals, were noted and compared in these three groups. Results: COPD patients were older and had higher rates of smoking habit, diabetes mellitus, and hypertension compared to the control group. Carotid intima-media thickness was increased bilaterally, and serum levels of Co, Cu, and Fe were higher in COPD patients. Left carotid intima-media thickness was increased, and serum levels of Cd, Co, and Fe were found to be higher in COPD cases with PH compared to COPD patients without PH. Conclusion: Our results show that serum levels of trace minerals and heavy metals may be altered in COPD and PH.

<https://www.dovepress.com/getfile.php?fileID=42412>

Aziz, F. and E. B. Lehman (2018). **"Preexisting Conditions Determine the Occurrence of Unplanned Readmissions after Procedures for Treatment of Peripheral Arterial Disease."** *Ann Vasc Surg* **50**: 60-72.

**BACKGROUND:** Readmissions after surgical procedures are increasingly considered a metric to indicate the quality of care received during the index hospitalization. Patients with peripheral arterial disease (PAD) requiring peripheral vascular interventions (PVI) or lower extremity bypasses (LEBs) often have several serious medical comorbidities. Risk factors associated with readmission after PVI and LEB have previously been identified. The purpose of this study is to compare the readmissions among patients receiving PVI and LEB procedures to identify risk factors associated with high risk of readmission. **METHODS:** The 2013 Procedure-targeted American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database and generalized 2013 general and vascular surgery ACS-NSQIP Program User Files were used for this study. Patient, diagnosis, and procedure characteristics of patients undergoing PVI and LEB were assessed. Odds ratios (ORs) with confidence intervals (CIs) for PVI versus LEB groups within the subgroups of these characteristics were then obtained where significant associations existed between the study groups. **RESULTS:** A total of 3,742 patients (males: 2,384 [63.7%] and females: 1,358 [36.3%]) underwent surgical procedures for lower extremity PAD during the year 2013. Among these patients, 1,096 (29.3%) were treated with endovascular interventions and 2,646 (70.7%) were treated with surgical bypasses. Patients were divided into 2 groups: PVI (n = 1,096) and LEB (n = 2,646) groups. Each group was further subdivided into 2 groups: readmission and no readmission. The incidence of readmission was as follows: PVI group (n = 147, 13.4%) and LEB (n = 425, 16.1%). The PVI and LEB groups showed a significant association with readmission within the following factors: dialysis dependency (PVI 32.6% vs. LEB 19.1%, OR: 2.06, CI: 1.13-3.75, P < 0.001), emergency operation (PVI 40.4% vs. LEB 18.7%, OR: 2.96, CI: 1.45-6.03, P < 0.001), chronic obstructive pulmonary disease (COPD; PVI 23.7% vs. LEB 14.6%, OR: 1.82, CI: 1.08-3.07, P = 0.001), cardiac arrest (PVI 45.5% vs. LEB 9.5%, OR: 7.92, CI: 1.21-51.9, P = 0.017), and body mass index > 30 (PVI 9.9% vs. LEB 18.4%, OR: 0.49, CI: 0.33-0.73, P = 0.009). **CONCLUSIONS:** Readmissions after lower extremity endovascular or surgical interventions can be used as a quality metric. Patients with dialysis dependency, COPD, in need of emergent operation, or having cardiac arrest are highly likely to be readmitted if treated with endovascular interventions. Similarly, patients with high body mass index are highly likely to be readmitted if treated with open surgical bypasses.

[https://www.annalsofvascularsurgery.com/article/S0890-5096\(18\)30149-3/fulltext](https://www.annalsofvascularsurgery.com/article/S0890-5096(18)30149-3/fulltext)

Backman, H., S. A. Jansson, et al. (2018). **"Chronic airway obstruction in a population-based adult asthma cohort: Prevalence, incidence and prognostic factors."** *Respir Med* **138**: 115-122.

**BACKGROUND:** Asthma and COPD may overlap (ACO) but information about incidence and risk factors are lacking. This study aimed to estimate prevalence, incidence and risk factors of chronic airway obstruction (CAO) in a population-based adult asthma cohort. **METHODS:** During 1986-2001 a large population-based asthma cohort was identified (n=2055, 19-72y). Subsamples have participated in clinical follow-ups during the subsequent years. The entire cohort was invited to a clinical follow-up including interview, spirometry, and blood sampling in 2012-2014 when n=983 subjects performed adequate spirometry. CAO was defined as post-bronchodilator FEV1/FVC < 0.7. **RESULTS:** At study entry, asthmatics with prevalent CAO (11.4%) reported more respiratory symptoms, asthma medication use, and ischemic heart disease than asthmatics without CAO (asthma only). Subjects who developed CAO during follow-up (17.6%; incidence rate of 16/1000/year) had a more rapid FEV1 decline and higher levels of neutrophils than asthma only. Smoking, older age and male sex were independently associated with increased risk for both prevalent and incident CAO, while obesity had a protective effect. **CONCLUSIONS:** In this prospective adult asthma cohort, the majority did not develop CAO. Smoking, older age and male sex were risk factors for prevalent and incident CAO, similar to risk factors described for COPD in the general population.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30108-2/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30108-2/fulltext)

Bayrak, M. and Y. Altintas (2018). **"Comparing laparoscopic cholecystectomy in patients with chronic obstructive pulmonary disease under spinal anesthesia and general anesthesia."** *BMC Surg* **18**(1): 65.

**BACKGROUND:** Epidemiological data demonstrate that the worldwide prevalence of chronic obstructive pulmonary disease is increasing. These patients have an increased risk of mortality and morbidity and have constant limitations in airflow. Comparing laparoscopic cholecystectomy (LC) in patients with chronic obstructive pulmonary disease (COPD) under spinal anesthesia (SA) and general anesthesia (GA). **METHODS:** We prospectively evaluated COPD patients who underwent laparoscopic cholecystectomy under general anesthesia (Group 1, n = 30) or spinal anesthesia (Group 2, n = 30) in our clinic between January 2016 and January 2018. Patients with COPD were further divided into groups according to their preoperative stages (Stage 1-4). Intraoperative vital findings, postoperative pain, complications, and length of hospitalization were compared between the general (GA) and spinal anesthesia (SA) groups. **RESULTS:** The mean age of the patients in the GA group was 61.0 +/- 6.7 years and was 61.0 +/- 7.7 years in the SA group. In the GA and SA groups, the mean ASA score was 2.8 +/- 0.6 and 2.9 +/- 0.6, respectively, the mean operation duration was 31.7 +/- 5.1 and 30.6 +/- 5.1 min, respectively, and the length of hospitalization was 3.2 +/- 1.7 and 1.5 +/- 0.5 days, respectively. The partial carbon dioxide rates (PaCO<sub>2</sub>) at the postoperative 5th and 20th minutes were lower in the SA group than in the GA group. Further, the requirement for postoperative analgesia was lower in the SA group, and the length of hospitalization was significantly shorter in the SA group. There was no significant difference between the two groups in terms of operation duration. **CONCLUSION:** Laparoscopic cholecystectomy is a rather safe procedure for COPD patients under general and spinal anesthesia. However, spinal anesthesia is preferred over general anesthesia as it has better postoperative analgesia and causes no impairment of pulmonary functions.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6102808/pdf/12893\\_2018\\_Article\\_396.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6102808/pdf/12893_2018_Article_396.pdf)

Bonnevie, T., F. E. Gravier, et al. (2018). **"Six-Minute Stepper Test to Set Pulmonary Rehabilitation Intensity in Patients with COPD."** *Copd* **15**(1): 91-92.

<https://www.tandfonline.com/doi/full/10.1080/15412555.2017.1419466>

Boutou, A. K., R. Franks, et al. (2017). **"Exercise-induced changes in QT interval are smaller in COPD patients and have no impact on mortality."** *Eur Respir J* **49**(3)

<https://erj.ersjournals.com/content/erj/49/3/1602394.full.pdf>

Chalmers, J. D., C. Poole, et al. (2018). **"Assessing the healthcare resource use associated with inappropriate prescribing of inhaled corticosteroids for people with chronic obstructive pulmonary disease (COPD) in GOLD groups A or B: an observational study using the Clinical Practice Research Datalink (CPRD)."** *Respir Res* **19**(1): 63.

**BACKGROUND:** Recent recommendations from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) position inhaled corticosteroids (ICS) for use in chronic obstructive pulmonary disease (COPD) patients experiencing exacerbations (>= 2 or >= 1 requiring hospitalisation); i.e. GOLD groups C and D. However, it is known that ICS is frequently prescribed for patients with less severe COPD. Potential drivers of inappropriate ICS use may be historical clinical guidance or a belief among physicians that intervening early with ICS would improve outcomes and reduce resource use. The objective of this study was to compare healthcare resource use in the UK for COPD patients in GOLD groups A and B (0 or 1 exacerbation not resulting in hospitalisation) who have either been prescribed an ICS-containing

regimen or a non-ICS-containing regimen. METHODS: Linked data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) database were used. For the study period (1 July 2005 to 30 June 2015) a total 4009 patients met the inclusion criteria; 1745 receiving ICS-containing therapy and 2264 receiving non-ICS therapy. Treatment groups were propensity score-matched to account for potential confounders in the decision to prescribe ICS, leaving 1739 patients in both treatment arms. Resource use was assessed in terms of frequency of healthcare practitioner (HCP) interactions and rescue therapy prescribing. Treatment acquisition costs were not assessed. RESULTS: Results showed no benefit associated with the addition of ICS, with numerically higher all-cause HCP interactions (72,802 versus 69,136; adjusted relative rate: 1.07 [p = 0.061]) and rescue therapy prescriptions (24,063 versus 21,163; adjusted relative rate: 1.05 [p = 0.212]) for the ICS-containing group compared to the non-ICS group. Rate ratios favoured the non-ICS group for eight of nine outcomes assessed. Outcomes were similar for subgroup analyses surrounding potential influential parameters, including patients with poorer lung function (FEV1 < 50% predicted), one prior exacerbation or elevated blood eosinophils. CONCLUSIONS: These data suggest that ICS use in GOLD A and B COPD patients is not associated with a benefit in terms of healthcare resource use compared to non-ICS bronchodilator-based therapy; using ICS according to GOLD recommendations may offer an opportunity for improving patient care and reducing resource use.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5896104/pdf/12931\\_2018\\_Article\\_767.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5896104/pdf/12931_2018_Article_767.pdf)

Cho, Y. H., S. M. Lee, et al. (2018). **"Quantitative assessment of pulmonary vascular alterations in chronic obstructive lung disease: Associations with pulmonary function test and survival in the KOLD cohort."** *Eur J Radiol* **108**: 276-282.

PURPOSE: Despite the high prevalence of pulmonary vascular alterations and their substantial impact on chronic obstructive pulmonary disease (COPD), tools for the direct in vivo assessment of pulmonary vascular alterations remain limited. Thus, the purpose of this study was to automatically extract pulmonary vessels from volumetric chest CT and evaluate the associations between the derived quantitative pulmonary vessel features and clinical parameters, including survival, in COPD patients. METHODS: This study included 344 adult COPD patients. Pulmonary vessels were automatically extracted from volumetric chest CT data. Quantitative pulmonary vessel features were obtained from various lung surface areas (LSAs), which are theoretical surface areas drawn at different depths from the pleural borders. The total number of vessels (Ntotal) and number of vessels with vessel area (VA) less than 5 mm<sup>2</sup> (N<5mm) were counted as both robust values and as values per 10 cm<sup>2</sup> of LSA (Ntotal/LSA; N<5mm/LSA). The average VA (VAmean) and percentage of measured VA in the corresponding LSA (%VA) were measured. Associations between quantitative pulmonary vessel features and clinical parameters, including survival and the pulmonary function test (PFT), were evaluated. RESULTS: The pulmonary vessels were automatically extracted with 100% technical success. Cox regression analysis showed Ntotal/LSA, N<5mm/LSA, VAmean, and %VA to be significant predictors of survival (hazard ratio (HR), 0.80, 0.75, 0.70, 0.49, respectively). Patients classified into high-risk groups by %VA18mm (cut-off = 3.258), chosen because it demonstrated the strongest statistical influence on survival in a univariate Cox analysis, were associated with worse overall survival before (HR, 4.83; p < 0.001) and after adjustment for patient age and BMI (HR, 2.18; p = 0.014). Of the quantitative pulmonary vessel features, Ntotal/LSA, N<5mm/LSA, and %VA were correlated with FEV1, FEV1/FVC, and DLCO in all LSAs. The strongest correlation with PFTs was noted at LSA9mm for both Ntotal (FEV1, r = 0.33; FEV1/FVC, r = 0.51) and N<5mm (FEV1, r = 0.35; FEV1/FVC, r = 0.52). For %VA, the association was most evident at LSA18mm (FEV1, r = 0.27; FEV1/FVC, r = 0.47). Significant moderate to strong correlations were consistently observed between the extent of emphysema and quantitative pulmonary vessel features (r = 0.44-0.66; all p < 0.001). CONCLUSIONS: The automated extraction of pulmonary vessels and their quantitative assessment are technically feasible. Various quantitative pulmonary vessel features demonstrated significant relationships with survival and PFT in COPD patients. Of the various quantitative features, the percentage of total VA measured at 18 mm depth from the pleural surface (%VA18mm) and the number of small vessels counted per 10 cm<sup>2</sup> of LSA at 9 mm depth from the pleural surface (N<5mm/LSA9mm) had the strongest predictability for the clinical parameters.

[https://www.ejradiology.com/article/S0720-048X\(18\)30318-8/fulltext](https://www.ejradiology.com/article/S0720-048X(18)30318-8/fulltext)

Comba, A., F. Demirbas, et al. (2018). "**Retrospective analysis of children with alpha-1 antitrypsin deficiency.**" Eur J Gastroenterol Hepatol **30**(7): 774-778.

BACKGROUND: alpha-1 Antitrypsin (AAT) deficiency is the most frequently occurring genetic liver disorder. The association among classical alpha-1 antitrypsin deficiency (AATD), chronic liver disease, and cirrhosis is common in adult patients but rare in children. AIM: To assess the clinical characteristics of children with AATD and to compare symptoms between homozygous and heterozygous children. MATERIALS AND METHODS: The study included 20 children who were found to have mutant Pi alleles. AAT phenotyping was conducted on patients with a low serum AAT level. The exclusion criteria included infectious, anatomic, and metabolic conditions. Symptoms on presentation, physical examination findings, laboratory values, liver biopsy results, and follow-up periods were recorded for each patient. RESULTS: The patients included six (30%) girls and 14 (70%) boys, with a mean age of 6.3+/-5.1 (1-16) years. The PiZZ phenotype was present in eight (40%) and PiMZ in 12 (60%) patients. The most frequent symptom was elevated liver function test results. Three patients were referred with neonatal cholestasis and one with compensated cirrhosis. Eight patients underwent liver biopsy; all patients except one had periodic acid-Schiff-positive diastase-resistant globules in the hepatocytes. The mean follow-up period was 34+/-33 (12-101) months. At the end of follow-up, all patients with PiZZ were found to have chronic hepatitis, and one with cirrhosis. On the contrary, two patients with PiMZ were found to have chronic hepatitis. CONCLUSION: Children with classical AATD commonly have chronic liver disease. In heterozygous (PiMZ) children with AATD, enzyme levels can normalize with occasional fluctuations, sometimes causing delayed diagnosis.

Cordoba-Lanus, E., C. Cabrera-Lopez, et al. (2018). "**Shorter telomeres in non-smoking patients with airflow limitation.**" Respir Med **138**: 123-128.

BACKGROUND: Cross-sectional and longitudinal studies describe shorter telomeres in patients with chronic obstructive pulmonary disease (COPD) compared to matched non-COPD controls, but the relationship is confounded by tobacco consumption. We hypothesized that telomere shortening would be similar between non-smoking and smoking individuals with airflow limitation and shorter than non-obstructed controls. METHODS: Telomere length (T/S) was measured by qPCR in blood leukocytes of 80 non-smoking patients and 80 age-matched smokers with airflow limitation. Forty non-smoker healthy individuals served as controls. Anthropometrics, lung function, previous and current comorbidities were recorded in all individuals. Relationship between telomere length and clinical and functional variables were explored in the three groups. RESULTS: Telomeres length was similar in non-smokers and smoker individuals with airflow limitation (T/S=0.61+/-0.19 vs. 0.60+/-0.23, p>0.05) respectively. Telomere length was significantly shorter in both groups compared to healthy controls (T/S 0.79+/-0.40; p=0.01) independent from age and sex. No significant association was found between the telomere length and clinical or lung function parameters. CONCLUSIONS: Telomere shortening is associated with airflow limitation independent of smoking status. Whether premature ageing or biologically determined shorter telomeres are responsible for this finding remain to be determined.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30110-0/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30110-0/fulltext)

de Miguel-Diez, J., A. Lopez-de-Andres, et al. (2018). "**Postoperative pneumonia among patients with and without COPD in Spain from 2001 to 2015.**" Eur J Intern Med **53**: 66-72.

BACKGROUND: To describe and compare incidence, characteristics and outcomes of postoperative pneumonia among patients with or without COPD. METHODS: We included hospitalized patients aged >/=40years whose medical diagnosis included pneumonia and ventilator-associated pneumonia in the secondary's

diagnosis field and who were discharged from Spanish hospitals from 2001 to 2015. Irrespectively of the position at the procedures coding list, we retrieved data about the type of surgical procedures using the enhanced ICD-9-CM codes. We grouped admissions by COPD status. The data were collected from the National Hospital Discharge Database. RESULTS: We included 117,665 hospitalizations of patients that developed postoperative pneumonia (18.06% of them had COPD). The incidence of postoperative pneumonia was significantly higher in COPD patients than in those without COPD (IRR 1.93, 95%CI 1.68-2.24). In-hospital mortality (IHM) was significantly lower in the first group of patients (29.79% vs 31.43%,  $p < 0.05$ ). Factors independently associated with IHM, among COPD and non-COPD patients, were older age, more comorbidities, mechanical ventilation, pleural drainage tube, red blood cell transfusion, dialysis and emergency room admission. Time trend analysis showed a significant decrease in IHM from 2001 to 2015. COPD was associated with lower IHM (OR 0.91, 95%CI 0.88-0.95). CONCLUSIONS: The incidence of postoperative pneumonia was higher in COPD patients than in those without this disease. However, IHM was lower among COPD patients. IHM decreased over time, regardless of the existence or not of COPD.

[https://www.ejinme.com/article/S0953-6205\(18\)30061-X/fulltext](https://www.ejinme.com/article/S0953-6205(18)30061-X/fulltext)

Demir, N., O. Ercen Diken, et al. (2017). "**Alpha-1 Antitrypsin Levels and Polymorphisms in Interstitial Lung Diseases.**" *Turk J Med Sci* **47**(2): 476-482.

BACKGROUND/AIM: Alpha-1 antitrypsin deficiency may be a potential predisposing factor for interstitial lung fibrosis. We investigated alpha-1 antitrypsin levels and its polymorphisms in patients with interstitial lung disease. MATERIALS AND METHODS: A total of 103 interstitial lung disease patients were compared. RESULTS: The mean alpha-1 antitrypsin level in idiopathic interstitial pneumonia patients was 1.67 +/- 0.33 g/L, and it was 1.54 +/- 0.37 g/L in patients with nonidiopathic interstitial pneumonia ( $P = 0.13$ ). Low alpha-1 antitrypsin levels were more frequently observed in nonidiopathic interstitial pneumonia patients compared with idiopathic interstitial pneumonia, but the difference was not statistically significant (8.9% vs. 0%, respectively,  $P = 0.4$ ). In 100 patients, the normal PiMM genotype was detected, while abnormal ones (PiMZ,  $n = 2$ , 1.9%; PiMS,  $n = 1$ , 0.97%) were determined in three cases. When the frequency of alpha-1 antitrypsin polymorphism in interstitial lung disease patients was compared with the data of the healthy population, no significant difference was detected for the PiMZ and PiMS variants ( $P = 0.15$  and  $P = 0.44$ , respectively). CONCLUSION: Lower levels of serum alpha-1 antitrypsin were more frequent in nonidiopathic interstitial pneumonia patients than idiopathic interstitial pneumonia without an increase in genetic polymorphism. The difference was not statistically significant.

de-Torres, J. P., P. Sanchez-Salcedo, et al. (2017). "**Telomere length, COPD and emphysema as risk factors for lung cancer.**" *Eur Respir J* **49**(1)

<https://erj.ersjournals.com/content/erj/49/1/1601521.full.pdf>

Di Stefano, A., T. Coccini, et al. (2018). "**Blood MCP-1 levels are increased in chronic obstructive pulmonary disease patients with prevalent emphysema.**" *Int J Chron Obstruct Pulmon Dis* **13**: 1691-1700.

Background and aims: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by different phenotypes with either bronchial airways alterations or emphysema prevailing. As blood biomarkers could be clinically useful for COPD stratification, we aimed at investigating the levels of blood biomarkers in COPD patients differentiated by phenotype: prevalent chronic airway disease versus emphysema. Methods: In 23 COPD patients with prevalent airway disease (COPD-B), 22 COPD patients with prevalent emphysema (COPD-E), 9 control smokers (CSs), and 18 control nonsmokers (CNSs), we

analyzed the expression levels of interleukin (IL)-1alpha, IL-1beta, IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, epidermal growth factor (EGF), monocyte chemotactic protein (MCP)-1, and vascular endothelial growth factor by enzyme-linked immunosorbent assay in plasma/serum; glutathione peroxidase and superoxide dismutase (SOD)-1 by immunochemical kits in plasma; and free F2-isoprostanes (F2-IsoPs) by gas chromatography in plasma. Results: F2-IsoPs level was increased in COPD-B and COPD-E compared with CSs and CNSs; in addition, CS showed higher levels than CNSs; SOD1 level was lower in COPD-B and COPD-E than that in CNSs. Interestingly, MCP-1 level was higher only in COPD-E versus CSs and CNSs; EGF and IL-8 levels were higher in COPD-B and COPD-E versus CNSs; IL-6 level was increased in all three smoking groups (COPD-B, COPD-E, and CSs) versus CNS; IFN-gamma and IL-1alpha levels were higher in CSs than in CNSs; and IL-1alpha level was also higher in CSs versus COPD-B and COPD-E. In all subjects, F2-IsoPs level correlated positively and significantly with MCP-1, IL-2, IL-1beta, IFN-gamma, and TNF-alpha and negatively with SOD1. When correlations were restricted to COPD-E and COPD-B groups, F2-IsoPs maintained the positive associations with IFN-gamma, TNF-alpha, and IL-2. Conclusion: We did not find any specific blood biomarkers that could differentiate COPD patients with prevalent airway disease from those with prevalent emphysema. The MCP-1 increase in COPD-E, associated with the imbalance of oxidant/antioxidant markers, may play a role in inducing emphysema.

<https://www.dovepress.com/getfile.php?fileID=42264>

Diaz, A. A., C. H. Martinez, et al. (2018). "**Pectoralis muscle area and mortality in smokers without airflow obstruction.**" *Respir Res* **19**(1): 62.

BACKGROUND: Low muscle mass is associated with increased mortality in the general population but its prognostic value in at-risk smokers, those without expiratory airflow obstruction, is unknown. We aimed to test the hypothesis that reduced muscle mass is associated with increased mortality in at-risk smokers. METHODS: Measures of both pectoralis and paravertebral erector spinae muscle cross-sectional area (PMA and PVMA, respectively) as well as emphysema on chest computed tomography (CT) scans were performed in 3705 current and former at-risk smokers ( $\geq 10$  pack-years) aged 45-80 years enrolled into the COPD Gene Study between 2008 and 2013. Vital status was ascertained through death certificate. The association between low muscle mass and mortality was assessed using Cox regression analysis. RESULTS: During a median of 6.5 years of follow-up, 212 (5.7%) at-risk smokers died. At-risk smokers in the lowest (vs. highest) sex-specific quartile of PMA but not PVMA had 84% higher risk of death in adjusted models for demographics, smoking, dyspnea, comorbidities, exercise capacity, lung function, emphysema on CT, and coronary artery calcium content (hazard ratio [HR] 1.85 95% Confidence interval [1.14-3.00]  $P = 0.01$ ). Results were consistent when the PMA index (PMA/height<sup>2</sup>) was used instead of quartiles. The association between PMA and death was modified by smoking status ( $P = 0.04$ ). Current smokers had a significantly increased risk of death (lowest vs. highest PMA quartile, HR 2.25 [1.25-4.03]  $P = 0.007$ ) while former smokers did not. CONCLUSIONS: Low muscle mass as measured on chest CT scans is associated with increased mortality in current smokers without airflow obstruction. TRIAL REGISTRATION: NCT00608764.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5894181/pdf/12931\\_2018\\_Article\\_771.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5894181/pdf/12931_2018_Article_771.pdf)

Epstein, D., R. Nasser, et al. (2018). "**Increased red cell distribution width: A novel predictor of adverse outcome in patients hospitalized due to acute exacerbation of chronic obstructive pulmonary disease.**" *Respir Med* **136**: 1-7.

BACKGROUND: Acute exacerbation of COPD (AECOPD) is one of the leading causes for hospitalization and readmission in developed countries. No laboratory indices were consistently found to be associated with readmission risk. Recent evidence attests that red blood cell distribution width (RDW), conveys important information for short and long term prognosis in a variety of medical conditions. Prognostic usefulness of RDW in patients with AECOPD has not been investigated. OBJECTIVE: To evaluate the usefulness of RDW in predicting early adverse outcomes in patients hospitalized due to AECOPD.

METHODS: Patients hospitalized for AECOPD between 2011 and 2013 were revised. Clinical and laboratory parameters were noted. Participants were followed to determine the incidence of readmission due to AECOPD, readmission from any cause and composite end point of readmission or death during 60 days after discharge. RESULTS: 539 patients were included in the study. The 60-day overall readmission rate was 26.35%, of that, 41.55% were due to AECOPD. The Presence of heart failure, pH below 7.35 at discharge and abnormal RDW were associated with the composite endpoint. The negative predictive value of normal RDW was 80.12%. CONCLUSION: Increased RDW is an independent negative prognostic factor associated with adverse outcomes after hospitalization due to AECOPD.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30019-2/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30019-2/fulltext)

Felisberto, R. M., C. F. de Barros, et al. (2018). **"Is the 6-minute pegboard and ring test valid to evaluate upper limb function in hospitalized patients with acute exacerbation of COPD?"** *Int J Chron Obstruct Pulmon Dis* **13**: 1663-1673.

Background: The 6-minute pegboard and ring test (6-PBRT) is a useful test for assessing the functional capacity of upper limbs in patients with stable COPD. Although 6-PBRT has been validated in stable patients, the possibility of a high floor effect could compromise the validity of the test in the hospital setting. The aim of this study was to verify the convergent validity of 6-PBRT in hospitalized patients with acute exacerbation of COPD (AECOPD). Methods: A cross-sectional study was conducted in a tertiary hospital. Patients who were hospitalized due to AECOPD and healthy elderly participants, voluntarily recruited from the community, were considered for inclusion. All participants underwent a 6-PBRT. Isokinetic evaluation to measure the strength and endurance of elbow flexors and extensors, handgrip strength (HGS), spirometry testing, the modified Pulmonary Functional Status Dyspnea Questionnaire (PFSDQ-M), the COPD assessment test (CAT), and symptoms of dyspnea and fatigue were all measured as comparisons for convergent validity. Good convergent validity was considered if >75% of these hypotheses could be confirmed (correlation coefficient > 0.50). Results: A total of 17 patients with AECOPD (70.9 +/- 5.1 years and forced expiratory volume in 1 second [FEV1] of 41.8% +/- 17.9% of predicted) and 11 healthy elderly subjects were included. The HGS showed a significant strong correlation with 6-PBRT performance ( $r=0.70$ ;  $p=0.002$ ). The performance in 6-PBRT presented a significant moderate correlation with elbow flexor torque peak ( $r=0.52$ ;  $p=0.03$ ) and elbow extensor torque peak ( $r=0.61$ ;  $p=0.01$ ). The total muscular work of the 15 isokinetic contractions of the elbow flexor and extensor muscles showed a significant moderate correlation with the performance in 6-PBRT ( $r=0.59$ ;  $p=0.01$  and  $r=0.57$ ;  $p=0.02$ , respectively). Concerning the endurance of elbow flexors and extensors, there was a significant moderate correlation with 6-PBRT performance ( $r=-0.50$ ;  $p=0.04$  and  $r=-0.51$ ;  $p=0.03$ , respectively). In relation to the upper-extremity physical activities of daily living (ADLs) assessed by means of PFSDQ-M, there was a significant moderate correlation of 6-PBRT with three domains: influence of dyspnea on ADLs ( $r=-0.66$ ;  $p<0.001$ ), influence of fatigue on ADLs ( $r=-0.60$ ;  $p=0.01$ ), and change in ADLs in relation to the period before the disease onset ( $r=-0.51$ ;  $p=0.03$ ). The CAT was also correlated with 6-PBRT ( $r=-0.51$ ;  $p=0.03$ ). Finally, the performance in 6-PBRT showed a significant moderate correlation with the increase in dyspnea ( $r=-0.63$ ;  $p=0.01$ ) and a strong correlation with the increase in fatigue of upper limbs ( $r=-0.76$ ;  $p<0.001$ ) in patients with AECOPD. Convergent validity was considered adequate, since 81% from 16 predefined hypotheses were confirmed. There was no correlation between 6-PBRT and patients' height. The performance in 6-PBRT was worse in patients with AECOPD compared to healthy elderly individuals (248.7 +/- 63.0 vs 361.6 +/- 49.9 number of moved rings;  $p<0.001$ ). Conclusion: The 6-PBRT is valid for the evaluation of functional capacity of upper limbs in hospitalized patients with AECOPD.

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Fiorelli, A., M. Santini, et al. (2018). **"When can computed tomography-fissure analysis replace Chartis collateral ventilation assessment in the prediction of patients with emphysema who might benefit from endobronchial valve therapy?"** *Interact Cardiovasc Thorac Surg* **26**(2): 313-318.

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was when can computed tomography-fissure analysis replace Chartis collateral ventilation assessment in the prediction of patients with emphysema who might benefit from endobronchial valve therapy? Twelve papers were chosen to answer the question. The authors, date, journal, country of publication and study type; patient group studied; relevant outcomes and results of these papers were tabulated. Five studies retrospectively compared the prognostic value of 2 methods. They found that when computed tomography-fissure analysis showed an intact fissure more than 95%, both methods were equivalent in correctly predicting a positive response to valve therapy. Concordant results were found in two-thirds of patients, and the additional evaluation with Chartis did not confer a significant advantage. Yet the increasing cost and time to procedure, the different ranges of Chartis findings patterns not correlated with lung volume reduction and the unfeasibility of the measurements (reported in 6-17% of the most series) due to difficult anatomy are additional limitations for its use. Conversely, in patients with fissure integrity between 75% and 90%, Chartis assessment could improve the patient selection, because the computed tomography-fissure analysis alone is unable to predict a successful treatment. In this situation, Chartis had a 31% ability to predict those patients who can be successfully treated. In BelieVer-Hifi Study, post hoc analysis revealed that the additional use of Chartis for patient selection significantly improved outcomes. Similarly, STELVIO, LIVE and IMPACT studies, where only patients with complete fissure and negative Chartis measurement were treated, showed significant benefits after valve treatment. Finally, in patients with fissure integrity below 75%, the negative predictive value for lobar atelectasis is 100%. Thus, in these patients, it could be futile even considering a Chartis assessment.

[https://watermark.silverchair.com/ivx272.pdf?token=AQECAHi208BE49Ooan9kkhW\\_Ercy7Dm3ZL\\_9Cf3qfKAc485ysgAAAIYwggJSBgkqhkiG9w0BBwagggJDMIICPwIBADCCAjgGCSqGSib3DQEHATAeBgIghkgBZQMEAS4wEQQMia4Aso17ttG6nLMBLAgEQgIICCQ2W90DPCugroiOjBqDqMB6-eS8zjyJKICTDyawRMErjDBE3hj\\_sACQ\\_Dkz\\_PkQq-Mr5jdpfvmcpddIOY2Oqc6GF3-kYFbmlc0MnmkUWtffMoqlKaeX2MIEXz98\\_9l0NemUsakQ8W0IUxjlKWlaq2\\_0y1cjaKzTPhWusuKk9bKtGomZH-WkbufLhwaFvgcx0FSGhfpEeEbJhAKLCr0uSzpOYoTx35EiS1pUOWyz0k41KxhXolgsIzIOIMrPce8GJanNeGK-dO6FiWwZiVxFs18YoRIMXh-CwAQ4p\\_SQV8xXdxENOljdyIJQTu3k8V4tsKncXW7dpJkACT9DtrlwR3wq0vZ4\\_gtOV\\_XLR8yTZPf0WMraFnl eUI04-iMvrnxVAQSeN1jQdxLZfVRJdBYyXCr8-a7FEpjELF8dOI3NyXZyuyA-vswwNqxcj9dZb5jPHy7zQAjjnaUWBY\\_jvKdde7wGWDy66ezWq\\_ZFiTyRHT7woP2\\_kRLgs9RNNemCxiQI1smlOYULxcgSgoQ1A3Sglf0XE9HYTzjtS-hXxtjSxQc3eC3ym95uuxaqzm56\\_sKxztu9zUsHp1d4H4DpS9EVxcjFVwMxz-auibDYI4NDffkeTILyKITB-kot40ckljYBjw80koBi5W0NNL5tQW6BD2l9Q933DPWvuOHxrrv4-k5FjNn7xRQS](https://watermark.silverchair.com/ivx272.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAIYwggJSBgkqhkiG9w0BBwagggJDMIICPwIBADCCAjgGCSqGSib3DQEHATAeBgIghkgBZQMEAS4wEQQMia4Aso17ttG6nLMBLAgEQgIICCQ2W90DPCugroiOjBqDqMB6-eS8zjyJKICTDyawRMErjDBE3hj_sACQ_Dkz_PkQq-Mr5jdpfvmcpddIOY2Oqc6GF3-kYFbmlc0MnmkUWtffMoqlKaeX2MIEXz98_9l0NemUsakQ8W0IUxjlKWlaq2_0y1cjaKzTPhWusuKk9bKtGomZH-WkbufLhwaFvgcx0FSGhfpEeEbJhAKLCr0uSzpOYoTx35EiS1pUOWyz0k41KxhXolgsIzIOIMrPce8GJanNeGK-dO6FiWwZiVxFs18YoRIMXh-CwAQ4p_SQV8xXdxENOljdyIJQTu3k8V4tsKncXW7dpJkACT9DtrlwR3wq0vZ4_gtOV_XLR8yTZPf0WMraFnl eUI04-iMvrnxVAQSeN1jQdxLZfVRJdBYyXCr8-a7FEpjELF8dOI3NyXZyuyA-vswwNqxcj9dZb5jPHy7zQAjjnaUWBY_jvKdde7wGWDy66ezWq_ZFiTyRHT7woP2_kRLgs9RNNemCxiQI1smlOYULxcgSgoQ1A3Sglf0XE9HYTzjtS-hXxtjSxQc3eC3ym95uuxaqzm56_sKxztu9zUsHp1d4H4DpS9EVxcjFVwMxz-auibDYI4NDffkeTILyKITB-kot40ckljYBjw80koBi5W0NNL5tQW6BD2l9Q933DPWvuOHxrrv4-k5FjNn7xRQS)

Flynn, R. W. V., T. M. MacDonald, et al. (2018). "**The effect of changes to GOLD severity stage on long term morbidity and mortality in COPD.**" *Respir Res* 19(1): 249.

**BACKGROUND:** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity stage classifies Chronic Obstructive Pulmonary Disease (COPD) into groups based on symptoms, exacerbations and forced expiratory volume in one second (FEV1). This allows patients to change to less severe COPD stages, a novel aspect of assessment not previously evaluated. We aimed to investigate the association between temporal changes in GOLD severity stage and outcomes in COPD patients. **METHODS:** This was a record-linkage study using patients registered with a Scottish regional COPD network 2000-2015. Annual spirometry & symptoms were recorded and linked to healthcare records to identify exacerbations, hospitalisations and mortality. Spirometry, modified Medical Research Council (mMRC) dyspnoea scale and acute exacerbations over the previous year were used to assign GOLD severity at each visit. A time-dependent Cox model was used to model time to death. Secondary outcomes were respiratory specific mortality and hospitalisations. Effect sizes are expressed as Hazard Ratios HR (95%CI). **RESULTS:** Four thousand, eight hundred and eighty-five patients (mean age 67.3 years; 51.3% female) with 21,348 visits were included. During a median 6.6 years follow-up there were 1530 deaths. For the secondary outcomes there were 712 respiratory deaths and 1629 first hospitalisations. Across 16,463 visit-pairs, improvement in COPD severity was seen in 2308 (14%), no change in 11,010 (66.9%) and worsening in 3145 (19.1). Compared to patients staying in GOLD stage A, those worsening had a stepwise increased mortality and hospitalisations. **CONCLUSIONS:** Improving COPD severity classification was associated

with reduced mortality and worsening COPD severity was associated with increased mortality and hospitalisations. Change in GOLD group has potential as monitoring tool and outcome measure in clinical trials.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6291946/pdf/12931\\_2018\\_Article\\_960.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6291946/pdf/12931_2018_Article_960.pdf)

Furuuchi, K., A. Ito, et al. (2018). "**Risk stratification for the development of chronic pulmonary aspergillosis in patients with Mycobacterium avium complex lung disease.**" *J Infect Chemother* **24**(8): 654-659.

BACKGROUND: The number of patients with pulmonary nontuberculous mycobacterial disease complicated by chronic pulmonary aspergillosis (CPA) has been increasing. Additionally, CPA is reportedly associated with mortality in patients with Mycobacterium avium complex lung disease (MAC-LD). In the present study, we aimed to identify risk factors for developing CPA and stratify the risk for CPA development in patients with MAC-LD. METHODS: We retrospectively examined 361 patients newly diagnosed with MAC-LD. Risk factors for CPA development were examined using multivariate Cox proportional hazards regression analyses. A risk stratification system was established using the risk factors and receiver operating characteristic curve analyses. RESULTS: CPA developed in 20 (5.5%) of the 361 patients. Independent risk factors for CPA development included the presence of pulmonary emphysema, baseline steroid use, a serum albumin level <3.5 g/dL, and the presence of MAC-LD cavities. A 4-point scoring system was established to stratify patients into low-risk (0-1 point) and high-risk (2-4 points) groups. The 5-year incidence rates of CPA were 2.2% and 31% in the low- and high-risk groups, respectively (P < 0.001). CONCLUSIONS: We identified independent predictors of CPA development and established a simple risk stratification system for identifying patients with MAC-LD who were at a high risk of developing CPA.

[https://www.jiac-j.com/article/S1341-321X\(18\)30106-5/fulltext](https://www.jiac-j.com/article/S1341-321X(18)30106-5/fulltext)

Grdic Rajkovic, M., S. Popovic-Grle, et al. (2018). "**PON1 gene polymorphisms in patients with chronic obstructive pulmonary disease.**" *J Clin Pathol* **71**(11): 963-970.

AIMS: Chronic obstructive pulmonary disease (COPD) is characterised with oxidative stress. Paraoxonase 1 (PON1) is an enzyme, coded by PON1 gene, with distinctive antiatherogenic and antioxidative roles. We aimed to investigate the frequencies of Q192R, L55M and -108C>T polymorphisms and association of those polymorphisms with paraoxonase and arylesterase activities in patients with COPD. METHODS: PON1 genotype was determined by PCR-restriction fragment length polymorphism method. PON1 activity was measured by paraoxon and phenylacetate. RESULTS: Only -108C>T polymorphism resulted in significantly different distribution of genotypes and alleles, with higher frequency of TT genotype and T allele in patients compared with control subjects. Moreover, T allele (OR 2.29 (95% CI 1.54 to 3.41); p<0.001) as well as TT genotype (OR 5.00 (95% CI 2.19 to 11.43); p<0.001) showed an association with the disease. -108C>T polymorphism was suggested as a significant diagnostic predictor for the disease (OR (95% CI) 2.65 (1.53 to 4.59), p=0.001), with an area under the receiver operating characteristic curve of 0.90 (95% CI 0.84 to 0.93) and with 83.90% of correctly classified cases. CONCLUSIONS: Higher frequency of TT genotype and T allele could contribute to the observed reduction of PON1 activity in patients with COPD. T allele and TT genotype are associated with COPD, and the PON1-108C>T polymorphism could be a potential predictor of the disease.

<https://jcp.bmj.com/content/71/11/963.long>

Gulsen, A. (2018). "**Importance of bronchoscopic lung volume reduction coil therapy in potential candidates for lung transplantation.**" *Biosci Trends* **12**(4): 395-402.

Bronchoscopic lung volume reduction (BLVR) coil treatment is an alternative and promising treatment modality for selected severe emphysema patients. The main indication of this treatment modality is a forced expiration volume in one second (FEV1) of 15-45% and a residual volume (RV) > 175%. The aim of this study was to investigate the efficacy of BLVR coil therapy in patients with end-stage emphysema who were potential candidates for lung transplantation and had FEV1 values less than 25%. Twenty-one patients who underwent bilateral BLVR coil therapy between September 2013 and May 2015 were retrospectively reviewed. We compared the changes in clinical and laboratory parameters at the baseline and 12 months after the treatment. Twelve months after the bilateral BLVR coil treatment, we observed an average increase in FEV1 (110 mL and 4.6%), a decrease in residual volume (660 mL and 33%), and an increase in 6-minute walk tests (67 m). The most common complications were chronic obstructive pulmonary disease exacerbation (47.6%) and pneumonia (23.8%). All patients tolerated the general anesthesia and procedure very well. BLVR coil therapy is safe and effective in patients with end-stage emphysema, who are potential candidates for lung transplantation within a short to medium period. The complication rates of this treatment were not different from those of the other coil treatments, and the improvements in the clinical parameters after the treatment resulted in gaining time for lung transplantation. Future research for evaluating the long-term efficacy of BLVR coil therapy in these patients is essential.

[https://www.jstage.jst.go.jp/article/bst/12/4/12\\_2018.01134/\\_pdf](https://www.jstage.jst.go.jp/article/bst/12/4/12_2018.01134/_pdf)

Hareendran, A., B. J. Make, et al. (2018). "**Evaluation of the psychometric properties of the Early Morning Symptoms of COPD Instrument (EMSCI).**" *Int J Chron Obstruct Pulmon Dis* **13**: 1633-1645.

Background: Early morning respiratory symptoms impact quality of life and are often the most troublesome for patients with COPD. Reduction in symptoms and their impact are important treatment outcomes for COPD. The Early Morning Symptoms of COPD Instrument (EMSCI) is a daily diary designed to collect patients' report of the occurrence, severity, and impact of morning COPD symptoms. Methods: To assess the psychometric properties of the EMSCI, a split-half sample of data from a COPD clinical trial where participants completed the EMSCI daily was used for conducting descriptive statistics, factor analyses, and Rasch model analyses to examine item performance and inform scoring. Once the final scoring algorithm was determined, data from the second split-half sample were used to examine the properties of the EMSCI. Test-retest reliability was assessed using intraclass correlation coefficient (ICC). Correlations with other study assessments were used to evaluate convergent and known-groups validity. Results: Data from 1,663 patients with COPD aged 40-93 years were analyzed. Factor analysis and Rasch analysis confirmed a one-factor structure for the 6 individual symptom items. Item analyses supported the generation of 4 scores. All scores demonstrated good test-retest reliability: 6-item symptom severity (ICC, 0.84); overall morning symptom severity (ICC, 0.84); activity limitation (ICC, 0.85); and rescue medication (ICC, 0.62). Significant correlations between EMSCI scores, St George's Respiratory Questionnaire scores, and EXacerbations of Chronic pulmonary disease Tool (EXACT)-Respiratory Symptoms scores supported the tool's convergent validity. Significant differences ( $p < 0.0001$ ) in all EMSCI domain scores were found between known-groups based on median split St George's Respiratory Questionnaire and EXACT-Respiratory Symptoms scores. Conclusion: The EMSCI consists of 4 scores: 6-item symptom severity, overall symptom severity, activity limitation, and rescue medication. The EMSCI is a reliable and valid instrument for evaluating patients' experience of early morning COPD symptoms.

<https://www.dovepress.com/getfile.php?fileID=42161>

Herer, B. and T. Chinet (2018). "**Acute exacerbation of COPD during pulmonary rehabilitation: outcomes and risk prediction.**" *Int J Chron Obstruct Pulmon Dis* **13**: 1767-1774.

Purpose: This study was performed to examine acute exacerbation of COPD (AECOPD) during pulmonary rehabilitation (PR) and the usefulness of multidimensional indices (MIs) to predict AECOPD at enrolment in PR. Patients and methods: A 4-week PR program (PRP) was implemented for 125 consecutive patients with COPD. At baseline and PRP completion, we recorded the FEV1, 6-minute walk test, peak work rate

at cardiopulmonary testing, modified Medical Research Council score, and COPD Assessment Test (CAT) score. The risk of AECOPDs at baseline was assessed using the body mass index, airway obstruction, dyspnea, Exercise capacity (BODE), dyspnea, obstruction, smoking, exacerbation (DOSE), and score to predict short-term risk of COPD exacerbations (SCOPEX) MIs. Results: Thirty-two episodes of AECOPD occurred. The COPD status was worse in patients with than without AECOPD at baseline (lower FEV<sub>1</sub>, 6-minute walk test, and peak work rate; higher modified Medical Research Council and CAT scores). The sensitivities of the BODE, DOSE, and SCOPEX MIs to predict the occurrence of AECOPD during PRP were 78.1%, 21.9%, and 84.4%, and the specificities were 73.6%, 87.1%, and 51.6%, respectively. Conclusion: The BODE and SCOPEX MIs help to predict the exacerbation risk during PR.

<https://www.dovepress.com/getfile.php?fileID=42355>

Iepsen, U. W., G. W. Munch, et al. (2018). "**Muscle alpha-adrenergic responsiveness during exercise and ATP-induced vasodilation in chronic obstructive pulmonary disease patients.**" *Am J Physiol Heart Circ Physiol* **314**(2): H180-h187.

Sympathetic vasoconstriction is blunted in exercising muscle (functional sympatholysis) but becomes attenuated with age. We tested the hypothesis that functional sympatholysis is further impaired in chronic obstructive pulmonary disease (COPD) patients. We determined leg blood flow and calculated leg vascular conductance (LVC) during 1) femoral-arterial Tyramine infusion (evokes endogenous norepinephrine release, 1 micromol.min<sup>-1</sup>.kg leg mass<sup>-1</sup>), 2) one-legged knee extensor exercise with and without Tyramine infusion [10 W and 20% of maximal workload (WL<sub>max</sub>)], 3) ATP (0.05 micromol.min<sup>-1</sup>.kg leg mass<sup>-1</sup>) and Tyramine infusion, and 4) incremental ATP infusions (0.05, 0.3, and 3.0 micromol.min<sup>-1</sup>.kg leg mass<sup>-1</sup>). We included 10 patients with moderate to severe COPD and 8 age-matched healthy control subjects. Overall, leg blood flow and LVC were lower in COPD patients during exercise (P < 0.05). Tyramine reduced LVC in both groups at 10-W exercise (COPD: -3 +/- 1 ml.min<sup>-1</sup>.mmHg<sup>-1</sup>) and controls: -3 +/- 1 ml.min<sup>-1</sup>.mmHg<sup>-1</sup>, P < 0.05) and 20% WL<sub>max</sub> (COPD: -4 +/- 1 ml.min<sup>-1</sup>.mmHg<sup>-1</sup>) and controls: -3 +/- 1 ml.min<sup>-1</sup>.mmHg<sup>-1</sup>, P < 0.05) with no difference between groups. Incremental ATP infusions induced dose-dependent vasodilation with no difference between groups, and, in addition, the vasoconstrictor response to Tyramine infused together with ATP was not different between groups (COPD: -0.03 +/- 0.01 l.min<sup>-1</sup>.kg leg mass<sup>-1</sup>) vs. CONTROLS: -0.04 +/- 0.01 l.min<sup>-1</sup>.kg leg mass<sup>-1</sup>, P > 0.05). Compared with age-matched healthy control subjects, the vasodilatory response to ATP is intact in COPD patients and their ability to blunt sympathetic vasoconstriction (functional sympatholysis) as evaluated by intra-arterial Tyramine during exercise or ATP infusion is maintained. **NEW & NOTEWORTHY** The ability to blunt sympathetic vasoconstriction in exercising muscle and ATP-induced dilation in chronic obstructive pulmonary disease patients remains unexplored. Chronic obstructive pulmonary disease patients demonstrated similar sympathetic vasoconstriction in response to intra-arterial Tyramine during exercise and ATP-induced vasodilation compared with age-matched healthy control subjects.

<https://www.physiology.org/doi/abs/10.1152/ajpheart.00398.2017>

Jetmalani, K., C. Thamrin, et al. (2018). "**Peripheral airway dysfunction and relationship with symptoms in smokers with preserved spirometry.**" *Respirology* **23**(5): 512-518.

**BACKGROUND AND OBJECTIVE:** Smokers develop respiratory symptoms and peripheral airway dysfunction even when spirometry is preserved. Multiple breath nitrogen washout (MBNW) and impulse oscillometry system (IOS) are potentially useful measures of peripheral airway function but they have not been compared in such subjects. We hypothesized that MBNW and IOS are jointly abnormal in smokers with normal spirometry and that these abnormalities relate to respiratory symptoms. **METHODS:** Eighty smokers with normal spirometry completed a symptom questionnaire, had ventilation heterogeneity in diffusion (Sacin) and convection-dependent (Scond) airways and trapped gas volume at functional residual capacity as a percentage of vital capacity (%V<sub>tr</sub>FRC/VC) measured by MBNW. Respiratory resistance and reactance at 5 and 20 Hz were measured using IOS. **RESULTS:** Respiratory symptoms were

reported in 55 (68%) subjects. Forty (50%) subjects had at least one abnormal MBNW parameter, predominantly in Sacin. Forty-one (51%) subjects had at least one abnormal IOS parameter, predominantly in resistance. Sixty-one (76%) subjects had an abnormality in either MBNW or IOS. Chronic bronchitis symptoms were associated with an increased Scond, while wheeze was associated with lower spirometry and an increased resistance. Abnormalities in MBNW and IOS parameters were unrelated to each other. CONCLUSIONS: Respiratory symptoms and peripheral airway dysfunction are common in smokers with normal spirometry. Symptoms of chronic bronchitis related to conductive airway abnormalities, while wheeze was related to spirometry and IOS. The clinical significance of abnormalities in peripheral airway function in smokers remains undetermined.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13215>

Jing, X., G. Zhang, et al. (2018). "**Efficacy and safety of low-dose urokinase for the treatment of hemodynamically stable AECOPD patients with acute pulmonary thromboembolism.**" *Clin Respir J* 12(5): 1882-1890.

PURPOSE: The aim of this study was to assess the incidence of pulmonary thromboembolism (PTE) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and to evaluate the efficacy and safety of low-dose urokinase (UK) thrombolysis therapy when treating hemodynamically stable AECOPD patients with acute PTE (AECOPD-PTE). METHODS: A total of 419 AECOPD patients, including 96 AECOPD-PTE, were enrolled. A total of 30 AECOPD-PTE patients were collected retrospectively, and 66 AECOPD-PTE patients were prospectively divided into anticoagulation-only, low-dose UK and standard-dose UK groups. Follow-up 1 year, we evaluated the efficacy and safety of low-dose UK therapy for hemodynamically stable AECOPD-PTE patients. RESULTS: The incidence of PTE in AECOPD patients was 22.9% (96/419), which increased with COPD severity degree ranging from 3.5% (2/57) in mild, 13.6% (19/140) in moderate and 33.8% (75/222) in severe subgroups ( $P < .05$ ). In the prospective study, the total effective rate of low-dose UK group 97.2% (35/36) was higher than that in anticoagulation 75.0% (12/16) and standard-dose UK group 78.6% (11/14) respectively ( $P < .05$ ). In the follow-up, the adverse events rate in low-dose UK group 8.3% (3/36) was significantly lower than that in anticoagulation group 25.0% (4/16) and standard-dose UK group 71.4% (10/14) respectively ( $P < .05$ ). In addition, the mean PTE recurrence time of low-dose UK group (9.0 +/- 0) months was longer than anticoagulation group (2.0 +/- 1.41) months ( $P < .05$ ). AECOPD relapse time in anticoagulation, low-dose UK and standard-dose UK groups corresponding to (8.5 +/- 2.12), (9.0 +/- 0) and (8.8 +/- 3.40) months were compared with no significant difference ( $P > .05$ ). CONCLUSIONS: The incidence of PTE in AECOPD patients was 22.9%, especially with higher occurrence rate in severe COPD. Compared with anticoagulation-only therapy, low-dose UK treatment (500 000 IU/day for 5-7 days) could obtain a better efficacy and safety in hemodynamically stable AECOPD patients with acute PTE, corresponding with a higher effective rate (97.2%) and lower adverse events rate (8.3%) respectively.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12751>

Johnson, E. F., S. N. Tolkachjov, et al. (2018). "**Alpha-1 antitrypsin deficiency panniculitis: clinical and pathologic characteristics of 10 cases.**" *Int J Dermatol* 57(8): 952-958.

BACKGROUND: Alpha-1 antitrypsin deficiency (AATD) may be associated with liver and lung disease and rarely causes panniculitis. OBJECTIVE: We evaluated the clinicopathologic and laboratory findings of AATD panniculitis in 10 patients. METHODS: We conducted a retrospective review of all cases of AATD panniculitis at Mayo Clinic, Rochester, MN, from 1989 to 2016. RESULTS: Ten patients with AATD panniculitis were included. Seven of ten were women. Clinical lesions were most commonly nodular (100%), erythematous (90%), ulcerated (90%), and painful (90%) subcutaneous nodules and plaques. Extracutaneous associations were rare. PiZZ phenotype was most commonly identified (50%). Histopathologically, lobular panniculitis (80%) with associated septal involvement (60%) and a predominant neutrophilic infiltrate (100%) were most common. Treatments varied; dapson and alpha-1 proteinase inhibitor infusions were each used in five (50%) patients, respectively. In patients with greater

than 6-month follow-up (n = 4), one patient continued to have disease activity despite treatment.  
CONCLUSION: AATD panniculitis should be considered in the differential for a painful, ulcerative panniculitis with a predominantly neutrophilic histopathologic infiltrate. Diagnosis can be made with clinicopathologic correlation and genetic and laboratory evaluations. Serum AAT level and phenotype assists in diagnosing patients with suspected AATD panniculitis.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/ijd.14012>

Kamei, T., Y. Yamamoto, et al. (2018). "**Detection of early-stage changes in people with chronic diseases: A telehome monitoring-based telenursing feasibility study.**" *Nurs Health Sci* 20(3): 313-322.

Chronic diseases, such as chronic obstructive pulmonary disease, amyotrophic lateral sclerosis, and diabetes mellitus, require long-term management, which daily telenurse monitoring can provide. The aim of the present feasibility study was to determine if using a telenursing protocol with home monitoring during a 12 week implementation could also identify early signs of deterioration and factors correlated with participants' change in status, while attaining patient acceptance and satisfaction. The purposive sample of 43 participants provided 4533 combined days of monitoring. Outcome feasibility indicators were the range of triggering protocol alerts (70~100%) and diagnoses with exacerbations (20~29.3%). Highly correlated were participants' activity limitation and palpitations with chronic obstructive pulmonary disease, activity limitation and ineffective sputum clearance with amyotrophic lateral sclerosis, and fatigue with diabetes. Acceptance and adherence were high with daily monitoring, including "feelings of safety," and "understanding own condition". Telenursing with home monitoring indicated a trend to accurately detect early-stage changes. Participant acceptance was acceptable. It would be feasible to conduct a randomized, controlled trial using this model with some modifications.

<https://onlinelibrary.wiley.com/doi/pdf/10.1111/nhs.12563>

Kamenskaya, O., I. Loginova, et al. (2018). "**Chronic obstructive pulmonary disease in patients with chronic thromboembolic pulmonary hypertension: Prevalence and implications for surgical treatment outcome.**" *Clin Respir J* 12(7): 2242-2248.

OBJECTIVE: The aim of our study was to investigate the prevalence of chronic obstructive pulmonary disease (COPD) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and examine their impact on the results of pulmonary thrombendarterectomy (PEA). METHODS: We enrolled 136 patients with CTEPH who scheduled for elective PEA. Pulmonary function tests (PFTs) including full-body plethysmography with bronchodilation test and lung diffusion capacity assessment were performed in all patients prior to surgery treatment. The diagnosis of COPD was verified in accordance with the recommendations of the Global Initiative for Chronic Obstructive Lung Disease 2017. The effect of COPD on perioperative characteristics, complications, in-hospital and one-year mortality of patients with CTEPH were analysed. RESULTS: In the study group with CTEPH the prevalence of COPD was 23%. In 13% of patients, COPD was first detected. The results of PFTs showed more severe airflow limitations with obstructive pattern in patients with concomitant COPD, as well as a more pronounced decrease in the lung diffusion capacity. The presence of COPD in patients with CTEPH significantly increases the risk of residual pulmonary hypertension in the early postoperative period of PEA (OR = 6.2 (1.90-10.27), P = .002), duration of hospital stay (OR = 1.1 (1.01-1.20), P = .020) and the risk of in-hospital mortality (OR = 4.4 (1.21-16.19), P = .023). The lung diffusion capacity revealed significant negative associations with the duration of hospital stay and in-hospital mortality (OR 0.87 (0.74-0.98), P = .012). CONCLUSION: COPD in patients with CTEPH significantly increases the risk of residual pulmonary hypertension, in-hospital mortality and increases the duration of hospital stay after PEA.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12898>

Karakoca, Y., G. Gogus, et al. (2018). **"Follow-up outcomes of chronic obstructive pulmonary disease patients who underwent dilatation and curettage with the Karakoca resector balloon: A 188-case series over 5 years."** *Medicine (Baltimore)* **97**(48): e13400.

We previously reported satisfactory results with the Karakoca resector balloon in 10 patients with stage IV chronic obstructive pulmonary disease (COPD) who did not respond to medical treatment. In this article, we present the outcomes of the Karakoca resector balloon dilatation and curettage technique in a larger case series (n = 188). A total of 188 COPD patients [mean age (SD): 69.2 (8.0) years; 46 females] classified as stage III to IV by the Global Initiative for Obstructive Lung Disease criteria underwent balloon desobstruction for segmental and subsegmental bronchi by therapeutic bronchoscopy. None of the patients could have achieved symptom relief even under high-dose inhaled bronchodilators and corticosteroids, oral corticosteroids, or oxygen and noninvasive mechanical ventilation therapy before the intervention. Forced expiratory volume in 1 s (FEV1) and oxygen saturation (SpO2) were measured, and modified Borg dyspnea scale (MBS) scores were determined before and 1 week and 1 month after the intervention. All patients were active smokers and 80% had concomitant chronic diseases. After the intervention, there was a notable reduction in the oxygen need of the patients. Comparison of lung function tests 1 week after the procedure with results before the procedure showed significant improvements in FEV1, MBS, and SpO2 levels (P < 0.001 for each), and the improvements were maintained for the entire postprocedural month (P < 0.001 for each). Except for 4 males, all patients were free of symptoms. These results confirmed our early observations that balloon dilatation and curettage is a safe and successful technique for medical treatment-resistant COPD.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6283145/pdf/medi-97-e13400.pdf>

Koehorst-Ter Huurne, K., C. G. Groothuis-Oudshoorn, et al. (2018). **"Association between poor therapy adherence to inhaled corticosteroids and tiotropium and morbidity and mortality in patients with COPD."** *Int J Chron Obstruct Pulmon Dis* **13**: 1683-1690.

**Aim:** The aim of this study was to analyze the association between therapy adherence to inhaled corticosteroids (ICSs) and tiotropium on the one hand and morbidity and mortality in COPD on the other hand.  
**Methods:** Therapy adherence to ICSs and tiotropium over a 3-year period of, respectively, 635 and 505 patients was collected from pharmacy records. It was expressed as percentage and deemed optimal at  $\geq 75\%$ - $\leq 125\%$ , suboptimal at  $\geq 50\%$ - $< 75\%$ , and poor at  $< 50\%$  (underuse) or  $> 125\%$  (overuse). The association between adherence and time to first hospital admission for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), community acquired pneumonia (CAP), and mortality was analyzed, with optimal use as the reference category. **Results:** Suboptimal use and underuse of ICSs and tiotropium were associated with a substantial increase in mortality risk: hazard ratio (HR) of ICSs was 2.9 (95% CI 1.7-5.1) and 5.3 (95% CI 3.3-8.5) and HR of tiotropium was 3.9 (95% CI 2.1-7.5) and 6.4 (95% CI 3.8-10.8) for suboptimal use and underuse, respectively. Suboptimal use and overuse of tiotropium were also associated with an increased risk of CAP, HR 2.2 (95% CI 1.2-4.0) and HR 2.3 (95% CI 1.2-4.7), respectively. Nonadherence to tiotropium was also associated with an increased risk of severe AECOPD: suboptimal use HR 3.0 (95% CI 2.01-4.5), underuse HR 1.9 (95% CI 1.2-3.1), and overuse HR 1.84 (95% CI 1.1-3.1). Nonadherence to ICSs was not related to time to first AECOPD or first CAP. **Conclusion:** Poor adherence to ICSs and tiotropium was associated with a higher mortality risk. Furthermore, nonadherence to tiotropium was associated with a higher morbidity. The question remains whether improving adherence can reduce morbidity and mortality.

<https://www.dovepress.com/getfile.php?fileID=42266>

Kunutsor, S. K., T. Laukkanen, et al. (2017). **"Sauna bathing reduces the risk of respiratory diseases: a long-term prospective cohort study."** *Eur J Epidemiol* **32**(12): 1107-1111.

Sauna bathing has been linked with numerous health benefits. Sauna bathing may reduce the risk of respiratory diseases; however, no prospective evidence exists to support this hypothesis. We aimed to assess the

association of frequency of sauna bathing with risk of respiratory diseases (defined as chronic obstructive pulmonary disease, asthma, or pneumonia). Baseline sauna bathing habits were assessed in a prospective cohort of 1935 Caucasian men aged 42-61 years. During a median follow-up of 25.6 years, 379 hospital diagnosed incident cases of respiratory diseases were recorded. In adjustment for several major risk factors for respiratory conditions and other potential confounders, the hazard ratios (HRs) 95% confidence intervals (CIs) of respiratory diseases were 0.73 (0.58-0.92) and 0.59 (0.37-0.94) for participants who had 2-3 and  $\geq 4$  sauna sessions per week respectively compared with participants who had  $\leq 1$  sauna session per week. The multivariate adjusted HR (95% CI) for pneumonia was 0.72 (0.57-0.90) and 0.63 (0.39-1.00) for participants who had 2-3 and  $\geq 4$  sauna sessions per week respectively. Frequent sauna baths may be associated with a reduced risk of acute and chronic respiratory conditions in a middle-aged male Caucasian population.

<https://link.springer.com/article/10.1007%2Fs10654-017-0311-6>

Lakhdar, R., D. McGuinness, et al. (2018). "**Role of accelerated aging in limb muscle wasting of patients with COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 1987-1998.

Purpose: Skeletal muscle wasting is an independent predictor of health-related quality of life and survival in patients with COPD, but the complexity of molecular mechanisms associated with this process has not been fully elucidated. We aimed to determine whether an impaired ability to repair DNA damage contributes to muscle wasting and the accelerated aging phenotype in patients with COPD. Patients and methods: The levels of phosphorylated H2AX (gammaH2AX), a molecule that promotes DNA repair, were assessed in vastus lateralis biopsies from 10 COPD patients with low fat-free mass index (FFMI; COPDL), 10 with preserved FFMI and 10 age- and gender-matched healthy controls. A panel of selected markers for cellular aging processes (CDKN2A/p16(ink4a), SIRT1, SIRT6, and telomere length) were also assessed. Markers of oxidative stress and cell damage and a panel of pro-inflammatory and anti-inflammatory cytokines were evaluated. Markers of muscle regeneration and apoptosis were also measured. Results: We observed a decrease in gammaH2AX expression in COPDL, which occurred in association with a tendency to increase in CDKN2A/p16(ink4a), and a significant decrease in SIRT1 and SIRT6 protein levels. Cellular damage and muscle inflammatory markers were also increased in COPDL. Conclusion: These data are in keeping with an accelerated aging phenotype as a result of impaired DNA repair and dysregulation of cellular homeostasis in the muscle of COPDL. These data indicate cellular degeneration via stress-induced premature senescence and associated inflammatory responses abetted by the senescence-associated secretory phenotype and reflect an increased expression of markers of oxidative stress and inflammation.

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Lane, D. C., S. Stemkowski, et al. (2018). "**Initiation of Triple Therapy with Multiple Inhalers in Chronic Obstructive Pulmonary Disease: An Analysis of Treatment Patterns from a U.S. Retrospective Database Study.**" *J Manag Care Spec Pharm* **24**(11): 1165-1172.

BACKGROUND: Evidence suggests that real-world treatment patterns of chronic obstructive pulmonary disease (COPD) do not always follow evidence-based treatment recommendations such as those of the Global Initiative for Chronic Obstructive Lung Disease, which recommends treatment escalation based on disease progression. This U.S. database study evaluated treatment patterns in patients with COPD, focusing on time to initiation of triple therapy using multiple inhalers. OBJECTIVES: To (a) estimate time from diagnosis to initiation of long-acting muscarinic antagonist (LAMA) monotherapy, inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) dual therapy, or LAMA/LABA dual therapy; (b) estimate time to initiation of triple therapy from LAMA monotherapy and ICS/LABA or LAMA/LABA dual therapies; and (c) estimate the likelihood of patient progression to triple therapy. METHODS: This study was a retrospective analysis of patients with COPD newly started on LAMA monotherapy, ICS/LABA, or LAMA/LABA therapy between July 1, 2010, and March 31, 2013, as identified in Humana's research database. Patients who were fully insured with commercial or Medicare Advantage insurance plans and

were aged  $\geq 40$  years at index with at least 1 hospitalization, 1 emergency department, or 1 medical office visit claim with a COPD diagnosis in the pre-index year were included in the analysis. Time from diagnosis to initiation of index therapy and time to triple therapy after index therapy were assessed. Multivariable logistic regression models were used to estimate the likelihood of progression to triple therapy. RESULTS: Of 13,541 patients with a confirmed diagnosis of COPD, 4,000 received LAMA monotherapy; 8,207 received ICS/LABA therapy; and 77 received LAMA/LABA therapy at index; mean time ( $\pm$  SD) from COPD diagnosis to initiation of triple therapy was 178 ( $\pm$  134) days, 185 ( $\pm$  130) days, and 252 ( $\pm$  124) days, respectively. During the study, 28% ( $n = 1,130$ ) of patients receiving LAMA monotherapy and 20% ( $n = 1,647$ ) of patients receiving dual therapy (ICS/LABA,  $n = 1,615$ ; LAMA/LABA,  $n = 32$ ) progressed to triple therapy. Of the patients who progressed to triple therapy, 63% and 57% of patients receiving monotherapy and dual therapy, respectively, progressed in the 12 months after the index date. In the 12 months before initiation of triple therapy, approximately 50% of patients in the LAMA monotherapy, ICS/LABA, and LAMA/LABA therapy groups had an exacerbation. In the multivariable analysis, discontinuation of therapy, smoking history, and concomitant use of xanthenes and short-acting beta2-agonists were significant predictors of progression from index therapy to triple therapy. CONCLUSIONS: Approximately 25% of patients with COPD progressed to triple therapy within 12 months of initiating treatment with monotherapy or dual therapy. Exacerbations were reported in only 50% of these patients, indicating that the other 50% may have escalated to triple therapy for other reasons. Treatment discontinuation, smoking history, the use of a LAMA, and concomitant medication use were significant predictors of progression to triple therapy. DISCLOSURES: This study was a GlaxoSmithKline-sponsored collaborative research study (HO-14-16145). GlaxoSmithKline funded this study and had a role in study design, data analysis, data interpretation, and writing of this report. Stemkowski is a paid employee of Comprehensive Health Insights, which is a wholly owned subsidiary of Humana and was contracted to conduct the study. No funding was provided to Comprehensive Health Insights for manuscript development. At the time of the study, Lane and Tao were paid employees of Comprehensive Health Insights. Stanford is an employee of and stockholder in GlaxoSmithKline.

Laribi, S., C. J. Pemberton, et al. (2017). **"Mortality and acute exacerbation of COPD: a pilot study on the influence of myocardial injury."** *Eur Respir J* 49(6)  
<https://erj.ersjournals.com/content/erj/49/6/1700096.full.pdf>

Lei, Y., Y. Gao, et al. (2017). **"GLCCI1 rs37973: a potential genetic predictor of therapeutic response to inhaled corticosteroids in Chinese chronic obstructive pulmonary disease patients."** *Sci Rep* 7: 42552.

Inhaled corticosteroids (ICSs) are widely prescribed in chronic obstructive pulmonary disease (COPD). However, little is known about predictors of ICSs therapeutic response. To investigate whether the variation in glucocorticoid-induced transcript 1 (GLCCI1) rs37973 is associated with ICS efficacy. A total of 204 clinically stable COPD patients were recruited and administered to inhaled fluticasone propionate/salmeterol combination (500/50 ug, twice daily) for 24 weeks. We genotyped the functional rs37973 and mainly assessed its effects on changes in lung function. In vitro, neutrophils isolated from parts of patients were incubated with various concentrations of dexamethasone (0, 10(-6) M and 10(-4) M) in the presence or absence of cigarette smoke extract, apoptosis was then assessed by flow cytometry. Patients with the homozygous GG genotype (increases of 15.3  $\pm$  33.2 mL) had significantly poorer improvement in FEV1 than those with the AA (92.7  $\pm$  29.6 mL;  $p < 0.001$ ) or AG (59.4  $\pm$  26.9 mL;  $p < 0.001$ ) genotypes after 24-week treatment. In vitro, dexamethasone had less inhibitory effect of neutrophil apoptosis on GG genotype, which further validated the presence of mutant allele 'G' might negatively affect glucocorticoid responsiveness irrespective of smoking status. The GG genotype of rs37973 may associated with decreased ICSs efficacy in Chinese COPD patients.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5301211/pdf/srep42552.pdf>

Leidy, N. K., F. J. Martinez, et al. (2018). **"Can CAPTURE be used to identify undiagnosed patients with mild-to-moderate COPD likely to benefit from treatment?"** *Int J Chron Obstruct Pulmon Dis* **13**: 1901-1912.

Background: COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) uses five questions and peak expiratory flow (PEF) thresholds (males  $\leq 350$  L/min; females  $\leq 250$  L/min) to identify patients with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC)  $< 0.70$  and FEV1  $< 60\%$  predicted or exacerbation risk requiring further evaluation for COPD. This study tested CAPTURE's ability to identify symptomatic patients with mild-to-moderate COPD (FEV1 60%-80% predicted) who may also benefit from diagnosis and treatment. Methods: Data from the CAPTURE development study were used to test its sensitivity (SN) and specificity (SP) differentiating mild-to-moderate COPD (n=73) from no COPD (n=87). SN and SP for differentiating all COPD cases (mild to severe; n=259) from those without COPD (n=87) were also estimated. The modified Medical Research Council (mMRC) dyspnea scale and COPD Assessment Test (CAT) were used to evaluate symptoms and health status. Clinical Trial Registration: NCT01880177, <https://ClinicalTrials.gov/ct2/show/NCT01880177?term=NCT01880177&rank=1>. Results: Mean age (+SD): 61 (+10.5) years; 41% male. COPD: FEV1/FVC=0.60 (+0.1), FEV1% predicted=74% (+12.4). SN and SP for differentiating mild-to-moderate and non-COPD patients (n=160): Questionnaire: 83.6%, 67.8%; PEF ( $\leq 450$  L/min;  $\leq 350$  L/min): 83.6%, 66.7%; CAPTURE (Questionnaire+PEF): 71.2%, 83.9%. COPD patients whose CAPTURE results suggested that diagnostic evaluation was warranted (n=52) were more likely to be symptomatic than patients whose results did not (n=21) (mMRC  $> 2$ : 37% vs 5%,  $p < 0.01$ ; CAT  $> 10$ : 86% vs 57%,  $p < 0.01$ ). CAPTURE differentiated COPD from no COPD (n=346): SN: 88.0%, SP: 83.9%. Conclusion: CAPTURE (450/350) may be useful for identifying symptomatic patients with mild-to-moderate airflow obstruction in need of diagnostic evaluation for COPD.

<https://www.dovepress.com/getfile.php?fileID=42592>

Li, J., H. Liu, et al. (2018). **"Estimation of PM2.5 mortality burden in China with new exposure estimation and local concentration-response function."** *Environ Pollut* **243**(Pt B): 1710-1718.

The estimation of PM2.5-related mortality is becoming increasingly important. The accuracy of results is largely dependent on the selection of methods for PM2.5 exposure assessment and Concentration-Response (C-R) function. In this study, PM2.5 observed data from the China National Environmental Monitoring Center, satellite-derived estimation, widely collected geographic and socioeconomic information variables were applied to develop a national satellite-based Land Use Regression model and evaluate PM2.5 exposure concentrations within 2013-2015 with the resolution of 1kmx1km. Population weighted concentration declined from 72.52 $\mu\text{g}/\text{m}^3$  in 2013 to 57.18 $\mu\text{g}/\text{m}^3$  in 2015. C-R function is another important section of health effect assessment, but most previous studies used the Integrated Exposure Regression (IER) function which may currently underestimate the excess relative risk of exceeding the exposure range in China. A new Shape Constrained Health Impact Function (SCHIF) method, which was developed from a national cohort of 189,793 Chinese men, was adopted to estimate the PM2.5-related premature deaths in China. Results showed that 2.19 million (2013), 1.94 million (2014), 1.65 million (2015) premature deaths were attributed to PM2.5 long-term exposure, different from previous understanding around 1.1-1.7 million. The top three provinces of the highest premature deaths were Henan, Shandong, Sichuan, while the least ones were Tibet, Hainan, Qinghai. The proportions of premature deaths caused by specific diseases were 53.2% for stroke, 20.5% for ischemic heart disease, 16.8% for chronic obstructive pulmonary disease and 9.5% for lung cancer. IER function was also used to calculate PM2.5-related premature deaths with the same exposed level used in SCHIF method, and the comparison of results indicated that IER had made a much lower estimation with less annual amounts around 0.15-0.5 million premature deaths within 2013-2015.

Li, P., J. Liu, et al. (2018). **"Effects of long-term home-based Liuzijue exercise combined with clinical guidance in elderly patients with chronic obstructive pulmonary disease."** *Clin Interv Aging* **13**: 1391-1399.

Purpose: This study was designed to investigate the effects of long-term home-based Liuzijue exercise combined with clinical guidance in elderly patients with chronic obstructive pulmonary disease (COPD). Methods: Forty patients with COPD at stages II-III of the Global Initiative for Chronic Obstructive Lung Disease were enrolled. The subjects were randomly allocated to the Liuzijue exercise group (LG) or control group (CG) in a 1:1 ratio. Participants in the LG performed six Liuzijue training sessions, including 4 days at home and 2 days in the hospital with clinical guidance for 60 minutes/day for 6 months. Participants in the CG conducted no exercise intervention. In addition, lung function test, 6-minute walking test (6MWT), 30-second sit-to-stand test (30 s SST), and the St George's Respiratory Questionnaire (SGRQ) were conducted at the baseline and at the end of the intervention. Results: Thirty-six patients completed the study. The patients' lung function improved significantly ( $p < 0.05$ ) in the LG as well as the 6MWT, 30 s SST, and SGRQ score ( $p < 0.01$ ). While the SGRQ total score, activity, and impact scores increased significantly ( $p < 0.05$ ) in the CG. In addition, there were significant differences between the groups ( $p < 0.01$ ) in regard to the values of forced expiratory volume in 1 second as a percentage of the predicted volume, 6MWT, 30 s SST, and SGRQ. Conclusions: Long-term home-based Liuzijue exercise combined with clinical guidance can effectively improve the pulmonary function, exercise capacity, and quality of life of elderly patients with moderate to severe COPD.

<https://www.dovepress.com/getfile.php?fileID=43487>

Liu, Z., Y. Wang, et al. (2018). **"Typing of chronic obstructive pulmonary disease using high-resolution computed tomography and the association with smoking, airway inflammation, and common comorbidities."** *Turk J Med Sci* **48**(5): 945-951.

Background/aim: This study performed typing of chronic obstructive pulmonary disease (COPD) using high-resolution computed tomography (HRCT) to determine the association with smoking, matrix metalloproteinases, and common comorbidities. Materials and methods: The study enrolled 94 hospitalized patients. Participants were divided into a group of 69 current and former smokers (group A) and a group of 25 that had never smoked (group B). Patients were also divided into 3 categories according to the degree of emphysema and bronchial wall thickness using HRCT to determine the association with levels of matrix metalloproteinase 9 (MMP-9) and TIMP-1, as well as associated comorbidities. These three categories were: type A - no or mild emphysema, with or without bronchial wall thickening; type E - emphysema without bronchial wall thickening; and type M - both emphysema and bronchial wall thickening. Results: The low attenuation area (LAA) scores in group A patients were higher than those in group B ( $t = 2.86$ ,  $P < 0.01$ ); correlation analysis showed that smoking was associated with a decline of the forced expiratory volume in 1 s and forced vital capacity ratio (FEV1/FVC%) and higher LAA scores in patients with COPD ( $F = 4.46$ ,  $F = 8.20$ ,  $P < 0.05$ ). The levels of MMP-9 in group A were higher than those in group B ( $t = 3.65$ ,  $P < 0.01$ ). Among COPD patients with more than 3 comorbidities, there were statistically significant differences in both the smoking group and the nonsmoking group ( $\chi^2 = 12.08$ ,  $P < 0.01$ ). When compared to type A patients, who had coincident cardiovascular diseases in the smoking group, patients of type M and E showed statistically significant differences ( $F = 2.42$  and  $2.12$ ,  $P < 0.05$ ). Conclusion: Emphysema was more severe in smokers. Metalloproteinase levels in smokers were higher than those in nonsmokers. Moreover, comorbidities were more severe in smokers.

Maamar, A., S. Chevalier, et al. (2018). **"COPD is independently associated with 6-month survival in patients who have life support withheld in intensive care."** *Clin Respir J* **12**(7): 2249-2256.

**BACKGROUND:** In-hospital outcomes following decisions of withholding or withdrawing in Intensive Care Unit (ICU) patients have been previously assessed, little is known about outcomes after ICU and hospital discharge. Our objective was to report the 6-month outcomes of discharged patients who had treatment limitations in a general ICU and to identify prognostic factors of survival. **METHODS:** We retrospectively collected the data of patients discharged from the ICU for whom life support was withheld from 2009 to 2011. We assessed the survival status of all patients at 6 months post-discharge and their duration of survival. Survivors and non-survivors were compared using univariate and multivariate analyses by Cox's proportional hazard model. **RESULTS:** One hundred fourteen patients were included. The survival rate at 6 months was 58.8%. Survival was associated with acute respiratory failure (48% vs 19%,  $P = .006$ ), a history of COPD (40% vs 21%,  $P = .03$ ) and a lower SAPS II score (44 vs 49,  $P = .006$ ). We identified a history of COPD as a prognostic factor for survival in the multivariate analysis (HR = 2.1; IC 95% 1.02-4.36,  $P = .04$ ). **CONCLUSION:** A total of 58.8% of patients for whom life-sustaining therapies were withheld in the ICU survived for at least 6 months after discharge. Patients with COPD appeared to have a significantly higher survival rate. The decision to withhold life support in patients should not lead to a cessation of post-ICU care and to non-readmission of COPD patients.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12899>

Makris, D., S. Leroy, et al. (2018). **"Changes in dynamic lung mechanics after lung volume reduction coil treatment of severe emphysema."** *Thorax* **73**(6): 584-586.

We assessed the relationships between changes in lung compliance, lung volumes and dynamic hyperinflation in patients with emphysema who underwent bronchoscopic treatment with nitinol coils (coil treatment) ( $n=11$ ) or received usual care (UC) ( $n=11$ ). Compared with UC, coil treatment resulted in decreased dynamic lung compliance (CL<sub>dyn</sub>) ( $p=0.03$ ) and increased endurance time ( $p=0.010$ ). The change in CL<sub>dyn</sub> was associated with significant improvement in FEV1 and FVC, with reduction in residual volume and intrinsic positive end-expiratory pressure, and with increased inspiratory capacity at rest/and at exercise. The increase in end-expiratory lung volume (EELV) during exercise (EELV<sub>dyn-ch</sub>=EELV<sub>isotime</sub> - EELV<sub>rest</sub>) demonstrated significant attenuation after coil treatment ( $p=0.02$ ).

<https://thorax.bmj.com/content/73/6/584.long>

Mei, L., S. Wu, et al. (2018). **"Epidemiology of Dementia in Elderly Chronic Obstructive Pulmonary Disease Patients Living in China's Northwestern High-Elevation Area."** *Med Sci Monit* **24**: 7742-7749.

**BACKGROUND** The aim of this study was to investigate the effects of oxygen and cholinesterase inhibitor (donepezil) therapy on dementia in patients with age-exacerbated chronic obstructive pulmonary disease (COPD) in China's northwestern high-altitude area. **MATERIAL AND METHODS** A total of 145 patients with acute exacerbation of COPD admitted to the Gerontology Department of the First People's Hospital of Xining City were initially retrospectively screened. From among these 145 patients, we selected 33 cases with dementia and 33 patients without dementia through use of the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and Activities of Daily Living (ADL) Scale evaluated before, 7 days after, and at the end of the treatment after 3 months. Both patient groups received oxygen therapy for 7 days, but patients with dementia in the intervention group were medicated additionally with donepezil (5 mg/day for 1 week, followed by 10 mg/day for another 12 weeks). **RESULTS** Mild dementia was found in 35 of the 145 COPD patients. ADL, MMSE, and ADAS-Cog scores were all significantly lower in the intervention group before treatment, improved after the first 7 days, and continued to improve significantly until week 12 in the intervention group, but were still significantly lower than in the control group. **CONCLUSIONS** Dementia in elderly COPD patients was mainly manifested as decreased executive function, attention, language, and delayed recall, while oxygen and donepezil therapy had beneficial effects on the symptoms.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6217287/pdf/medscimonit-24-7742.pdf>

Miro, O., J. Tost, et al. (2018). **"The BRONCH-AHF study: effects on short-term outcome of nebulized bronchodilators in emergency department patients diagnosed with acute heart failure."** Eur J Heart Fail **20**(4): 822-826.

<https://onlinelibrary.wiley.com/doi/abs/10.1002/ejhf.1028>

Montserrat-Capdevila, J., P. Godoy, et al. (2018). **"Mental disorders in chronic obstructive pulmonary diseases."** Perspect Psychiatr Care **54**(3): 398-404.

PURPOSE: Anxiety and depression are underdiagnosed in chronic obstructive pulmonary disease (COPD) patients. Few studies have tried to identify their association with hospitalization (severe exacerbation). The objective of this study was to determine whether the anxiety/depression was associated with severe exacerbation. DESIGN AND METHODS: A prospective cohort study, based on a sample of 512 patients diagnosed with COPD originating from primary care in a rural area in Lleida (Spain) and monitored between November 1, 2012 and October 31, 2014. For each patient, variables of interest were recorded; they were administered the HADS (Hospital Anxiety and Depression Scale) test to determine the possible presence of anxiety/depression, and its association with severe exacerbation was analyzed using a logistic regression model. FINDINGS: Initially, the prevalence of anxiety/depression was 15.6%. The incidence of global hospitalization in the first year was 8.2% and 11.3% in the second year. In patients with anxiety/depression, it increased to 17.5% in the first year and 18.8% in the second year. In the multivariate regression model, the diagnosis of anxiety/depression almost doubled the risk of hospitalization (OR = 1.94) ( $p < .041$ ). PRACTICE IMPLICATIONS: Anxiety and depression are associated with an increased risk of hospitalization. Intervention studies are needed to evaluate the effects of anxiety/depression in the hospitalization.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/ppc.12274>

Morita, A. A., L. K. O. Silva, et al. (2018). **"Heart Rate Recovery, Physical Activity Level, and Functional Status in Subjects With COPD."** Respir Care **63**(8): 1002-1008.

BACKGROUND: A normal heart rate reflects the balance between the sympathetic and parasympathetic autonomic nervous system. When the difference between heart rate at the end of an exercise test and after 1 min of recovery, known as the 1-min heart rate recovery, is  $\leq 12$  beats/min, this may indicate an abnormal delay. We sought to compare physical activity patterns and subjects' functional status with COPD with or without delayed 1-min heart rate recovery after the 6-min walk test (6MWT). METHODS: 145 subjects with COPD (78 men, median [interquartile range (IQR)] age 65 [60-73] y, body mass index 25 [21-30] kg/m<sup>2</sup>, FEV1 45  $\pm$  15% predicted) were underwent the following assessments: spirometry, 6MWT, functional status, and physical activity in daily life (PADL). A delayed heart rate recovery of 1 min was defined as  $\leq 12$  beats/min. RESULTS: Subjects with delayed 1-min heart rate recovery walked a shorter distance in the 6MWT compared to subjects without delayed heart rate recovery (median [IQR] 435 [390-507] m vs 477 [425-515] m,  $P = .01$ ; 81 [71-87] vs 87 [79-98]% predicted,  $P = .002$ ). Regarding PADL, subjects with delayed heart rate recovery spent less time in the standing position (mean  $\pm$  SD 185  $\pm$  89 min vs 250  $\pm$  107 min,  $P = .002$ ) and more time in sedentary positions (472  $\pm$  110 min vs 394  $\pm$  129 min,  $P = .002$ ). Scores based on the self-care domain of the London Chest Activity of Daily Living questionnaire and the activity domain of the Pulmonary Functional Status and Dyspnea questionnaire were also worse in the group with delayed heart rate recovery (6  $\pm$  2 points vs 5  $\pm$  2 points;  $P = .039$  and 29  $\pm$  24 points vs 19  $\pm$  17 points;  $P = .037$ , respectively). CONCLUSIONS: Individuals with COPD who exhibit delayed 1-min heart rate recovery after the 6MWT exhibited worse exercise capacity as well as a more pronounced sedentary lifestyle and worse functional status than those without delayed heart rate recovery. Despite its assessment simplicity, heart rate recovery after the 6MWT can be further explored as a promising outcome in COPD.

<http://rc.rcjournal.com/content/63/8/1002.short>

Mouronte-Roibas, C., V. Leiro-Fernandez, et al. (2018). "**Chronic Obstructive Pulmonary Disease in Lung Cancer Patients: Prevalence, Underdiagnosis, and Clinical Characterization.**" *Respiration* **95**(6): 414-421.

**BACKGROUND:** Lung cancer (LC) and chronic obstructive pulmonary disease (COPD) are associated with increased morbidity and mortality. The differential clinical and functional features among LC patients with or without COPD have not been defined. **OBJECTIVES:** The aims of this study were to examine the prevalence and underdiagnosis rate of COPD in LC patients and to compare the clinical and functional features of LC patients with and without COPD. **METHODS:** We designed a multicenter hospital-based study including all LC cases diagnosed from January 2014 to August 2016. We assessed epidemiological, clinical, radiological, functional, and histological variables in all cases. **RESULTS:** We recruited 602 patients with LC, most of them men (77.9%), with a median age of 67 +/- 15 years. The COPD prevalence among LC patients was 51.5%, with a underdiagnosis rate of 71.6%. The LC+COPD patients were older and the proportion of men was higher compared with the LC-only patients. The LC+COPD patients had more pack-years, more squamous LC, a lower monoxide transfer coefficient (KCO), and higher Charlson index scores than patients with LC only. The median survival of LC-only patients was 37% longer than that of LC+COPD patients (22 vs. 16 months), but this difference was not statistically significant. **CONCLUSIONS:** Among LC patients, COPD is prevalent and underdiagnosed. Patients with LC+COPD more often have squamous LC, have greater comorbidities, and have a lower KCO. More effort should be made for an early diagnosis of COPD to select patients at higher risk of developing LC.

<https://www.karger.com/Article/Abstract/487243>

Nikolic, E., T. Brandmajer, et al. (2018). "**Prevalence of Escherichia coli Resistant to Beta-Lactam Antibiotics among Patients with Chronic Obstructive Pulmonary Disease and Urinary Tract Infection.**" *Tohoku J Exp Med* **244**(4): 271-277.

Urinary tract infection (UTI), which is typically caused by *Escherichia coli* (*E. coli*), is an insufficiently recognized co-morbidity among patients with chronic obstructive pulmonary disease (COPD). Adequate treatment can be complicated by resistance of the causative pathogen to beta-lactam antibiotics, which often produce beta-lactamase enzymes that destroy the antibiotic. The beta-lactamase family of enzymes is extremely diverse, including different types of enzyme and mutant forms. In this study, we analyzed 580 patients with COPD (236 females and 344 males) and thus found 218 patients with co-morbid UTIs, including 58 patients with UTI caused by *E. coli* (38 females and 20 males). We also investigated cases of uncomplicated symptomatic and asymptomatic UTI caused by *E. coli* and the presence of resistance to beta-lactam antibiotics among those patients. The *E. coli* strains resistant to beta-lactam antibiotics were selected for their ability to grow on selective media, before DNA microarrays were applied for specific identification of three beta-lactamase gene types (i.e., TEM, SHV and CTX-M). Overall, 83% of *E. coli* strains responsible for UTIs in COPD patients carried extended-spectrum beta-lactamase genes. The most prevalent were those producing CTX-M, with CTX-M-15 being predominant. The rare CTX-M-27 and TEM-15 genes were also detected in two samples. Three samples contained several extended-spectrum beta-lactamase genes simultaneously (CTX-M-15 or CTX-M-14 plus SHV-5 or TEM-15). This high prevalence of resistant *E. coli* strains necessitates rational antibiotic selection when treating UTI to prevent COPD exacerbations. Additionally, antibiotic therapy should be aligned with and adapted to existing and potential COPD co-morbidities.

[https://www.jstage.jst.go.jp/article/tjem/244/4/244\\_271/\\_pdf](https://www.jstage.jst.go.jp/article/tjem/244/4/244_271/_pdf)

Ohno, Y., Y. Fujisawa, et al. (2018). "**Comparison of Xenon-Enhanced Area-Detector CT and Krypton Ventilation SPECT/CT for Assessment of Pulmonary Functional Loss and Disease Severity in Smokers.**" *AJR Am J Roentgenol* **210**(2): W45-w53.

OBJECTIVE: The objective of this study was to compare the capability of xenon-enhanced area-detector CT (ADCT) performed with a subtraction technique and coregistered (81m)Kr-ventilation SPECT/CT for the assessment of pulmonary functional loss and disease severity in smokers. SUBJECTS AND METHODS: Forty-six consecutive smokers (32 men and 14 women; mean age, 67.0 years) underwent prospective unenhanced and xenon-enhanced ADCT, (81m)Kr-ventilation SPECT/CT, and pulmonary function tests. Disease severity was evaluated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. CT-based functional lung volume (FLV), the percentage of wall area to total airway area (WA%), and ventilated FLV on xenon-enhanced ADCT and SPECT/CT were calculated for each smoker. All indexes were correlated with percentage of forced expiratory volume in 1 second (%FEV1) using step-wise regression analyses, and univariate and multivariate logistic regression analyses were performed. In addition, the diagnostic accuracy of the proposed model was compared with that of each radiologic index by means of McNemar analysis. RESULTS: Multivariate logistic regression showed that %FEV1 was significantly affected ( $r = 0.77$ ,  $r(2) = 0.59$ ) by two factors: the first factor, ventilated FLV on xenon-enhanced ADCT ( $p < 0.0001$ ); and the second factor, WA% ( $p = 0.004$ ). Univariate logistic regression analyses indicated that all indexes significantly affected GOLD classification ( $p < 0.05$ ). Multivariate logistic regression analyses revealed that ventilated FLV on xenon-enhanced ADCT and CT-based FLV significantly influenced GOLD classification ( $p < 0.0001$ ). The diagnostic accuracy of the proposed model was significantly higher than that of ventilated FLV on SPECT/CT ( $p = 0.03$ ) and WA% ( $p = 0.008$ ). CONCLUSION: Xenon-enhanced ADCT is more effective than (81m)Kr-ventilation SPECT/CT for the assessment of pulmonary functional loss and disease severity.

Oliveira, A., J. Rodrigues, et al. (2018). "**Enhancing our understanding of computerised adventitious respiratory sounds in different COPD phases and healthy people.**" *Respir Med* **138**: 57-63.

BACKGROUND: Timely diagnosis of acute exacerbations of COPD (AECOPD) is challenging as it depends on patients' reports. AECOPD are characterised by increased airway obstruction, mucus and air trapping, which results in changes in lung acoustics. Thus, adventitious respiratory sounds (ARS) may be useful to detect/monitor AECOPD. OBJECTIVE: To evaluate computerised ARS changes during AECOPD. METHODS: 25 non-hospitalised patients with AECOPD (16male symbol, 70 [62.5-77.0]yrs, FEV1 59 [31.5-73.0]%predicted) and 34 healthy volunteers (17male symbol, 63.5 [57.7-72.3]yrs, FEV1 103.0 [88.8-125.3]%predicted) were enrolled. ARS at anterior and posterior right and left chest were recorded at hospital presentation (T1), 15 days (T2) and 45 days (T3) after hospital presentation from patients with AECOPD and only once from healthy participants. A subsample of 9 patients (7male symbol; 66 [60.0-76.0]yrs; FEV1 62 [26.5-74.0]%predicted) was also included to study ARS pre-AECOPD (T0). Number of crackles and wheeze occupation rate (%Wh) were processed using validated algorithms. RESULTS: During AECOPD, patients presented more inspiratory crackles at T1 than T3 ( $p=0.013$ ) and more inspiratory %Wh at T1 than T2 ( $p=0.006$ ), at posterior chest. Patients with stable COPD presented more inspiratory crackles ( $p=0.012$ ), at posterior chest, and more expiratory %Wh, both at anterior ( $p<0.001$ ) and posterior ( $p=0.001$ ) chest, than healthy participants. No differences were observed for the remaining ARS parameters or subsamples ( $p>0.05$ ). CONCLUSIONS: Inspiratory crackles seem to persist until 15 days post exacerbation whilst inspiratory %Wh decreased after this period. ARS seem to be sensitive to monitor AECOPD. This information may allow advances in monitoring the recovery time of patients with AECOPD across all clinical and non-clinical settings.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30094-5/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30094-5/fulltext)

Ovali, C. and A. Sahin (2018). "**Chronic Obstructive Pulmonary Disease and Off-Pump Coronary Surgery.**" *Ann Thorac Cardiovasc Surg* **24**(4): 193-199.

**PURPOSE:** To determine to what extent chronic obstructive pulmonary disease (COPD) affects mortality and morbidity rates in patients treated with off-pump coronary artery bypass graft (CABG). **METHODS:** A total of 321 patients treated with off-pump CABG were included in the present study. Of the 321 patients, 46 patients had COPD and they were designated as Group 1 and the remaining 275 patients did not have COPD and they were considered as Group 2. We compared the data obtained from the patients in both groups. **RESULTS:** While preoperative spirometry values and arterial blood gas oxygen saturation levels were significantly lower, the partial values of carbon dioxide were higher in Group 1. Likewise, extubation time, the amount of drainage and blood transfusion, inotropic support, prolonged intubation, pulmonary complications, the use of bronchodilators, and steroids were statistically higher in Group 1 when compared with Group 2. Overall, there was no marked difference between the two groups in terms of mortality incidence. **CONCLUSION:** We found similar morbidity and mortality rates among the patients with COPD and without COPD when they were treated with off-pump CABG. Therefore, the present results indicate that the presence of COPD is not associated with in-hospital mortality or severe morbidity post-CABG by off-pump approach.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6102600/pdf/atcs-24-193.pdf>

Pan, L., S. Wu, et al. (2018). **"The short-term effects of indoor size-fractioned particulate matter and black carbon on cardiac autonomic function in COPD patients."** *Environ Int* **112**: 261-268.

**BACKGROUND:** Previous studies have reported adverse health effects of indoor air pollutants especially particulate matter (PM) and black carbon (BC). Patients with chronic obstructive pulmonary disease (COPD) have been shown to be more likely with cardiovascular comorbidities in which cardiac autonomic dysfunction plays an important role. However, there is little evidence for the effect of indoor PM and BC exposures on cardiac autonomic function in COPD patients. **OBJECTIVES:** To evaluate the association between exposure to indoor size-fractioned PM and BC and changes in HRV and HR in COPD patients. **METHODS:** Forty-three doctor diagnosed, stable COPD patients were recruited and measured for 24-h HRV and HR. Real-time indoor size-fractioned PM and BC were monitored on the day before and the day of performing health measurements. Mixed-effects models were used to estimate the associations between indoor PM and BC and HRV indices and HR after controlling for potential confounders. **RESULTS:** Increasing levels of size-fractioned PM and BC were associated with decreased HRV indices and increased HR. An IQR (3.14 $\mu\text{g}/\text{m}^3$ ) increase in 8-h BC moving average and an IQR (20.72 $\mu\text{g}/\text{m}^3$ ) increase in 5-min PM<sub>0.5</sub> moving average concentrations were associated with declines of 7.45% (95% CI: -10.89%, -3.88%) and 16.40% (95% CI: -21.06%, -11.41%) in LF, respectively. The smaller the particles size, the greater effects on HRV indices and HR. Patients' BMI modified the associations between size-fractioned PM and BC and their HRV and HR. For an IQR increase in PM<sub>0.5</sub>, there was decline in HF of 34.85% (95% CI: -39.08%, -30.33%) in overweight patients, compared to a 2.01% (95% CI: -6.44%, 11.19%) increase in normal-weight patients. **CONCLUSIONS:** Exposures to indoor PM and BC were associated with altered cardiac autonomic function in COPD patients, and the associations for HRV measures of parasympathetic activity (e.g., HF) were more apparent in overweight patients.

Regan, J., S. Lawson, et al. (2017). **"The Eating Assessment Tool-10 Predicts Aspiration in Adults with Stable Chronic Obstructive Pulmonary Disease."** *Dysphagia* **32**(5): 714-720.

Adults with COPD frequently present with dysphagia, which often leads to clinical complications and hospital admissions. This study investigates the ability of the Eating Assessment Tool (EAT-10) to predict aspiration during objective dysphagia evaluation in adults with stable COPD. Thirty adults (20 male, 10 female; mean age = 69.07 +/- 16.82) with stable COPD attended an outpatient dysphagia clinic for a fiberoptic endoscopic evaluation of swallowing (FEES) in an acute teaching hospital (January 2015- November 2016). During evaluations, individuals completed an EAT-10 rating scale followed immediately by a standardised FEES exam. Aspiration status during FEES was rated using the

penetration-aspiration scale by clinicians blinded to EAT-10 scores. Data were retrospectively analysed. Significant differences in mean EAT-10 scores were found between aspirators (16.3; SEM = 2.165) and non-aspirators (7.3; SEM = 1.009) ( $p = 0.000$ ). The EAT-10 predicted aspiration with a high level of accuracy (AUC = 0.88). An EAT-10 cut-off value of  $>9$  presented a sensitivity of 91.67, specificity of 77.78 with positive and negative likelihood ratios of 4.12 and 0.11, respectively. Positive and negative predictive values were 73.30 and 93.30, respectively. Diagnostic odds ratio was 38.50 ( $p < 0.01$ , CI 3.75-395.42). EAT-10 is a quick, easy to administer tool, which can accurately predict the presence of aspiration in adults with COPD. The scale can also very accurately exclude the absence of aspiration, helping clinicians to determine the need for onward referral for a comprehensive dysphagia evaluation. This may ultimately reduce clinical complications and hospital admissions resulting from dysphagia in this clinical population.

<https://link.springer.com/article/10.1007%2Fs00455-017-9822-2>

Rorth, R., E. L. Fosbol, et al. (2018). "**Employment status at time of first hospitalization for heart failure is associated with a higher risk of death and rehospitalization for heart failure.**" *Eur J Heart Fail* **20**(2): 240-247.

AIMS: Employment status at time of first heart failure (HF) hospitalization may be an indicator of both self-perceived and objective health status. In this study, we examined the association between employment status and the risk of all-cause mortality and recurrent HF hospitalization in a nationwide cohort of patients with HF. METHODS AND RESULTS: We identified all patients of working age (18-60 years) with a first HF hospitalization in the period 1997-2015 in Denmark, categorized according to whether or not they were part of the workforce at time of the index admission. The primary outcome was death from any cause and the secondary outcome was readmission for HF. Cumulative incidence curves, binomial regression and Cox regression models were used to assess outcomes. Of 25 571 patients with a first hospitalization for HF, 15 428 (60%) were part of the workforce at baseline. Patients in the workforce were significantly younger (53 vs. 55 years) more likely to be male (75% vs 64%) and less likely to have diabetes (13% vs 22%) and chronic obstructive pulmonary disease (5% vs 10%) (all  $P < 0.0001$ ). Not being part of the workforce was associated with a significantly higher risk of death [hazard ratio (HR) 1.59; 95% confidence interval (CI) 1.50-1.68] and rehospitalization for HF (HR 1.09; 95% CI 1.05-1.14), in analyses adjusted for age, sex, co-morbidities, education level, calendar time, and duration of first HF hospitalization. CONCLUSION: Not being part of the workforce at time of first HF hospitalization was independently associated with increased mortality and recurrent HF hospitalization.

<https://onlinelibrary.wiley.com/doi/abs/10.1002/ejhf.1046>

Saji, H., T. Miyazawa, et al. (2018). "**Survival significance of coexisting chronic obstructive pulmonary disease in patients with early lung cancer after curative surgery.**" *Thorac Cancer* **9**(1): 19-24.

BACKGROUND: The impact of chronic obstructive pulmonary disease (COPD) severity on survival after curative resection of early-stage lung cancer (NSCLC) has not been sufficiently elucidated. METHODS: We retrospectively reviewed 250 consecutive patients who underwent lobectomy with lymph nodal dissection for pathological stage I-II NSCLC. RESULTS: Among the COPD patients, 28 were classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1, 21 as GOLD 2, and one as GOLD 3. The cumulative overall survival (OS) of the non-COPD, GOLD 1, and GOLD 2-3 groups at five years was 90.7%, 85.7%, and 55.3%, respectively, ( $P < 0.0001$ ), while recurrence-free survival (RFS) between the groups at five years was 84.7%, 80.7%, and 72.9%, respectively. Although RFS in the GOLD 2-3 group tended to indicate a poor prognosis, there was no statistical difference between the groups ( $P = 0.385$ ). In multivariate analysis, age  $\geq 75$  years, pN1, and GOLD 2-3 COPD were independent factors for a poor prognosis ( $P = 0.034$ ,  $P = 0.010$ , and  $P = 0.030$ , respectively). CONCLUSIONS: Our results indicate that early stage NSCLC patients with COPD had a significantly increased risk of poorer OS and potentially an increased risk of poor RFS.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5754300/pdf/TCA-9-19.pdf>

Sakornsakolpat, P., J. D. Morrow, et al. (2018). **"Integrative genomics identifies new genes associated with severe COPD and emphysema."** *Respir Res* **19**(1): 46.

**BACKGROUND:** Genome-wide association studies have identified several genetic risk loci for severe chronic obstructive pulmonary disease (COPD) and emphysema. However, these studies do not fully explain disease heritability and in most cases, fail to implicate specific genes. Integrative methods that combine gene expression data with GWAS can provide more power in discovering disease-associated genes and give mechanistic insight into regulated genes. **METHODS:** We applied a recently described method that imputes gene expression using reference transcriptome data to genome-wide association studies for two phenotypes (severe COPD and quantitative emphysema) and blood and lung tissue gene expression datasets. We further tested the potential causality of individual genes using multi-variant colocalization. **RESULTS:** We identified seven genes significantly associated with severe COPD, and five genes significantly associated with quantitative emphysema in whole blood or lung. We validated results in independent transcriptome databases and confirmed colocalization signals for PSMA4, EGLN2, WNT3, DCBLD1, and LILRA3. Three of these genes were not located within previously reported GWAS loci for either phenotype. We also identified genetically driven pathways, including those related to immune regulation. **CONCLUSIONS:** An integrative analysis of GWAS and gene expression identified novel associations with severe COPD and quantitative emphysema, and also suggested disease-associated genes in known COPD susceptibility loci. **TRIAL REGISTRATION:** NCT00608764 , Registry: ClinicalTrials.gov, Date of Enrollment of First Participant: November 2007, Date Registered: January 28, 2008 (retrospectively registered); NCT00292552 , Registry: ClinicalTrials.gov, Date of Enrollment of First Participant: December 2005, Date Registered: February 14, 2006 (retrospectively registered).

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863845/pdf/12931\\_2018\\_Article\\_744.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863845/pdf/12931_2018_Article_744.pdf)

Savaria, F., M. F. Beauchesne, et al. (2017). **"Polypharmacy, chronic kidney disease, and benign prostatic hyperplasia in patients with chronic obstructive pulmonary disease newly treated with long-acting anticholinergics."** *Respir Med* **132**: 195-202.

[https://www.resmedjournal.com/article/S0954-6111\(17\)30362-1/fulltext](https://www.resmedjournal.com/article/S0954-6111(17)30362-1/fulltext)

Schafer, M., S. Humphries, et al. (2018). **"4D-flow cardiac magnetic resonance-derived vorticity is sensitive marker of left ventricular diastolic dysfunction in patients with mild-to-moderate chronic obstructive pulmonary disease."** *Eur Heart J Cardiovasc Imaging* **19**(4): 415-424.

**Aims:** To investigate the possibility that vorticity assessed by four-dimensional flow cardiac magnetic resonance (4D-Flow CMR) in the left ventricle of patients with mild-to-moderate chronic obstructive pulmonary disease (COPD) is a potential marker of early LV diastolic dysfunction (LVDD) and more sensitive than standard echocardiography, and whether changes in vorticity are associated with quantitative computed tomography (CT) and clinical markers of COPD, and right ventricular (RV) echocardiographic markers indicative of ventricular interdependency. **Methods and results:** Sixteen COPD patients with presumptive LVDD and 10 controls underwent same-day 4D-Flow CMR and Doppler echocardiography to quantify early and late diastolic vorticity as well as standard evaluation for LVDD. Furthermore, all patients underwent detailed CT analysis for COPD markers including percent emphysema and air trapping. The 4D-Flow CMR derived diastolic vorticity measures were correlated with CT measures, standard clinical and CMR markers, and echocardiographic diastolic RV metrics. Early diastolic vorticity was significantly reduced in COPD patients ( $P < 0.0001$ ) with normal left ventricular (LV) mass, geometry, systolic function, and no or mild signs of Doppler LVDD when compared with controls. Vorticity significantly differentiated COPD patients without echocardiographic signs of LVDD ( $n = 11$ ) from controls ( $P < 0.0001$ ), and from

COPD patients with stage I LVDD (n = 5) (P < 0.0180). Vorticity markers significantly correlated with CT computed measures, CMR-derived RV ejection fraction, echocardiographic RV diastolic metrics, and 6-minute walk test. Conclusion: 4D-Flow CMR derived diastolic vorticity is reduced in patients with mild-to-moderate COPD and no or mild signs of LVDD, implying early perturbations in the LV flow domain preceding more obvious mechanical changes (i.e. stiffening and dilation). Furthermore, reduced LV vorticity appears to be driven by COPD induced changes in lung tissue and parallel RV dysfunction.

[https://watermark.silverchair.com/jex069.pdf?token=AQECAHi208BE49Ooan9kkhW\\_Ercy7Dm3ZL\\_9Cf3qfKAc485ysgAAAmIwggJeBgkqhkiG9w0BBwagggJPMIICSwiBADCCAKQGCSqGSib3DQEHATAeBglghkgBZQMEAS4wEQQMJQYvxefUfgAxBZSeAgEQgIICFfRo6zW5JLKHrOWmRMY5rkv1TStHp2B5HXPVTquiFwgkRK26eYsXtqLmV6if0wbGENn9njygmizNwccWe5FCoNtbUMiWAtagp\\_Zbjb1U6KEGh0laGgDYKrEuhLoHvcxhyv1RVctMvWwMW52PN\\_ngeO5CqhT6mEqKbrC2W4-pg1F8SShdSW31NnwDSCuc52boBPriWQeTuDqvwXaxUQ\\_drfyhSOjvsOg3KgR1kqF4AuFtVFPX-M702cpz2vm\\_dPBFepFc7neOz6Bir8IFlvkDVxSKbjneT6lGBHC-5aUjugWbbtWFFvrSstoUah6vw9u6LRIAnRRZwG9-umHUKu682eAyYTMMG5jhhb-zkl2ybTfpTsbQZErNpu3QbEPT8OIkaTUdcZL0XdA6ZpnAKUwVY4yH668mh0sf5uRpMVQk\\_6vbW2UHBiEufE25ycQD7OYVJvboh8MgW6zIUZw8ErXr5f4TdjlrTvZfYM5SgRFsOx4FyeOvTB3kuoXFaexKLCDnzd1WmCGd81A72skiOFw-uk-tVB5SBihMAEJ2lq7SDz12-vHHWBq1ekqWMxD\\_DLa0ogN23D8vXFWVydNmNxz1QBW7ljrCVzCdwTKA8EEly94dqN6UaN7EzbHh7yr8GNTZQZGqlpVoBYhtEwf0FA9lfDsL2qFVOxm0hbEXMVoLgy2VXuNbQEJFXCo-Cyj0lqsnLjkNH2h](https://watermark.silverchair.com/jex069.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAmIwggJeBgkqhkiG9w0BBwagggJPMIICSwiBADCCAKQGCSqGSib3DQEHATAeBglghkgBZQMEAS4wEQQMJQYvxefUfgAxBZSeAgEQgIICFfRo6zW5JLKHrOWmRMY5rkv1TStHp2B5HXPVTquiFwgkRK26eYsXtqLmV6if0wbGENn9njygmizNwccWe5FCoNtbUMiWAtagp_Zbjb1U6KEGh0laGgDYKrEuhLoHvcxhyv1RVctMvWwMW52PN_ngeO5CqhT6mEqKbrC2W4-pg1F8SShdSW31NnwDSCuc52boBPriWQeTuDqvwXaxUQ_drfyhSOjvsOg3KgR1kqF4AuFtVFPX-M702cpz2vm_dPBFepFc7neOz6Bir8IFlvkDVxSKbjneT6lGBHC-5aUjugWbbtWFFvrSstoUah6vw9u6LRIAnRRZwG9-umHUKu682eAyYTMMG5jhhb-zkl2ybTfpTsbQZErNpu3QbEPT8OIkaTUdcZL0XdA6ZpnAKUwVY4yH668mh0sf5uRpMVQk_6vbW2UHBiEufE25ycQD7OYVJvboh8MgW6zIUZw8ErXr5f4TdjlrTvZfYM5SgRFsOx4FyeOvTB3kuoXFaexKLCDnzd1WmCGd81A72skiOFw-uk-tVB5SBihMAEJ2lq7SDz12-vHHWBq1ekqWMxD_DLa0ogN23D8vXFWVydNmNxz1QBW7ljrCVzCdwTKA8EEly94dqN6UaN7EzbHh7yr8GNTZQZGqlpVoBYhtEwf0FA9lfDsL2qFVOxm0hbEXMVoLgy2VXuNbQEJFXCo-Cyj0lqsnLjkNH2h)

Schwarzkopf, L., S. Witt, et al. (2018). "**Associations between comorbidities, their treatment and survival in patients with interstitial lung diseases - a claims data analysis.**" *Respir Res* 19(1): 73.

BACKGROUND: Interstitial lung diseases (ILDs) are associated with a high burden of disease. However, data on the prognostic impact of comorbidities and comorbidity-related pharmaceutical treatments in patients with various ILDs remain sparse. METHODS: Using longitudinal claims data from a German Statutory Health Insurance Fund, we assessed comorbidity in ILD subtypes and associated drug treatments. Baseline comorbidity was assessed via the Elixhauser Comorbidity Index that was amended by ILD-relevant conditions. Drug treatment was assessed on the substance level using the ATC-codes of drugs prescribed at the time of ILD diagnosis. Subsequently, the comorbid conditions (main analysis) and pharmaceutical substances (secondary analysis) with a meaningful association to survival were identified for the complete ILD cohort and within the subtype strata. For this, we applied multivariate Cox models using a LASSO selection process and visualized the findings within comorbidomes. RESULTS: In the 36,821 patients with ILDs, chronic obstructive pulmonary disease (COPD), arterial hypertension, and ischaemic heart disease (IHD) were the most prevalent comorbidities. The majority of patients with cardiovascular diseases received pharmaceutical treatment, while, in other relevant comorbidities, treatment quotas were low (COPD 46%, gastro-oesophageal reflux disease 65%). Comorbidities had a clinically meaningful detrimental effect on survival that tended to be more pronounced in the case of untreated conditions (e.g. hazard ratios for treated IHD 0.97 vs. 1.33 for untreated IHD). Moreover, comorbidity impact varied substantially between distinct subtypes. CONCLUSIONS: Our analyses suggest that comorbid conditions and their treatment profile significantly affect mortality in various ILDs. Therefore, comprehensive comorbidity assessment and management remains important in any ILD.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5918773/pdf/12931\\_2018\\_Article\\_769.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5918773/pdf/12931_2018_Article_769.pdf)

Shah, S., C. M. Blanchette, et al. (2018). "**Healthcare utilization and costs associated with COPD among SEER-Medicare beneficiaries with NSCLC.**" *J Med Econ* 21(9): 861-868.

AIM: To estimate the healthcare utilization and costs in elderly lung cancer patients with and without pre-existing chronic obstructive pulmonary disease (COPD). METHODS: Using Surveillance, Epidemiology and End Results (SEER)-Medicare data, this study identified patients with lung cancer between 2006-2010, at least 66 years of age, and continuously enrolled in Medicare Parts A and B in the 12 months prior to cancer diagnosis. The diagnosis of pre-existing COPD in lung cancer patients was identified using ICD-9 codes.

Healthcare utilization and costs were categorized as inpatient hospitalizations, skilled nursing facility (SNF) use, physician office visits, ER visits, and outpatient encounters for every stage of lung cancer. The adjusted analysis was performed using a generalized linear model for healthcare costs and a negative binomial model for healthcare utilization. RESULTS: Inpatient admissions in the COPD group increased for each stage of non-small cell lung cancer (NSCLC) compared to the non-COPD group per 100 person-months (Stage I: 14.67 vs 9.49 stays,  $p < .0001$ ; Stage II: 14.13 vs 10.78 stays,  $p < .0001$ ; Stage III: 28.31 vs 18.91 stays,  $p < .0001$ ; Stage IV: 49.5 vs 31.24 stays,  $p < .0001$ ). A similar trend was observed for outpatient visits, with an increase in utilization among the COPD group (Stage I: 1136.04 vs 796 visits,  $p < .0001$ ; Stage II: 1325.12 vs 983.26 visits,  $p < .0001$ ; Stage III: 2025.47 vs 1656.64 visits,  $p < .0001$ ; Stage IV: 2825.73 vs 2422.26 visits,  $p < .0001$ ). Total direct costs per person-month in patients with pre-existing COPD were significantly higher than the non-COPD group across all services (\$54,799.16 vs \$41,862.91). Outpatient visits represented the largest cost category across all services in both groups, with higher costs among the COPD group (\$41,203 vs \$31,140.08). CONCLUSION: Healthcare utilization and costs among lung cancer patients with pre-existing COPD was approximately 2-3-times higher than the non-COPD group.

<https://www.tandfonline.com/doi/full/10.1080/13696998.2018.1484370>

Sharif, K., A. Watad, et al. (2018). **"The link between COPD and ankylosing spondylitis: A population based study."** *Eur J Intern Med* **53**: 62-65.

BACKGROUND: Ankylosing spondylitis (AS) is one of the most common and severe subtypes of the spondyloarthropathies. Extra-articular involvement among AS patients, including lung disease, has been described widely. Chronic obstructive pulmonary disease (COPD) has been linked to several autoimmune diseases, however, very few studies have investigated the association between AS and COPD. OBJECTIVE: To assess whether an association exists between AS and COPD. MATERIAL AND METHODS: A population-based cross-sectional study was conducted using data retrieved from the largest electronic medical records database in Israel, the Clalit Health Services (CHS). Patients were defined as having AS or COPD when there was at least one such documented diagnosis in their medical records. The proportion of COPD was compared between AS patients and controls. A logistic regression model was used to estimate the association between AS and COPD in a multivariate analysis adjusted for age, gender and smoking status. RESULTS: The study included 4076 patients with AS and 20,290 age- and sex-frequency matched controls. The proportion of COPD in AS patients was higher than in controls (46% vs. 18%, respectively,  $p < .001$ ). Multivariate logistic regression demonstrated a robust independent association between AS and COPD (OR 1.225,  $p = .031$ ). CONCLUSION: Our study supports an association between AS and COPD, further extending the link between COPD and autoimmune diseases. This finding highlights the importance of smoking cessation in AS patients and raises the question of whether COPD screening may be warranted.

[https://www.ejinme.com/article/S0953-6205\(18\)30139-0/fulltext](https://www.ejinme.com/article/S0953-6205(18)30139-0/fulltext)

Simon, M., L. Harbaum, et al. (2018). **"Endoscopic lung volume reduction coil treatment in patients with very low FEV1: an observational study."** *Ther Adv Respir Dis* **12**: 1753466618760133.

BACKGROUND: Endoscopic lung volume reduction coil (LVRC) treatment is a therapeutic option for selected patients with advanced emphysema. The effects and the safety of endoscopic lung volume reduction in patients with very low forced expired volume in one second (FEV1) remain to be determined. This study was conducted to assess the effects and the safety of LVRC treatment in patients with very low FEV1. METHODS: The study was performed as a retrospective observational study in the Department of Respiratory Medicine at the University Medical Center Hamburg-Eppendorf on patients with very low FEV1, defined as an FEV1 20% of predicted at baseline in whom LVRC treatment was performed between 1 April 2012 and 28 February 2017. RESULTS: LVRC treatment was performed in 33 patients with very low FEV1. Of these, 45.5% were female and 54.5% were male. At baseline, mean FEV1 was 0.46 +/- 0.12 liters (15 +/- 3% of predicted), mean forced vital capacity (FVC) was 1.61 +/- 0.62 liters (42 +/- 13% of

predicted), mean residual volume (RV) was 6.03 +/- 0.81 liters (275 +/- 51% of predicted) and 6-minute walk distance was 229 +/- 102 m. Bilateral LVRC treatment was completed in 21 of these patients (63.6%). Bilateral LVRC treatment led to significant improvements in functional parameters with an increase in mean FEV1 from 0.44 +/- 0.11 liters to 0.54 +/- 0.12 liters ( p = 0.001), equivalent to a relative improvement of 24.5 +/- 26.9%, an increase in mean FVC from 1.49 +/- 0.54 liters to 1.84 +/- 0.49 liters ( p = 0.001), a decrease in mean RV from 6.27 +/- 0.83 liters to 5.83 +/- 1.09 liters ( p = 0.004) and an improvement in 6-minute walk distance from 218 +/- 91 m to 266 +/- 96 m ( p = 0.01). There were no cases of respiratory failure requiring mechanical ventilation and no deaths. CONCLUSIONS: LVRC treatment was effective and safe in patients with very low FEV1.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5937153/pdf/10.1177\\_1753466618760133.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5937153/pdf/10.1177_1753466618760133.pdf)

Sprooten, R. T. M., K. Lenaerts, et al. (2018). "**Increased Small Intestinal Permeability during Severe Acute Exacerbations of COPD.**" *Respiration* **95**(5): 334-342.

BACKGROUND: Disturbances of intestinal integrity, manifested by increased gastro-intestinal (GI) permeability, have been found in chronic obstructive pulmonary disease (COPD) patients during physical activity, often associated with intermittent hypoxic periods. Evidence about extrapulmonary organ disturbances, especially of the GI tract, during hospitalised acute exacerbation of COPD (AE-COPD) with hypoxaemic respiratory failure (RF) is lacking. OBJECTIVE: The aim was to assess changes in GI permeability in patients with AE-COPD and during recovery 4 weeks later. METHODS: All patients admitted to our hospital with AE-COPD accompanied by hypoxaemia at admission (PaO<sub>2</sub> <8.7 kPa or O<sub>2</sub> saturation <93%) were screened between October 2013 and February 2014. Patients with a history of GI or renal disease, chronic heart failure, or use of non-steroidal anti-inflammatory drugs in the 48 h before the test were excluded. GI permeability was assessed by evaluating urinary excretion ratios of the orally ingested sugars lactulose/L-rhamnose (L/R ratio), sucrose/L-rhamnose (Su/R ratio) and sucralose/erythritol (S/E ratio). RESULTS: Seventeen patients with severe to very severe COPD completed the study. L/R ratio (x103) at admission of AE-COPD was significantly higher than in the recovery condition (40.9 [29.4-49.6] vs. 27.3 [19.5-47.7], p = 0.039), indicating increased small intestinal permeability. There were no significant differences in the individual sugar levels in urine nor in the 0- to 5-h urinary S/E and Su/R ratios between the 2 visits. CONCLUSION: This is the first study showing increased GI permeability during hospitalised AE-COPD accompanied by hypoxaemic RF. Therefore, GI integrity in COPD patients is an attractive target for future research and for the development of interventions to alleviate the consequences of AE-COPD.

<https://www.karger.com/Article/Pdf/485935>

Steinemann, N., L. Grize, et al. (2018). "**Associations between Dietary Patterns and Post-Bronchodilation Lung Function in the SAPALDIA Cohort.**" *Respiration* **95**(6): 454-463.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is not restricted to smokers. Dietary habits may contribute to the disease occurrence. Epidemiological studies point to a protective effect of fruit and vegetable intake against COPD. OBJECTIVE: To investigate the associations between dietary patterns and parameters of lung function related to COPD in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA). METHODS: Data were included from the second follow-up assessment of the SAPALDIA cohort in 2010-2011 using a food frequency questionnaire. Principal component factor analysis was used to derive dietary patterns, whose association with FEV1, FEV1/FVC, FEF2575, and COPD was investigated by applying multivariate regression analyses. RESULTS: After adjustment for potential confounders, the "prudent dietary pattern" characterised by the predominant food groups vegetables, fruits, water, tea and coffee, fish, and nuts was positively associated with FEV1 (increase of 40 mL per SD, p < 0.001). Also for factor 3 ("high-carbohydrate diet"), we found a significant positive association with FEV1 (with an increase per SD of 36 mL, p = 0.006). CONCLUSIONS: The main results are consistent with a protective effect of a diet rich in fruits, vegetables, fish, and nuts against

age-related chronic respiratory disease. If confirmed in prospective cohorts, our results may guide nutritional counselling towards respiratory health promotion.

<https://www.karger.com/Article/Pdf/488148>

Stephenson, S. E., C. L. Wilson, et al. (2018). "**Impact of HIV infection on alpha1-antitrypsin in the lung.**" *Am J Physiol Lung Cell Mol Physiol* **314**(4): L583-L592.

Emphysema is one of the most common lung diseases in HIV(+) individuals. The pathogenesis of HIV-associated emphysema remains unclear; however, radiographic distribution and earlier age of presentation of emphysema in the lungs of HIV(+) patients are similar to deficiency of alpha1-antitrypsin (A1AT), a key elastase inhibitor in the lung. Reduced levels of circulating A1AT in HIV(+) patients suggest a potential mechanism for emphysema development. In the present study we asked if A1AT levels and activity in the bronchoalveolar lavage fluid (BALF) differ in HIV(+) and HIV(-) patients with and without emphysema. A1AT levels were measured by ELISA in plasma and BALF from a cohort of 21 HIV(+) and 29 HIV(-) patients with or without emphysematous changes on chest CT scan. To analyze A1AT function, we measured elastase activity in the BALF and assessed oxidation and polymerization of A1AT by Western blotting. Total A1AT was increased in the BALF, but not in the plasma, of HIV(+) compared with HIV(-) patients, regardless of the presence or absence of emphysema. However, antielastase activity was decreased in BALF from HIV(+) patients, suggesting impaired A1AT function. Higher levels of the oxidized form of A1AT were detected in BALF from HIV(+) than HIV(-) patients, which may account for the decreased antielastase activity. These findings suggest that, in the lungs of HIV(+) patients, posttranslational modifications of A1AT produce a "functional deficiency" of this critical elastase inhibitor, which may contribute to emphysema development.

<https://www.physiology.org/doi/abs/10.1152/ajplung.00214.2017>

Stockley, R. A., R. G. Edgar, et al. (2018). "**Health status decline in alpha-1 antitrypsin deficiency: a feasible outcome for disease modifying therapies?**" *Respir Res* **19**(1): 137.

**BACKGROUND:** Trials of disease modifying therapies in Chronic Obstructive Pulmonary Disease (COPD) provide challenges for detecting physiological and patient centred outcomes. The purpose of the current study was to monitor decline in health status in Alpha-1 antitrypsin deficiency (AATD) and determine its' relationship to conventional physiology. **METHODS:** Patients recruited to the UK-AATD database with a median follow up of 7 years (IQR 5-10) were studied to determine annual change in St George's Respiratory Questionnaire (SGRQ), FEV1, gas transfer and their feasibility of use in future trials. **RESULTS:** Annual decline in SGRQ had a wide range, was greater for patients with established COPD and correlated with decline in FEV1 ( $p < 0.0001$ ). Total score decline was greater ( $p < 0.05$ ) for those with accelerated FEV1 decline (median = 1.07 points/year) compared to those without (median = 0.51). Power calculations indicated effective intervention would not achieve MCID for the SGRQ unless the timeframe was extended for up to 8 years. More than 5000 patients/arm would be required for a statistically significant modest effect over 3 years even in those with rapid FEV1 decline. **CONCLUSION:** Despite AATD being a rapidly declining form of COPD, deterioration in SGRQ was slow consistent with ageing and the chronic nature of disease progression. Power calculations indicate the numbers needed to detect a difference with disease modifying therapies would be prohibitive especially in this rare cause of COPD. These data have important implications for future study design of disease modifying therapies even in COPD not associated with AATD.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6053712/pdf/12931\\_2018\\_Article\\_844.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6053712/pdf/12931_2018_Article_844.pdf)

Stroda, A., V. Brandenburg, et al. (2018). "**Serum phosphate and phosphate-regulatory hormones in COPD patients.**" *Respir Res* **19**(1): 183.

**BACKGROUND:** Fibroblast growth factor 23 (FGF23) regulates phosphate metabolism by increasing renal phosphate excretion and decreasing 1.25-dihydroxyvitamin D synthesis. Reports about hypophosphatemia in patients with chronic obstructive pulmonary disease (COPD) suggest altered phosphate metabolism. Therefore, we hypothesized that disturbances in phosphate-regulatory hormones such as FGF23 and parathyroid hormone (PTH) are present in COPD patients. **METHODS:** We investigated 40 COPD patients (63.5 +/- 9.9 years, 27 male), each matched with two age- and sex-matched controls without any primary lung disease. COPD patients underwent lung function testing in advance. All patients had a glomerular filtration rate (GFR) > 60 mL/min/1.73m<sup>2</sup>. We measured concentrations of intact FGF23 (iFGF23) and c-terminal FGF23 (c-term FGF23), phosphate, parathyroid hormone (PTH) and C-reactive protein (CRP) levels in COPD patients and controls. **RESULTS:** Phosphate (1.0 +/- 0.2 vs. 1.1 +/- 0.2 mmol/L; p = 0.027), PTH (54.2 +/- 29.4 vs. 68.7 +/- 31.8 pg/mL; p = 0.002) and iFGF23 (46.3 +/- 29.0 vs. 57.5 +/- 33.5 pg/mL; p = 0.026) levels were significantly lower in COPD patients compared with controls. There was a significant negative correlation between c-term FGF23 and total lung capacity (r = - 0.4; p = 0.01), and between c-term FGF23 and CRP in COPD patients (r = 0.48; p = 0.002). iFGF23 and c-term FGF23 were positively correlated with phosphate and PTH in the control group. **CONCLUSION:** We confirmed lower average serum phosphate levels in COPD patients compared with controls. However, our data do not suggest a causative role for FGF23 or PTH in COPD because levels of both phosphate-lowering hormones appear to be adaptively decreased as well. Therefore, further investigations are needed to identify the pathogenesis of low phosphate levels in patients with COPD and the relationship between phosphate-regulatory hormones and disease progression.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6149072/pdf/12931\\_2018\\_Article\\_889.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6149072/pdf/12931_2018_Article_889.pdf)

Swanson, J. O., V. Vogt, et al. (2018). "**Continuity of care and its effect on readmissions for COPD patients: A comparative study of Norway and Germany.**" *Health Policy* **122**(7): 737-745.

**BACKGROUND:** This study compares continuity of care between Germany - a social health insurance country, and Norway - a national health service country with gatekeeping and patient lists for COPD patients before and after initial hospitalization. We also investigate how subsequent readmissions are affected. **METHODS:** Continuity of Care Index (COCI), Usual Provider Index (UPC) and Sequential Continuity Index (SECON) were calculated using insurance claims and national register data (2009-14). These indices were used in negative binomial and logistic regressions to estimate incident rate ratios (IRR) and odds ratios (OR) for comparing readmissions. **RESULTS:** All continuity indices were significantly lower in Norway. One year readmissions were significantly higher in Germany, whereas 30-day rates were not. All indices measured one year after discharge were negatively associated with one-year readmissions for both countries. Significant associations between indices measured before hospitalization and readmissions were only observed in Norway - all indices for one-year readmissions and SECON for 30-day readmissions. **CONCLUSION:** Our findings indicate higher continuity is associated with reductions in readmissions following initial COPD admission. This is observed both before and after hospitalization in a system with gatekeeping and patient lists, yet only after for a system lacking such arrangements. These results emphasize the need for policy strategies to further investigate and promote care continuity in order to reduce hospital readmission burden for COPD patients.

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Tee, A., W. L. Chow, et al. (2018). "**Cost-effectiveness of indacaterol/glycopyrronium in comparison with salmeterol/fluticasone combination for patients with moderate-to-severe chronic obstructive pulmonary disease: a LANTERN population analysis from Singapore.**" *Singapore Med J* **59**(7): 383-389.

**INTRODUCTION:** In light of the growing evidence base for better clinical results with the use of the dual bronchodilator indacaterol/glycopyrronium (IND/GLY) over inhaled corticosteroid-containing salmeterol/fluticasone combination (SFC), this study aimed to evaluate the cost-effectiveness of IND/GLY over SFC in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) who are at low risk of exacerbations, in the Singapore healthcare setting. **METHODS:** A previously published patient-level simulation model was adapted for use in Singapore by applying local unit costs. The model was populated with clinical data from the LANTERN and ECLIPSE studies. Both costs and health outcomes were predicted for the lifetime horizon from a payer's perspective and were discounted at 3% per annum. Costs were expressed in 2015 USD exchange rates. Uncertainty was assessed through probabilistic sensitivity analysis. **RESULTS:** Compared to SFC, use of IND/GLY increased mean life expectancy by 0.316 years and mean quality-adjusted life years (QALYs) by 0.246 years, and decreased mean total treatment costs (drug costs and management of associated events) by USD 1,474 over the entire lifetime horizon. IND/GLY was considered to be 100% cost-effective at a threshold of 1 x gross domestic product per capita. The cost-effectiveness acceptability curve showed that IND/GLY was 100% cost-effective at a willingness-to-pay threshold of USD 0 (additional cost) when compared to SFC. **CONCLUSION:** IND/GLY was estimated to be highly cost-effective compared to SFC in patients with moderate-to-severe COPD who are not at high risk of exacerbations in the Singapore healthcare setting.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6056374/pdf/SMJ-59-383.pdf>

Tonga, K. O., G. G. King, et al. (2018). "**Steroid insensitive fixed airflow obstruction is not related to airway inflammation in older non-smokers with asthma.**" *Respir Res* **19**(1): 176.

There is limited evidence linking airway inflammation and lung function impairment in older non-smoking asthmatics with fixed airflow obstruction (FAO), which can develop despite treatment with inhaled corticosteroids (ICS). We assessed lung function (spirometry, forced oscillation technique (FOT)), lung elastic recoil and airway inflammation using bronchoalveolar lavage (BAL) in non-smoking adult asthmatics with FAO, following 2 months treatment with high-dose ICS/long-acting beta-agonist. Subjects demonstrated moderate FAO, abnormal FOT indices and loss of lung elastic recoil. This cross-sectional study showed a lack of a relationship between BAL neutrophils, eosinophils, inflammatory cytokines and lung function impairment. Other inflammatory pathways or the effect of inflammation on lung function over time may explain FAO development.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142701/pdf/12931\\_2018\\_Article\\_880.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142701/pdf/12931_2018_Article_880.pdf)

Tuluze, D. and S. Kutluturkan (2018). "**The effect of health coaching on treatment adherence, self-efficacy, and quality of life in patients with chronic obstructive pulmonary disease.**" *Int J Nurs Pract* **24**(4): e12661.

**AIM:** The aim of this study was to determine the impact of health coaching on respiratory functions, treatment adherence, self-efficacy, and quality of life in chronic obstructive pulmonary disease patients. **METHODS:** This study was conducted as an experimental study with non-randomized control group in chronic obstructive pulmonary disease individuals. The study group included a total of 54 chronic obstructive pulmonary disease patients (27 patients both health coaching and control groups), was selected between 13 July 2016 and 2 July 2017. Data were collected by using a questionnaire form, St. George Respiratory Questionnaire, 8-Item Morisky Adherence Scale, and chronic obstructive pulmonary disease Self-Efficacy Scale. A total of 12 coaching interviews were conducted with the patients in the health coaching group. **RESULTS:** After health coaching intervention, self-efficacy scale general score, and St. George Respiratory Questionnaire, total scores were found statistically significant different between 2 groups in interaction values. There was a significant difference in the 8-Item Morisky Adherence Scale scores for degree of treatment adherence between the groups. **CONCLUSION:** The health coaching intervention is recommended, as it contributes to facilitate the treatment adherence and increase the self-efficacy skills by improving the quality of life of the chronic obstructive pulmonary disease patients.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/ijn.12661>

Ugur, M. G., R. Kutlu, et al. (2018). "**The effects of smoking on vascular endothelial growth factor and inflammation markers: A case-control study.**" *Clin Respir J* **12**(5): 1912-1918.

BACKGROUND AND AIMS: Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease characterized by long-term poor airflow. Tobacco smoking is the most common cause of COPD. In this study, we aimed to assess the vascular endothelial growth factor (VEGF) and inflammation markers on smokers and non-smoking individuals. METHODS: Our study was a case-control study and 175 individuals who want to give up smoking constituted the case group. As a control group, 175 individuals who never smoked. RESULTS: The mean age of 350 participants was 35.83 +/- 13.11 years. Educational status of the non-smokers was significantly higher than that of the smoking group ( $P < .001$ ). When smoking and non-smoking groups were compared in terms of VEGF and interleukin-6 (IL-6), it was found that these values were statistically higher in smokers than non-smokers ( $P < .001$ ). The levels of IL-10 were found to be higher in non-smokers than in smokers ( $P < .001$ ). Although a moderate positive correlation was found between VEGF and IL-6 levels ( $r = .486$ ,  $P < .001$ ), there was a weak negative correlation between VEGF and IL-10 ( $r = -.210$ ,  $P < .001$ ). A weak negative correlation was found between IL-6 and IL-10 ( $r = -.185$ ,  $P < .001$ ). CONCLUSIONS: In our study, IL-6 inflammatory marker and VEGF levels were found to be high and IL-10 anti-inflammatory marker was discovered to be low in smokers. For this reason, raising awareness in the society about the harms of smoking and encouraging people to give it up have become more challenging to counteract the inflammatory effects of smoking in human body and to prevent many smoking-related diseases.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12755>

van Geffen, W. H., B. Hajian, et al. (2018). "**Functional respiratory imaging: heterogeneity of acute exacerbations of COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 1783-1792.

Background: Exacerbations of COPD are a major burden to patients, and yet little is understood about heterogeneity. It contributes to the current persistent one-size-fits-all treatment. To replace this treatment by more personalized, precision medicine, new insights are required. We assessed the heterogeneity of exacerbations by functional respiratory imaging (FRI) in 3-dimensional models of airways and lungs. Methods: The trial was designed as a multicenter trial of patients with an acute exacerbation of COPD who were assessed by FRI, pulmonary function tests, and patient-reported outcomes, both in the acute stage and during resolution. Results: Forty seven patients were assessed. FRI analyses showed significant improvements in hyperinflation (a decrease in total volume at functional residual capacity of  $-0.25 \pm 0.61$  L,  $p < 0.01$ ), airway volume at total lung capacity ( $+1.70 \pm 4.65$  L,  $p = 0.02$ ), and airway resistance. As expected, these improvements correlated partially with changes in the quality of life and in conventional lung function test parameters. Patients with the same changes in pulmonary function differ in regional disease activity measured by FRI. Conclusion: FRI is a useful tool to get a better insight into exacerbations of COPD, and significant improvements in its indices can be demonstrated from the acute phase to resolution even in relatively small groups. It clearly visualizes the marked variability within and between individuals in ventilation and resistance during exacerbations and is a tool for the assessment of the heterogeneity of COPD exacerbations.

<https://www.dovepress.com/getfile.php?fileID=42379>

Vanzella, L. M., A. F. B. Bernardo, et al. (2018). "**Complexity of autonomic nervous system function in individuals with COPD.**" *J Bras Pneumol* **44**(1): 24-30.

OBJECTIVE: To evaluate autonomic modulation in individuals with COPD, compared with healthy controls, via recurrence plots (RPs) and linear heart rate variability (HRV) indices. METHODS: We analyzed data on 74

volunteers, who were divided into two groups: COPD (n = 43) and control (n = 31). For calculation of HRV indices, heart rate was measured beat-by-beat during 30 min of supine rest using a heart-rate meter. We analyzed linear indices in the time and frequency domains, as well as indices derived from the RPs. RESULTS: In comparison with the control group, the COPD group showed significant increases in the indices derived from the RPs, as well as significant reductions in the linear indices in the time and frequency domains. No significant differences were observed in the linear indices in the frequency domains expressed in normalized units or in the low frequency/high frequency ratio. CONCLUSIONS: Individuals with COPD show a reduction in both sympathetic and parasympathetic activity, associated with decreased complexity of autonomic nervous system function, as identified by RPs, which provide important complementary information in the detection of autonomic changes in this population.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6104537/pdf/1806-3713-jbpneu-44-01-00024.pdf>

Varmaghani, M., A. Kebriaeezadeh, et al. (2018). "**Death-specific rate due to asthma and chronic obstructive pulmonary disease in Iran.**" *Clin Respir J* 12(6): 2075-2083.

BACKGROUND AND OBJECTIVE: Asthma and chronic obstructive pulmonary disease (COPD) could be considered as a major health problem in industrialized and developing countries. This study was designed to analyze the trends of mortality from asthma and COPD at national and subnational levels in Iran based on National Death Registry, from 2001 to 2015. MATERIALS AND METHODS: We used Death Registration System (DRS) as the basic source of data. Death Registration System data were available from 1995 to 2010 in Iran's Ministry of Health. Although, Tehran and Isfahan, 2 most populated cities in Iran, had independent death registry systems in their cemeteries, by combining their data we achieved more comprehensive and representative data on death among Iranian people. We addressed incompleteness and misclassification of death registry system using demographic and statistical methods. We also employed spatio-temporal and Gaussian process regression to extrapolate and interpolate mortality rates for the missing data. RESULTS: Age-standardized asthma mortality rate was 7.2 (5.6-9.2) in females and 8.8 (6.9-11.1) in males at the national level in 2015. Age-standardized COPD mortality rates in females and males, respectively, were 8.46 (6.6-10.9) and 12.38 (9.8-15.6) during the studied years. A reduction in age-standardized asthma mortality was observed during the period of study. In addition, the trend of COPD mortality was increasing. CONCLUSIONS: It seems that mortality rate attributable to COPD has risen during the past 15 years in Iran. It could have increased because of increased exposure of people to related risk factors such as air pollution which is a common problem in larger cities and border provinces.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12776>

Varol, Y., C. Anar, et al. (2017). "**Sex-related differences in COPD Assessment Test scores of COPD population with or without significant anxiety and/or depression.**" *Turk J Med Sci* 47(1): 61-68.

BACKGROUND/AIM: Sex-related differences have not been thoroughly explored in chronic obstructive pulmonary disease (COPD). We aimed to evaluate possible sex-related differences in COPD Assessment Test (CAT) scores of COPD patients with or without significant anxiety and/or depression. MATERIALS AND METHODS: Stable COPD patients were prospectively enrolled in the study between July 2013 and April 2014. Levels of anxiety, depression, dyspnea, and health-related quality of life parameters were assessed using specific questionnaires, including the CAT and others. Demographic and clinical data were recorded and physiological tests were performed. All the data were compared to determine any sex-related differences. RESULTS: A total of 128 COPD patients (86 men, 42 women, mean age: 60.5 +/- 9.3 years) were included. The women were significantly younger and had lower pack-years of cigarette smoking, and higher biomass smoke exposure, but displayed similarly severe COPD as compared to men. Beck anxiety (13.5-11) and Beck depression (15-11) inventory results were significantly higher in women than men (P = 0.04, P = 0.01). No statistically significant difference was found between the sexes in terms of CAT score, Modified Medical Research Council score, or COPD stage parameters (P > 0.05).

CONCLUSION: Female patients have higher levels of depression and anxiety scores but present the same CAT scores related to COPD severity as compared to men.

Wada, Y., Y. Kitaguchi, et al. (2018). "**Diversity of respiratory impedance based on quantitative computed tomography in patients with COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 1841-1849.

Introduction: This study was conducted in order to investigate the diversity of respiratory physiology, including the respiratory impedance and reversibility of airway obstruction, based on quantitative computed tomography (CT) in patients with COPD. Patients and methods: Medical records of 174 stable COPD patients were retrospectively reviewed to obtain the patients' clinical data, including the pulmonary function and imaging data. According to the software-based quantification of the degree of emphysema and airway wall thickness, the patients were classified into the "normal by CT" phenotype, the airway-dominant phenotype, the emphysema-dominant phenotype, and the mixed phenotype. The pulmonary function, including the respiratory impedance evaluated by using the forced oscillation technique (FOT) and the reversibility of airway obstruction in response to inhaled short-acting beta2-agonists, was then compared among the four phenotypes. Results: The respiratory system resistance at 5 and 20 Hz (R5 and R20) was significantly higher, and the respiratory system reactance at 5 Hz (X5) was significantly more negative in the airway-dominant and mixed phenotypes than in the other phenotypes. The within-breath changes of X5 (DeltaX5) were significantly greater in the mixed phenotype than in the "normal by CT" and emphysema-dominant phenotypes. The FOT parameters (R5, R20, and X5) were significantly correlated with indices of the degree of airway wall thickness and significantly but weakly correlated with the reversibility of airway obstruction. There was no significant correlation between the FOT parameters (R5, R20, and X5) and the degree of emphysema. Conclusion: There is a diversity of respiratory physiology, including the respiratory impedance and reversibility of airway obstruction, based on quantitative CT in patients with COPD. The FOT measurements may reflect the degree of airway disease and aid in detecting airway remodeling in patients with COPD.

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Wang, J., H. Lv, et al. (2018). "**Plasma YKL-40 and NGAL are useful in distinguishing ACO from asthma and COPD.**" *Respir Res* **19**(1): 47.

BACKGROUND: Asthma-chronic obstructive pulmonary disorder (COPD) overlap (ACO) is characterized by the coexistence of features of both asthma and COPD and is associated with rapid progress and a poor prognosis. Thus, the early recognition of ACO is crucial. OBJECTIVES: We sought to explore the plasma levels of biomarkers associated with asthma (periostin, TSLP and YKL-40), COPD (NGAL) and their possible correlation with lung function, the bronchodilator response and radiographic imaging in patients with asthma, COPD and with features of ACO. METHODS: We enrolled 423 subjects from 6 clinical centers. All participants underwent blood collection, lung function measurements, bronchodilator response tests and high-resolution CT. Correlations of the plasma biomarkers with lung function, the bronchodilator response and percentemphysema were calculated by Spearman's rank correlation and multivariate stepwise regression analysis. RESULTS: 1) Patients with features of ACO had lower plasma YKL-40 than COPD patients and a moderate elevated plasma level of NGAL compared with asthma patients. 2) Patients with features of ACO had an intermediate degree of airflow obstruction, the bronchodilator response and emphysema between patients with COPD and asthma. 3) Plasma YKL-40 was negatively correlated with lung function and with the bronchodilator response, and plasma NGAL was positively correlated with the extent of emphysema. CONCLUSIONS: Plasma YKL-40 is a promising candidate for distinguishing between patients with features of ACO and COPD patients, while plasma NGAL may be a valuable biomarker for differentiating between patients with features of ACO and asthma patients. CLINICAL TRIAL REGISTRATION: ChiCTR-OOC-16009221.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5870925/pdf/12931\\_2018\\_Article\\_755.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5870925/pdf/12931_2018_Article_755.pdf)

Wang, Y., N. Liu, et al. (2019). "**Respiratory electrophysiologic studies in chronic obstructive pulmonary disease.**" *Medicine (Baltimore)* **98**(1): e13993.

Respiratory failure is common during acute exacerbation of chronic obstructive pulmonary disease (AE-COPD). Phrenic nerve conduction (PNC), transcranial magnetic stimulation (TMS), and cervical magnetic stimulation (CMS) are of great value in identifying the feature and site of AE-COPD. PNC, TMS, and CMS were performed in 20 AE-COPD patients with respiratory failure, and re-examined after weaning. Latencies and amplitudes of the diaphragmatic compound muscle action potential (dCMAP), motor evoked potential of the diaphragm (dMEP) evoked by TMS and CMS, and central motor conduction time (CMCT) were measured. Blood gas analysis and serum electrolyte levels were also evaluated. The results were compared with those from 20 healthy subjects. AE-COPD patients showed prolonged CMCT and latencies of dCMAP and dMEP, decreased amplitudes of dCMAP and dMEP evoked by CMS, while CMCT and the latency of dMEP evoked by TMS were shortened after weaning. Significant correlation was identified between arterial blood gas analysis, serum electrolyte levels, disease duration, the duration of mechanical ventilation and the electrophysiological findings in AE-COPD patients prior to weaning. The central and peripheral respiratory pathway is involved in AE-COPD. Central respiratory pathway function is improved after weaning in AE-COPD patients with respiratory failure.

Weir-McCall, J. R., P. S. Liu-Shiu-Cheong, et al. (2018). "**Disconnection of pulmonary and systemic arterial stiffness in COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 1755-1765.

Background: Both pulmonary arterial stiffening and systemic arterial stiffening have been described in COPD. The aim of the current study was to assess pulse wave velocity (PWV) within these two arterial beds to determine whether they are separate or linked processes. Materials and methods: In total, 58 participants with COPD and 21 healthy volunteers (HVs) underwent cardiac magnetic resonance imaging (MRI) and were tested with a panel of relevant biomarkers. Cardiac MRI was used to quantify ventricular mass, volumes, and pulmonary (pulse wave velocity [pPWV] and systemic pulse wave velocity [sPWV]). Results: Those with COPD had higher pPWV (COPD: 2.62 vs HV: 1.78 ms<sup>-1</sup>, p=0.006), higher right ventricular mass/volume ratio (RVMVR; COPD: 0.29 vs HV: 0.25 g/mL, p=0.012), higher left ventricular mass/volume ratio (LVMVR; COPD: 0.78 vs HV: 0.70 g/mL, p=0.009), and a trend toward a higher sPWV (COPD: 8.7 vs HV: 7.4 ms<sup>-1</sup>, p=0.06). Multiple biomarkers were elevated: interleukin-6 (COPD: 1.38 vs HV: 0.58 pg/mL, p=0.02), high-sensitivity C-reactive protein (COPD: 6.42 vs HV: 2.49 mg/L, p=0.002), surfactant protein D (COPD: 16.9 vs HV: 9.13 ng/mL, p=0.001), N-terminal pro-brain natriuretic peptide (COPD: 603 vs HV: 198 pg/mL, p=0.001), and high-sensitivity troponin I (COPD: 2.27 vs HV: 0.92 pg/mL, p<0.001). There was a significant relationship between sPWV and LVMVR (p=0.01) but not pPWV (p=0.97) nor between pPWV and RVMVR (p=0.27). Conclusion: Pulmonary arterial stiffening and systemic arterial stiffening appear to be disconnected and should therefore be considered independent processes in COPD. Further work is warranted to determine whether both these cause an increased morbidity and mortality and whether both can be targeted by similar pharmacological therapy or whether different strategies are required for each.

<https://www.dovepress.com/getfile.php?fileID=42347>

Wu, Y. K., W. L. Su, et al. (2018). "**Treatment of chronic obstructive pulmonary disease in patients with different fractional exhaled nitric oxide levels.**" *Medicine (Baltimore)* **97**(47): e11922.

Some patients with chronic obstructive pulmonary disease (COPD) have eosinophilic inflammation which may be evaluated via the measurement of fractional exhaled nitric oxide (FeNO) like asthma. The aim of this prospective study was to assess whether FeNO levels can be used to identify patients with COPD with

eosinophilic inflammation who may respond to inhaled corticosteroid (ICS) therapy. This study included patients (N = 112) with COPD (age > 18 years) who were divided into 4 groups depending upon whether they had high ( $\geq 25$  parts per billion [ppb]) or low (<25 ppb) pretreatment (baseline) FeNO and if they were treated with either ICS plus long-acting beta-agonist (ICS + LABA) or a long-acting muscarinic antagonist (LAMA). The 4 groups were: high FeNO/ICS + LABA, high FeNO/LAMA, low FeNO/ICS + LABA, and low FeNO/LAMA. Outcomes assessed included FeNO, COPD assessment test (CAT), and pulmonary function. The high FeNO/ICS + LABA group had the greatest reduction from baseline in FeNO levels (-25.80 ppb +/- 27.14) compared with the high FeNO/LAMA, low FeNO/ICS + LABA, and low FeNO/LAMA groups (range, -4.45 to 1.31 ppb;  $P < .001$ ). The high FeNO/ICS + LABA group also showed the greatest improvement in CAT (-7.20), which was statistically larger than the low FeNO/ICS + LABA and low FeNO/LAMA groups (-1.72 and -2.03, respectively). No difference in pulmonary function following treatment was observed across the 4 groups. This study found that patients with high FeNO showed the greatest reduction in FeNO and improvement in CAT with ICS + LABA therapy, supporting the use of FeNO to identify patients who would benefit from ICS use.

Xu, S., A. Tsai, et al. (2018). **"Decreased microbiome diversity in the HIV small airway epithelium."** *Respir Res* **19**(1): 140.

**BACKGROUND:** Persons living with human immunodeficiency virus (PLWH) face an increased burden of chronic obstructive pulmonary disease (COPD). Repeated pulmonary infections, antibiotic exposures, and immunosuppression may contribute to an altered small airway epithelium (SAE) microbiome. **METHODS:** SAE cells were collected from 28 PLWH and 48 HIV- controls through bronchoscopic cytologic brushings. DNA extracted from SAE cells was subjected to 16S rRNA amplification and sequencing. Comparisons of alpha and beta diversity between HIV+ and HIV- groups were performed and key operational taxonomic units (OTUs) distinguishing the two groups were identified using the Boruta feature selection after Random Forest Analysis. **RESULTS:** PLWH demonstrated significantly reduced Shannon diversity compared with HIV- volunteers (1.82 +/- 0.10 vs. 2.20 +/- 0.073,  $p = 0.0024$ ). This was primarily driven by a reduction in bacterial richness (23.29 +/- 2.75 for PLWH and 46.04 +/- 3.716 for HIV-,  $p < 0.0001$ ). Phyla distribution was significantly altered among PLWH, with an increase in relative abundance of Proteobacteria ( $p = 0.0003$ ) and a decrease in Bacteroidetes ( $p = 0.0068$ ) and Firmicutes ( $p = 0.0002$ ). Six discriminative OTUs were found to distinguish PLWH from HIV- volunteers, aligning to Veillonellaceae, Fusobacterium, Verrucomicrobiaceae, Prevotella, Veillonella, and Campylobacter. **CONCLUSIONS:** Compared to HIV- controls, PLWH's SAE microbiome is marked by reduced bacterial diversity and richness with significant differences in community composition.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6062954/pdf/12931\\_2018\\_Article\\_835.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6062954/pdf/12931_2018_Article_835.pdf)

Xu, S., E. A. Vucic, et al. (2018). **"Decreased telomere length in the small airway epithelium suggests accelerated aging in the lungs of persons living with human immunodeficiency virus (HIV)."** *Respir Res* **19**(1): 117.

Human immunodeficiency virus (HIV) infection is associated with an increased risk of chronic obstructive pulmonary disease (COPD) independent of cigarette smoke exposure. Previous studies have demonstrated that decreased peripheral leukocyte telomere length is associated with HIV, suggesting an accelerated aging phenomenon. We demonstrate that this process of telomere shortening also occurs in the lungs, with significant decreases in telomere length observed in small airway epithelial cells collected during bronchoscopy. Molecular evidence of accelerated aging in the small airway epithelium of persons living with HIV may be one clue into the predisposition for chronic lung disease observed in this population.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5998581/pdf/12931\\_2018\\_Article\\_821.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5998581/pdf/12931_2018_Article_821.pdf)

Zhao, D., Y. Zhou, et al. (2018). **"Small airway disease: A different phenotype of early stage COPD associated with biomass smoke exposure."** *Respirology* **23**(2): 198-205.

**BACKGROUND AND OBJECTIVE:** Chronic exposure to biomass smoke (BS) can significantly compromise pulmonary function and lead to chronic obstructive pulmonary disease (COPD). To determine whether BS exposure induces a unique phenotype of COPD from an early stage, with different physiopathological features compared with COPD associated with smoking (cigarette-smoke (CS) COPD), we assessed the physiopathology of early COPD associated with BS exposure (BS COPD) by incorporating spirometry, high-resolution computed tomography (HRCT) imaging, bronchoscopy and pathological examinations. **METHODS:** In this cross-sectional study, we recruited 29 patients with BS COPD, 31 patients with CS COPD and 22 healthy controls, including 12 BS-exposed subjects who did not smoke and 10 healthy smokers without BS exposure. Spirometry, HRCT scans, bronchoscopy and bronchial mucosa biopsies were performed to assess lung function, emphysema and air trapping, as well as the pathological characteristics and levels of inflammatory cells in bronchoalveolar lavage fluid (BALF). **RESULTS:** Among COPD patients with mild-to-moderate airflow limitation, BS exposure caused greater small airway dysfunction in BS COPD patients, although these patients had less emphysema and air trapping, as detected by HRCT ( $P < 0.05$ ). We also observed significantly thicker basement membranes and greater endobronchial pigmentation in BS COPD than in CS COPD ( $P < 0.05$ ). Moreover, patients with BS COPD exhibited greater macrophage and lymphocyte infiltration but reduced neutrophil infiltration in their BALF ( $P < 0.05$ ). **CONCLUSION:** We used both radiology and pathology to document a distinct COPD phenotype associated with BS exposure. This is characterized by small airway disease.

<https://onlinelibrary.wiley.com/doi/pdf/10.1111/resp.13176>

Zhou, Z., A. Zhou, et al. (2018). **"A comparison of the assessment of health status between CCQ and CAT in a Chinese COPD clinical population: a cross-sectional analysis."** *Int J Chron Obstruct Pulmon Dis* **13**: 1675-1682.

**Background:** Both the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ) were recommended as comprehensive symptom measures by the Global Initiative for Chronic Obstructive Lung disease. The main objective of this work was to compare the evaluation of symptom severity with the CAT and the CCQ and find a cutoff value of the CCQ for the Chinese clinical population. **Methods:** Patients diagnosed with stable COPD in the outpatient department who completed the CAT and CCQ were enrolled from November 2015 to December 2016. Scores of 0-10, 11-20, 21-30, and 31-40 represent low, medium, high, and very high impact level, respectively, by CAT. Scores of the CCQ can be considered as acceptable ( $CCQ < 1$ ), acceptable for moderate disease ( $1 \leq CCQ < 2$ ), instable-severe limited ( $2 \leq CCQ < 3$ ), and very instable-very severe limited ( $CCQ \geq 3$ ). **Results:** According to the CAT, only 20.4% of patients belonged to the high ( $21 \leq CAT < 30$ ) and very high ( $31 \leq CAT < 40$ ) impact levels, which were statistically lower than those of the CCQ, which classified over half of the population (51.1%) into the instable-severe limited ( $2 \leq CCQ < 3$ ) and very instable-very severe limited ( $CCQ \geq 3$ ) categories ( $P < 0.001$ ). The kappa of agreement for the symptom groups by CAT and CCQ (cutoff point 1.5) was 0.495, but only slight agreement (0.144) was found between the CAT and CCQ with the cutoff point of 1.0. The CAT and the total CCQ had a strong correlation ( $\rho = 0.776$ ,  $P < 0.01$ ). The CCQ 1.0 and 1.5 corresponded to CAT 4.2 and 9.7, respectively. The CAT 10.0 was equivalent to 1.53 of the CCQ. In addition, with higher scores of the CAT and CCQ, subjects displayed more impairment in lung function, higher levels on modified Medical Research Council, and higher exacerbation rates in the last year ( $P < 0.001$ ). Similarly, patients with more exacerbations presented worse scores on the CAT and total CCQ as well as its 3 domains ( $P < 0.001$ ). **Conclusion:** Compared with the CAT, the CCQ was more likely to classify the patients into more severe categories, and 1.5 might be a better cutoff point for the CCQ than 1.0. Both the CAT and the overall CCQ with its 3 domains were able to discriminate between groups of patients that differ in COPD severity.

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## **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 ("meta-analysis"[All Fields] OR "meta-analyses"[All Fields] OR "randomised"[All] OR "random"[All Fields]) AND English[lang]

Aalstad, L. T., J. A. Hardie, et al. (2018). **"Lung hyperinflation and functional exercise capacity in patients with COPD - a three-year longitudinal study."** *BMC Pulm Med* **18**(1): 187.

**BACKGROUND:** Lung hyperinflation contributes to dyspnea, morbidity and mortality in chronic obstructive pulmonary disease (COPD). The inspiratory-to-total lung capacity (IC/TLC) ratio is a measure of lung hyperinflation and is associated with exercise intolerance. However, knowledge of its effect on longitudinal change in the 6-min walk distance (6MWD) in patients with COPD is scarce. We aimed to study whether the IC/TLC ratio predicts longitudinal change in 6MWD in patients with COPD. **METHODS:** This prospective cohort study included 389 patients aged 40-75 years with clinically stable COPD in Global Initiative for Chronic Obstructive Lung Disease stages II-IV. The 6MWD was measured at baseline, and after one and 3 years. We performed generalized estimating equation regression analyses to examine predictors for longitudinal change in 6MWD. Predictors at baseline were: IC/TLC ratio, age, gender, pack years, fat mass index (FMI), fat-free mass index (FFMI), number of exacerbations within 12 months prior to inclusion, Charlson index for comorbidities, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and light and hard self-reported physical activity. **RESULTS:** Reduced IC/TLC ratio ( $p < 0.001$ ) was a statistically significant predictor for decline in 6MWD. With a 0.1-unit decrease in baseline IC/TLC ratio, the annual decline in 6MWD was 12.7 m ( $p < 0.001$ ). Study participants with an IC/TLC ratio in the upper quartiles maintained their 6MWD from baseline to year 3, while it was significantly reduced for the patients with an IC/TLC ratio in the lower quartiles. Absence of light and hard physical activity, increased age and FMI, decreased FEV1 and FVC, more frequent exacerbations and higher Charlson comorbidity index were also predictors for lower 6MWD at any given time, but did not predict higher rate of decline over the timespan of the study. **CONCLUSION:** Our findings demonstrated that patients with less lung hyperinflation at baseline maintained their functional exercise capacity during the follow-up period, and that it was significantly reduced for patients with increased lung hyperinflation.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6282360/pdf/12890\\_2018\\_Article\\_747.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6282360/pdf/12890_2018_Article_747.pdf)

Abukhalaf, J., R. Davidson, et al. (2018). **"Chronic obstructive pulmonary disease mortality, a competing risk analysis."** *Clin Respir J* **12**(11): 2598-2605.

**BACKGROUND:** Current risk factors for Chronic Obstructive Pulmonary Disease mortality focus only on overall and respiratory death. We investigated whether risk factors for each specific cause of mortality are different depending on the outcome under consideration. **METHODS:** This retrospective cohort study included patients with a clinical diagnosis of COPD, older than 40, greater than 20 pack-years smoking history, and obstructive pattern on spirometry. Collected data included baseline spirometry, comorbidities, medication use, tobacco exposure, severe exacerbations, and cause-specific mortality. **RESULTS:** This 512 patient cohort of heavy smokers included 277 (54.1%) males, was on average 66.4 +/- 9.4 years of age and primarily non-Hispanic white, 395 (83.2%). The average FEV1% was 52.1% (SD = 16.9%) and the median COTE score was 2 (IQR: 0-6). A total of 67 deaths were of respiratory causes in 26 patients (38.8%), malignancies in 21 (31.1%), cardiovascular causes in 6 (9%), and from other etiologies in 14 patients (20.1%). COTE index, low predicted FEV1%, and lower body mass index were significant predictors of overall mortality. Predictors of respiratory deaths were significantly impacted by lower FEV1%, history of COPD exacerbations, lower BMI, and higher number of pack-years smoked. Risk factors for all other cause-specific mortality combined included history of malignancy or cardiovascular disease and smoking status. **CONCLUSION:** Cause-specific mortality risk factors differ in patients with COPD.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12963>

Ajala, O., Y. Zhang, et al. (2018). "**Decreased serum TRAIL is associated with increased mortality in smokers with comorbid emphysema and coronary artery disease.**" *Respir Med* **145**: 21-27.

BACKGROUND: Smokers are highly susceptible to lung and cardiovascular disease that can reduce their survival.

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a protein in the circulation that may suppress vascular and pulmonary inflammation. Therefore, we hypothesized that diminished circulating TRAIL levels would be associated with poor survival in smokers with lung and cardiovascular disease. METHODS: Serum TRAIL level was measured by immunoassay in 474 smokers. Coronary atherosclerosis was assessed by coronary artery calcium scoring along with emphysema, lung function, and survival. RESULTS: The 474 smokers were 65.7+/-6.3 years old and 52.2% male with 55.3+/-31.5 pack-years of tobacco-exposure. 83 of them died during 3588.2 person-years of follow up. At baseline, lower TRAIL level was associated with more coronary artery calcium (OR=1.2 per SD, 95%CI 1.1-1.5, p=0.02), and with history of myocardial infarction (OR=2.3 per SD, 95%CI 1.2-4.5, p=0.02), angina (OR=1.6 per SD, 95%CI 1.1-2.6, p=0.03), and angioplasty (OR=1.8 per SD, 95%CI 1.0-3.1, p=0.04) in models adjusted for cardiovascular risk-factors, FEV1, and emphysema. Also, lower TRAIL level was associated with emphysema severity independent of demographics and tobacco exposure (beta=0.11 sq. root units, 95% CI 0.01-0.22, p=0.03). Further, TRAIL level was lowest in smokers with comorbid emphysema and coronary artery calcification rather than either condition alone. Finally, lower TRAIL level was independently associated with increased mortality in smokers particularly in those with comorbid emphysema and coronary artery calcification (HR=1.38, 95% CI 1.01-1.90). CONCLUSIONS: TRAIL level is reduced in smokers with comorbid emphysema and coronary artery disease, and is associated with reduced survival.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30324-X/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30324-X/fulltext)

Assenzo, V., C. Assenzo, et al. (2018). "**The feasibility of extubation in the operating room after bilateral lung transplantation in adult emphysema patients: an observational retrospective study.**" *Eur J Cardiothorac Surg* **54**(6): 1128-1133.

OBJECTIVES: We introduced an extubation strategy for emphysema patients after bilateral lung transplantation. Patients who met the extubation criteria were extubated in the operating room (OR) followed by non-invasive ventilation, and the other patients were extubated in the intensive care unit (ICU). The primary objective was to determine the extubation rate. The secondary outcomes were to determine the factors allowing for extubation in the OR and the postoperative course. METHODS: This study is a single-centre retrospective database analysis of 96 patients. Anaesthesia was performed using automated titration of total intravenous anaesthesia combined with thoracic epidural analgesia. Extubation criteria included arterial partial pressure oxygen (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio, chest radiograph, oedema and haemodynamic stability. Data were compared using non-parametric tests and expressed as median (interquartile ranges) or number (%). RESULTS: Fifty-three (55%) patients were extubated in the OR (the OR group) with 1 requiring reintubation and 43 (45%) patients were extubated in the ICU (the ICU group). Preoperative pulmonary hypertension, the requirement for intraoperative extracorporeal membrane oxygenation (ECMO), bleeding and ex vivo lung reconditioning donors were lower in the OR group. At the end of the procedure, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was better [352 (289-437) vs 206 (144-357), P = 0.004], and the need for postoperative ECMO, mechanical ventilation duration, length of stay in the ICU [5 (4-7) vs 12 (8-20) days, P < 0.0001], Grade 3 primary graft dysfunction at 72 h [1 (2%) vs 10 (24%), P = 0.002] and 1-year mortality [5 (9%) vs 11 (26%) patients, P = 0.014] were lower in the OR group than in the ICU group. CONCLUSIONS: Half of patients were extubated in the OR, and this strategy does not require additional ICU resources.

<https://academic.oup.com/ejcts/article-abstract/54/6/1128/5001777?redirectedFrom=fulltext>

Baillargeon, J., R. J. Urban, et al. (2019). **"Testosterone replacement therapy and hospitalization rates in men with COPD."** *Chron Respir Dis* **16**: 1479972318793004.

Testosterone deficiency is common in men with chronic obstructive pulmonary disease (COPD) and may exacerbate their condition. Research suggests that testosterone replacement therapy (TRT) may have a beneficial effect on respiratory outcomes in men with COPD. To date, however, no large-scale nationally representative studies have examined this association. The objective of the study was to assess whether TRT reduced the risk of respiratory hospitalizations in middle-aged and older men with COPD. We conducted two retrospective cohort studies. First, using the Clinformatics Data Mart-a database of one of the largest commercially insured populations in the United States-we examined 450 men, aged 40-63 years, with COPD who initiated TRT between 2005 and 2014. Second, using the national 5% Medicare database, we examined 253 men, aged  $\geq 66$  years, with COPD who initiated TRT between 2008 and 2013. We used difference-in-differences (DID) statistical modeling to compare pre- versus post-respiratory hospitalization rates in TRT users versus matched TRT nonusers over a parallel time period. DID analyses showed that TRT users had a greater relative decrease in respiratory hospitalizations compared with nonusers. Specifically, middle-aged TRT users had a 4.2% greater decrease in respiratory hospitalizations compared with nonusers (-2.4 decrease vs. 1.8 increase;  $p = 0.03$ ); and older TRT users had a 9.1% greater decrease in respiratory hospitalizations compared with nonusers (-0.8 decrease vs. 8.3 increase;  $p = 0.04$ ). These findings suggest that TRT may slow disease progression in patients with COPD. Future studies should examine this association in larger cohorts of patients, with particular attention to specific biological pathways.

Bhatt, S. P., H. P. Nath, et al. (2018). **"Centrilobular emphysema and coronary artery calcification: mediation analysis in the SPIROMICS cohort."** *Respir Res* **19**(1): 257.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is associated with a two-to-five fold increase in the risk of coronary artery disease independent of shared risk factors. This association is hypothesized to be mediated by systemic inflammation but this link has not been established. METHODS: We included 300 participants enrolled in the SPIROMICS cohort, 75 each of lifetime non-smokers, smokers without airflow obstruction, mild-moderate COPD, and severe-very severe COPD. We quantified emphysema and airway disease on computed tomography, characterized visual emphysema subtypes (centrilobular and paraseptal) and airway disease, and used the Weston visual score to quantify coronary artery calcification (CAC). We used the Sobel test to determine whether markers of systemic inflammation mediated a link between spirometric and radiographic features of COPD and CAC. RESULTS: FEV1/FVC but not quantitative emphysema or airway wall thickening was associated with CAC ( $p = 0.036$ ), after adjustment for demographics, diabetes mellitus, hypertension, statin use, and CT scanner type. To explain this discordance, we examined visual subtypes of emphysema and airway disease, and found that centrilobular emphysema but not paraseptal emphysema or bronchial thickening was independently associated with CAC ( $p = 0.019$ ). MMP3, VCAM1, CXCL5 and CXCL9 mediated 8, 8, 7 and 16% of the association between FEV1/FVC and CAC, respectively. Similar biomarkers partially mediated the association between centrilobular emphysema and CAC. CONCLUSIONS: The association between airflow obstruction and coronary calcification is driven primarily by the centrilobular subtype of emphysema, and is linked through bioactive molecules implicated in the pathogenesis of atherosclerosis. TRIAL REGISTRATION: ClinicalTrials.gov: Identifier: NCT01969344 .

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6299495/pdf/12931\\_2018\\_Article\\_946.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6299495/pdf/12931_2018_Article_946.pdf)

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

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is characterized by airway remodeling. Characterization of airway changes on computed tomography has been challenging due to the

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

<https://dm5migu4zj3pb.cloudfront.net/manuscripts/120000/120693/JC1120693.v4.pdf>

Boer, L. M., M. van der Heijden, et al. (2018). "**Validation of ACCESS: an automated tool to support self-management of COPD exacerbations.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3255-3267.

Background: To support patients with COPD in their self-management of symptom worsening, we developed Adaptive Computerized COPD Exacerbation Self-management Support (ACCESS), an innovative software application that provides automated treatment advice without the interference of a health care professional. Exacerbation detection is based on 12 symptom-related yes-or-no questions and the measurement of peripheral capillary oxygen saturation (SpO<sub>2</sub>), forced expiratory volume in one second (FEV<sub>1</sub>), and body temperature. Automated treatment advice is based on a decision model built by clinical expert panel opinion and Bayesian network modeling. The current paper describes the validity of ACCESS. Methods: We performed secondary analyses on data from a 3-month prospective observational study in which patients with COPD registered respiratory symptoms daily on diary cards and measured SpO<sub>2</sub>, FEV<sub>1</sub>, and body temperature. We examined the validity of the most important treatment advice of ACCESS, ie, to contact the health care professional, against symptom- and event-based exacerbations. Results: Fifty-four patients completed 2,928 diary cards. One or more of the different pieces of ACCESS advice were provided in 71.7% of all cases. We identified 115 symptom-based exacerbations. Cross-tabulation showed a sensitivity of 97.4% (95% CI 92.0-99.3), specificity of 65.6% (95% CI 63.5-67.6), and positive and negative predictive value of 13.4% (95% CI 11.2-15.9) and 99.8% (95% CI 99.3-99.9), respectively, for ACCESS' advice to contact a health care professional in case of an exacerbation. Conclusion: In many cases (71.7%), ACCESS gave at least one self-management advice to lower symptom burden, showing that ACCESS provides self-management support for both day-to-day symptom variations and exacerbations. High sensitivity shows that if there is an exacerbation, ACCESS will advise patients to contact a health care professional. The high negative predictive value leads us to conclude that when ACCESS does not provide the advice to contact a health care professional, the risk of an exacerbation is very low. Thus, ACCESS can safely be used in patients with COPD to support self-management in case of an exacerbation.

<https://www.dovepress.com/getfile.php?fileID=45184>

Bogart, M., M. B. Glassberg, et al. (2018). "Impact of prompt versus delayed initiation of triple therapy post COPD exacerbation in a US-managed care setting." *Respir Med* 145: 138-144.

**BACKGROUND:** It is unknown whether there is a benefit to initiating triple therapy (TT; inhaled corticosteroids combined with long-acting beta2-agonists and long-acting muscarinic antagonists) promptly (within 30 days) following a chronic obstructive pulmonary disease (COPD)-related hospitalization or emergency-department (ED) visit compared with delaying treatment (31-180 days). **METHODS:** This retrospective, observational study (GSK: HO-15-15256) used healthcare claims from a commercial and Medicare claims database (January 1, 2008-December 31, 2015). **PATIENTS:**  $\geq 40$  years of age, diagnosed with COPD and no history of TT 12 months pre-index. Patients experiencing a COPD-related hospitalization or ED visit (index) who initiated TT  $\leq 6$  months following index were included (January 1, 2009-December 31, 2014). Patients initiating TT  $\leq 30$  or 31-180 days following index were included in the Prompt or Delayed cohorts, respectively. All-cause and COPD-related costs (total, medical and prescription), and exacerbations (severe and moderate) per patient per year were determined for 12 months post index. Outcomes were adjusted by cohort, weighted for a balanced distribution of baseline covariates between cohorts using inverse probability weights. **RESULTS:** Overall, 10,902 patients were identified (Prompt: n=5701; Delayed: n=5201). Total, medical and prescription all-cause costs were significantly higher in the Delayed versus Prompt cohorts (percent increase: 18.7%, 22.8% and 8.8%, respectively; all  $p < 0.0001$ ). COPD-related total, medical and prescription costs were 49.3%, 66.3% and 10.3% higher in the Delayed versus Prompt cohorts, respectively (all  $p < 0.0001$ ). Total and severe COPD-related exacerbation rates were 28.2% and 64.7% higher in the Delayed versus Prompt cohorts ( $p < 0.0001$ ). **CONCLUSION:** Prompt use of TT following a COPD-inpatient or ED visit may reduce future costs and subsequent exacerbations compared with delaying the initiation of TT.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30319-6/pdf](https://www.resmedjournal.com/article/S0954-6111(18)30319-6/pdf)

Bolund, A. C. S., M. R. Miller, et al. (2018). "New-onset COPD and Decline in Lung Function Among Wood Dust-Exposed Workers: Re-analysis of a 6-year Follow-up Study." *Ann Work Expo Health* 62(9): 1064-1076.

**Objectives:** There is a lack of longitudinal studies exploring the association between organic wood dust exposure and new-onset chronic obstructive pulmonary disease (COPD) and change in lung function. We have re-investigated these associations in a 6-year follow-up cohort of furniture workers exposed to wood dust using improved outcome measures and methods. **Methods:** A large follow-up study of 1112 woodworkers (63%) from the Danish furniture industry and 235 controls (57%) was conducted between 1998 and 2004. Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and the ratio (FEV1/FVC) standardized for age, height, and sex using the Global Lung Function Initiative 2012 equations were assessed at baseline and follow-up. Questionnaires on respiratory symptoms, wood dust exposure, and smoking habits were collected. Exposure was assessed as exposure level at baseline and as cumulative exposure in the follow-up period from quantitative task specific job exposure matrix available at both baseline and follow-up based on personal dust sampling using passive dust monitors. The association between exposure to wood dust and new-onset COPD was assessed with logistic regression, whereas the association between wood dust and the longitudinal change in z-score for lung function was assessed with linear regression. **Results:** Similar associations were seen for different exposure metrics. An exposure-response relation was seen for new-onset COPD for female smokers with an odds ratio (OR) (95% confidence interval [CI]) of 8.47 (0.9-82.4) in the highest exposed group compared to controls, and a significant test for trend  $P = 0.049$ . No such association was seen among males for whom only smoking was strongly associated to new-onset COPD. For change in lung function, a significant exposure-response was seen for females, confirming previous findings, with increasing levels of wood dust exposure showing larger decline in lung function (beta [95% CI]: -0.32 DeltazFEV1 (-0.56 to -0.08,  $P = 0.009$ ) for third quartile exposure compared to controls, test for trend,  $P = 0.005$ , equivalent to an excess loss of 125 ml in the 6 years of follow-up). An opposite association was seen for men. **Conclusion:** In conclusion, we found that female woodworkers have a dose-dependent increased OR of new-onset COPD and an excess decline in lung function suggesting that female woodworkers may

be more susceptible to wood dust exposure than male woodworkers. Among male woodworkers, only smoking and asthma were significant predictors for new-onset COPD and excess decline in lung function. These results emphasize that reduction in both smoking and wood dust exposure should continuously be an effort to prevent adverse pulmonary health effects.

[https://watermark.silverchair.com/wxy075.pdf?token=AQECAHi208BE49Ooan9kKhW\\_Ercy7Dm3ZL\\_9Cf3qfKAc485y sgAAAlowggJWBgkqhkiG9w0BBwagggJHMIICQwIBADCCAjwGCSqGSIb3DQEHATAeBgIghkgBZQMEAS4wEQQMzq4TcdhICDvzE739AgEQgIICDYANPI7J5yO\\_kpFezGEmB465Z5-Yy22D6X1U0pfr7T-ifZETVCXWs7RzpuHihYoODXbY4rb0pudlNtlmJ6xg3iDsm\\_UFWHAeXT1zJoNs0-hptva2EBvT98O32KpxCWd\\_ft-MjmFukG1T2NXwGjQGzfyR8824C5Q01A\\_wkiyDk-5ii1Zioy-iWTEQzpJXADAWNBRofVulD4CO4dmGBn0w3uyC2xl60h2E4ldpzYCn3TIFXbRI0oxytQ8cW3wPVOUfwUgXRA8toxL8ZD-MOdBtYtcBGAACvYoWL4-kATNr2GfHSpMFqFL5VdNIL6GfAeurRaV7CdU8EFuvJd76P6J5AAocF11Pk1F3yvo788itEf6HVk51GgV0Mt-v0kr5giN4ha2\\_mXJV5LRydxrtu9jU-Tv6M5kC0reGQpq0jmXpVHwk-AbhxbX75DswJvsIYVJlpB9yj8aGsWaXbzpPF6lqnEvRxa6xfj0LbrfzRYSshv3fvkDRU1DiPPvaM9i8ZwYBi16fslNHkm7KS9r4FG7\\_Rw4D0jZSb0BGBE5J1\\_hp9LHkpkic93nOc0ly9etCS3F9naa52Jf3KPPHhxMg\\_qq4QS3DYH4l-AhJs21zv0Mjs4GXBPkDroyn7Kqfz2g2yuFQ9U1uKmKZx\\_GzjZxA4g71Cwj6YvwFuLUNHgf6\\_KaUYNgPm76Q2oJupWkbOovA](https://watermark.silverchair.com/wxy075.pdf?token=AQECAHi208BE49Ooan9kKhW_Ercy7Dm3ZL_9Cf3qfKAc485y sgAAAlowggJWBgkqhkiG9w0BBwagggJHMIICQwIBADCCAjwGCSqGSIb3DQEHATAeBgIghkgBZQMEAS4wEQQMzq4TcdhICDvzE739AgEQgIICDYANPI7J5yO_kpFezGEmB465Z5-Yy22D6X1U0pfr7T-ifZETVCXWs7RzpuHihYoODXbY4rb0pudlNtlmJ6xg3iDsm_UFWHAeXT1zJoNs0-hptva2EBvT98O32KpxCWd_ft-MjmFukG1T2NXwGjQGzfyR8824C5Q01A_wkiyDk-5ii1Zioy-iWTEQzpJXADAWNBRofVulD4CO4dmGBn0w3uyC2xl60h2E4ldpzYCn3TIFXbRI0oxytQ8cW3wPVOUfwUgXRA8toxL8ZD-MOdBtYtcBGAACvYoWL4-kATNr2GfHSpMFqFL5VdNIL6GfAeurRaV7CdU8EFuvJd76P6J5AAocF11Pk1F3yvo788itEf6HVk51GgV0Mt-v0kr5giN4ha2_mXJV5LRydxrtu9jU-Tv6M5kC0reGQpq0jmXpVHwk-AbhxbX75DswJvsIYVJlpB9yj8aGsWaXbzpPF6lqnEvRxa6xfj0LbrfzRYSshv3fvkDRU1DiPPvaM9i8ZwYBi16fslNHkm7KS9r4FG7_Rw4D0jZSb0BGBE5J1_hp9LHkpkic93nOc0ly9etCS3F9naa52Jf3KPPHhxMg_qq4QS3DYH4l-AhJs21zv0Mjs4GXBPkDroyn7Kqfz2g2yuFQ9U1uKmKZx_GzjZxA4g71Cwj6YvwFuLUNHgf6_KaUYNgPm76Q2oJupWkbOovA)

Casas-Mendez, F., M. J. Abadias, et al. (2018). **"Treatment strategies after acute exacerbations of chronic obstructive pulmonary disease: Impact on mortality."** *PLoS One* **13**(12): e0208847.

INTRODUCTION: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common reason for presentation to emergency departments (ED), but the management of these episodes is often heterogeneous regardless of their potential impact on short-term adverse outcomes. METHODS: This was a longitudinal, retrospective study of all patients >40 years old admitted to the ED of two Spanish teaching hospitals for an AECOPD between January 1st and May 31st, 2016. All data were collected from electronic medical records. The primary outcomes were patient treatment at discharge and 90-day mortality. Logistic regression was used to model the determinants of 90-day mortality. RESULTS: Of the 465 included patients, 56% were prescribed a 3-drug combination at hospital discharge, 22% a 2-drug combination, 19% a single drug, and 4% other or no treatment. Approximately 8% of patients died within 90 days after an AECOPD. Multivariate logistic models revealed that having more than 2 severe exacerbations within the last 12 months (OR (95% CI): 15.12 (4.22-54.22)) and being prescribed a single drug at discharge (OR (95% CI): 7.23 (2.44-21.38)) were the main determinants of 90-day mortality after an AECOPD. CONCLUSIONS: This study reflects the real-life heterogeneity in the pharmacological treatments prescribed after an ED admission for an AECOPD and suggests the potential impact of suboptimal inhaled treatment strategies on 90-day mortality rates.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6294427/pdf/pone.0208847.pdf>

Chen, W., K. M. Johnson, et al. (2018). **"Long-term effects of inhaled corticosteroids on bone mineral density in older women with asthma or COPD: a registry-based cohort study."** *Arch Osteoporos* **13**(1): 116.

We assessed the association between long-term inhaled corticosteroid (ICS) use and bone mineral density (BMD) in older women with chronic respiratory disease. Women with > 50% adherence to ICS use had very slightly accelerated BMD loss at the total hip compared with those with lower or ICS use.

INTRODUCTION: This study evaluated the impact of long-term ICS therapy on bone loss in older women with asthma or chronic obstructive pulmonary disease (COPD). METHODS: We used a population-based bone densitometry registry linked with administrative health data covering the province of Manitoba, Canada (1999-2013), to identify women aged > 40 years who had diagnosed asthma or COPD. ICS exposure was defined as cumulative dispensed days and medication possession ratio (MPR). Associations were examined both cross-sectionally and longitudinally, and results were covariate adjusted. RESULTS: Among 6561 women with asthma and/or COPD (mean age 65 years [SD = 11]),

compared to no ICS treatment, those in the highest tertile of prior ICS use ( $\geq 720$  days) had lower BMD at the femoral neck (- 0.09 T-score, 95% CI - 0.16, - 0.02) and total hip (- 0.14 T-score, 95% CI - 0.22, - 0.05), but not at the lumbar spine. Over a mean of 5 years of follow-up, the highest tertile of ICS exposure (MPR > 0.5) was associated with a - 0.02 SD/year (95% CI - 0.04, - 0.01) greater decline in total hip BMD relative to non-users, with no significant effect at the femoral neck or lumbar spine. Middle and lower tertiles of ICS use were not associated with baseline or longitudinal change in BMD.

CONCLUSIONS: The highest tertile of ICS use was associated with a slightly lower hip BMD at baseline and slightly greater reduction in total hip BMD over time in older women with asthma or COPD. No adverse effects on BMD were seen from low to moderate ICS exposure.

<https://link.springer.com/article/10.1007%2Fs11657-018-0537-2>

Cherneva, R. V. and D. T. Kostadinov (2018). "**Biomarkers in COPD - Challenging, Real or Illusive.**" *Folia Med (Plovdiv)* **60**(3): 351-363.

Biomarker research in COPD is becoming the most rapidly progressing sphere in respiratory medicine. Although "omics" generate a huge amount of biomarkers, fibrinogen is the only one validated by the European Medicines Agency. Thousands of studies analyzing different biological samples from the respiratory tract, collected in different ways, using various kits and techniques are generating more and more data, rendering biomarkers very confusing rather than having practical value. It seems that in order to be applicable and validated, biomarkers should be analysed in an accurately described cohort of patients, homogeneous in disease severity and activity. As COPD has multiple mechanisms of pathobiology it raises the issue of which is the most appropriate biological sample reflecting each of them. Unified criteria for tissue sampling, validated kits for respiratory tract probes and standardized technologies should be announced. The review presents the biomarkers that are currently validated and raises the problem of standardization.

Conley, P., T. J. Kelechi, et al. (2018). "**Chronic Obstructive Pulmonary Disease Discharge Education and Quality of Life Evaluation: A Feasibility Study.**" *Res Theory Nurs Pract* **32**(3): 328-348.

BACKGROUND AND PURPOSE: Discharge instructions provided to hospitalized participants with chronic obstructive pulmonary disease (COPD) are essential to promote improved health outcomes, reduce incidence of hospitalization, and enhance quality of life (QOL). This study evaluated the feasibility of implementing the American Lung Association's COPD Action Plan and assessment of QOL among participants hospitalized for acute exacerbation of COPD or COPD as a primary or secondary diagnosis. METHODS: The study was conducted on a cohort of critically ill participants hospitalized on a progressive care unit. The Principal Investigator administered the WHOQOL-BREF Questionnaire to assess QOL before discharge and 30 days after discharge via phone call. Reach, Effectiveness, Adoption, Implementation, and Maintenance was used to evaluate outcomes from the discharge study. RESULTS: Among participants enrolled (n = 50), 13 completed the in-hospital and follow-up phone call. Participants scored (12; 92% answered "yes") that they learned appropriate COPD self-management skills, such as change in respiratory symptoms and appropriate actions to take. At 30-day follow-up: number of rehospitalizations (12; 99%), no emergency department visits, and (1; 1%) emergency department visit for insulin reaction, not COPD. Most frequent principal admitted diagnosis was acute respiratory failure, and secondary diagnosis was COPD. There was no significant difference in QOL comparing scores at discharge to 30-day follow-up, using the Wilcoxon signed-rank test. IMPLICATIONS FOR PRACTICE: COPD education can increase participant satisfaction in receiving self-management instructions from an action plan near the time of discharge based on a small sample.

<http://connect.springerpub.com/content/sgrtnp/32/3/328>

Crisafulli, E., A. Ielpo, et al. (2018). "**Clinical variables predicting the risk of a hospital stay for longer than 7 days in patients with severe acute exacerbations of chronic obstructive pulmonary disease: a prospective study.**" *Respir Res* **19**(1): 261.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) patients may experience an acute exacerbation (AECOPD) that requires hospitalisation. The length of hospital stay (LHS) has a great economic impact on the health-care system. Knowing the predictors of prolonged LHS could help to identify possible interventions. METHODS: We performed a prospective study to identify the clinical predictors of prolonged LHS in patients hospitalised for AECOPD. We divided the study sample by LHS into normal ( $\leq 7$  days) and prolonged LHS ( $> 7$  days) groups. Outcomes were the need for non-invasive and invasive mechanical ventilation (NIMV and IMV), intensive care unit (ICU) admission, and the 3-year mortality. RESULTS: We enrolled 437 patients, of which 213 and 224 had normal LHS and prolonged LHS, respectively. Patients with a prolonged LHS had more prior hospitalisations for AECOPD, a worse mMRC (modified Medical Research Council) dyspnoea score, a higher prevalence of long-term oxygen therapy and a higher rate of congestive heart disease. During the current admission, this group also tended to require NIMV, IMV and ICU admission and the mortality risks at 6 months, 1 year and 3 years were higher. In the multivariate regression analysis, an mMRC dyspnoea score  $\geq 2$  (odds ratio-OR 2.24; 95% confidence interval-CI 1.34 to 3.74;  $p = 0.002$ ) and the presence of acute respiratory acidosis (OR 2.75; 95% CI 1.49 to 5.05;  $p = 0.001$ ) predicted a prolonged LHS at admission. CONCLUSIONS: The presence of an mMRC  $\geq 2$  and acute respiratory acidosis at admission independently increased the risk of a prolonged LHS for AECOPD.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6307152/pdf/12931\\_2018\\_Article\\_951.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6307152/pdf/12931_2018_Article_951.pdf)

de Miguel-Diez, J., A. Lopez-de-Andres, et al. (2018). "**Clostridium difficile infection in hospitalized patients with COPD in Spain (2001-2015).**" *Eur J Intern Med* **57**: 76-82.

BACKGROUND: The objectives of this study were to examine incidence and in-hospital outcomes of Clostridium difficile infection (CDI) among patients with COPD, to compare clinical variables among COPD patients with matched non-COPD patients hospitalized with CDI, and to identify factors associated with in-hospital mortality (IHM) among COPD patients. METHODS: We performed a retrospective study using the Spanish National Hospital Discharge Database from 2001 to 2015. We included patients aged 40 years or over with a primary or secondary diagnosis of CDI. For each COPD patient, we selected a sex, age, readmission status and year-matched non-COPD patient. RESULTS: We identified 44,695 patients with CDI (19.36% with COPD). Incidence of CDI has increased significantly from 2001 to 2015 besides COPD status. Incidence was higher in COPD patients than in patients without this disease (IRR 2.24; 95%CI 2.18-2.29). IHM decreased significantly over time in patients without COPD (from 13.98% in 2001-03 to 10.99% in 2013-15), but there were no changes in those with COPD (from 12.93% in 2001-03 to 13.37% in 2013-15). In COPD patients, higher mortality rates were associated with older age, comorbidities, severe CDI, longer length of hospital stay and readmission. Primary diagnosis of CDI was associated with lower IHM in this group of patients (OR 0.66; 95%CI 0.56-0.77) in comparison with secondary diagnosis. CONCLUSIONS: Incidence of CDI was twice higher in COPD patients than in matched non-COPD controls and is increasing overtime in both groups. Our results suggest that the management of CDI has improved in Spain during the study period.

[https://www.ejinme.com/article/S0953-6205\(18\)30272-3/fulltext](https://www.ejinme.com/article/S0953-6205(18)30272-3/fulltext)

Dong, W., Y. Du, et al. (2018). "**Impact of chemotherapy in the prognosis of non-small-cell lung cancer patients with severe to very severe COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3805-3812.

Background: The aim of the study was to investigate if first-line chemotherapy improves total survival time in non-small-cell lung cancer (NSCLC) patients complicated with severe to very severe COPD. Materials and methods: This retrospective observational clinical study included 267 consecutive NSCLC patients with

COPD complications at the Department of Respiratory and Critical Care Medicine of Tianjin Chest Hospital between January 2009 and January 2018. Sixty-nine evaluable patients were included. The clinical characteristics, toxicity profile, objective response rate, and prognosis were analyzed and compared between patients receiving and those not receiving chemotherapy. Results: Forty-five and 24 patients received first-line chemotherapy plus supportive care and supportive care alone, respectively. Kaplan-Meier curves showed that patients receiving chemotherapy had a statistically significant 6-month longer median overall survival (OS) than that of patients receiving supportive care alone (14.0, 95% CI: 8.5-19.5 vs 8.0, 95% CI: 6.4-9.6, respectively) ( $\chi^2=8.857$ ,  $P=0.003$ ). In the multivariate Cox proportional hazard model adjusted for the most relevant variables, the adjusted hazard ratio (HRadj) differed significantly for the receipt of chemotherapy (HRadj=0.4464, 95% CI: 0.2495-0.7988;  $P=0.0066$ ) but not for gender (HRadj=0.8527, 95% CI: 0.4461-1.6298;  $P=0.6297$ ), age (HRadj=1.0021, 95% CI: 0.9609-1.0451;  $P=0.9214$ ), histology (HRadj=1.4422, 95% CI: 0.6959-2.9889;  $P=0.3247$ ), cancer stage (HRadj=1.9098, 95% CI: 0.8607-4.2375;  $P=0.1116$ ), performance status score (HRadj=1.5155, 95% CI: 0.7523-3.0529;  $P=0.2446$ ), lung function (HRadj=1.3856, 95% CI: 0.7149-2.6857;  $P=0.3341$ ), or respiratory symptoms (HRadj=1.0518, 95% CI: 0.6032-1.8342;  $P=0.8586$ ). Patients with grade 3/4 adverse reactions accounted for 29% (13/45) of the chemotherapy group. Conclusion: The results indicated that chemotherapy may improve the OS of NSCLC patients with severe to very severe COPD.

<https://www.dovepress.com/getfile.php?fileID=46376>

Dunican, E. M. (2018). "**Seeing the forest for the trees: fractal dimensions measure COPD airway remodeling.**" *J Clin Invest* **128**(12): 5203-5205.

Chronic obstructive pulmonary disease (COPD) is extremely heterogeneous in its effects on airway remodeling. Parsing the complex and interrelated morphologic changes and understanding their contribution to disease severity has posed a significant challenge to the field. In the current issue of the JCI, Bodduluri et al. measured the complex effects of COPD on the airway tree using airway fractal dimension (AFD) on computerized tomography in a large cohort of smokers with and without COPD. They found that lower AFD was independently associated with disease severity and mortality in COPD. This work highlights AFD as a noninvasive approach to analyze complex changes in airway geometry.

<https://dm5migu4zj3pb.cloudfront.net/manuscripts/124000/124776/JCI124776.v2.pdf>

Durheim, M. T., D. N. Holmes, et al. (2018). "**Characteristics and outcomes of adults with chronic obstructive pulmonary disease and atrial fibrillation.**" *Heart* **104**(22): 1850-1858.

**OBJECTIVE:** Chronic obstructive pulmonary disease (COPD) is associated with the development of atrial fibrillation (AF), and may complicate treatment of AF. We examined the association between COPD and symptoms, quality of life (QoL), treatment and outcomes among patients with AF. **METHODS:** We compared patients with and without a diagnosis of COPD in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, a prospective registry that enrolled outpatients with AF not secondary to reversible causes, from both academic and community settings. **RESULTS:** Among 9749 patients with AF, 1605 (16%) had COPD. Relative to patients without COPD, those with COPD were more likely to be older, current/former smokers (73% vs 43%), have heart failure (54% vs 29%) and coronary artery disease (49% vs 34%). Oral anticoagulant and beta blocker use were similar, whereas digoxin use was more common among patients with COPD. Symptom burden was generally higher, and QoL worse, among patients with COPD (median Atrial Fibrillation Effect on Quality-of-Life score 76 vs 83). Patients with COPD had higher risk of all-cause mortality (adjusted HR 1.52 (95% CI 1.32 to 1.74)), cardiovascular mortality (adjusted HR 1.51 (95% CI 1.24 to 1.84)) and cardiovascular hospitalisation (adjusted HR 1.15 (95% CI 1.05 to 1.26)). Patients with COPD also had higher risk of major bleeding events (adjusted HR 1.25 (95% CI 1.05 to 1.50)). There did not appear to be associations between COPD and AF progression, ischaemic events or new-onset heart failure. **CONCLUSIONS:** Among patients with AF, COPD is associated with higher symptom burden, worse QoL, and worse cardiovascular and bleeding outcomes. These

associations were not fully explained by cardiovascular risk factors, AF treatment or smoking history.  
CLINICAL REGISTRATION NUMBER: NCT01165710.

<https://heart.bmj.com/content/104/22/1850.long>

Ediboglu, O. and C. Kirakli (2018). "**Can NT-pro BNP Levels Predict Prognosis of Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease in the Intensive Care Unit?**" Balkan Med J **35**(6): 422-426.

Background: The prognostic value of amino terminal pro-brain natriuretic peptide levels in patients with acute exacerbation of chronic obstructive pulmonary disease has not been fully established. Aims: To investigate the predictive value of amino terminal pro-brain natriuretic peptide levels in terms of mortality, need for noninvasive mechanical ventilation, invasive mechanical ventilation, and weaning success. Study Design: Cohort study. Methods: Patients who were admitted to intensive care unit between December 2015 and December 2016 due to acute exacerbation of chronic obstructive pulmonary disease were included in the study. Demographic data, noninvasive mechanical ventilation application, need for invasive mechanical ventilation, amino terminal pro-brain natriuretic peptide level, duration of mechanical ventilation, intensive care unit and hospital stay, weaning success, and mortality rates were recorded. Results: A total of 110 patients (75 males) were included in the study. The mean age of the participants was 69 (61-76) years, and the mean Acute Physiology and Chronic Health Evaluation II score was 19 (15-23). The mean amino terminal pro-brain natriuretic peptide level was found to be lower in cases with noninvasive mechanical ventilation success than those with noninvasive mechanical ventilation failure ( $p=0.053$ ). In addition, the mean amino terminal pro-brain natriuretic peptide level was significantly higher (4740 pg/mL vs. 3004 pg/mL,  $p=0.001$ ) in patients who needed invasive mechanical ventilation support than in patients who did not. The mortality rate was significantly higher in patients who had an increasing trend of amino terminal pro-brain natriuretic peptide levels during hospitalization than in patients who had decreasing levels (59% vs. 23%,  $p=0.015$ ). Based on the receiver operating characteristic analysis, the increasing trend of amino terminal pro-brain natriuretic peptide levels during intensive care unit stay predicted mortality with area under curve of 0.84 ( $p<0.0001$ , 95% CI: 0.75-0.93) and predicted invasive mechanical ventilation need with area under curve of 0.68. Conclusion: In cases of acute exacerbation of chronic obstructive pulmonary disease requiring mechanical ventilation, amino terminal pro-brain natriuretic peptide measurement and monitoring of its trend may be a valuable asset in predicting mortality, noninvasive mechanical ventilation, weaning success, and need for invasive mechanical ventilation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6251376/pdf/BMJ-35-422.pdf>

Ferreira, L., A. C. Moniz, et al. (2019). "**The impact of glycemic variability on length of stay and mortality in diabetic patients admitted with community-acquired pneumonia or chronic obstructive pulmonary disease.**" Diabetes Metab Syndr **13**(1): 149-153.

AIM: To investigate the influence of glycemic variability (GV) on length of stay and in-hospital mortality in non-critical diabetic patients. METHODS: A observation retrospective study was performed. Diabetic patients admitted between January and June 2016 with the diagnosis of community-acquire pneumonia (CAP) and/or acute exacerbation of chronic obstructive pulmonary disease (COPD) were enrolled and glycemic control (persistent hyperglycemia, hypoglycemia, mean glucose level (MGL) and respective standard deviation (SD) and coefficient of variation (CV)) were evaluated. Primary outcomes were length of stay and in-hospital mortality. RESULTS: Data from 242 patients were analyzed. Fifty-eight percent of the patients were male, with a median age of 77 years (min-max, 29-98). Patients had on average 2.1 glucose readings-day and the MGL was 193.3mg/dl (min-max, 84.3-436.6). Hypoglycemia was documented in 13.4% of the patients and 55.4% had persistent hyperglycemia. The median length of hospital stay was 10 days (min-max, 1-66) and in-hospital mortality was 7.4%. We found a significant higher in-hospital mortality in older patients, with history of cancer and with nosocomial infections. We did not find any correlation between MGL, SD, CV, hypoglycemia or persist hyperglycemia and in-

hospital mortality. A longer length of stay was observed in patients with heavy alcohol consumption and nosocomial infections. The length of stay was negatively correlated with the mean glucose level ( $r(2) = -0.147$ ;  $p < 0.05$ ) and positively correlated with the coefficient of variation ( $p = 0.162$ ;  $p < 0.05$ ). **CONCLUSION:** This study confirmed the negative impact of the glycemic variability in the outcomes of diabetic patients admitted with CAP or acute exacerbation of COPD.

[https://ac.els-cdn.com/S1871402118303412/1-s2.0-S1871402118303412-main.pdf?\\_tid=9a42fd33-eb91-4d6d-a5a8-e119c07b49ef&acdnat=1547773053\\_6cd950a1ce045fc7a28676aa7c4b972e](https://ac.els-cdn.com/S1871402118303412/1-s2.0-S1871402118303412-main.pdf?_tid=9a42fd33-eb91-4d6d-a5a8-e119c07b49ef&acdnat=1547773053_6cd950a1ce045fc7a28676aa7c4b972e)

Frith, P. A., S. Ashmawi, et al. (2018). **"Efficacy and safety of the direct switch to indacaterol/glycopyrronium from salmeterol/fluticasone in non-frequently exacerbating COPD patients: The FLASH randomized controlled trial."** *Respirology* **23**(12): 1152-1159.

**BACKGROUND AND OBJECTIVE:** Combination long-acting beta<sub>2</sub>-agonist/long-acting muscarinic antagonist (LABA/LAMA) has demonstrated superior clinical outcomes over LABA/inhaled corticosteroid (ICS) in chronic obstructive pulmonary disease (COPD) patients; however, data from blinded randomized controlled trials on direct switching from LABA/ICS to LABA/LAMA are lacking. FLASH (Assessment of switching salmeterol/Fluticasone to indacaterol/glycopyrronium in A Symptomatic COPD patient cohort) investigated if direct switch, without a washout period, from salmeterol/fluticasone (SFC) to indacaterol/glycopyrronium (IND/GLY) in COPD patients improves lung function and is well tolerated. **METHODS:** In this 12-week, multicentre, double-blind study, patients with moderate-to-severe COPD and up to one exacerbation in previous year, receiving SFC for  $\geq 3$  months, were randomized to continue SFC 50/500  $\mu\text{g}$  twice daily (bd) or switch to IND/GLY 110/50  $\mu\text{g}$  once daily (od). Primary endpoint was pre-dose trough forced expiratory volume in 1 s (FEV<sub>1</sub>) at Week 12. **RESULTS:** In total, 502 patients were randomized (1:1) to IND/GLY or SFC. Patients switched to IND/GLY demonstrated superior lung function (pre-dose trough FEV<sub>1</sub>) versus SFC at Week 12 (treatment difference ( $\Delta$ ) = 45 mL;  $P = 0.028$ ). IND/GLY provided significant improvements in pre-dose trough forced vital capacity (FVC;  $\Delta = 102$  mL;  $P = 0.002$ ) and numerical improvements in transition dyspnoea index (TDI;  $\Delta = 0.46$ ;  $P = 0.063$ ). Rescue medication use and COPD assessment test (CAT) scores were comparable between groups. Both treatments had similar safety profiles. **CONCLUSION:** FLASH demonstrated that a direct switch to IND/GLY from SFC improved pre-dose FEV<sub>1</sub> and FVC in COPD patients with up to one exacerbation in the previous year. No new safety signals were identified.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13374>

Gauthier, A., S. Bernard, et al. (2019). **"Adherence to long-term oxygen therapy in patients with chronic obstructive pulmonary disease."** *Chron Respir Dis* **16**: 1479972318767724.

Long-term oxygen therapy (LTOT) has beneficial effects on survival in patients with chronic obstructive pulmonary disease (COPD) and severe hypoxemia at rest. Two landmark trials suggested that these benefits depend on the time of exposure to oxygen. Patients are usually prescribed LTOT for at least 15-18 hours/day. The primary objective of this study was to determine the average daily exposure to supplemental oxygen in patients with severely hypoxemic COPD who were newly prescribed LTOT and the proportion of patients who were adherent to their prescription. The secondary objective was to identify predictors of compliance to LTOT. We performed a retrospective observational study of patients newly registered in a regional home oxygen program in Quebec, Canada, between July 1, 2013, and December 31, 2014. Daily exposure to oxygen was objectively measured from the concentrator's counter clock. From 196 patients registered in the program during the study period, 115 contributed to the analysis. Most patients ( $n = 84$ ; 73%) were prescribed oxygen for  $\geq 18$  hours/day. Overall, the 115 patients were exposed to home oxygen for 17.8 hours/day; 60% of the patients were compliant according to our definition. Increasing age and ambulatory oxygen utilization predicted adherence to oxygen therapy. Adherence to home oxygen therapy is suboptimal. Behavioral and psychological interventions to improve compliance to LTOT should be investigated.

Giezeman, M., M. Hasselgren, et al. (2018). **"Influence of comorbid heart disease on dyspnea and health status in patients with COPD - a cohort study."** *Int J Chron Obstruct Pulmon Dis* **13**: 3857-3865.

Purpose: The aim of this study was to examine the changing influence over time of comorbid heart disease on symptoms and health status in patients with COPD. Patients and methods: This is a prospective cohort study of 495 COPD patients with a baseline in 2005 and follow-up in 2012. The study population was divided into three groups: patients without heart disease (no-HD), those diagnosed with heart disease during the study period (new-HD) and those with heart disease at baseline (HD). Symptoms were measured using the mMRC. Health status was measured using the Clinical COPD Questionnaire (CCQ) and the COPD Assessment Test (CAT; only available in 2012). Logistic regression with mMRC  $\geq 2$  and linear regression with CCQ and CAT scores in 2012 as dependent variables were performed unadjusted, adjusted for potential confounders, and additionally adjusted for baseline mMRC, respectively, CCQ scores. Results: Mean mMRC worsened from 2005 to 2012 as follows: for the no-HD group from 1.8 (+/- 1.3) to 2.0 (+/-1.4), (P=0.003), for new-HD from 2.2 (+/-1.3) to 2.4 (+/-1.4), (P=0.16), and for HD from 2.2 (+/-1.3) to 2.5 (+/-1.4), (P=0.03). In logistic regression adjusted for potential confounding factors, HD (OR 1.71; 95% CI: 1.03-2.86) was associated with mMRC  $\geq 2$ . Health status worsened from mean CCQ as follows: for no-HD from 1.9 (+/-1.2) to 2.1 (+/-1.3) with (P=0.01), for new-HD from 2.3 (+/-1.5) to 2.6 (+/-1.6) with (P=0.07), and for HD from 2.4 (+/-1.1) to 2.5 (+/-1.2) with (P=0.57). In linear regression adjusted for potential confounders, HD (regression coefficient 0.12; 95% CI: 0.04-5.91) and new-HD (0.15; 0.89-5.92) were associated with higher CAT scores. In CCQ functional state domain, new-HD (0.14; 0.18-1.16) and HD (0.12; 0.04-0.92) were associated with higher scores. After additional correction for baseline mMRC and CCQ, no statistically significant associations were found. Conclusion: Heart disease contributes to lower health status and higher symptom burden in COPD but does not accelerate the worsening over time.

<https://www.dovepress.com/getfile.php?fileID=46585>

Goedemans, L., R. Abou, et al. (2019). **"Left ventricular global longitudinal strain and long-term prognosis in patients with chronic obstructive pulmonary disease after acute myocardial infarction."** *Eur Heart J Cardiovasc Imaging* **20**(1): 56-65.

Aims: Left ventricular (LV) systolic function is a known prognostic factor after ST-segment elevation myocardial infarction (STEMI). We evaluated the prognostic value of LV global longitudinal strain (GLS) in patients with chronic obstructive pulmonary disease (COPD) after STEMI. Methods and results: One hundred and forty-three STEMI patients with COPD (mean age 70 +/- 11 years, 71% male), were retrospectively analysed. Left ventricular ejection fraction (LVEF) and LV GLS were measured on transthoracic echocardiography within 48 h of admission. Patients were followed for the occurrence of all-cause mortality and the combined endpoint of all-cause mortality and heart failure hospitalization. After a median follow-up of 68 (interquartile range 38.5-99) months, 66 (46%) patients died and 70 (49%) patients reached the combined endpoint. The median LV GLS was -14.4%. Patients with LV GLS  $> -14.4\%$  (more impaired) showed higher cumulative event rates of all-cause mortality (19%, 26%, and 44% vs. 7%, 8%, and 18% at 1, 2, and 5 years follow-up; log-rank P = 0.004) and the combined endpoint (26%, 34%, and 50% vs. 8%, 10%, and 20% at 1, 2, and 5 years follow-up; log-rank P = 0.001) as compared to patients with LV GLS  $\leq -14.4\%$ . In multivariate analysis, LV GLS  $> -14.4\%$  was independently associated with increased all-cause mortality and the combined endpoint [hazard ratio (HR) 2.07; P = 0.02 and HR 2.20; P = 0.01, respectively] and had incremental prognostic value over LVEF demonstrated by a significant increase in chi2 (P = 0.023 and P = 0.011, respectively). Conclusion: Impaired LV GLS is independently associated with worse long-term survival in STEMI patients with COPD and has incremental prognostic value over LVEF.

<https://academic.oup.com/ehjcmaging/article-abstract/20/1/56/4911134?redirectedFrom=fulltext>

Grymonprez, M., V. Vakaet, et al. (2019). "**Chronic obstructive pulmonary disease and the development of atrial fibrillation.**" *Int J Cardiol* **276**: 118-124.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) has been associated with atrial fibrillation (AF). More insight into the epidemiology and underlying mechanisms is required to optimize management. METHODS: The Rotterdam Study is a large, population-based cohort study with long-term follow-up. Time dependent Cox proportional hazard models were constructed to study the effect of COPD on incident AF, adjusted for age, sex and pack years of cigarette smoking, and additionally stratified according to exacerbation frequency, left atrial size and baseline systemic inflammatory levels. RESULTS: 1369 of 10,943 subjects had COPD, of whom 804 developed AF. The AF incidence rate was 14 per 1000 person years in COPD and 8 per 1000 person years in subjects without COPD. The adjusted hazard ratio (HR) for COPD subjects to develop AF as compared to subjects without COPD was 1.28 (95%CI [1.04, 1.57]). COPD subjects with frequent exacerbations had a twofold increased AF risk (HR 1.99 [1.42, 2.79]) and COPD subjects with a left atrial size  $\geq 40$ mm also had an elevated AF risk (HR 1.77 [1.07, 2.94]). COPD subjects with baseline systemic inflammatory levels above the median had significantly increased AF risks (hsCRP  $\geq 1.83$ mg/L: HR 1.51 [1.13, 2.03] and IL6  $\geq 1.91$ ng/L: HR 2.49 [1.18, 5.28]), whereas COPD subjects below the median had in both analyses no significantly increased AF risk. CONCLUSIONS: COPD subjects had a 28% increased AF risk, which further increased with frequent exacerbations and an enlarged left atrium. The risk was driven by COPD subjects having elevated systemic inflammatory levels.

[https://www.internationaljournalofcardiology.com/article/S0167-5273\(18\)32860-2/pdf](https://www.internationaljournalofcardiology.com/article/S0167-5273(18)32860-2/pdf)

Gupta, A., N. J. Greening, et al. (2019). "**Prospective risk of osteoporotic fractures in patients with advanced chronic obstructive pulmonary disease.**" *Chron Respir Dis* **16**: 1479972318769763.

Despite the high prevalence of osteoporosis in chronic obstructive pulmonary disease (COPD) patients, the fracture risk prediction tools are not routinely undertaken in the management of COPD. We quantified fracture risk using a validated risk prediction tool (Fracture Risk Assessment (FRAX(R))) and determined potential bone-protection treatment needs in patients with advanced COPD. The 10-year probability of major osteoporotic or hip fracture was calculated using the FRAX tool in a cohort of patients attending a hospital complex COPD service. Patients were identified to be at low, intermediate and high risk based on their FRAX scores, in accordance with the National Osteoporosis Guideline Group recommendations, to assess the number of patients requiring bone mineral density (BMD) testing or bone protection therapy. Two hundred forty-seven patients [mean (standard deviation (SD)) age 66 (9.1) years, 26% current smokers, 40% women and median (interquartile range (IQR)) Medical Research Council (MRC) breathlessness scale 4 (0)] had a 10-year probability of 9.5% (6.1) and 3.8% (4.6) for major osteoporotic and hip fractures, respectively. Thirty-six percentage of patients were identified to be at intermediate risk of developing fragility fracture, requiring BMD assessment, while 9% were at high risk, requiring treatment. Thirty-two percentage of high-risk patients were on bisphosphonates. The FRAX score can be used to assess the fracture risk within the COPD cohort and assist with decision-making about BMD measurement and provision of bone protection therapy.

Han, M. Z., T. R. Hsiue, et al. (2018). "**Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3425-3433.

Background and objective: A multidimensional assessment of COPD was recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2013 and revised in 2017. We examined the ability of the GOLD 2017 and the new 16 subgroup (1A-4D) classifications to predict clinical outcomes, including exacerbation and mortality, and compared them with the GOLD 2013 classifications. Methods: Patients

with COPD were recruited from January 2006 to December 2017. The predictive abilities of grades 1-4 and groups A-D were examined through a logistic regression analysis with receiver operating curve estimations and area under the curve (AUC). Results: A total of 553 subjects with COPD were analyzed. The mortality rate was 48.6% during a median follow-up period of 5.2 years. Both the GOLD 2017 and the 2013 group A-D classifications had good predictive ability for total and severe exacerbations, for which the AUCs were 0.79 vs 0.77 and 0.79 vs 0.78, respectively. The AUCs for the GOLD 2017 groups A-D, grades 1-4, and the GOLD 2013 group A-D classifications were 0.70, 0.66, and 0.70 for all-cause mortality and 0.73, 0.71, and 0.74 for respiratory cause mortality, respectively. Combining the spirometric staging with the grouping for the GOLD 2017 subgroups (1A-4D), the all-cause mortality rate for group B and D patients was significantly increased from subgroups 1B-4B (27.7%, 50.6%, 53.3%, and 69.2%, respectively) and groups 1D-4D (55.0%, 68.8%, 82.1%, and 90.5%, respectively). The AUCs of subgroups (1A-4D) were 0.73 and 0.77 for all-cause and respiratory mortality, respectively; the new classification was determined more accurate than the GOLD 2017 for predicting mortality ( $P < 0.0001$ ). Conclusion: The GOLD 2017 classification performed well by identifying individuals at risk of exacerbation, but its predictive ability for mortality was poor among COPD patients. Combining the spirometric staging with the grouping increased the predictive ability for all-cause and respiratory mortality. Summary at a glance: We validate the ability of the GOLD 2017 and 16 subgroup (1A-4D) classifications to predict clinical outcome for COPD patients. The GOLD 2017 classification performed well by identifying individuals at risk of exacerbation, but its predictive ability for mortality was poor. The new 16 subgroup (1A-4D) classification combining the spirometric 1-4 staging and the A-D grouping increased the predictive ability for mortality and was better than the GOLD 2017 for predicting all-cause and respiratory mortality among COPD patients.

<https://www.dovepress.com/getfile.php?fileID=45466>

Hoffmann, C., M. Hanisch, et al. (2018). **"Increased vulnerability of COPD patient groups to urban climate in view of global warming."** *Int J Chron Obstruct Pulmon Dis* **13**: 3493-3501.

Purpose: Patients with COPD show an increase in acute exacerbations (AECOPD) during the cold season as well as during heat waves in the summer months. Due to global climate changes, extreme weather conditions are likely to occur more frequently in the future. The goal of this study was to identify patient groups most at risk of exacerbations during the four seasons of the year and to determine at which temperature threshold the daily hospital admissions due to AECOPD increase during the summer. Patients and methods: We analyzed retrospective demographic and medical data of 990 patients, who were hospitalized for AECOPD in Berlin, Germany. The cases were grouped into the following cohorts: "spring" (admission between March and May), "summer" (June - August), "autumn" (September - November), and "winter" (December - February). AECOPD hospital admissions from 2006 and 2010 were grouped into a "hot summer" cohort and cases from 2011 and 2012 into a "cold summer" data-set. Climate data were obtained from the German Meteorological Office. Results: Patients hospitalized for a COPD exacerbation during winter were significantly older than summertime patients ( $P=0.040$ ) and also thinner than patients exacerbating in spring ( $P=0.042$ ). COPD exacerbations during hot summer periods happened more often to patients with a history of myocardial infarction ( $P=0.014$ ) or active smokers ( $P=0.011$ ). An AECOPD during colder summers occurred in patients with a higher Charlson index, who suffered in increased numbers from peripheral vascular diseases ( $P=0.016$ ) or tumors ( $P=0.004$ ). Summertime hospital admissions increased above a daily minimum temperature of 18.3 degrees C ( $P=0.006$ ). Conclusion: The identification of COPD patient groups most at risk for climate related exacerbations enables climate-adapted prevention through patient guidance and treatment. In view of global climate changes, discovering vulnerabilities and implementing adaptive measures will be of growing importance.

<https://www.dovepress.com/getfile.php?fileID=45525>

Hwang, J., Y. M. Oh, et al. (2019). "**Low morphometric complexity of emphysematous lesions predicts survival in chronic obstructive pulmonary disease patients.**" *Eur Radiol* **29**(1): 176-185.

**OBJECTIVES:** To investigate whether morphometric complexity in the lung can predict survival and act as a new prognostic marker in patients with chronic obstructive pulmonary disease (COPD). **METHODS:** COPD (n = 302) patients were retrospectively reviewed. All patients underwent volumetric computed tomography and pulmonary function tests at enrollment (2005-2015). For complexity analysis, we applied power law exponent of the emphysema size distribution (Dsize) as well as box-counting fractal dimension (Dbox3D) analysis. Patients' survival at February 2017 was ascertained. Univariate and multivariate Cox proportional hazards analyses were performed, and prediction performances of various combinatorial models were compared. **RESULTS:** Patients were 66 +/- 6 years old, had 41 +/- 28 pack-years' smoking history and variable GOLD stages (n = 20, 153, 108 and 21 in stages I-IV). The median follow-up time was 6.1 years (range: 0.2-11.6 years). Sixty-three patients (20.9%) died, of whom 35 died of lung-related causes. In univariate Cox analysis, lower Dsize and Dbox3D were significantly associated with both all-cause and lung-related mortality (both p < 0.001). In multivariate analysis, the backward elimination method demonstrated that Dbox3D, along with age and the BODE index, was an independent predictor of survival (p = 0.014; HR, 2.08; 95% CI, 1.16-3.71). The contributions of Dsize and Dbox3D to the combinatorial survival model were comparable with those of the emphysema index and lung-diffusing capacity. **CONCLUSIONS:** Low morphometric complexity in the lung is a predictor of survival in patients with COPD. **KEY POINTS:** \* A newly suggested method for quantifying lung morphometric complexity is feasible. \* Morphometric complexity measured on chest CT images predicts COPD patients' survival. \* Complexity, diffusing capacity and emphysema index contribute similarly to the survival model.

<https://link.springer.com/article/10.1007%2Fs00330-018-5551-7>

Inabnit, L. S., C. Blanchette, et al. (2018). "**Comorbidities and length of stay in chronic obstructive pulmonary disease patients.**" *Copd* **15**(4): 355-360.

Chronic Obstructive Pulmonary Disease (COPD) has a significant burden on patients and the healthcare system. There is a link between COPD and comorbidities such as congestive heart failure (CHF), fluid and electrolyte disorders, and renal failure. This adds to the complexity of healthcare in these patients. The objective of this study is to determine if certain comorbidities affect length of stay. A sample of 3,399 patients with COPD were assessed from the Premier((c)) healthcare database. The cohort had a mean (standard deviation (SD)) age of 68.41 (10.85) years. The average number of comorbidities was 24.83 (10.46) with a mean length of stay (SD) of 11.64 (9.40) days. A negative binomial regression model was used to evaluate the impact that comorbidities have on the length of hospital stay. The authors found that the number of comorbidities was associated with an increased length of stay (r = .4596, p < .0001). Having at least one comorbidity was associated with a 13% greater length of stay (IRR = 1.13, 95% CI 1.11-1.15, p < 0.0001). CHF was associated with a 28% greater length of stay (IRR = 1.28, 95% CI 1.24-1.31, p < 0.0001). Fluid and electrolyte disorders were associated with a 2-fold greater length of stay (IRR = 2.57, 95% CI 2.52-2.62, p < 0.0001). Renal failure was associated with a 50% greater length of stay (IRR = 1.50, 95% CI 1.45-1.55, p < 0.0001). However, uncomplicated diabetes was associated with 13% shorter length of stay than not having uncomplicated diabetes (IRR = .87, 95% CI .82-.91, p < .0001). This study demonstrated that specific comorbidities have an impact on length of stay.

<https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1513470>

Ishii, T., M. Nishimura, et al. (2018). "**Understanding low COPD exacerbation rates in Japan: a review and comparison with other countries.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3459-3471.

COPD is associated with significant morbidity and is one of the leading causes of death worldwide. Periods of exacerbation, the acute worsening of symptoms, are interspersed throughout the disease's natural history and can result in increased treatment burden and hospitalization for patients with COPD. The frequency of exacerbations varies between countries, with both epidemiological studies and randomized controlled trials (RCTs) showing significant differences in observed prevalence rates. Differences in study

design and the healthcare setting are likely to contribute to differences in exacerbation frequency, however the perceived rate of exacerbations in Japan is currently lower than the rest of the world. This review identified nine cohort studies and five RCTs that reported COPD annual exacerbation rates in Japan in the ranges of 0.1-2.1 and 0.33-1.79, respectively. The difference in exacerbation rate between studies appeared greater than the difference between Japan and Western countries, likely because of disparities between settings, design, and inclusion criteria. Of these, only one (Understanding the Long-Term Impacts of Tiotropium) had uniform inclusion criteria across different regions. This study found that the annual rate of exacerbation events per patient in Japan was 0.61, compared with 0.85 worldwide in the placebo groups. This review summarizes the published rates of COPD exacerbations in Japan and the rest of the world and explores the hypotheses as to why rates in Japan might be lower than other countries. These include access to medical care, variance in the associated morbidity profile, environmental factors, diagnostic crossover with related diseases, and differences in study design (including the underreporting of COPD exacerbations in Japan). Understanding the reasons why COPD exacerbation rates appear lower in Japan could help clinicians to recognize and modify treatment behaviors, which may lead to improved patient outcomes in all populations.

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Jang, S. M., K. U. Kim, et al. (2019). "**Depression is a major determinant of both disease-specific and generic health-related quality of life in people with severe COPD.**" Chron Respir Dis **16**: 1479972318775422.

The quality of life of patients with chronic obstructive pulmonary disease (COPD) decreases significantly as the disease progresses; those with severe COPD are affected most. This article investigates predictors of the disease-specific and generic health-related quality of life (HRQL) in patients with severe COPD. This multicentre prospective cross-sectional study enrolled 80 patients with severe COPD. At enrolment, all patients completed a disease-specific instrument, the St George's Respiratory Questionnaire (SGRQ), and a generic instrument, the Short Form 36 Health Survey Questionnaire (SF-36). The data were analyzed by Pearson's correlation and multiple linear regression. The mean age of the patients was 66 +/- 8 years; 93% were males. The SGRQ and SF-36 scores were not influenced by age or sex. Depression, dyspnea, the number of exacerbations, and exercise capacity significantly predicted the total SGRQ score (  $p < 0.05$ ). Depression was the strongest determinant of the total SGRQ score. The SF-36 physical component summary scores were related to depression, dyspnea, and the number of exacerbations (  $p < 0.05$ ). In comparison, the SF-36 mental component summary scores were related to depression and anxiety (  $p < 0.05$ ). Depression is a significant determinant of both the disease-specific and generic HRQL in patients with severe COPD. Screening and early intervention for depression in patients with severe COPD could improve the HRQL.

Jo, T., N. Michihata, et al. (2019). "**Reduction in exacerbation of COPD in patients of advanced age using the Japanese Kampo medicine Dai-kenchu-to: a retrospective cohort study.**" Int J Chron Obstruct Pulmon Dis **14**: 129-139.

Purpose: Patients with symptomatic COPD are recommended to use inhaled bronchodilators containing long-acting muscarinic receptor antagonists (LAMAs). However, bronchodilators may cause gastrointestinal adverse effects due to anticholinergic reactions, especially in advanced-age patients with COPD. Dai-kenchu-to (TU-100, Da Jian Zhong Tang in Chinese) is the most frequently prescribed Japanese herbal Kampo medicine and is often prescribed to control abdominal bloating and constipation. The purpose of this study was to evaluate the role of Dai-kenchu-to as a supportive therapy in advanced-age patients with COPD. Patients and methods: We used the Japanese Diagnosis Procedure Combination inpatient database and identified patients aged  $\geq 75$  years who were hospitalized for COPD exacerbation. We then compared the risk of re-hospitalization for COPD exacerbation or death between patients with and without Dai-kenchu-to using 1-to-4 propensity score matching. A Cox proportional hazards model was used to compare the two groups. We performed subgroup analyses for patients with and without LAMA

therapy. Results: Patients treated with Dai-kenchu-to had a significantly lower risk of re-hospitalization or death after discharge; the HR was 0.82 (95% CI, 0.67-0.99) in 1-to-4 propensity score matching. Subgroup analysis of LAMA users showed a significant difference in re-hospitalization or death, while subgroup analysis of LAMA non-users showed no significant difference. Conclusion: Our findings indicate that Dai-kenchu-to may have improved the tolerability of LAMA in advanced-age patients with COPD and, therefore, reduced the risk of re-hospitalization or death from COPD exacerbation. Dai-kenchu-to may be recommended as a useful supportive therapy for advanced-age patients with COPD.

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Johnson, K. M., A. Safari, et al. (2018). "**Heterogeneity in the respiratory symptoms of patients with mild-to-moderate COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3983-3995.

Background: The burden of symptoms varies markedly between patients with COPD and is only weakly correlated with lung function impairment. While heterogeneity in lung function decline and exacerbations have been previously studied, the extent of heterogeneity in symptoms and the factors associated with this heterogeneity are not well understood. Methods: A sample of the general Canadian population  $\geq 40$  years with persistent airflow limitation was followed for up to 3 years. Participants reported whether they experienced chronic coughing, phlegm, wheezing, or dyspnea during visits at 18-month intervals. We used mixed-effect logistic regression models (separately for each symptom) to assess overall heterogeneity in the occurrence of symptoms between individuals, and the proportion of variation in symptom burden explained by lung function vs all other clinical characteristics of participants. Results: Four hundred forty-nine participants (53% male, mean age 67 years) contributed 968 visits in total, and 89% of patients reported at least one symptom during follow-up. There was substantial heterogeneity in the individual-specific probabilities for the occurrence of symptoms. This heterogeneity was highest for wheeze and dyspnea (IQR of probabilities: 0.13-0.78 and 0.19-0.81, respectively). FEV1 explained 28% of the variation between individuals in the occurrence of dyspnea, 8% for phlegm, 3% for cough, and 2% for wheeze. All clinical characteristics of participants (including FEV1) explained between 26% of heterogeneity in the occurrence of cough to 49% for dyspnea. Conclusion: There is marked heterogeneity in the burden of respiratory symptoms between COPD patients. The ability of lung function and other commonly measured clinical characteristics to explain this heterogeneity differs between symptoms.

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Jouleh, B., M. Erdal, et al. (2018). "**Guideline adherence in hospital recruited and population based COPD patients.**" *BMC Pulm Med* **18**(1): 195.

BACKGROUND: Evidence from several studies show poor guideline adherence to COPD treatment, but no such study has been undertaken in Norway. The objectives of this study, was to estimate and compare the guideline adherence to COPD treatment in general population-based and hospital-recruited COPD patients, and find possible predictors of guideline adherence. METHODS: From the prospective, observational EconCOPD-study, we analysed guideline adherence for 90 population-based COPD cases compared to 245 hospital-recruited COPD patients. Overall guideline adherence was defined as correct pharmacological treatment, and influenza vaccination the preceding year, and having received smoking cessation advice. Multivariate logistic regression analysis was performed with the dichotomous outcome overall guideline adherence adjusting for relevant variables. RESULTS: The overall guideline adherence for population-based COPD cases was 6.7%, significantly lower than the 29.8% overall guideline-adherence amongst hospital-recruited COPD patients. Adherence to pharmacological treatment guidelines was 10.0 and 35.5%, for the two recruitment sources, respectively. GOLD-stage 3 to 4 was associated with significantly better guideline adherence compared to GOLD-stage 2 (OR (95% CI) 18.9 (8.37,42.7)). The unadjusted difference between the two recruitment sources was completely explained by degree of airflow obstruction. CONCLUSION: Overall guideline adherence was very low for both

recruitment sources. We call for increased attention from authorities and healthcare personnel to improve the quality of care given to this patient group.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6302492/pdf/12890\\_2018\\_Article\\_756.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6302492/pdf/12890_2018_Article_756.pdf)

Kahnert, K., B. Jobst, et al. (2019). "**Relationship of spirometric, body plethysmographic, and diffusing capacity parameters to emphysema scores derived from CT scans.**" *Chron Respir Dis* **16**: 1479972318775423.

Phenotyping of chronic obstructive pulmonary disease (COPD) with computed tomography (CT) is used to distinguish between emphysema- and airway-dominated type. The phenotype is reflected in correlations with lung function measures. Among these, the relative value of body plethysmography has not been quantified. We addressed this question using CT scans retrospectively collected from clinical routine in a large COPD cohort. Three hundred and thirty five patients with baseline data of the German COPD cohort COPD and Systemic Consequences-Comorbidities Network were included. CT scans were primarily evaluated using a qualitative binary emphysema score. The binary score was positive for emphysema in 52.5% of patients, and there were significant differences between the positive/negative groups regarding forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity (FVC), intrathoracic gas volume (ITGV), residual volume (RV), specific airway resistance (sRaw), transfer coefficient (KCO), transfer factor for carbon monoxide (TLCO), age, pack-years, and body mass index (BMI). Stepwise discriminant analyses revealed the combination of FEV1/FVC, RV, sRaw, and KCO to be significantly related to the binary emphysema score. The additional positive predictive value of body plethysmography, however, was only slightly higher than that of the conventional combination of spirometry and diffusing capacity, which if taken alone also achieved high predictive values, in contrast to body plethysmography. The additional information on the presence of CT-diagnosed emphysema as conferred by body plethysmography appeared to be minor compared to the well-known combination of spirometry and CO diffusing capacity.

Kalhan, R. and R. K. Mutharasan (2018). "**Reducing Readmissions in Patients With Both Heart Failure and COPD.**" *Chest* **154**(5): 1230-1238.

Patients with both COPD and heart failure (HF) pose particularly high costs to the health-care system. These diseases arise from similar root causes, have overlapping symptoms, and share similar clinical courses. Because of these strong parallels, strategies to reduce readmissions in patients with both conditions share synergies. Here we present 10 practical tips to reduce readmissions in this challenging population: (1) diagnose the population accurately, (2) detect admissions for exacerbations early and consider risk stratification, (3) use specialist management in hospital, (4) modify the underlying disease substrate, (5) apply and intensify evidence-based therapies, (6) activate the patient and develop critical health behaviors, (7) setup feedback loops, (8) arrange an early follow-up appointment prior to discharge, (9) consider and address other comorbidities, and (10) consider ancillary support services at home. The multidisciplinary care teams needed to support these care models pose expense to the health-care system. Although these costs may more easily be recouped under financial models such as accountable care organizations and bundled payments, the opportunity cost of an admission for COPD or HF may represent an underrecognized financial lever.

[https://journal.chestnet.org/article/S0012-3692\(18\)30891-2/fulltext](https://journal.chestnet.org/article/S0012-3692(18)30891-2/fulltext)

Kaluza, J., H. R. Harris, et al. (2018). "**Long-term consumption of fruits and vegetables and risk of chronic obstructive pulmonary disease: a prospective cohort study of women.**" *Int J Epidemiol* **47**(6): 1897-1909.

Background: Fruits and vegetables, due to high antioxidant capacity, may protect the lung from oxidative damage caused by tobacco smoke and potentially prevent chronic obstructive pulmonary disease (COPD). Only one study based on baseline diet has examined fruit and vegetable consumption in relation to risk of COPD, and no previous studies have examined long-term diet. Methods: We investigated whether long-term fruit and vegetable consumption was associated with COPD incidence among 34 739 women (age 48-83 years) in the population-based prospective Swedish Mammography Cohort. Fruit and vegetable consumption was assessed twice (1987, 1997) with a self-administered questionnaire. Cases of COPD were identified by linkage to the Swedish health register. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Results: During follow-up from 2002 to 2014, 1512 women were diagnosed with COPD. Long-term fruit was associated with lower risk of COPD; women in the highest vs lowest quintile of consumption ( $\geq 2.5$  vs  $< 0.8$  servings/day) had a 37% lower risk of COPD (95% CI: 25-48%; P-trend  $< 0.0001$ ). No association was observed with long-term vegetable intake. Current and ex-smokers with low long-term consumption of fruits ( $< 1$  serving/day) in comparison to never smokers with high consumption ( $\geq 3$  servings/day) had a 38-fold (HR: 38.1; 95% CI: 20.2-71.7) and 13-fold (HR: 12.5, 95% CI: 6.5-24.1) higher risk of COPD, respectively. However, no significant interaction between smoking status and fruit intake in relation to COPD incidence was observed (P-interaction = 0.95). Conclusions: In this prospective cohort of middle-age and older women, long-term consumption of fruits but not vegetables was inversely associated with COPD incidence.

<https://academic.oup.com/ije/article-abstract/47/6/1897/5101395?redirectedFrom=fulltext>

Kanar, B. G., I. Ozmen, et al. (2018). "**Right Ventricular Functional Improvement after Pulmonary Rehabilitation Program in Patients with COPD Determined by Speckle Tracking Echocardiography.**" *Arq Bras Cardiol* **111**(3): 375-381.

BACKGROUND: Although right ventricular (RV) dysfunction in pulmonary diseases has been associated with increased morbidity, tools for RV dysfunction identification are not well defined. OBJECTIVE: The aim of this study was to evaluate the magnitude of RV dysfunction by means of speckle tracking echocardiography (STE) in patients with chronic obstructive pulmonary disease (COPD) and to investigate whether STE could be used as an index of RV improvement after a pulmonary rehabilitation (PR) program. METHODS: Forty-six patients with COPD undergoing PR program and 32 age-sex matched healthy subjects were enrolled. RV function was evaluated at admission and after PR program by conventional two-dimensional echocardiography (2DE) and STE. In addition, exercise tolerance of subjects was evaluated using the six-minute walk test (6MWT). RESULTS: COPD patients had worse RV function according to STE and 2DE as well. STE was more sensitive than conventional 2DE in determining RV improvement after PR program - RV global longitudinal strain (LS): 20.4 +/- 2.4% vs. 21.9 +/- 2.9%  $p < 0.001$  and RV free wall LS: 18.1 +/- 3.4% vs. 22.9 +/- 3.7%,  $p < 0.001$ ). RV free wall LS was directly related to distance walked at baseline 6MWT ( $r = 0.58$ ,  $p < 0.001$ ) and to the change in the 6MWT distance (6MWTD) ( $r = 0.41$ ,  $p = 0.04$ ). CONCLUSIONS: We conclude that STE might be as effective as 2DE for evaluation of global and regional RV functions. STE may become an important tool for assessment and follow-up of COPD patients undergoing PR program to determine the relationship between RV function and exercise tolerance.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6173336/pdf/abc-111-03-0375.pdf>

Kasymjanova, G., R. T. Jagoe, et al. (2018). "**Does the presence of emphysema increase the risk of radiation pneumonitis in lung cancer patients?**" *Curr Oncol* **25**(6): e610-e614.

Introduction: Radiotherapy (rt) plays an important role in the treatment of lung cancer. One of the most common comorbidities in patients with lung cancer is pulmonary emphysema. The literature offers conflicting

data about whether emphysema increases the occurrence and severity of radiation pneumonitis (rp). As a result, whether high doses of rt (with curative intent) should be avoided in patients with emphysema is still unclear. Objective: We measured the documented incidence of rp in patients with and without emphysema who received curative radiation treatment. Methods: This retrospective cohort study considered patients in the lung cancer clinical database of the Peter Brojde Lung Cancer Centre. Data from the database has been used previously for research studies, including a recent publication about emphysema grading, based on the percentage of lung occupied by emphysema on computed tomography (ct) imaging. Results: Using previously published methods, chest ct imaging for 498 patients with lung cancer was scored for the presence of emphysema. The analysis considered 114 patients who received at least 30 Gy radiation. Of those 114 patients, 64 (56%) had emphysema, with approximately 23% having severe or very severe disease. The incidence of rp was 34.4% in patients with emphysema (n = 22) and 32.0% in patients with no emphysema (n = 16, p = 0.48). No difference in the incidence of rp was evident between patients with various grades of emphysema (p = 0.96). Similarly, no difference in the incidence of rp was evident between the two treatment protocols-that is, definitive rt 17 (37%) and combined chemotherapy-rt 21 (31%, p = 0.5). Conclusions: In our cohort, the presence of emphysema on chest ct imaging was not associated with an increased risk of rp. That finding suggests that patients with lung cancer and emphysema should be offered rt when clinically indicated. However, further prospective studies will be needed for confirmation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6291283/pdf/conc-25-e610.pdf>

Kaszuba, E., H. Odeberg, et al. (2018). "**Impact of heart failure and other comorbidities on mortality in patients with chronic obstructive pulmonary disease: a register-based, prospective cohort study.**" BMC Fam Pract **19**(1): 178.

BACKGROUND: Multimorbidity has already become common in primary care and will be a challenge in the future. Primary care in Sweden participates to a great extent in the care of patients with two severe, chronic conditions: chronic obstructive pulmonary disease (COPD) and heart failure. Both conditions are characterized by high mortality and often coexist. Age, sex, heart failure and other comorbidities are considered to be the major predictors of mortality in patients with COPD. We aimed to study the impact of heart failure, other comorbidities, age and sex on mortality in patients with COPD. METHODS: A register-based, prospective cohort study conducted in Blekinge County in Sweden with about 150,000 inhabitants. The study population was comprised of people aged  $\geq 35$  years. The data about diagnoses of COPD and heart failure came from the 2007 health care register, in which we found 984 individuals with a diagnosis of COPD. Date of death was collected from January 1st, 2008 -August 31st, 2015. The diagnosis-based Adjusted Clinical Groups (ACG) Case-Mix System 7.1 was used to describe comorbidity. Each individual was assigned one of six comorbidity levels called resource utilization bands (RUB) graded from 0 to 5. RESULTS: Estimated eight year mortality in patients with COPD and coexisting heart failure was seven times higher than in patients with COPD alone - odds ratio 7.06 (95% CI 3.88-12.84). Adjusting for age and male sex resulted in odds ratio 3.75 (95% CI 1.97-7.15). Further adjusting for other comorbidities resulted in odds ratio 3.26 (95% CI 1.70-6.25). The mortality was strongly associated with the highest comorbidity level - RUB 5 where the odds ratio was 5.19 (95% CI 2.59-10.38). CONCLUSION: Heart failure has an important impact on mortality in patients with COPD. The mortality in patients with COPD and coexisting heart failure was strongly associated with age, male sex and other comorbidities. Of those three predictors, only other comorbidities can be influenced. Heart failure and other comorbidities should be recognized early and properly treated in order to improve survival in patients with coexisting COPD and heart failure.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6260666/pdf/12875\\_2018\\_Article\\_865.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6260666/pdf/12875_2018_Article_865.pdf)

Kobayashi, S., M. Hanagama, et al. (2018). "**Clinical characteristics and outcomes in Japanese patients with COPD according to the 2017 GOLD classification: the Ishinomaki COPD Network Registry.**" Int J Chron Obstruct Pulmon Dis **13**: 3947-3955.

Purpose: The GOLD report provides a framework for classifying COPD in a way that reflects its clinical impact and allows treatment recommendations. The GOLD 2017 proposes a new classification whereby patients are grouped as A-D according to their symptoms and history of exacerbations. However, the clinical characteristics and outcomes in these patients are not well documented. Patients and methods: In this prospective observational study, we analyzed data from the Ishinomaki COPD Network Registry. All patients with stable COPD were classified into the four groups defined by GOLD 2017. The patient demographics, clinical characteristics, number of exacerbations, and mortality rate during 1 year of follow-up were compared between the groups. Results: Four hundred and one patients with stable COPD were identified. There were 240 patients (59.9%) in group A, 122 (30.4%) in group B, 16 (4.0%) in group C, and 23 (5.7%) in group D. Patients in groups B, C, and D had ORs of 2.95, 3.92, and 5.45, respectively, for risk of exacerbation relative to group A. Groups C and D experienced exacerbations more frequently, including exacerbations leading to hospital admission, than groups A and B (both  $P < 0.001$ ) during the 1-year follow-up period. Patients with a high risk of exacerbation (groups C and D) had a lower body mass index, showed more symptoms, used more respiratory medications, and had more severe airflow limitation than patients at low risk of exacerbation (groups A and B). Mortality was not different between the high-risk and low-risk groups. Conclusion: The results of our study provide evidence that the GOLD 2017 classification identifies patients with COPD at risk of exacerbations, including those requiring hospitalization, but has a poor ability to predict mortality.

<https://www.dovepress.com/getfile.php?fileID=46785>

Kostikas, K., C. Brindicci, et al. (2018). "**Blood Eosinophils as Biomarkers to Drive Treatment Choices in Asthma and COPD.**" *Curr Drug Targets* **19**(16): 1882-1896.

BACKGROUND: Asthma and COPD are complex, heterogeneous conditions comprising a wide range of phenotypes, some of which are refractory to currently available treatments. Elucidation of these phenotypes and identification of biomarkers with which to recognize them and guide appropriate treatment remain a priority. OBJECTIVE: This review describes the utility of blood eosinophils as a surrogate biomarker of eosinophilic airway inflammation, a common feature of specific asthma and COPD phenotypes. The role of blood eosinophils in airway disease is described, as is their relevance in reflecting airway eosinophilia. Each disease is discussed separately as the manner in which blood eosinophils might be used as biomarkers differs. Focusing on patients with severe disease (persistent eosinophilic asthma and exacerbating COPD), we evaluate evidence examining eosinophils as biomarkers. RESULTS: In asthma, the rationale for using blood eosinophils to guide treatment is clearly defined, backed by prospective, well-controlled studies. Higher eosinophil counts identify patients with more severe disease and poorer outcomes, patients for whom biologic therapies targeting allergic and/or eosinophilic pathways are recommended. In COPD, the evidence is less robust. High blood eosinophil counts are a modest predictor of future exacerbations, and may predict a favourable response to ICS on top of LABA/LAMA, especially in patients with a history of frequent exacerbations. CONCLUSION: Before extensive application in clinical practice, further evaluation of these findings in prospective clinical studies, and standardization of the appropriate thresholds of clinically relevant eosinophilia are needed, together with establishing whether single or multiple measurements are required in different clinical settings.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225326/pdf/CDT-19-1882.pdf>

Lai, C. C., Y. H. Wang, et al. (2019). "**Risk of Sepsis and Mortality Among Patients With Chronic Obstructive Pulmonary Disease Treated With Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers.**" *Crit Care Med* **47**(1): e14-e20.

OBJECTIVES: This study aimed to compare the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk and outcomes of sepsis in patients with chronic obstructive pulmonary disease. DESIGN: A retrospective study. SETTING: Taiwan's National Health Insurance Research Database. PATIENTS: All patients with chronic obstructive pulmonary disease who received angiotensin-converting

enzyme inhibitors or angiotensin receptor blockers for more than 90 days between 2000 and 2005 were recruited for this study. Pairwise matching (1:1) of the angiotensin-converting enzyme inhibitor and angiotensin receptor blocker groups resulted in two similar subgroups with 5,959 patients in each. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: The primary outcome was sepsis, and the secondary outcome was death. The occurrence rate of sepsis was 3.67 per 100 person-years for the patients receiving angiotensin-converting enzyme inhibitors and 2.87 per 100 person-years for those receiving angiotensin receptor blockers. In addition, the patients receiving angiotensin-converting enzyme inhibitors had a higher risk of septic shock (adjusted hazard ratio, 1.45; 95% CI, 1.26-1.67) and mortality (adjusted hazard ratio, 1.31; 95% CI, 1.22-1.40) than those receiving angiotensin receptor blockers. No matter whether the patients had prior severe exacerbation before the index date, those receiving angiotensin-converting enzyme inhibitors had a higher risk of sepsis, septic shock, and mortality than those receiving angiotensin receptor blockers (all  $p < 0.001$ ). CONCLUSIONS: Angiotensin receptor blockers were associated with lower rates of sepsis and mortality than angiotensin-converting enzyme inhibitors in the patients with chronic obstructive pulmonary disease. The similar findings were also noted in subgroup analysis.

Lawson, C. A., M. A. Mamas, et al. (2018). "**Association of Medication Intensity and Stages of Airflow Limitation With the Risk of Hospitalization or Death in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease.**" *JAMA Netw Open* 1(8): e185489.

Importance: In heart failure (HF), chronic obstructive pulmonary disease (COPD) increases the risk of poor outcomes, but the effect of COPD severity is unknown. This information is important for early intervention tailored to the highest-risk groups. Objectives: To determine the associations between COPD medication intensity or stage of airflow limitation and the risk of hospitalization or death in patients with HF. Design, Setting, and Participants: This UK population-based, nested case-control study with risk-set sampling used the Clinical Practice Research Datalink linked to Hospital Episode Statistics between January 1, 2002, to January 1, 2014. Participants included patients aged 40 years and older with a new diagnosis of HF in their family practice clinical record. Data analysis was conducted from 2017 to 2018. Exposures: In patients with HF, those with COPD were compared with those without it. International COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD]) guidelines were used to stratify patients with COPD by 7 medication intensity levels and 4 airflow limitation severity stages using automatically recorded prescriptions and routinely requested forced expiratory volume in 1 second (FEV1) data. Main Outcomes and Measures: First all-cause admission or all-cause death. Results: There were 50114 patients with new HF (median age, 79 years [interquartile range, 71-85 years]; 46% women) during the study period. In patients with HF, COPD (18478 [13.8%]) was significantly associated with increased mortality (adjusted odds ratio [AOR], 1.31; 95% CI, 1.26-1.36) and hospitalization (AOR, 1.33; 95% CI, 1.26-1.39). The 3 most severe medication intensity levels showed significantly increasing mortality associations from full inhaler therapy (AOR, 1.17; 95% CI, 1.06-1.29) to oral corticosteroids (AOR, 1.69; 95% CI, 1.57-1.81) to oxygen therapy (AOR, 2.82; 95% CI, 2.42-3.28). The respective estimates for hospitalization were AORs of 1.17 (95% CI, 1.03-1.33), 1.75 (95% CI, 1.59-1.92), and 2.84 (95% CI, 1.22-3.63). Availability of spirometry data was limited but showed that increasing airflow limitation was associated with increased risk of mortality, with the following AORs: FEV1 80% or more, 1.63 (95% CI, 1.42-1.87); FEV1 50% to 79%, 1.69 (95% CI, 1.56-1.83); FEV1 30% to 49%, 2.21 (95% CI, 2.01-2.42); FEV1 less than 30%, 2.93 (95% CI, 2.49-3.43). The strength of associations between FEV1 and hospitalization risk were similar among stages ranging from FEV1 80% or more (AOR, 1.48; 95% CI, 1.31-1.68) to FEV1 less than 30% (AOR, 1.73; 95% CI, 1.40-2.12). Conclusions and Relevance: In the UK HF community setting, increasing COPD severity was associated with increasing risk of mortality and hospitalization. Prescribed COPD medication intensity and airflow limitation provide the basis for targeting high-risk groups.

[https://jamanetwork.com/journals/jamanetworkopen/articlepdf/2718091/lawson\\_2018\\_oi\\_180236.pdf](https://jamanetwork.com/journals/jamanetworkopen/articlepdf/2718091/lawson_2018_oi_180236.pdf)

Li, M., F. Wang, et al. (2018). **"Factors contributing to hospitalization costs for patients with COPD in China: a retrospective analysis of medical record data."** *Int J Chron Obstruct Pulmon Dis* **13**: 3349-3357.

Purpose: Hospitalization brings considerable economic pressure on COPD patients in China. A clear understanding of hospitalization costs for patients with COPD is warranted to improve treatment strategies and to control costs. Currently, investigation on factors contributing to hospitalization costs for patients with COPD in China is limited. This study aimed to measure the hospitalization costs of COPD and to determine the contributing factors. Patients and methods: Medical record data from the First Affiliated Hospital of Guangzhou Medical University from January 2016 to December 2016 were used for a retrospective analysis. Patients who were hospitalized with a diagnosis of COPD were included. Patient characteristics, medical treatment, and hospitalization costs were analyzed by descriptive statistics and multivariable regression. Results: Among the 1,943 patients included in this study, 87.85% patients were male; the mean (SD) age was 71.15 (9.79) years; 94.49% patients had comorbidities; and 82.30% patients had health insurance. Regarding medical treatment, the mean (SD) length of stay was 9.38 (7.65) days; 11.12% patients underwent surgery; 87.91% used antibiotics; and 4.53% underwent emergency treatment. For hospitalization costs, the mean (SD) of the total costs per COPD patient per admission was 24,372.75 (44,173.87) CNY (3,669.33 [6,650.38] USD), in which Western medicine fee was the biggest contributor (45.53%) followed by diagnosis fee (27.00%) and comprehensive medical fee (12.04%). Regression found that reimbursement (-0.032; 95% CI -0.046 to 0.007), length of stay (0.738; 95% CI 0.832-0.892), comorbidity (0.044; 95% CI 0.029-0.093), surgery (0.145; 95% CI 0.120-0.170), antibiotic use (0.086; 95% CI 0.060-0.107), and emergency treatment (0.121; 95% CI 0.147-0.219) were significantly ( $P < 0.01$ ) associated with total hospitalization costs. Conclusion: To control hospitalization costs for COPD patients in China, the significance of comorbidity, length of stay, antibiotic use, surgery, and emergency treatment suggests the importance of controlling the COPD progression and following clinical guidelines for inpatients. Interventions such as examination of pulmonary function for early detection, quality control of medical treatment, and patient education warrant further investigation.

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Luo, Z., C. Wu, et al. (2018). **"High-intensity versus low-intensity noninvasive positive pressure ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease (HAPPEN): study protocol for a multicenter randomized controlled trial."** *Trials* **19**(1): 645.

BACKGROUND: Despite the positive outcomes of the use of noninvasive positive pressure ventilation (NPPV) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), NPPV fails in approximately 15% of patients with AECOPD, possibly because the inspiratory pressure delivered by conventional low-intensity NPPV is insufficient to improve ventilatory status for these patients. High-intensity NPPV, a novel form that delivers high inspiratory pressure, is believed to more efficiently augment alveolar ventilation than low-intensity NPPV, and it has been shown to improve ventilatory status more than low-intensity NPPV in stable AECOPD patients. Whether the application of high-intensity NPPV has therapeutic advantages over low-intensity NPPV in patients with AECOPD remains to be determined. The high-intensity versus low-intensity NPPV in patients with AECOPD (HAPPEN) study will examine whether high-intensity NPPV is more effective for correcting hypercapnia than low-intensity NPPV, hence reducing the need for intubation and improving survival. METHODS/DESIGN: The HAPPEN study is a multicenter, two-arm, single-blind, prospective, randomized controlled trial. In total, 600 AECOPD patients with low to moderate hypercapnic respiratory failure will be included and randomized to receive high-intensity or low-intensity NPPV, with randomization stratified by study center. The primary endpoint is NPPV failure rate, defined as the need for endotracheal intubation and invasive ventilation. Secondary endpoints include the decrement of arterial carbon dioxide tension from baseline to 2 h after randomization, in-hospital and 28-day mortality, and 90-day survival. Patients will be followed up for 90 days after randomization. DISCUSSION: The HAPPEN study will be the first randomized controlled study to investigate whether high-intensity NPPV better corrects hypercapnia and reduces the need for intubation and mortality in AECOPD patients than low-intensity NPPV. The results will help critical care physicians decide the intensity of NPPV delivery to patients with AECOPD. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02985918 . Registered on 7 December 2016.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6249746/pdf/13063\\_2018\\_Article\\_2991.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6249746/pdf/13063_2018_Article_2991.pdf)

Matthes, S., J. Stadler, et al. (2018). "**Asthma features in severe COPD: Identifying treatable traits.**" *Respir Med* **145**: 89-94.

AIM: Biological therapies developed for severe asthma may have a role in COPD patients with asthma features.

METHOD: We carried out a prospective, consecutive, cross-sectional analysis of 80 patients with severe COPD GOLD IV/D. RESULTS: We studied 80 patients (48.8% female), aged 57.6+/-5.1 years, ex-smokers with 35.7+/-21.2 pack years, BMI 22.3+/-3.5kg/m(2), FEV1 of 0.61+/-0.2L (21.1+/-5.6% pred), pO2 52.4+/-8.4mmHg, and BODE 6.9+/-1.7. 68% had >2 moderate or severe exacerbations annually. 16.1% (5/31) patients showed FEV1 reversibility of >12% and >200ml despite maximal therapy, 33% (15/45) had FENO >=22.5ppb, 33% (24/73) had serum IgE >=100 I.E./ml and there was positive allergen sensitization in 51.5% (35/68). Blood eosinophilia of >=150cells/mul was seen in 47% (35/74). Induced sputum showed eosinophilia of >=2% in 56% (14/24) with respiratory pathogens in 63.8% (30/47). We identified 12 (15%) patients with asthma-COPD overlap. Of these, 10 (83.3%) had frequent exacerbations and these patients had significantly more severe exacerbations requiring NIV or ICU than those without asthma features (p<0.005). CONCLUSION: We detected asthma features in a substantial subset of stable patients with severe COPD. Asthma features were associated with more severe exacerbation despite optimal COPD therapy, representing potential candidates for targeted therapy with anti- IgE or anti-IL5.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30343-3/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30343-3/fulltext)

Meeraus, W., R. Wood, et al. (2019). "**COPD treatment pathways in France: a retrospective analysis of electronic medical record data from general practitioners.**" *Int J Chron Obstruct Pulmon Dis* **14**: 51-63.

Background: Increasing availability of therapeutic options for COPD may drive new treatment pathways. This study describes COPD treatment in France, focusing on identifying initial treatment modifications in patients with COPD who either initiated long-acting bronchodilator (LABD)-based therapy or escalated to triple therapy (long-acting muscarinic antagonist [LAMA] + long-acting beta2-agonist [LABA] + inhaled corticosteroid [ICS]). Methods: This retrospective analysis of patients with COPD in a large general practitioner database (IQVIA Longitudinal Patient Database) in France included two cohorts: Cohort 1 - new initiators of LABD-based therapy (LAMA, LABA, LAMA + LABA, LAMA + ICS, LABA + ICS or LAMA + LABA + ICS); Cohort 2 - patients escalating to triple therapy from mono- or dual-bronchodilator-based maintenance treatment. Both cohorts were indexed on the date of initiation/escalation (January 2008-December 2013), and the first treatment modification (at class level) within the 18-month post-index observational period was described. Five mutually exclusive outcomes were defined: continuous use (no modification), discontinuation (permanent [ $\geq$ 91 days with no restart] or temporary [ $\geq$ 91 days with subsequent restart]), switch, and augmentation (Cohort 1 only). Exploratory analysis of Cohort 1 explored potential drivers of treatment initiation. Results: Overall, 5,065 patients initiated LABD-based therapy (Cohort 1), and 501 escalated to triple therapy (Cohort 2). In Cohort 1, 7.0% of patients were continuous users, 46.5% discontinued permanently, 28.5% discontinued temporarily, 2.8% augmented (added LAMA and/or LABA and/or ICS), and 15.2% switched therapy. In Cohort 2, 18.2% of patients were continuous users, 7.2% discontinued permanently, 27.9% discontinued temporarily, and 46.7% switched therapy. Exploratory analyses showed that time since COPD diagnosis was first recorded, pre-index exacerbation events, and concomitant medical conditions were potential drivers of initial maintenance treatment choices. Conclusion: Discontinuation among new initiators of LABD-based therapy was high in France, whereas few switched or augmented treatment. In comparison, permanent discontinuation within 18 months was low in patients escalating to triple therapy.

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Mesquita, C. B., C. Knaut, et al. (2018). "Impact of adherence to long-term oxygen therapy on patients with COPD and exertional hypoxemia followed for one year." *J Bras Pneumol* **44**(5): 390-397.

**OBJECTIVE:** To determine the impact of adherence to long-term oxygen therapy (LTOT) on quality of life, dyspnea, and exercise capacity in patients with COPD and exertional hypoxemia followed for one year. **METHODS:** Patients experiencing severe hypoxemia during a six-minute walk test (6MWT) performed while breathing room air but not at rest were included in the study. At baseline and after one year of follow-up, all patients were assessed for comorbidities, body composition, SpO<sub>2</sub>, and dyspnea, as well as for anxiety and depression, having also undergone spirometry, arterial blood gas analysis, and the 6MWT with supplemental oxygen. The Saint George's Respiratory Questionnaire (SGRQ) was used in order to assess quality of life, and the Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE) index was calculated. The frequency of exacerbations and the mortality rate were noted. Treatment nonadherence was defined as LTOT use for < 12 h per day or no LTOT use during exercise. **RESULTS:** A total of 60 patients with COPD and exertional hypoxemia were included in the study. Of those, 10 died and 11 experienced severe hypoxemia during follow-up, 39 patients therefore being included in the final analysis. Of those, only 18 (46.1%) were adherent to LTOT, showing better SGRQ scores, higher SpO<sub>2</sub> values, and lower PaCO<sub>2</sub> values than did nonadherent patients. In all patients, SaO<sub>2</sub>, the six-minute walk distance, and the BODE index worsened after one year. There were no differences between the proportions of adherence to LTOT at 3 and 12 months of follow-up. **CONCLUSIONS:** Quality of life appears to be lower in patients with COPD and exertional hypoxemia who do not adhere to LTOT than in those who do. In addition, LTOT appears to have a beneficial effect on COPD symptoms (as assessed by SGRQ scores). (Brazilian Registry of Clinical Trials - ReBEC; identification number RBR-9b4v63 [<http://www.ensaiosclinicos.gov.br>]).

Milkowska-Dymanowska, J., A. J. Bialas, et al. (2018). "The usefulness of soluble receptor for advanced glycation end-products in the identification of COPD frequent exacerbator phenotype." *Int J Chron Obstruct Pulmon Dis* **13**: 3879-3884.

**Introduction:** Exacerbations of COPD (ECOPDs) are important events in the course of COPD, accelerating the rate of decline in lung function and increasing the mortality risk. A growing body of evidence suggests the significance of the "frequent exacerbator" phenotype. This phenotype seems to be associated with a more severe airflow limitation, symptoms, health-related quality of life impairment, and higher mortality. However, there is no described biomarker that would help to identify this group of patients. **Patients and methods:** Patients with COPD in "D" GOLD category were monitored for 3 years according to events of ECOPD. Serum samples were collected from the patients. Circulating level of plasma soluble receptor for advanced glycation end-products (sRAGE) was measured using commercially available high sensitivity kits. The receiver operating characteristic (ROC) curve analysis was used to assess the usefulness of sRAGE to identify frequent exacerbator phenotype. Log-rank test was used in the analysis of time to the subsequent exacerbation. Pearson (R) or Spearman's rank (R<sub>S</sub>) correlation coefficients were used for correlation analysis. **Results:** Nineteen patients were enrolled. The area under the ROC curve (AUROC) for sRAGE for the identification of frequent exacerbator phenotype was 0.81. Analysis identified the cutoff point as 850.407 pg/mL, characterized by a sensitivity of 0.80 (95% CI: 0.28-1.0) and specificity of 0.93 (95% CI: 0.66-1.0). Additionally, in the group with sRAGE  $\leq$  850.407 pg/mL, we observed significantly shorter time to the subsequent exacerbation: median of 32 vs 105.5 days (P=0.03). Correlation analysis revealed significant negative correlation between sRAGE and the number of exacerbations requiring hospitalization during the whole time of follow-up (R<sub>S</sub> = -0.53; P=0.02) and significant positive correlation with FEV<sub>1</sub> expressed as the percentage of reference value (R=0.6; P=0.006). **Conclusion:** sRAGE seems to be useful in the identification of frequent exacerbator phenotype. This parameter may also be used in the prediction of time to ECOPD. Our findings should be confirmed in a sufficiently powered larger sample.

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Mohamed-Hussein, A. A. R., H. A. Makhoulf, et al. (2018). **"Association between hand grip strength with weaning and intensive care outcomes in COPD patients: A pilot study."** *Clin Respir J* 12(10): 2475-2479.

**BACKGROUND:** In COPD, weight loss and muscle wasting contribute significantly to morbidity, disability, and handicap. Dominant-handgrip strength for evaluation of muscle strength has not been tested as a parameter to predict outcome of weaning from mechanical ventilation (MV). **OBJECTIVES:** To evaluate the association between handgrip strength and the duration and success of weaning and extubation outcome. **MATERIALS AND METHODS:** This prospective study included 34 COPD patients requiring MV for at least 48 hours. Recovery from sedation and muscle relaxants was assessed before recruitment. Serial measurement of handgrip strength were assessed by trained personnel. **RESULTS:** There was a significant negative correlation between baseline hand grip and duration of MV ( $P = .047$ ,  $r = -.343$ ). The mean day 5 hand grip was significantly lower in person who died compared to survivors ( $5.7 \pm 5.5$  vs  $18.2 \pm 14.5$ ,  $P = .044$ ). The mean day 5 hand grip was significantly lower in patients who needed reintubation compared to those in patients who did not need reintubation ( $2.8 \pm 2$  vs  $17.2 \pm 13.9$ ,  $P = .029$ ). There was no significant difference in the mean baseline, day 2, day 3, day 4 and day 5 hand grip in weaning success compared to those in failure ( $P > .05$ ). **CONCLUSION:** Handgrip strength may be good predictor for duration of MV, extubation outcome, ICU mortality and prognosis.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12921>

Mohedano Del Pozo, R. B., M. Rubio Alonso, et al. (2018). **"Diagnosis of invasive fungal disease in hospitalized patients with chronic obstructive pulmonary disease."** *Rev Iberoam Micol* 35(3): 117-122.

**BACKGROUND:** The role of culture-independent techniques (galactomannan, (1-3)-beta-d-glucan) in the early diagnosis of invasive fungal diseases (IFD) is well assessed in hematological patients, but there are no clear conclusions in patients with chronic obstructive pulmonary disease (COPD). **AIMS:** To study the usefulness of nonculture-based techniques in the diagnosis of IFD in COPD-patients at risk for IFD. **METHODS:** A prospective observational study based on monitoring COPD patients at risk for IFD during 2007-2010 was carried out. The presence of galactomannan, (1-3)-beta-d-glucan and an indirect immunofluorescence of *Candida albicans* germ tube specific antibodies (CAGTA) were performed. **RESULTS:** Among 43 COPD patients, 16 (37.2%) were diagnosed with IFD: seven cases were proven IFD (five invasive candidemia - IC, one invasive aspergillosis - IA and a rhinocerebral zygomycosis) and nine probable IFD (seven IA and two IC). In the diagnosis of IC and IA, the negative predictive value (NPV) of (1-3)-beta-d-glucan was 100%. Regarding CAGTA in IC, NPV was 96.2%. Finally, NPV of galactomannan in IA was 91.2%. The area under the ROC curve for (1-3)-beta-d-glucan in IC and for the rest of the IFD cases was 0.86 (95% CI, 0.79-0.93) and 0.60 (95% CI, 0.43-0.77), for CAGTA in IC was 0.83 (95% CI, 0.74-0.91) and for galactomannan in IA was 0.71 (95% CI, 0.56-0.85). Positive (1-3)-beta-d-glucan preceded the growth of *Candida* (average of 1.7 days) in blood culture. **CONCLUSIONS:** In COPD patients at risk for IFD the assayed techniques are especially useful to rule out the presence of IFD.

Mondonedo, J. R., S. Sato, et al. (2019). **"CT Imaging-Based Low-Attenuation Super Clusters in Three Dimensions and the Progression of Emphysema."** *Chest* 155(1): 79-87.

**BACKGROUND:** Distributions of low-attenuation areas in two-dimensional (2-D) CT lung slices are used to quantify parenchymal destruction in patients with COPD. However, these segmental approaches are limited and may not reflect the true three-dimensional (3-D) tissue processes that drive emphysematous changes in the lung. The goal of this study was to instead evaluate distributions of 3-D low-attenuation volumes, which we hypothesized would follow a power law distribution and provide a more complete assessment of the mechanisms underlying disease progression. **METHODS:** CT scans and pulmonary

function test results were acquired from an observational database for N = 12 patients with COPD and N = 12 control patients. The data set included baseline and two annual follow-up evaluations in patients with COPD. Three-dimensional representations of the lungs were reconstructed from 2-D axial CT slices, with low-attenuation volumes identified as contiguous voxels < -960 Hounsfield units. RESULTS: Low-attenuation sizes generally followed a power law distribution, with the exception of large, individual outliers termed "super clusters," which deviated from the expected distribution. Super cluster volume was correlated with disease severity (% total low attenuation, rho = 0.950) and clinical measures of lung function including FEV1 (rho = -0.849) and diffusing capacity of the lung for carbon monoxide Dlco (rho = -0.874). To interpret these results, we developed a personalized computational model of super cluster emergence. Simulations indicated disease progression was more likely to occur near existing emphysematous regions, giving rise to a biomechanical, force-induced mechanism of super cluster growth. CONCLUSIONS: Low-attenuation super clusters are defining, quantitative features of parenchymal destruction that dominate disease progression, particularly in advanced COPD.

[https://journal.chestnet.org/article/S0012-3692\(18\)32496-6/pdf](https://journal.chestnet.org/article/S0012-3692(18)32496-6/pdf)

Mouronte-Roibas, C., A. Fernandez-Villar, et al. (2018). **"Influence of the type of emphysema in the relationship between COPD and lung cancer."** *Int J Chron Obstruct Pulmon Dis* **13**: 3563-3570.

Introduction: There are no studies analyzing the relationship between emphysema and lung cancer (LC). With this aim and in order to make some comparisons between different clinical variables, we carried out the present study. Methods: This is a case-control study, patients with COPD and LC being the cases and subjects with stable COPD being the controls. Clinical and functional parameters, as well as the existence of radiological emphysema, were evaluated in a qualitative and quantitative way, using a radiological density of -950 Hounsfield units as a cutoff point in the images. The existence of several different types of emphysema (centrilobular, paraseptal, panacinar, or bullae) was analyzed, allowing patients to have more than one simultaneously. The extent to which lobes were involved was evaluated and the extension of emphysema was graduated for each type and location, following a quantitative scale. Differences between cases and controls were compared by using bivariate and multivariate analyzes with results expressed as OR and 95% CI. Results: We included 169 cases and 74 controls, 84% men with a FEV1 (%) of 61.7+/-18.5, with 90.1% non-exacerbators. Most of them (50%) were active smokers and 47.2% were ex-smokers. Emphysema was found in 80.2% of the subjects, the most frequent type being centrilobular (34.4%). The only significantly different factor was the presence of paraseptal emphysema (alone or combined; OR =2.2 [95% CI =1.1-4.3, P = 0.03]), with adenocarcinoma being significantly more frequent in paraseptal emphysema with respect to other types (67.2% vs 32.8%, P =0.03). Conclusion: Patients with COPD and paraseptal emphysema could be a risk group for the development of LC, especially adenocarcinoma subtype.

<https://www.dovepress.com/getfile.php?fileID=45728>

Mulpuru, S., L. Li, et al. (2019). **"Effectiveness of Influenza Vaccination on Hospitalizations and Risk Factors for Severe Outcomes in Hospitalized Patients With COPD."** *Chest* **155**(1): 69-78.

BACKGROUND: The effectiveness of influenza vaccination in reducing influenza-related hospitalizations among patients with COPD is not well described, and influenza vaccination uptake remains suboptimal. METHODS: Data were analyzed from a national, prospective, multicenter cohort study including patients with COPD, hospitalized with any acute respiratory illness or exacerbation between 2011 and 2015. All patients underwent nasopharyngeal swab screening with polymerase chain reaction (PCR) testing for influenza. The primary outcome was an influenza-related hospitalization. We identified influenza-positive cases and negative control subjects and used multivariable logistic regression with a standard test-negative design to estimate the vaccine effectiveness for preventing influenza-related hospitalizations. RESULTS: Among 4,755 hospitalized patients with COPD, 4,198 (88.3%) patients with known vaccination status were analyzed. The adjusted analysis showed a 38% reduction in influenza-related hospitalizations in vaccinated vs unvaccinated individuals. Influenza-positive patients (n = 1,833 [38.5%]) experienced

higher crude mortality (9.7% vs 7.9%;  $P = .047$ ) and critical illness (17.2% vs 12.1%;  $P < .001$ ) compared with influenza-negative patients. Risk factors for mortality in influenza-positive patients included age  $> 75$  years (OR, 3.7 [95% CI, 0.4-30.3]), cardiac comorbidity (OR, 2.0 [95% CI, 1.3-3.2]), residence in long-term care (OR, 2.6 [95% CI, 1.5-4.5]), and home oxygen use (OR, 2.9 [95% CI, 1.6-5.1]). CONCLUSIONS: Influenza vaccination significantly reduced influenza-related hospitalization among patients with COPD. Initiatives to increase vaccination uptake and early use of antiviral agents among patients with COPD could reduce influenza-related hospitalization and critical illness and improve health-care costs in this vulnerable population. TRIAL REGISTRY: ClinicalTrials.govNo.:NCT01517191; URL [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

[https://journal.chestnet.org/article/S0012-3692\(18\)32725-9/pdf](https://journal.chestnet.org/article/S0012-3692(18)32725-9/pdf)

Naya, I. P., L. Tombs, et al. (2018). **"Long-term outcomes following first short-term clinically important deterioration in COPD."** *Respir Res* **19**(1): 222.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is characterized by varying trajectories of decline. Information regarding the prognostic value of preventing short-term clinically important deterioration (CID) in lung function, health status, or first moderate/severe exacerbation as a composite endpoint of worsening is needed. We evaluated post hoc the link between early CID and long-term adverse outcomes. METHODS: CID was defined as  $\geq 100$  mL decrease in forced expiratory volume in 1 s (FEV1),  $\geq 4$ -unit increase in St George's Respiratory Questionnaire (SGRQ) score from baseline, and/or a moderate/severe exacerbation during enrollment in two 3-year studies. Presence of CID was assessed at 6 months for the principal analysis (TORCH) and 12 months for the confirmatory analysis (ECLIPSE). Association between presence (+) or absence (-) of CID and long-term deterioration in FEV1, SGRQ, future risk of exacerbations, and all-cause mortality was assessed. RESULTS: In total, 2870 (54%; TORCH) and 1442 (73%; ECLIPSE) patients were CID+. At 36 months, in TORCH, CID+ patients (vs CID-) had sustained clinically significant worsening of FEV1 ( $- 117$  mL; 95% confidence interval [CI]:  $- 134, - 100$  mL;  $P < 0.001$ ) and SGRQ score ( $+ 6.42$  units; 95% CI: 5.40, 7.45;  $P < 0.001$ ), and had higher risk of exacerbations (hazard ratio [HR]: 1.61 [95% CI: 1.50, 1.72];  $P < 0.001$ ) and all-cause mortality (HR: 1.41 [95% CI: 1.15, 1.72];  $P < 0.001$ ). Similar risks post-CID were observed in ECLIPSE. CONCLUSIONS: A CID within 6-12 months of follow-up was consistently associated with increased long-term risk of exacerbations and all-cause mortality, and predicted sustained meaningful loss in FEV1 and health status amongst survivors. TRIAL REGISTRATION: NCT00268216 ; NCT00292552 .

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6245880/pdf/12931\\_2018\\_Article\\_928.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6245880/pdf/12931_2018_Article_928.pdf)

Ogasawara, T., S. Marui, et al. (2018). **"Effect of eicosapentaenoic acid on prevention of lean body mass depletion in patients with exacerbation of chronic obstructive pulmonary disease: A prospective randomized controlled trial."** *Clin Nutr ESPEN* **28**: 67-73.

BACKGROUND & AIMS: Systemic inflammation plays an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD), resulting in depletion of lean body mass (LBM) and muscle mass. Both frequent exacerbation of COPD and low LBM are associated with poor prognosis. This study aimed to evaluate whether supplementation of eicosapentaenoic acid (EPA) prevents depletion of LBM and muscle mass in hospitalized patients with exacerbation of COPD. METHODS: This was a prospective randomized controlled trial, conducted between November 2014 and October 2017. Fifty patients were randomly assigned to receive 1 g/day of EPA-enriched oral nutrition supplementation (ONS) (EPA group) or EPA-free ONS of similar energy (control group) during hospitalization. The LBM index (LBMI) and the skeletal muscle mass index (SMI) were measured using a bioelectrical impedance analyzer at the time of admission and at the time of discharge. Patients underwent pulmonary rehabilitation and wore a pedometer to measure step counts and physical activity. RESULTS: Forty-five patients that completed the experiment were analyzed. Baseline characteristics were similar between the EPA ( $n = 24$ ) and control groups ( $n = 21$ ). There were no significant differences in energy intake, step counts, physical activity, or length of hospitalization between the two groups. Although the plasma levels of EPA significantly increased only in the EPA group, we found an insignificant increase in LBMI and SMI in the EPA group

compared with the control group (LBM: +0.35 vs. +0.19 kg/m<sup>2</sup>, P = 0.60, and SMI: +0.2 vs. -0.3 kg/m<sup>2</sup>, P = 0.17, respectively). The change in the SMI was significantly correlated with the length of hospitalization in the EPA group, but not in the control group (r = 0.53, P = 0.008, and r = -0.09, P = 0.70, respectively). CONCLUSIONS: EPA-enriched ONS in patients with exacerbation of COPD during short-time hospitalization had no significant advantage in preservation of LBM and muscle mass compared with EPA-free ONS. EPA supplementation for a longer duration might play an important role in the recovery of skeletal muscle mass after exacerbation of COPD.

[https://clinicalnutritionespen.com/article/S2405-4577\(18\)30453-4/fulltext](https://clinicalnutritionespen.com/article/S2405-4577(18)30453-4/fulltext)

Oh, J. Y., Y. S. Lee, et al. (2018). "**Decreased serum club cell secretory protein in asthma and chronic obstructive pulmonary disease overlap: a pilot study.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3411-3417.

Purpose: Improvement in the diagnosis of asthma and chronic obstructive pulmonary disease (COPD) overlap (ACO), and identification of biomarkers for phenotype recognition will encourage good patient care by providing optimal therapy. We investigated club cell secretory protein (CC-16), a protective and anti-inflammatory mediator, as a new candidate biomarker for diagnosing ACO. Patients and methods: We performed a multicenter cohort study. A total of 107 patients were divided into three groups - asthma, COPD, and ACO - according to the Spanish guidelines algorithm, and enrolled into the study. Serum CC-16 levels were measured using commercial ELISA kits. Results: Serum CC-16 levels were the lowest in patients with ACO. Low serum CC-16 levels were a significant marker for the ACO even after adjustment for age, sex, and smoking intensity. Serum CC-16 levels were positively correlated with forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), forced expiratory flow at 25%-75% of FVC, FEV1/FVC, vital capacity, and diffusing capacity of the lung for carbon monoxide, and were negatively correlated with smoking amount (pack-years), bronchodilator response, fractional residual capacity, residual volume, and number of exacerbations per year. FEV1 and serum CC-16 levels were significantly lower in patients with frequent exacerbations. Conclusion: Serum CC-16 has the potential to be a biomarker for ACO diagnosis and also treat frequent exacerbations in patients with chronic inflammatory airway diseases.

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Oh, J. Y., Y. S. Lee, et al. (2018). "**Difference in systemic inflammation and predictors of acute exacerbation between smoking-associated COPD and tuberculosis-associated COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3381-3387.

Purpose: Tuberculosis-associated COPD (T-COPD) has clinical characteristics similar to those of smoking-associated COPD (S-COPD), such as dyspnea, sputum production, and acute exacerbation (AE). However, the degree of systemic inflammation and prognosis might be different because of difference in the pathophysiology. The aim of this study was to compare the lung function, systemic inflammatory markers, and their impacts on AE in patients with S-COPD and T-COPD. Patients and methods: We performed a multicenter cross-sectional cohort study. We evaluated clinical characteristics, pulmonary function tests, levels of inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and IL-6, and the association of these markers with AE in patients with S-COPD and T-COPD. Results: Patients with T-COPD included more women and had lesser smoking history and higher St George Respiratory Questionnaire score than did patients with S-COPD. Although the FEV1 of both groups was similar, FVC, vital capacity, total lung capacity, and functional residual capacity were lower in patients with T-COPD than in those with S-COPD. CRP, ESR, and IL-6 levels were significantly higher in patients with T-COPD compared to patients with S-COPD. According to a multivariate logistic regression analysis, FEV1 was a significant factor predicting AE in S-COPD, and IL-6 was a significant factor predicting AE in T-COPD. IL-6 level greater than 2.04 pg/mL was a cutoff for predicting exacerbation of T-COPD (sensitivity 84.8%, specificity 59.3%, P<0.001). Conclusion: Patients with T-COPD have higher levels of inflammatory markers, and IL-6 has a predictive value for AE in T-COPD.

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Oh, Y. M., K. S. Lee, et al. (2018). "**Blood eosinophil count as a prognostic biomarker in COPD.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3589-3596.

Background: High blood eosinophil count is a predictive biomarker for response to inhaled corticosteroids in prevention of acute exacerbation of COPD, and low blood eosinophil count is associated with pneumonia risk in COPD patients taking inhaled corticosteroids. However, the prognostic role of blood eosinophil count remains underexplored. Therefore, we investigated the associated factors and mortality based on blood eosinophil count in COPD. Methods: Patients with COPD were recruited from 16 hospitals of the Korean Obstructive Lung Disease cohort (n=395) and COPD in Dusty Area cohort (n=234) of Kangwon University Hospital. The two merged cohorts were divided based on blood eosinophil count into three groups: high ( $\geq 5\%$ ), middle (2%-5%), and low ( $< 2\%$ ). Results: The high group had longer six-minute walk distance (high =445.8 $\pm$ 81.4, middle =428.5 $\pm$ 88.0, and low =414.7 $\pm$ 86.3 m), higher body mass index (23.3 $\pm$ 3.1, 23.1 $\pm$ 3.1, and 22.5 $\pm$ 3.2 kg/m<sup>2</sup>), lower emphysema index (18.5 $\pm$ 14.1, 22.2 $\pm$ 15.3, and 23.7 $\pm$ 16.3), and higher inspiratory capacity/total lung capacity ratio (32.6 $\pm$ 7.4, 32.4 $\pm$ 9.2, and 29.9%  $\pm$  8.9%) (P<0.05). The survival period increased with increasing blood eosinophil count (high =9.52 $\pm$ 0.23, middle =8.47 $\pm$ 1.94, and low =7.42 $\pm$ 0.27 years, P<0.05). Multivariate linear regression analysis revealed that the emphysema index was independently and negatively correlated with blood eosinophil count (P<0.05). Conclusion: In COPD, the severity of emphysema was independently linked with low blood eosinophil count and the longer survival period was associated with increased blood eosinophil count, though it was not proven in the multivariate analysis.

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Oliveira, A., V. Afreixo, et al. (2018). "**Enhancing our understanding of the time course of acute exacerbations of COPD managed on an outpatient basis.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3759-3766.

Purpose: Acute exacerbations of COPD (AECOPD) are associated with pulmonary/systemic changes; however, quantification of those changes during AECOPD managed on an outpatient basis and factors influencing recovery are lacking. This study aimed to characterize patients' changes during AECOPD and identify factors influencing their recovery. Methods: Body mass index, the modified British Medical Research Council questionnaire, number of exacerbations in the previous year, and the Charlson comorbidity index (independent variables) were collected within 24-48 hours of hospital presentation (T0). Peripheral oxygen saturation (SpO<sub>2</sub>), forced expiratory volume in one second, percentage predicted (FEV1% predicted), maximum inspiratory pressure, quadriceps muscle strength, 5 times sit-to-stand, and COPD assessment test (CAT) (dependent variables) were collected at T0 and approximately at days 8 (T1), 15 (T2), and 45 (T3) after T0. Results: A total of 44 outpatients with AECOPD (31 male symbol; 68.2 $\pm$ 9.1 years; 51.1 $\pm$ 20.3 FEV1% predicted) were enrolled. All variables improved overtime (P<0.05); however, at day 8, only SpO<sub>2</sub> and CAT (P $\leq$ 0.001) showed significant improvements. Changes in FEV1% predicted and SpO<sub>2</sub> were not influenced by any independent measure, while changes in other outcome measures were influenced by at least one of the independent measures. Independently of the time of data collection, being underweight or overweight and having increased dyspnea, previous exacerbations, and severe comorbidities negatively affected patients' outcomes. Conclusion: FEV1% predicted and SpO<sub>2</sub> were not influenced by any independent measure and, thus, seem to be robust measures to follow-up outpatients with AECOPD. No single indicator was able to predict patients' recovery for all measures; thus, a comprehensive assessment at the onset of the AECOPD is required to personalize interventions.

<https://www.dovepress.com/getfile.php?fileID=46326>

Orea-Tejeda, A., A. G. Navarrete-Penaloza, et al. (2018). **"Right heart failure as a risk factor for severe exacerbation in patients with chronic obstructive pulmonary disease: Prospective cohort study."** *Clin Respir J* **12**(12): 2635-2641.

**BACKGROUND:** The prognosis in patients with Chronic Obstructive Pulmonary Disease (COPD) depends, in large part, on the frequency of exacerbations. Cardiovascular diseases, including heart failure (HF), are the risk factors for exacerbations. However, the importance of HF type over the exacerbations in COPD patients is unknown. **OBJECTIVE:** To determine whether right heart failure (RHF) is an independent risk factor for severe exacerbations in patients with COPD. **METHODS:** A prospective cohort study of 133 patients diagnosed with COPD with a follow-up period from 2010 to 2016. Patients with bronchial hyperreactivity, asthma, or pulmonary embolism were excluded. **RESULTS:** The mean age was 74.7 +/- 8.2 years and 43.6% were men, 69.9% had severe exacerbations during follow-up. Subjects with RHF had lower FEV1 (50.2 +/- 19.9 vs 57.4 +/- 16.9, P = .006) and greater incidence of stroke (15.4% vs 1.8%, P = .009) compared to those without RHF. Subjects with RHF were at higher risk of severe exacerbations (HR, 2.46; CI 95%, 1.32-4.58, P = .005) compared to those without RHF after adjusting for confounding variables. **CONCLUSION:** In patients with COPD, RHF is an independent risk factor for suffering severe exacerbations.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12969>

Osadnik, C. R., M. Loeckx, et al. (2018). **"The likelihood of improving physical activity after pulmonary rehabilitation is increased in patients with COPD who have better exercise tolerance."** *Int J Chron Obstruct Pulmon Dis* **13**: 3515-3527.

**Purpose:** Pulmonary rehabilitation (PR) enhances exercise tolerance in patients with COPD; however, improvements in physical activity (PA) are not guaranteed. This study explored the relationship between baseline exercise tolerance and changes in PA after PR. **Materials and methods:** Patient data from prospective clinical trials in the PR settings of Athens and Leuven (2008-2016) were analyzed. Validated PA monitors were worn for 1 week before and after a 12-week program. The proportion of patients who improved PA levels  $\geq 1,000$  steps/day ("PA responders") after PR was compared between those with initial 6-minute walk distance [6MWDi]  $< 350$  m and  $\geq 350$  m. Baseline predictors of PA change were evaluated via univariate and multivariate logistic regression analyses. **Results:** Two hundred thirty-six patients with COPD (median [IQR] FEV1 44 [33-59] % predicted, age 65 +/- 8 years, 6MWDi 416 [332-486] m) were included. The proportion of "PA responders" after PR was significantly greater in those with higher vs lower 6MWDi (37.9% vs 16.4%, respectively;  $P < 0.001$ ). 6MWDi group classification was the strongest baseline independent predictor of PA improvement (univariate OR 3.10, 95% CI 1.51-6.36). **Conclusion:** The likelihood of improving PA after PR is increased with greater 6MWDi. Baseline exercise tolerance appears as an important stratification metric for future research in this field.

<https://www.dovepress.com/getfile.php?fileID=45612>

Oshagbemi, O. A., F. M. E. Franssen, et al. (2018). **"Blood eosinophilia, use of inhaled corticosteroids, and risk of COPD exacerbations and mortality."** *Pharmacoepidemiol Drug Saf* **27**(11): 1191-1199.

**PURPOSE:** It remains unclear whether eosinophilia is useful for in guiding inhaled corticosteroid (ICS) therapy in chronic obstructive pulmonary disease (COPD) patients. The goal of this study is to evaluate the risk of acute exacerbations, COPD-related hospitalisations/accident and emergency visits, and all-cause mortality with various levels of eosinophil counts among COPD patients using ICS. **METHODS:** A cohort study was conducted using the UK Clinical Practice Research Datalink. Patients were aged 40+ and had COPD (n = 32 693). Current users of ICS were stratified by relative and absolute eosinophil counts to determine the risk of outcomes with blood eosinophilia using Cox regression analysis. **RESULTS:** Among COPD patients, current use of ICS was not associated with a reduced risk of acute COPD exacerbations, COPD-related hospitalisations/accident and emergency visits, and all-cause mortality. Stratification of

ICS use by absolute or relative eosinophil counts did not result in significant differences in risk of COPD exacerbations or hospitalisations/accident and emergency visits. However, all-cause mortality was reduced by 12% to 24% among patients with eosinophilia. CONCLUSIONS: COPD-related acute exacerbations or hospitalisations/accident and emergency visits were not reduced with eosinophilia among users of ICS with COPD. However, all-cause mortality was reduced by 12% to 24%. These findings are potentially important and require further evaluation in prospective studies.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6282838/pdf/PDS-27-1191.pdf>

Oshagbemi, O. A., S. J. Keene, et al. (2018). **"Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013."** *Respir Med* **144**: 1-6.

INTRODUCTION: Exacerbations of chronic obstructive pulmonary disease are characterised by increased symptoms such as dyspnoea, cough and sputum production and/or purulence, leading to greater risk of hospitalisation and mortality. Very few studies have measured long term trends in the incidence of exacerbations of chronic obstructive pulmonary disease. We therefore investigated the incidence of moderate and severe exacerbations in the UK general population. METHODS: A population based-study including Clinical Practice Research Datalink (CPRD) patients  $\geq 40$  years of age with a current diagnosis of COPD within the United Kingdom from 2004 to 2013 was conducted. Individuals with a history of asthma were excluded from main analyses. We calculated the incidence rates for any, moderate, and severe exacerbations. Patients contributed time at risk from January 1st up to the date of the first outcome within each year. The incidence rate for any, moderate and severe exacerbations for COPD in each calendar year was calculated as follows: the sum of any or moderate or severe exacerbations for COPD in that year divided by the total duration of follow-up in the same calendar year from 2005 through to 2013. We then analysed these rates by gender and age categories (40-59 years, 60-79 years and  $\geq 80$  years). RESULTS: Among 213,561 with incident COPD diagnosis, 86,300 patients were included in the study. From 2005 to 2013, the incidence rate of any exacerbations increased from 89 to 98 per 1000 person years (PYs) ( $p = 0.005$ ). Women had significantly higher incidence rates of any exacerbation for each calendar year when compared to men ( $p < 0.0001$ ). The incidence rate of any and moderate exacerbations increased with age from 2005 to 2007. For severe exacerbations incidence decreased from 2005 to 2007 before increasing from 2008 until the end of follow-up (43 per 1000 PYs (95% confidence interval, 42-45/1000PYs) in 2013). Incidence rates of severe exacerbations were similar by gender and patients aged 80 + years had a higher incidence rate of severe exacerbation from 2005 to 2008 after which their incident rate dropped in subsequent years. CONCLUSION: This is the first study that reports the long-term changes in the incidence rates of moderate and severe exacerbations within the UK general practice. Women showed a substantially higher risk of any COPD exacerbations, and their risk is increasing. The incidence rates of any exacerbations increased during the study period, while severe exacerbations were variable. Furthermore, incidence rates varied substantially by age group.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30292-0/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30292-0/fulltext)

Pang, H., L. Wang, et al. (2018). **"The prevalence and risk factors of venous thromboembolism in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease."** *Clin Respir J* **12**(11): 2573-2580.

INTRODUCTION: Venous thromboembolism (VTE) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is not rare, which would affect the patient's prognosis. OBJECTIVES: To examine the prevalence, risk factors and clinical characteristics of AECOPD patients with VTE. METHODS: We performed this multi-center, prospective, observational study that involved 16 hospitals in China. Patients admitted to hospital due to AECOPD were consecutively enrolled. Baseline characteristics, VTE risk factors, symptoms, signs and auxiliary examination results were collected. Lower limb venous ultrasound and computed tomography pulmonary angiography were examined. RESULTS: Between June 2009 and October 2010, a total of 1144 AECOPD patients (the average age 72.0  $\pm$  9.1 years, 761 males) were enrolled in this study. Seventy-eight (6.8%) were diagnosed with VTE, including 24 PE, 64 DVT, 10

combined PE and DVT. VTE patients were older than non-VTE patients. History of venous thromboembolism and lower extremity varicose vein, and presence of longer immobility ( $\geq 3$  days), lower limbs problems of swelling, pain and walking difficulties, diuretics use, fever, syncope, higher d-dimer and lower hemoglobin were more common in VTE patients than in non-VTE patients. After adjusting the covariates, venous thrombosis history, prolonged immobility ( $\geq 3$  days), lower limb pain before hospitalization, higher d-dimer independently associated with VTE development. Regular glucocorticoid use was not associated with increased risk of VTE in this set of patients. CONCLUSION: VTE is relatively common among hospitalized AECOPD patients. Conventional prophylactic anticoagulant therapy may be considered for those hospitalized AECOPD patients with risk factors.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12959>

Pavic, T., D. Dilber, et al. (2018). "**N-glycosylation patterns of plasma proteins and immunoglobulin G in chronic obstructive pulmonary disease.**" *J Transl Med* **16**(1): 323.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a complex condition, whose diagnosis requires spirometric assessment. However, considering its heterogeneity, subjects with similar spirometric parameters do not necessarily have the same functional status. To overcome this limitation novel biomarkers for COPD have been investigated. Therefore, we aimed to explore the potential value of N-glycans as COPD biomarkers and to examine the individual variation of plasma protein and immunoglobulin G (IgG) glycosylation profiles in subjects with COPD and healthy controls. METHODS: Both the total plasma protein and IgG N-glycome have been profiled in the total of 137 patients with COPD and 95 matching controls from Croatia. Replication cohort consisted of 61 subjects with COPD and 148 controls recruited at another Croatian medical centre. RESULTS: Plasma protein N-glycome in COPD subjects exhibited significant decrease in low branched and conversely, an increase in more complex glycan structures (tetragalactosylated, trisialylated, tetrasialylated and antennary fucosylated glycoforms). We also observed a significant decline in plasma monogalactosylated species, and the same change replicated in IgG glycome. N-glycans also showed value in distinguishing subjects in different COPD GOLD stages, where the relative abundance of more complex glycan structures increased as the disease progressed. Glycans also showed statistically significant associations with the frequency of exacerbations and demonstrated to be affected by smoking, which is the major risk factor for COPD development. CONCLUSIONS: This study showed that complexity of glycans associates with COPD, mirroring also the disease severity. Moreover, changes in N-glycome associate with exacerbation frequency and are affected by smoking. In general, this study provided new insights into plasma protein and IgG N-glycome changes occurring in COPD and pointed out potential novel markers of the disease progression and severity.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6249776/pdf/12967\\_2018\\_Article\\_1695.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6249776/pdf/12967_2018_Article_1695.pdf)

Pedersen, J. E., K. Ugelvig Petersen, et al. (2018). "**Risk of asthma and chronic obstructive pulmonary disease in a large historical cohort of Danish firefighters.**" *Occup Environ Med* **75**(12): 871-876.

OBJECTIVE: Firefighters are exposed to numerous respiratory hazards, but large studies on the risk of pulmonary disease are scarce. The objective of this study was to examine incidence of asthma and chronic obstructive pulmonary disease (COPD) in a nationwide cohort of Danish firefighters. METHODS: We used individual historical employment records on 11 968 Danish male firefighters primarily supplied by trade unions and fire agencies. Furthermore, we used the Supplementary Pension Fund Register to form an occupational reference group consisting of military employees. Information on respiratory incidence was retrieved from the nationwide Danish National Patient Registry. Age and calendar time standardised incidence ratio (SIR) and Poisson regression analyses (incidence rate ratio) were used for estimation of risks, including 95% CIs. RESULTS: Compared with military employees, the overall age and calendar-time adjusted risk for asthma was significantly increased among full-time firefighters (SIR=1.58, 95% CI 1.32 to 1.88), but not among part-time/volunteer firefighters. Full-time firefighters' risk for asthma did not vary by duration of employment. No consistent evidence of an increased risk for chronic obstructive

pulmonary disease was detected. CONCLUSION: Danish firefighters have an increased risk of asthma, but the causes, whether occupational or not, remain to be established.

<https://oem.bmj.com/content/75/12/871.long>

Perez-Padilla, R., F. C. Wehrmeister, et al. (2018). "**Outcomes for symptomatic non-obstructed individuals and individuals with mild (GOLD stage 1) COPD in a population based cohort.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3549-3561.

Background: We aimed to study the adverse outcomes of symptomatic and asymptomatic non-obstructed individuals and those with mild COPD longitudinally in participants from three Latin-American cities. Methods: Two population-based surveys of adults with spirometry were conducted for these same individuals with a 5- to 9-year interval. We evaluated the impact of respiratory symptoms (cough, phlegm, wheezing or dyspnea) in non-obstructed individuals, and among those classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1, COPD on exacerbation frequency, mortality and FEV1 decline, compared with asymptomatic individuals without airflow obstruction or restriction. Results: Non-obstructed symptomatic individuals had a marginal increased risk of mortality (HR 1.3; 95% CI 0.9-1.94), increased FEV1 decline (-4.5 mL/year; 95% CI -8.6, -0.4) and increased risk of 2+ exacerbations in the previous year (OR 2.6; 95% CI 1.2-6.5). Individuals with GOLD stage 1 had a marginal increase in mortality (HR 1.5; 95% CI 0.93-2.3) but a non-significant impact on FEV1 decline or exacerbations compared with non-obstructed individuals. Conclusions: The presence of respiratory symptoms in non-obstructed individuals was a predictor of mortality, lung-function decline and exacerbations, whereas the impact of GOLD stage 1 was mild and inconsistent. Respiratory symptoms were associated with asthma, current smoking, and the report of heart disease. Spirometric case-finding and treatment should target individuals with moderate-to-severe airflow obstruction and those with restriction, the groups with consistent increased mortality.

<https://www.dovepress.com/getfile.php?fileID=45678>

Pervez, M. O., J. A. Winther, et al. (2018). "**Prognostic and diagnostic significance of mid-regional pro-atrial natriuretic peptide in acute exacerbation of chronic obstructive pulmonary disease and acute heart failure: data from the ACE 2 Study.**" *Biomarkers* **23**(7): 654-663.

PURPOSE: To compare the diagnostic and prognostic value of mid-regional pro-ANP (MR-proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with acute dyspnea. METHODS: MR-proANP and NT-proBNP were measured with commercial immunoassays at hospital admission (n = 313), on day 2 (n = 234), and before discharge (n = 91) and compared for diagnosing acute heart failure (HF; n = 143) and to predict mortality among patients with acute HF and acute exacerbation of chronic obstructive pulmonary disease (AECOPD; n = 84) separately. RESULTS: The correlation coefficient between MR-proANP and NT-proBNP was 0.89 ( $p < 0.001$ ) and the receiver-operating area under the curve (AUC) was 0.85 (95% CI 0.81-0.89) for MR-proANP and 0.86 (0.82-0.90) for NT-proBNP to diagnose acute HF. During a median follow-up of 816 days, mortality rates were 46% in acute HF patients and 42% in AECOPD patients. After adjustment for other risk variables by multivariate Cox regression analysis, MR-proANP and NT-proBNP concentrations were associated with mortality in patients with acute HF, but only MR-proANP were associated with mortality among patients with AECOPD: hazard ratio (lnMR-proANP) 1.98 (95% CI 1.17-3.34). CONCLUSION: MR-proANP and NT-proBNP concentrations provide similar diagnostic and prognostic information in patients with acute HF. In contrast to NT-proBNP, MR-proANP measurements also provided independent prognostic information in AECOPD patients.

<https://www.tandfonline.com/doi/full/10.1080/1354750X.2018.1474258>

Pirard, L. and E. Marchand (2018). "**Reassessing the BODE score as a criterion for listing COPD patients for lung transplantation.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3963-3970.

Background: The BODE score (incorporating body mass index, airflow obstruction, dyspnea and exercise capacity) is used for the timing of listing for lung transplantation (LTx) in COPD, based on survival data from the original BODE cohort. This has limitations, because the original BODE cohort differs from COPD patients who are candidates for LTx and the BODE does not include parameters that may influence survival. Our goal was to assess whether parameters such as age, smoking status and diffusion indices significantly influence survival in the absence of LTx, independently of the BODE. Methods: In the present cohort study, the BODE was prospectively assessed in COPD patients followed in a tertiary care hospital with an LTx program. The files of 469 consecutive patients were reviewed for parameters of interest (age, gender, smoking status and diffusing capacity of the lungs for carbon monoxide [DL,CO]) at the time of BODE assessment, as well as for survival status. Their influence on survival independent of the BODE score was assessed, as well as their ability to predict survival in patients aged less than 65 years. Results: A Cox regression model showed that the BODE score, age and DL,CO were independently related to survival (P-values <0.001), as opposed to smoking status. Survival was better in patients aged less than 65 in the first (P=0.004), third (P=0.002) and fourth BODE quartiles (P=0.008). The difference did not reach significance in the second quartile (P=0.13). Median survival for patients aged less than 65 in the fourth BODE quartile was 55 months. According to a receiver operating characteristic curve analysis, the BODE score as well as FEV1 and DL,CO fared similarly in predicting survival status at 5 years in patients aged less than 65 years. Conclusion: Age and DL,CO add to the BODE score to predict survival in COPD. Assessing survival using tools tested in cohorts of patients younger than 65 years is warranted for improving the listing of patients for LTx.

<https://www.dovepress.com/getfile.php?fileID=46856>

Plachi, F., F. M. Balzan, et al. (2018). "**Characteristics associated with mortality in patients with chronic obstructive pulmonary disease (COPD)-heart failure coexistence.**" *Prim Health Care Res Dev* **19**(6): 570-574.

AimTo investigate if cardiac/pulmonary functional tests and variables obtained from clinical practice (body mass index, dyspnea, functional class, clinical judgment of disability to perform an exercise test and previous hospitalization rate) are related to mortality in patients with overlap chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF). BACKGROUND: Although the coexistence of COPD and CHF has been growingly reported, description of survival predictors considering the presence of both conditions is still scarce. METHODS: Using a cohort design, outpatients with the previous diagnosis of COPD and/or CHF that performed both spirometry and echocardiography in the same year were followed-up during a mean of 20.9+/-8.5 months. FindingsOf the 550 patients initially evaluated, 301 had both spirometry and echocardiography: 160 (53%) with COPD on isolation; 100 (33%) with CHF on isolation; and 41 (14%) with overlap. All groups presented similar mortality: COPD 17/160 (11%); CHF 12/100 (12%); and overlap 7/41 (17%) (P=0.73). In the overlap group (n=41), inability to exercise and hospitalization rate were the unique parameters associated with higher mortality (seven events) in univariate analyses. In conclusion, inability to exercise and hospitalization rate emerged as the unique parameters associated with mortality in our sample.

<https://www.cambridge.org/core/services/aop-cambridge-core/content/view/B564D764AFBFA5A25A1E1934DD97FED7/S1463423618000117a.pdf/div-class-title-characteristics-associated-with-mortality-in-patients-with-chronic-obstructive-pulmonary-disease-copd-heart-failure-coexistence-div.pdf>

Pleguezuelos, E., P. Casarramona, et al. (2018). "**How whole-body vibration can help our COPD patients. Physiological changes at different vibration frequencies.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3373-3380.

**Objective:** Evaluate cardiac, metabolic, and ventilatory changes during a training session with whole-body vibration training (WBVT) with 3 different frequencies in patients with chronic obstructive pulmonary disease (COPD). **Methods:** This was a prospective, interventional trial in outpatients with severe COPD. Participants performed 3 vertical WBVT sessions once a week using frequencies of 35, 25 Hz and no vibration in squatting position (isometric). Cardiac, metabolic, and ventilator parameters were monitored during the sessions using an ergospirometer. Changes in oxygen pulse response (VO<sub>2</sub>/HR) at the different frequencies were the primary outcome of the study. **Results:** Thirty-two male patients with a mean forced expiratory volume in 1 second of 39.7% completed the study. Compared to the reference of 35 Hz, VO<sub>2</sub>/HR at no vibration was 10.7% lower (P=0.005); however, no statistically significant differences were observed on comparing the frequencies of 35 and 25 Hz. The median oxygen uptake (VO<sub>2</sub>) at 25 Hz and no vibration was 9.43% and 13.9% lower, respectively, compared to that obtained at 35 Hz (both comparisons P<0.0001). The median expiratory volume without vibration was 9.43% lower than the VO<sub>2</sub> at the end of the assessment at 35 Hz vibration (P=0.002). **Conclusion:** Vertical WBVT training sessions show greater cardiac, metabolic, and respiratory responses compared with the squat position. On comparing the 2 frequencies used, we observed that the frequency of 35 Hz provides higher cardiorespiratory adaptation.

<https://www.dovepress.com/getfile.php?fileID=45478>

Pleguezuelos, E., L. Guirao, et al. (2018). **"Ischiocrural Strength May Be a Better Prognostic Marker Than Quadriceps Strength in COPD."** *Lung* **196**(6): 665-668.

It is well known that chronic obstructive pulmonary disease (COPD) patients present with muscle dysfunction that may not correlate with the degree of severity of airflow obstruction. Historically, the strength deficit of the knee extensor musculature (quadriceps) has been described as an independent factor of mortality in COPD. We present the results of a retrospective study with longitudinal follow-up of 60 patients with severe COPD followed for 7 years. During follow-up 22 patients died, mainly of respiratory cause. We have observed that the strength of knee flexor muscles (ischiocrural) and dominant handgrip were independent predictors of mortality in severe COPD patients. However, knee extensor strength (quadriceps) was not an independent predictor of mortality. This is the first study which highlights the importance of knee flexor musculature as a prognostic factor in COPD.

<https://link.springer.com/article/10.1007%2Fs00408-018-0164-0>

Poder, T. G., N. Carrier, et al. (2018). **"Eosinophil counts in first COPD hospitalizations: a 1-year cost analysis in Quebec, Canada."** *Int J Chron Obstruct Pulmon Dis* **13**: 3065-3076.

**Background:** Exacerbations explain much of the cost of COPD. Higher blood eosinophil cell counts at admission for acute exacerbation of COPD increase the risk of subsequent exacerbations and hospitalizations. However, there is no literature on the economic burden of patients with this inflammatory profile. The objective of this study is to assess the cost of health-care service utilization according to different counts of blood eosinophils. **Methods:** The observational retrospective cohort included all first hospitalizations for COPD exacerbation between April 2006 and March 2013. The eosinophilic group was defined by blood eosinophil counts on admission  $\geq 200$  cells/microL and/or  $\geq 2\%$  of the total white blood cell count. Study outcomes were: total costs (2016 Canadian dollars) (index hospitalization and 1-year follow-up), total index hospitalization costs, total 1-year costs (all-cause readmissions, ambulatory and emergency service use), and 1-year COPD-related costs (only cost for COPD after initial discharge). Sensitivity analyses were conducted to evaluate the impact of different eosinophil cut-offs on outcomes. **Results:** In total, 479 patients were included, 173 in the eosinophilic group (92 in the higher cut-off). The average total cost was \$18,263 (\$6,706 for the index hospitalization), without significant difference between groups (P=0.3). The average 1-year COPD-related cost was higher in the eosinophilic group (\$3,667 vs \$2,472, P=0.006), with an adjusted mean difference of \$1,416. Analysis of data using the higher cut-off of  $\geq 400$  cells or  $\geq 3\%$  was associated with a slightly larger difference in 1-year COPD-related costs between groups (\$4,060 vs \$2,629, P=0.003), with an adjusted mean difference of \$1,640.

Conclusion: A higher blood eosinophil cell count at admission for a first hospitalization is associated with an increase in total 1-year COPD-related costs.

<https://www.dovepress.com/getfile.php?fileID=45073>

Ponte, E. V., A. A. Cruz, et al. (2018). **"Greater Access to Long Acting Beta2 Agonists Is Associated with Less Hospital Admissions Due to COPD: A Longitudinal Nation-Wide Study."** *Lung* **196**(6): 643-648.

PURPOSE: Long Acting Beta2 Agonists (LABA) prevent COPD exacerbations in strictly standardized clinical trials. Our aim was to evaluate the relationship between the amount of LABA provided by the government and the trend in COPD hospital admission (HA) rate in Brazil. METHODS: This is a longitudinal large-scale real-life study. We calculated COPD HA rate and the number of subjects per 10(5) inhabitant who received LABA supplied by the government in each Brazilian municipality, between years 2004 and 2013. We used Poisson Multilevel Regression analysis to calculate the rate ratio between LABA dispensation rate and COPD HA rate. RESULTS: In Brazil, COPD HA rate reduced 59% among subjects between 40 and 59 years of age and 60% among subjects older than 59 years of age. Most of the 5506 Brazilian municipalities reduced COPD HA rate [4149 (75%) municipalities & 1357 (25%) municipalities]. The dispensation of LABA was greater among municipalities that reduced COPD HA rate. In the 40-59 age group, the gap in LABA dispensation between the two groups of municipalities increased during the study period from 90.40 to 614.28 subjects per 10(5) inhabitants. In the > 59 age group, the gap in LABA dispensation increased from 35.87 to 912.99 subjects per 10(5) inhabitants. For each one hundred subjects who received LABA there was less one HA (RR 0.99, 95 CI 0.99-0.99). CONCLUSIONS: COPD HA rate reduced in Brazil. LABA dispensation growth was associated with COPD HA rate reduction.

<https://link.springer.com/article/10.1007%2Fs00408-018-0158-y>

Porta, A. S., N. Lam, et al. (2019). **"Low income as a determinant of exercise capacity in COPD."** *Chron Respir Dis* **16**: 1479972318809491.

Exercise capacity (EC) is a critical outcome in chronic obstructive lung disease (chronic obstructive pulmonary disease (COPD)). It measures the impact of the disease and the effect of specific interventions like pulmonary rehabilitation (PR). EC determines COPD prognosis and is associated with health-care utilization and quality of life. Field walking tests and cardiopulmonary exercise test (CPET) are two ways to measure EC. The 6-minute walking test (6MWT) is the commonest and easiest field test. CPET has the advantage of assessing maximal aerobic capacity. Determinants of EC include age, gender, breathlessness, and lung function. Previous research suggests that socioeconomic status (SES), a meaningful factor in COPD, may also be associated with EC. However, those findings have not been replicated. We aimed to determine whether SES is an independent factor associated with EC in COPD. For this analysis, we used the National Emphysema Treatment Trial (NETT) database. NETT was a multicenter clinical trial where severe COPD patients were randomized to lung volume reduction surgery or medical therapy. Measures used were taken at baseline, postrehabilitation. Patients self-reported their income and were divided in two groups whether it was less or above US\$30,000. Patients with a lower income had worse results in 6MWT ( $p < 0.0001$ ). We found an independent association between income and the 6MWT in patients with severe COPD after adjusting for age, gender, lung function, dyspnea, and living conditions ( $p < 0.0007$ ). One previous publication stated the relationship between income and EC. Our research confirms and extends previous publications associating EC with income by studying a large and well characterized cohort of severe COPD patients, also addressing EC by two different methods (maximal watts and 6MWT). Our results highlight the importance of addressing social determinants of health such as income when assessing COPD patients.

Pothirat, C., W. Chaiwong, et al. (2019). **"Influence of Particulate Matter during Seasonal Smog on Quality of Life and Lung Function in Patients with Chronic Obstructive Pulmonary Disease."** *Int J Environ Res Public Health* **16**(1) The impact of outdoor air pollution on the quality of life (QoL) of chronic obstructive pulmonary disease (COPD) patients, as measured by the COPD assessment test (CAT) questionnaire, is limited. The aim of this study was to determine the impact of a short-term increase in outdoor particulate matter in which the particles are less than 10 microns in diameter (PM10) during a seasonal smog period on QoL, symptoms, and lung function in COPD patients. This prospective observational study was conducted at Chiang Dao Hospital, Chiang Mai, Thailand between March and August 2016. Measurement of QoL, severity of dyspnea, forced vital capacity (FVC), and forced expiratory volume in the first second (FEV(1)) were performed at both high and low PM10 periods. Fifty-nine patients met the inclusion criteria for enrollment into the study, with the mean age being 71.5 +/- 8.0 years. Total CAT score, but not mMRC score, was statistically higher during the high PM10 period. The two lung function parameters, FVC and FEV(1), were significantly lower at the high PM10 compared to the low PM10 period. We concluded that exposure to PM10 during the seasonal smog period resulted in short-term negative impact on the quality of life and lung function in COPD patients.

[https://res.mdpi.com/ijerph/ijerph-16-00106/article\\_deploy/ijerph-16-00106.pdf?filename=&attachment=1](https://res.mdpi.com/ijerph/ijerph-16-00106/article_deploy/ijerph-16-00106.pdf?filename=&attachment=1)

Price, D. B., S. Yang, et al. (2018). **"Physiological predictors Of peak inspiRatory flow using Observed lung function resultS (POROS): evaluation at discharge among patients hospitalized for a COPD exacerbation."** *Int J Chron Obstruct Pulmon Dis* **13**: 3937-3946.

Background: Peak inspiratory flow (PIF) as generated through the resistance of a dry powder inhaler (DPI) device is a critical patient-dependent maneuver impacting the success of DPI medication delivery. Despite its importance, it is not routinely measured in clinical practice. Little is currently known about the relationship, if any, between PIF through DPI devices, routine spirometry and disease outcomes. Aim: The aim of this study was to identify potential predictors of PIF for different DPIs from spirometric parameters and patient characteristics and explore the association between PIF and follow-up events. Patients and methods: A retrospective observational study at discharge among patients hospitalized for a COPD exacerbation at Attikon hospital, Athens, Greece. Spirometry was performed using an Easy on-PC spirometer. PIF was measured through four DPI resistances using the In-Check DIAL. Regression analyses were used to investigate the association between PIF through resistances and spirometric parameters obtained at discharge, comorbidities and demographic parameters. Results: Forty-seven COPD patients (mean [+/-SD], age 71 [+/-9] years, 72% males, 51% current smokers) were included in this study. Overall, 85% and 15% were classified as GOLD (2017) groups D and C, respectively. Most prevalent comorbidities were hypertension (70%) and cardiovascular disease (53%). In the final regression model, higher PIF was significantly associated with the following: higher FEV1 and % predicted peak expiratory flow (PEF) for Turbohaler((R)) (R-squared value 0.374); higher FEV1 and diagnosis of gastroesophageal reflux disease (GERD) for Aerolizer((R)) (R-squared value 0.209) and higher FEV1, younger age and diagnosis of ischemic heart disease (IHD) for Diskus((R)) (R-squared value 0.350). However, R-squared values for all three devices were weak (<0.4). Conclusion: The study did not provide evidence to support the use of surrogate measurements for PIF through device resistance, which could assist in determining the appropriateness of inhaler device type. Although PIF measurement is feasible in patients at discharge and could be a valuable addition to the standard of care in COPD management, it needs to be measured directly.

<https://www.dovepress.com/getfile.php?fileID=46948>

Prudente, R., E. A. T. Franco, et al. (2018). **"Predictors of mortality in patients with COPD after 9 years."** *Int J Chron Obstruct Pulmon Dis* **13**: 3389-3398.

Background: COPD is one of the leading causes of morbidity and mortality in the world; however, the most varied amounts of clinical and laboratory characteristics acts in different ways in the mortality among over time.

Therefore, this study aimed to evaluate the predictors of mortality in patients with COPD after 9 years. Patients and methods: One hundred and thirty-three patients with COPD were assessed at baseline by spirometry, pulse oximetry (SpO<sub>2</sub>), body composition, intensity of dyspnea, distance walked in the 6-minute walk test (6MWT), and Charlson Comorbidity Index (CCI). Results: After 9 years, it was not possible to identify the lifetime of 4 patients who died and of 19 patients who stopped follow-up; thus, 110 patients were included in the analysis of predictors of mortality (67% male, 65+/-9 years old, and FEV<sub>1</sub>: 52.5 [40%-73%]). Male sex, age, SpO<sub>2</sub>, Body mass index, airway Obstruction, Dyspnea, and Exercise capacity (BODE) index, and frequency of exacerbations in the first 3 years of follow-up were considered in the model. Patients classified at baseline with BODE class 2 (HR: 2.62, 95% CI: 1.36-5.04; P=0.004), BODE class 3 (HR: 2.54, 95% CI: 1.15-5.61; P=0.02), and BODE class 4 (HR: 15.35, 95% CI: 3.11-75.75; P=0.001) showed increased risk of death compared to those with BODE class 1. The CCI (HR: 1.29, 95% CI: 1.00-1.68; P=0.04) and the number of exacerbations in the first 3 years (HR: 1.32, 95% CI: 1.00-1.76; P=0.04) also showed increased risk of death. By replacing the BODE index for the variables that compose it, those with body mass index  $\leq 21$  kg/m<sup>2</sup> showed increased risk of death compared to those with body mass index (BMI)  $> 21$  kg/m<sup>2</sup> (HR: 2.70, 95% CI: 1.38-5.25; P=0.003). Conclusion: After 9 years, we identified that those with high BODE index, greater CCI, greater frequency of exacerbations in the first 3 years, and BMI  $\leq 21$  kg/m<sup>2</sup> showed increased risk of death.

<https://www.dovepress.com/getfile.php?fileID=45405>

Rassouli, F., D. Boutellier, et al. (2018). "**Digitalizing multidisciplinary pulmonary rehabilitation in COPD with a smartphone application: an international observational pilot study.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3831-3836.

Background: Concerning COPD, pulmonary rehabilitation (PR) has a positive effect on disease progression and mortality, is cost-effective, and is a part of recommendations of international guidelines. Only a minority of patients profit from conventional PR due to a lack of resources, physicians' guideline adherence, or patients' motivation. Novel digital therapies like Kaia COPD, a smartphone application that digitizes PR in COPD, are promising solutions to fill this void. Methods: Kaia COPD provides a digital version of PR and is certified as a class-I medical device in the European Union. We investigated anonymized data from users of the Kaia COPD app on in-app retention and the change in health-related quality of life (COPD assessment test and Chronic Respiratory Disease Questionnaire [CRQ]) during a period of 20 exercise days with the app. Results: Of 349 app downloads, 56 users fulfilled inclusion criteria and 34 (61%) had finished day 20 at the time of analysis and were included. Users took 33+/-11 days to complete the 20-day core program. Users finishing the program reduced their COPD assessment test scores (mean 2.5 units from 21.6+/-7.7 to 19.1+/-8.4 units, P=0.008). In finishers, there was a statistically significant effect above the minimum clinically important threshold of the CRQ score on the domains of fatigue, mastery, and emotional function. There was a statistically significant but not clinically relevant effect on the domain of dyspnea of CRQ. Conclusion: Digitalizing PR with a smartphone app is feasible and accepted by selected patients. The app leads to short-term improvement of health-related quality of life in patients completing a 20-day core program. Due to its observational character, this study has several methodological limitations and was intended to show the feasibility and to extrapolate effect sizes for planned prospective randomized-controlled trials to confirm these findings.

<https://www.dovepress.com/getfile.php?fileID=46472>

Raveling, T., G. Bladder, et al. (2018). "**Improvement in hypercapnia does not predict survival in COPD patients on chronic noninvasive ventilation.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3625-3634.

Purpose: It has recently been shown that chronic noninvasive ventilation (NIV) improves a number of outcomes including survival, in patients with stable hypercapnic COPD. However, the mechanisms responsible for these improved outcomes are still unknown. The aim of the present study was to identify parameters associated with: 1) an improved arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) and 2) survival, in a cohort of hypercapnic COPD patients treated with chronic NIV. Patients and methods: Data from 240

COPD patients treated with chronic NIV were analyzed. Predictors for the change in PaCO<sub>2</sub> and survival were investigated using multivariate linear and Cox regression models, respectively. Results: A higher level of bicarbonate before NIV initiation, the use of higher inspiratory ventilator pressures, the presence of anxiety symptoms, and NIV initiated following an exacerbation compared to NIV initiated in stable disease were associated with a larger reduction in PaCO<sub>2</sub>. A higher body mass index, a higher FEV<sub>1</sub>, a lower bicarbonate before NIV initiation, and younger age and NIV initiation in stable condition were independently associated with better survival. The change in PaCO<sub>2</sub> was not associated with survival, neither in a subgroup of patients with a PaCO<sub>2</sub> >7.0 kPa before the initiation of NIV. Conclusion: Patients with anxiety symptoms and a high bicarbonate level at NIV initiation are potentially good responders in terms of an improvement in hypercapnia. Also, higher inspiratory ventilator pressures are associated with a larger reduction in PaCO<sub>2</sub>. However, the improvement in hypercapnia does not seem to be associated with an improved survival and emphasizes the need to look beyond PaCO<sub>2</sub> when considering NIV initiation.

<https://www.dovepress.com/getfile.php?fileID=45867>

Rodrigo-Troyano, A., V. Melo, et al. (2018). "**Pseudomonas aeruginosa in Chronic Obstructive Pulmonary Disease Patients with Frequent Hospitalized Exacerbations: A Prospective Multicentre Study.**" *Respiration* **96**(5): 417-424.

BACKGROUND: *Pseudomonas aeruginosa* (PA) is a common microorganism related to severe exacerbations in Chronic Obstructive Pulmonary Disease (COPD). However, their role in COPD patients with frequent hospitalized exacerbations (FHE) is not well described. OBJECTIVES: We aimed to determine prevalence, risk factors, susceptibility patterns and impact on outcomes of PA in COPD patients with FHE. METHODS: Prospective observational multicentre study that included COPD patients with FHE. The cohort was stratified in 2 groups according to the presence or absence of PA isolation in sputum. Patients were followed up for 12 months. RESULTS: We enrolled 207 COPD patients with FHE. In 119 patients (57%), a valid sputum culture was collected. Of them, PA was isolated in 21 patients (18%). The risk factors associated with PA were prior use of systemic corticosteroids (OR 3.3, 95% CI 1.2-9.7,  $p = 0.01$ ) and prior isolation of PA (OR 4.36, 95% CI 1.4-13.4,  $p < 0.01$ ). Patients with PA had an increased risk of having  $\geq 3$  readmissions (OR 4.1, 95% CI 1.3-12.8,  $p = 0.01$ ) and higher PA isolation rate (OR 7.7, 95% CI 2.4-24.6,  $p < 0.001$ ) during the follow-up period. In 14 patients (67%), PA was resistant to at least one antibiotic tested. PA persisted in the sputum in 70% of patients. CONCLUSIONS: The presence of PA was related to 3 or more readmissions during the 1-year follow-up and PA persisted in the sputum despite an appropriate antibiotic treatment. This finding suggested an important role of PA in the course of the disease of COPD patients with FHE.

<https://www.karger.com/Article/Abstract/490190>

Rodrigues, A., C. A. Camillo, et al. (2019). "**Cluster analysis identifying patients with COPD at high risk of 2-year all-cause mortality.**" *Chron Respir Dis* **16**: 1479972318809452.

The objective of the article is to identify clusters of patients with COPD according to factors known to be associated with mortality and to verify whether clusters' assignment is associated with 2-year mortality. Patients ( $n = 141$ ) were evaluated by bioelectrical impedance, maximal inspiratory pressure (MIP), one-repetition maximum test of the quadriceps femoris (1RMQF) and BODE index (body mass index; airflow obstruction (spirometry); dyspnea (modified Medical Research Council scale); and exercise capacity (6-minute walk test (6MWT) distance). Vital status was retrospectively checked 2 years after the assessments, and time to death was quantified for those deceased in this period. K-means analysis identified two clusters. Patients in cluster one (CL I,  $n = 69$ ) presented an impaired clinical status in comparison to cluster two (CL II,  $n = 72$ ). Receiver operating characteristics curves identified the cutoffs discriminating patients composing CL I: forced expiratory volume in the first second  $< 44\%$ pred; 6MWT  $< 479$  m; 1RMQF  $< 19$  kg; and maximum inspiratory pressures  $< 73$  cmH<sub>2</sub>O (area under the curve range 0.750-0.857). During the follow-up, 19 (13%) patients deceased, 15 in CL I (22%) and 4 in CL II (0.06%) ( $p$

= 0.005). CL I was associated with a higher risk of 2-year mortality (hazard ratio (95% confidence interval): 4.3 (1.40-12.9),  $p = 0.01$ ). A cluster of patients with COPD highly associated with 2-year mortality was statistically identified, and cutoffs to identify these subjects were provided.

Rong, B., Y. Liu, et al. (2018). "**Correlation of serum levels of HIF-1alpha and IL-19 with the disease progression of COPD: a retrospective study.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3791-3803.

Background: The aim of this study was to disclose the correlation between the serum levels of hypoxia-inducible factor 1 alpha (HIF-1alpha) and IL-19 and stable COPD. Methods: The serum levels of HIF-1alpha and IL-19 were tested by ELISA. The relationships between their levels and clinical parameters of stable COPD patients were analyzed by linear regression methods. Results: Patients with stable COPD showed higher serum levels of HIF-1alpha and IL-19 compared with healthy control group ( $P < 0.001$ ), and serum levels of HIF-1alpha and IL-19 had a positive linear correlation ( $P < 0.05$ ). In stable COPD patients, increased serum levels of HIF-1alpha and IL-19 were positively correlated with the GOLD grading ( $P < 0.005$ ), modified British Medical Research Council (mMRC) score ( $P < 0.05$ ), and medical history ( $P < 0.05$ ) but negatively related to the pulmonary function ( $P < 0.05$ ). The serum level of HIF-1alpha ( $P < 0.05$ ) was affected by the patient's FEV1/FVC value and COPD grading, and the serum level of IL-19 was associated with the mMRC scores and the serum level of HIF-1alpha ( $P < 0.05$ ). Conclusion: Increased serum levels of HIF-1alpha and IL-19 correlated with the disease progression of COPD, suggesting that they can be used as indicators to help us understand the COPD.

<https://www.dovepress.com/getfile.php?fileID=46373>

Rusnak, J., M. Behnes, et al. (2018). "**COPD increases cardiac mortality in patients presenting with ventricular tachyarrhythmias and aborted cardiac arrest.**" *Respir Med* **145**: 153-160.

OBJECTIVES: The study sought to assess the prognostic impact of COPD in patients presenting with ventricular tachyarrhythmias and sudden cardiac arrest (SCA) on admission. BACKGROUND: Data regarding the outcome of patients with COPD presenting with ventricular tachyarrhythmias and SCA is limited. METHODS: A large retrospective registry was used including all consecutive patients presenting with ventricular tachycardia (VT), fibrillation (VF) and SCA from 2002 to 2016. Patients with COPD were compared to patients without COPD applying multivariable Cox regression models and propensity-score matching for evaluation of the primary prognostic endpoint defined as long-term all-cause mortality at 2 years. Secondary endpoints were all-cause mortality at index, at 30 days and after discharge, cardiac death at 24h, rehospitalization related to cardiac causes and the composite endpoint of cardiac death at 24h, recurrences of ventricular tachyarrhythmias and appropriate ICD therapies at 2 years. RESULTS: In 2813 unmatched high-risk patients with ventricular tachyarrhythmias and SCA, COPD was present in 9%. VF was less common in COPD (28% versus 39%;  $p = 0.001$ ). Multivariable Cox regression models revealed that COPD was associated with the primary endpoint of long-term all-cause mortality (HR= 1.245; 95% CI 1.001-1.549;  $p = 0.001$ ), which was also proven after propensity score matching (log rank  $p = 0.001$ ). The secondary endpoints of all-cause mortality at index, at 30 days, after discharge, cardiac death at 24h, as well as the composite endpoint of cardiac death at 24h, recurrences of ventricular tachyarrhythmias and appropriate ICD therapies were higher in COPD ( $p < 0.033$ ). CONCLUSION: In high-risk patients presenting with ventricular tachyarrhythmias and SCA, COPD was associated with higher long-term all-cause mortality, cardiac death at 24h and higher rates of the composite endpoint of cardiac death at 24h, recurrences of ventricular tachyarrhythmias and appropriate ICD therapies at 2 years.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30325-1/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30325-1/fulltext)

Rysiak, E., I. Prokop, et al. (2018). **"Estimates of Medication Expenditure for Ischemic Heart Disease Accompanying Chronic Obstructive Pulmonary Disease."** *Adv Exp Med Biol* **1114**: 49-55.

Ischemic heart disease (IHD) is a frequent accompaniment of chronic obstructive pulmonary disease (COPD). Co-occurrence of these two diseases is associated with many risk factors, difficulties in implementing appropriate therapies, numerous complications, and high spending for treatment. All these elements significantly reduce the quality of life of patients. The aim of this study was to estimate the expenditure for medications involved with IHD pharmacotherapy in the course of COPD. This retrospective study was based on the review of medical files of 57 patients, 27 women and 30 men, diagnosed with IHD, according to the severity classification, in the course of COPD which was staged according to the GOLD criteria. We found a considerable increase in per capita per year retail spending for drugs. The spending increased with the severity class of IHD; from 27.41 EUR in Class I to 142.30 EUR in Class IV. This spending did not include the treatment cost for the basic disease, i.e., COPD. A high individual cost burden was decreased by a discounting intervention of the National Health Fund. Despite a relatively high drug expenditure, we consider the treatment being cost-effective since we noticed a reduction in the classical risk factors for IHD, related to metabolic disturbances and lifestyle features, as soon as 2 months after treatment initiation. This study confirms that heart disease accompanying COPD is a frequent occurrence, generating high costs of treatment, which relates to the severity of this comorbidity.

[https://link.springer.com/chapter/10.1007%2F5584\\_2018\\_201](https://link.springer.com/chapter/10.1007%2F5584_2018_201)

Scalone, G., S. Nava, et al. (2018). **"Pharmacological approach and adherence to treatment recommendations in frequently and non-frequently exacerbating COPD patients from Italy: MISTRAL - The prospective cohort, observational study."** *Pulm Pharmacol Ther* **53**: 68-77.

**BACKGROUND:** Several documents and guidelines provide recommendations for effective management of COPD patients. However, there is often a significant imbalance between recommended treatment of COPD patients and the actual care provided both in primary care and specialty setting. This imbalance could result in a significant negative impact on patients' health status and quality of life, leading to increased hospitalisations and health resource utilisation in COPD patients **METHODS:** MISTRAL was an observational, longitudinal, prospective cohort study, designed to assess the overall pharmacological approach of COPD in routine clinical practice in Italy. Eligible patients were divided into two cohorts based on their exacerbation history in the year prior to the enrolment, frequent exacerbators (FEs;  $\geq 2$  exacerbations), and non-frequent exacerbators (NFEs;  $< 1$  exacerbation). The primary objective was to assess adherence to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 treatment recommendations in FEs and NFEs at baseline and follow-up visits **RESULTS:** Of the 1489 enrolled patients, 1468 (98.6%; FEs, 526; NFEs, 942) were considered evaluable for analyses. At baseline, 57.8% of patients were treated according to GOLD 2011 recommendations; a greater proportion of FEs were treated according to GOLD recommendations, compared with NFEs patients at baseline (77.1% versus 46.7%;  $P < 0.0001$ ), and all study visits. At baseline, GOLD group D patients were the most adherent (81.2%) to treatment recommendations, while group A patients were the least adherent (30.3%) at baseline, attributed mainly to overuse of inhaled corticosteroids in less severe GOLD groups. Triple therapy with long-acting muscarinic antagonist (LAMA) + long-acting beta<sub>2</sub>-agonist/inhaled corticosteroid (LABA/ICS) was the most frequent prescribed treatment at all study visits, irrespective of patient's exacerbation history. Changes in treatment were more frequent in FEs versus NFEs **CONCLUSIONS:** The Mistral study reports a scarce adherence to the GOLD 2011 treatment recommendations in routine clinical practice in Italy. The adherence was particularly low in less severe, non-frequent exacerbating patients mostly for ICS overuse, and was higher in high-risk, frequent exacerbating COPD patients.

[https://ac.els-cdn.com/S1094553918301494/1-s2.0-S1094553918301494-main.pdf?\\_tid=a6fee81a-4fa2-418f-93ce-ba7105b138ea&acdnat=1547773384\\_5c017cf6b8eb467bb96ab93aa05536ef](https://ac.els-cdn.com/S1094553918301494/1-s2.0-S1094553918301494-main.pdf?_tid=a6fee81a-4fa2-418f-93ce-ba7105b138ea&acdnat=1547773384_5c017cf6b8eb467bb96ab93aa05536ef)

Schreiber, A., F. Cemmi, et al. (2018). "**Prevalence and Predictors of Obstructive Sleep Apnea in Patients with Chronic Obstructive Pulmonary Disease Undergoing Inpatient Pulmonary Rehabilitation.**" *Copd* **15**(3): 265-270.

The aim of our study was to evaluate the prevalence and predictors of obstructive sleep apnea (OSA) in patients with chronic obstructive pulmonary disease (COPD) undergoing inpatient pulmonary rehabilitation programs (PRPs). A retrospective data review of consecutive stable patients with a known diagnosis of COPD, admitted for PRP between January 2007 and December 2013. Full overnight polysomnography (PSG) and Epworth Sleepiness Scale (ESS) were assessed in all patients. Out of 422 evaluated patients, 190 (45%) showed an Apnea Hypopnea Index (AHI)  $\geq 15$  events/hour and underwent OSA treatment. Patients with OSA were significantly younger and had a less severe airway obstruction as compared to patients without OSA. There were no significant differences in cardiac comorbidities nor in arterial blood gases. As expected, patients with OSA showed significantly more severe diurnal symptoms, as assessed by the ESS and higher body mass index (BMI). However, only 69 out of 190 patients with OSA (36.3%) showed an ESS  $> 10$ , whereas 25% of them had BMI  $\leq 25$  and 41% of them had a BMI  $< 30$ . In all, 68% of patients with OSA were discharged with continuous positive airway pressure (CPAP), 15% with Bilevel ventilation, and 17% without any ventilatory treatment. In conclusion, in the population studied, the combination of OSA and COPD was frequent. BMI and ESS values commonly considered cutoff values for the prediction of OSA in the general population may not be accurate in a subgroup of patients with COPD.

<https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1500533>

Seo, M., W. Qiu, et al. (2018). "**Genomics and response to long-term oxygen therapy in chronic obstructive pulmonary disease.**" *J Mol Med (Berl)* **96**(12): 1375-1385.

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide, and long-term oxygen therapy has been shown to reduce mortality in COPD patients with severe hypoxemia. However, the Long-term Oxygen Treatment Trial (LOTT), a large randomized trial, found no benefit of oxygen therapy in COPD patients with moderate hypoxemia. We hypothesized that there may be differences in response to oxygen which depend on genotype or gene expression. In a genome-wide time-to-event analysis of the primary outcome of death or hospitalization in 331 subjects, 97 single nucleotide polymorphisms (SNPs) showed evidence of interaction with oxygen therapy at  $P < 1e-5$ , including 7 SNPs near arylsulfatase B (ARSB;  $P = 6e-6$ ). In microarray expression profiling on 51 whole blood samples from 37 individuals, at screening and/or at 12-month follow-up, ARSB expression was associated with the primary outcome depending on oxygen treatment. The significant SNPs were conditional expression quantitative trait loci for ARSB expression. In a network analysis of genes affected by long-term oxygen, two observed clusters including 26 co-expressed genes were enriched in mitochondrial function. Using data from the observational COPD Gene Study, we validated the expression of 25 of these 26 genes, plus ARSB. The effect of long-term oxygen therapy in COPD varied based on ARSB expression and genotype. ARSB has previously been shown to be associated with hypoxemia in human bronchial and colonic epithelial cells and in a mouse model. In peripheral blood, long-term oxygen treatment affected expression of mitochondrial-related genes, a biologically relevant pathway in COPD. SNPs and expression of ARSB are associated with response to long-term oxygen in COPD. The ARSB SNPs were expression quantitative trait loci depending on oxygen therapy. Genes differentially expressed by long-term oxygen were enriched in mitochondrial functions. This suggests a potential biomarker to personalize use of long-term oxygen in COPD.

<https://link.springer.com/article/10.1007%2Fs00109-018-1708-8>

Serra-Picamal, X., R. Roman, et al. (2018). "**Hospitalizations due to exacerbations of COPD: A big data perspective.**" *Respir Med* **145**: 219-225.

BACKGROUND: Patients with Chronic Obstructive Pulmonary Disease (COPD) may suffer episodes of exacerbation (ECOPD) that require hospitalization and worsen their health status, and prognosis. We hypothesized

that a detailed interrogation of health-care "big data" databases can provide valuable information to better understand the risk factors and outcomes of these episodes. MATERIAL AND METHODS: We interrogated four databases of the Catalan health-care system (>8,000,000 registries) to identify patients hospitalized because of ECOPD for the first time (index event) between 2010 and 2012. Analysis was carried forward since the index event until the end of 2014 or the death of the patient. The two years that preceded the index event were also investigated. RESULTS: We identified 17,555 patients, (>=50 years of age) hospitalized because of ECOPD (ICD9 v.9 codes at discharge) for the first time between 2010 and 2012. In this population we observed that: (1) 23% of patients die within a year after being discharged from their first ECOPD hospitalization; (2) in the remaining patients, all-cause mortality was related to the number of re-hospitalizations, particularly with early (<30 days) readmissions; (3) despite this being a 'respiratory' cohort, prescription and dispensation of drugs for cardiovascular diseases was higher than for obstructive airway diseases; and, finally, (4) lower winter ambient temperatures are associated with hospital admissions for ECOPD particularly in early re-admitters. CONCLUSIONS: Overall these results indicate under appreciation of the burden of COPD in patients hospitalized for the first time because ECOPD.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30009-X/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30009-X/fulltext)

Shafuddin, E., C. L. Chang, et al. (2018). **"Changes in biomarkers of cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease."** *Respir Med* **145**: 192-199.

BACKGROUND: Cardiac dysfunction is associated with a higher mortality in exacerbations of chronic obstructive pulmonary disease (COPD). It is unknown how the heart responds to treatment of COPD exacerbations. We followed cardiac biomarker levels during hospital admissions for exacerbations of COPD and hypothesised that these biochemical markers of cardiac dysfunction might be affected the severity and treatment of exacerbations of COPD. METHODS: N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T were measured at admission, 12h, 72h, and clinical stability in 176 patients. In a second cohort (n=93), associations between blood salbutamol concentrations and biomarker changes at 12h were analysed. RESULTS: NT-proBNP increased from a geometric mean of 43pmol/L at admission to 56pmol/L at 12h ( $p<0.001$ ), 53pmol/L at 72h ( $p=0.045$ ), and decreased to 25pmol/L ( $p<0.001$ ) at stability. Troponin T levels decreased at 12h ( $p<0.001$ ), but 15/174 (9%) patients had a clinically significant rise. Nebulised bronchodilator treatment and blood salbutamol concentrations were associated with greater increases in NT-proBNP rise at 12h independently of baseline COPD or exacerbation severity and other treatments ( $p<0.05$ ). Nebulised bronchodilator and blood salbutamol concentrations also predicted rises in troponin T in univariate analyses ( $p<0.05$ ). CONCLUSIONS: NT-proBNP continues to rise after admission to hospital for COPD exacerbations and a minority of patients have clinically significant rises in cardiac troponins. These rises were associated with nebulised beta2-agonist treatment. These findings suggest that high doses of beta2-agonists may exacerbate cardiac dysfunction in COPD.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30367-6/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30367-6/fulltext)

Shin, B., S. H. Kim, et al. (2019). **"Early readmission and mortality in acute exacerbation of chronic obstructive pulmonary disease with community-acquired pneumonia."** *Chron Respir Dis* **16**: 1479972318809480.

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are important causes of hospital admission and mortality. Pneumonia is a major contributor to hospitalization for AECOPD and has a close relationship with poor outcomes. We performed a prospective cohort study to evaluate the prognosis of AECOPD patients with or without community-acquired pneumonia (CAP) who hospitalized from January 2012 to December 2015. We investigated mortality and readmission rates within 6 months after the first admission between two groups and analyzed the difference of survival rate according to readmission duration (<=30 vs. >30 days) or intensive care unit (ICU) treatment. Total 308 AECOPD patients (134 with CAP and 174 without CAP) were enrolled. The mean age was 72.3 +/- 9.5 years old, and 235 patients (76.3%) were male. The 180-day mortality was higher in AECOPD with CAP than

without CAP (24.6% vs. 13.2%; hazard ratio (HR): 1.982; 95% CI: 1.164-3.375;  $p = 0.012$ ). However, readmission rate showed no significant difference between two groups (51.5% vs. 46.6%; HR: 1.172; 95% CI: 0.850-1.616;  $p = 0.333$ ). It showed a significantly lower survival rate in AECOPD with CAP rather than without CAP when were readmitted within 30 days (HR: 1.738; 95% CI:1.063-3.017;  $p = 0.031$ ). According to ICU treatment, survival rate was not significantly different between two groups. Multivariate analysis revealed the readmission within 30 days ( $p < 0.001$ ), serum hemoglobin concentration ( $p = 0.010$ ), and albumin level ( $p = 0.049$ ) were significantly associated with 180-day mortality of AECOPD with CAP. AECOPD with CAP showed lower survival rate than AECOPD without CAP during 6 months. Early readmission within 30 days was significantly associated with an increased risk of mortality.

Siddiqui, S. H., I. D. Pavord, et al. (2018). "**Blood eosinophils: a biomarker of COPD exacerbation reduction with inhaled corticosteroids.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3669-3676.

Background: Growing evidence suggests that blood eosinophil count is associated with patient responsiveness to inhaled corticosteroids (ICS). We performed post hoc predictive modeling on data from the FORWARD study and two replicate studies by Dransfield, to evaluate the relationships between baseline eosinophil count and the effect of ICS on exacerbations and lung function in patients with COPD. Methods: The studies assessed ICS/long-acting beta2 agonist (LABA) combinations vs LABA alone. Using data from each study, we modeled COPD exacerbation rates, predose FEV1, and St George's Respiratory Questionnaire score ([FORWARD only]) over a continuous range of eosinophils (0-1,000 eosinophils/microL in FORWARD, 0-993 eosinophils/microL in Dransfield). Results: In all studies, ICS/LABA reduced exacerbations versus LABA alone across all eosinophil levels, with progressively greater reductions at increasing baseline blood eosinophil counts. In FORWARD, annual exacerbation rates ranged from 0.78 to 0.83 per year between 0 and 1,000 eosinophils/microL in the ICS/LABA arm, and from 0.81 to 1.54 per year in the LABA-only arm. In the Dransfield studies, exacerbation rates ranged from 0.54 to 1.02 per year in the ICS/LABA arm between 0 and 993 eosinophils/microL, and from 0.56 to 1.75 per year in the LABA-only arm. Change in FEV1 was not associated with eosinophil count in ICS-treated patients in FORWARD, whereas an increased treatment benefit in terms of FEV1 was observed at higher eosinophil levels in the Dransfield studies. ICS/LABA led to greater improvements in St George's Respiratory Questionnaire total scores compared to LABA alone in patients in FORWARD with  $\geq 67$  eosinophils/microL. Conclusion: Higher blood eosinophil count in patients with COPD is associated with an increased beneficial effect from ICS in terms of exacerbation reduction. Further prospective data are required to assess the role of blood eosinophils as a biomarker for therapeutic recommendations.

<https://www.dovepress.com/getfile.php?fileID=45958>

Siddiqui, T. and B. I. Morshed (2018). "**Severity Classification of Chronic Obstructive Pulmonary Disease and Asthma with Heart Rate and SpO2 Sensors.**" *Conf Proc IEEE Eng Med Biol Soc* **2018**: 2929-2932.

Asthma and Chronic Obstructive Pulmonary Disease are chronic and long-term lung diseases. Disease monitoring with minimal sensors with high efficacy can make the disease control simple and practical for patients. We propose a model for the severity assessment of the diseases through wearables and compatible with mobile health applications, using only heart rate and SpO2 (from pulse oximeter sensor). Patient data were obtained from the MIMIC- III Waveform Database Matched Subset. The dataset consists of 158 subjects. Both heart rate and SpO2 signal of patients are analyzed via the proposed algorithm to classify the severity of the diseases. Strategically, a rule-based threshold approach in real time evaluation is considered for the categorization scheme. Furthermore, a method is proposed to assess severity as an Event of Interest (EOI) from the computed metrics in retrospective. This type of autonomous system for real-time evaluation of patient's condition has the potential to improve individual health through continual monitoring and self- management, as well as improve the health status of the overall Smart and Connected Community (SCC).

<https://ieeexplore.ieee.org/document/8512927/>

Silva, I. G., B. S. A. Silva, et al. (2018). **"Functionality of patients with Chronic Obstructive Pulmonary Disease at 3 months follow-up after elastic resistance training: a randomized clinical trial."** *Pulmonology* **24**(6): 354-357.

[https://ac.els-cdn.com/S2531043718301491/1-s2.0-S2531043718301491-main.pdf?\\_tid=bb93c8a1-4d42-48bd-b255-1108cbd1fa03&acdnat=1547773107\\_f6134e717887addac1a360e19bc87fb4](https://ac.els-cdn.com/S2531043718301491/1-s2.0-S2531043718301491-main.pdf?_tid=bb93c8a1-4d42-48bd-b255-1108cbd1fa03&acdnat=1547773107_f6134e717887addac1a360e19bc87fb4)

Singh, A., C. Liu, et al. (2018). **"Predictors of Asthma/COPD Overlap in FDNY Firefighters With World Trade Center Dust Exposure: A Longitudinal Study."** *Chest* **154**(6): 1301-1310.

BACKGROUND: Previously healthy firefighters with World Trade Center (WTC) dust exposure developed airway disease. Risk factors for irritant-associated asthma/COPD overlap are poorly defined. METHODS: This study included 2,137 WTC-exposed firefighters who underwent a clinically indicated bronchodilator pulmonary function test (BD-PFT) between 9/11/2001 and 9/10/2017. A post-BD FEV1 increase of > 12% and 200 mL from baseline defined asthma, and a post-BD FEV1/FVC ratio < 0.7 identified COPD cases. Participants who met both criteria had asthma/COPD overlap. Eosinophil levels were measured on screening blood tests performed shortly after 9/11/2001 and prior to BD-PFT; a subgroup of participants also had serum IgE and 21 cytokines measured (n = 215). Marginal Cox regression models for multiple events assessed the associations of eosinophil levels or serum biomarkers with subsequent diagnosis, with age, race, smoking, WTC exposure, first post-9/11 FEV1/FVC ratio, and BMI included as covariates. RESULTS: BD-PFT diagnosed asthma/COPD overlap in 99 subjects (4.6%), isolated-asthma in 202 (9.5%), and isolated-COPD in 215 (10.1%). Eosinophil concentration  $\geq 300$  cells/ $\mu$ L was associated with increased risk of asthma/COPD overlap (hazard ratio [HR], 1.85; 95% CI, 1.16-2.95) but not with isolated-asthma or isolated-COPD. Serum IL-4 also predicted asthma/COPD overlap (HR, 1.51 per doubling of cytokine concentration; 95% CI, 1.17-1.95). Greater IL-21 concentration was associated with both isolated-asthma and isolated-COPD (HRs of 1.73 [95% CI, 1.27-2.35] and 2.06 [95% CI, 1.31-3.23], respectively). CONCLUSIONS: In WTC-exposed firefighters, elevated blood eosinophil and IL-4 levels are associated with subsequent asthma/COPD overlap. Disease-specific T-helper cell type 2 biomarkers present years before diagnosis suggest patient-intrinsic predisposition to irritant-associated asthma/COPD overlap.

[https://journal.chestnet.org/article/S0012-3692\(18\)31055-9/fulltext](https://journal.chestnet.org/article/S0012-3692(18)31055-9/fulltext)

Singh, U., V. Wangia-Anderson, et al. (2019). **"Chronic Rhinitis Is a High-Risk Comorbidity for 30-Day Hospital Readmission of Patients with Asthma and Chronic Obstructive Pulmonary Disease."** *J Allergy Clin Immunol Pract* **7**(1): 279-285.e6.

BACKGROUND: Early hospital readmissions for asthma and chronic obstructive pulmonary disease (COPD), measured as hospital readmission within 30 days from the last discharge, is a major economic burden to our health care system. The association of this measure with comorbid chronic rhinitis (CR) has not been investigated before despite significant clinical association between CR and asthma or COPD. OBJECTIVE: To investigate the association of CR with the risk of asthma or COPD-related early hospital readmission rates. METHODS: This retrospective cohort study was performed using the asthma- and COPD-related hospital encounter and patient comorbidity data between June 15, 2012, and July 19, 2017, from a large hospital care system in Cincinnati, Ohio. Patients (any sex, race or socioeconomic status, and of all ages) with a primary discharge diagnosis of asthma (n = 4754 patients, 10,111 encounters) and COPD (n = 2176 patients, 4748 encounters) based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes were included. Relevant comorbidities, including comorbid allergic rhinitis (AR) or nonallergic rhinitis (NAR), in such patients were identified using ICD-10-CM codes. The

association between 30-day asthma or COPD-related hospital readmission (1670 such encounters for asthma and 736 for COPD) and comorbid CR in the affected patients were determined using Cox proportional hazards models. Multivariate-adjusted hazard ratios (HRs), adjusted for relevant patient comorbidities, compared 30-day asthma- and COPD-related readmissions of patients with CR with those patients without a CR diagnosis. RESULTS: Analysis was performed on 4754 patients with asthma and 2176 patients with COPD. The median follow-up period (+interquartile range) for asthma was 980 (+760) days and for COPD was 553 (+827) days. The HRs for 30-day asthma- or COPD-related readmission rates were significantly higher in patients with AR (HR = 4.4 [3.9, 5.0] and 2.4 [1.7, 3.2], respectively) or NAR (HR = 3.7 [2.9, 4.9] and 2.6 [1.8, 3.7], respectively) compared with patients without rhinitis. For asthma, both AR and NAR had higher HRs compared with all other comorbidities analyzed. For COPD, both AR and NAR had HRs to the magnitude as obesity and hypertension. CONCLUSIONS: Comorbid CR is significantly associated with 30-day asthma- and COPD-related readmissions. These findings are useful for guiding health care professionals to focus on outpatient management of both the upper and lower respiratory tracts to reduce early readmission of patients with asthma and COPD.

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Soler-Cataluna, J. J., M. Marzo, et al. (2018). "**Validation of clinical control in COPD as a new tool for optimizing treatment.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3719-3731.

Background: It has recently been proposed that the concept of clinical control in COPD may be useful for deciding treatment in COPD, but the original control criteria (OCC) were considered too restrictive. Objective: Define and subsequently validate "modified" control criteria (MCC) of COPD. Method: Prospective observational study in COPD patients with a 1-year follow-up. Control was defined as the presence of low clinical impact and clinical stability. To evaluate clinical impact, the following clinical parameters were assessed: the degree of dyspnea, use of rescue medication, physical activity, and sputum color. Stability was assessed by clinical changes and exacerbations in the last 3 months. The COPD assessment test score and their changes were also evaluated as alternative control criteria. To define the MCC, adjustment for disease severity using BODEx index (MCC-B) or FEV1 (MCC-F) was evaluated, and the best cutoff point was established. Time to first combined event (emergency visit, hospitalization, or death) was analyzed to evaluate the predictive capacity of risk of the OCC, MCC-B, and MCC-F. Results: We included 265 patients, 224 (83.9%) men, with a mean age (+/-SD) of 68 +/- 9 years and FEV1 of 58% +/- 17%. The proportion of controlled patients was higher using clinical MCC-B or MCC-F (61.5% and 59.6%) than OCC (27.5%). Similar percentages were found using COPD assessment test scores. The time to the first combined event was significantly greater in controlled patients using MCC criteria (P<0.001, all cases). The predictive capacity of risk was similar in MCC-B (c-statistic [C]=0.639) and MCC-F (C=0.637) and higher than OCC (C=0.589). Conclusions: The new MCC identified a higher number of controlled COPD patients. These patients have a better quality of life and lower risk of poor outcomes. The concept of control and the new MCC could be a useful tool to optimize therapy.

<https://www.dovepress.com/getfile.php?fileID=46165>

Stanford, R. H., M. S. Lau, et al. (2019). "**External Validation of a COPD Risk Measure in a Commercial and Medicare Population: The COPD Treatment Ratio.**" *J Manag Care Spec Pharm* **25**(1): 58-69.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) exacerbations can accelerate disease progression and lead to higher health care costs. To improve patient survival and reduce cost, risk assessment measures should be developed to identify patients at risk for exacerbations and prevent future exacerbations. OBJECTIVES: To (a) externally validate the COPD treatment ratio (CTR) as a measure of COPD exacerbation risk based on predictive models previously tested and (b) assess the measure's capability to assess risk using only pharmacy claims for use in Medicare Part D programs. METHODS: This was a retrospective observational study conducted using the Humana research datasets. Separate assessments were performed using pharmacy-only models that excluded risk factors derived from

medical claims. Patients were aged  $\geq 40$  years, with  $\geq 1$  inpatient hospitalization or  $\geq 2$  physician's office, emergency department, or urgent care visits with a COPD diagnosis. Using logistic regression models, risk factors (age, exacerbation history, COPD and concomitant medication use, and comorbidities) were assessed during the baseline period (year 1) and were used to predict the risk of exacerbation during year 2. Continuous and dichotomized CTRs were analyzed. A cut-point of 0.3 was initially used for dichotomizing CTR, and subsequently receiver operating characteristics (ROC) analysis was used to determine the optimal cut-point for CTR. RESULTS: A total of 92,496 patients were identified, the majority of which (96.2%) were Medicare members with a mean age of 69 years. During the baseline period, 14.0% and 11.2% of patients had  $\geq 1$  moderate or severe exacerbation, respectively. Overall, the CTR performed well in predicting future COPD exacerbations, especially severe exacerbations. ROC analysis suggested that 0.7 was the optimal cut-point for dichotomizing CTR. Patients with a CTR  $\geq 0.7$  had a 7.9% (OR = 0.921; 95% CI = 0.852-0.995) lower risk of a severe exacerbation, compared with those with a CTR  $< 0.7$ . Stronger effects were seen in pharmacy-only models, with patients 17% less likely to experience a severe exacerbation with a CTR  $\geq 0.7$  compared with patients with a CTR  $< 0.7$ . CONCLUSIONS: This study validated the use of CTR as a modifiable measure of risk of COPD exacerbation in a large commercial and Medicare population and remained a robust predictor when pharmacy-only claims data were available. A CTR of  $\geq 0.7$  may be a useful target to help reduce the risk of severe exacerbations, and its use by payer or quality organizations has the potential to improve COPD management. DISCLOSURES: This study was funded by GlaxoSmithKline (GSK; study number HO-15-16651). GSK had a role in the study design, collection, analysis, and interpretation of data and in the writing of the study report but did not place any restrictions on access to the data or on the statements made in the manuscript. The authors were in full editorial control of publication target journal and content and conclusions, accepted full responsibility for final approval of a manuscript describing this GSK-sponsored research, and had final responsibility for the decision to submit for publication. Stanford and Lau are employees of GSK and hold GSK stocks/shares. Li and Stemkowski are employees of Comprehensive Health Insights, which was contracted to conduct the study but did not receive funding for manuscript development. This manuscript was presented in part at the American Thoracic Society 2017 International Conference; May 19-24, 2017; Washington, DC.

Stiell, I. G., J. J. Perry, et al. (2018). "**Clinical validation of a risk scale for serious outcomes among patients with chronic obstructive pulmonary disease managed in the emergency department.**" *Cmaj* 190(48): E1406-e1413.

BACKGROUND: The Ottawa chronic obstructive pulmonary disease (COPD) Risk Scale (OCRS), which consists of 10 criteria, was previously derived to identify patients in the emergency department with COPD who were at high risk for short-term serious outcomes. We sought to validate, prospectively and explicitly, the OCRS when applied by physicians in the emergency department. METHODS: We conducted this prospective cohort study involving patients in the emergency departments at 6 tertiary care hospitals and enrolled adults with acute exacerbation of COPD from May 2011 to December 2013. Physicians evaluated patients for the OCRS criteria, which were recorded on a data form along with the total risk score. We followed patients for 30 days and the primary outcome, short-term serious outcomes, was defined as any of death, admission to monitored unit, intubation, noninvasive ventilation, myocardial infarction (MI) or relapse with hospital admission. RESULTS: We enrolled 1415 patients with a mean age of 70.6 (SD 10.6) years and 50.2% were female. Short-term serious outcomes occurred in 135 (9.5%) cases. Incidence of short-term serious outcomes ranged from 4.6% for a total score of 0 to 100% for a score of 10. Compared with current practice, an OCRS score threshold of greater than 1 would increase sensitivity for short-term serious outcomes from 51.9% to 79.3% and increase admissions from 45.0% to 56.6%. A threshold of greater than 2 would improve sensitivity to 71.9% with 47.9% of patients being admitted. INTERPRETATION: In this clinical validation of a risk-stratification tool for COPD in the emergency department, we found that OCRS showed better sensitivity for short-term serious outcomes compared with current practice. This risk scale can now be used to help emergency department disposition decisions for patients with COPD, which should lead to a decrease in unnecessary admissions and in unsafe discharges.

Su, V. Y., K. Y. Yang, et al. (2018). **"Use of ICS/LABA Combinations or LAMA Is Associated with a Lower Risk of Acute Exacerbation in Patients with Coexistent COPD and Asthma."** *J Allergy Clin Immunol Pract* **6**(6): 1927-1935.e3.

**BACKGROUND:** Based on current guidelines, more research is urgently needed to guide appropriate treatment for patients with asthma-chronic obstructive pulmonary disease (COPD) overlap. **OBJECTIVE:** The objective of this study was to investigate medication effects on acute exacerbation in patients with coexistent COPD and asthma. **METHODS:** Using Taiwan's National Health Insurance Research Database, we conducted a nationwide population-based study to evaluate medication effects in patients with COPD and asthma. Patients diagnosed with both asthma and COPD between 1997 and 2012 were enrolled as the COPD + asthma cohort. The primary endpoint was acute exacerbation. The definitions of COPD and asthma were validated. The validation study confirmed the accuracy of definitions of COPD (86.2% sensitivity) and asthma (92.0% sensitivity). **RESULTS:** The study included 251,398 patients with COPD + asthma and 514,522 patients with COPD alone, with a mean follow-up period of 9.85 years. After adjustment, hazard ratios (HRs) for long-acting muscarinic antagonist (LAMA) and inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) combinations were lower (time-dependent model, 1 year: LAMA, HR 0.51, 95% confidence interval [CI] 0.49-0.54; ICS/LABA combinations, HR 0.61, 95% CI 0.60-0.62; all  $P < .0001$ ) than were those for LABAs or ICSs in patients with COPD and asthma. **CONCLUSIONS:** The use of LAMA or ICS/LABA combinations was associated with a lower risk of acute exacerbation in patients with COPD and asthma in this study.

Suissa, S., S. Dell'Aniello, et al. (2018). **"Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study."** *Lancet Respir Med* **6**(11): 855-862.

**BACKGROUND:** Long-acting beta2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are the recommended initial maintenance treatment for chronic obstructive pulmonary disease (COPD), with almost all LABAs dispensed in fixed combination with inhaled corticosteroids (LABA-ICS). We compared the effectiveness and safety of LABA-ICS versus LAMA treatment initiation as a function of blood eosinophilia, a potential biomarker of ICS effectiveness, in a real-world setting. **METHODS:** In this population-based cohort study, we identified a cohort of patients with COPD initiating treatment with a LAMA or LABA-ICS during 2002-15, age 55 years or older, from the UK's Clinical Practice Research Datalink. We excluded patients who initiated treatment with both bronchodilators on the same date. All patients required at least 1 year of medical history and a measure of blood eosinophil concentration before cohort entry, defined by the date of the first cohort-defining bronchodilator prescription. Patients initiating a LAMA were matched on high-dimensional propensity scores with patients initiating a LABA-ICS. They were followed up for 1 year for the occurrence of a moderate or severe COPD exacerbation and for severe pneumonia. Sensitivity analyses included, among others, repeating the analysis among patients with two blood eosinophil concentration measures and stratification by concurrent asthma and previous exacerbations. **FINDINGS:** The base cohort included 539 643 patients with a prescription for LABAs or LAMAs from Jan 1, 2002, to Dec 31, 2015, of whom 18 500 were initiated on LABA-ICS and 13 870 on LAMAs. Propensity score analysis resulted in 12 366 initiators of LAMAs (mainly tiotropium) matched to 12 366 initiators of LABA-ICS. The hazard ratio (HR) of COPD exacerbation associated with LABA-ICS initiation, relative to LAMA initiation, was 0.95 (95% CI 0.90-1.01). In patients with blood eosinophil concentrations of less than 2% of white blood cell count, the HR was 1.03 (95% CI 0.93-1.13) and for those with eosinophil concentrations of 2-4%, the HR was 1.00 (0.91-1.10). For patients with eosinophil concentrations of more than 4%, the HR was 0.79 (0.70-0.88). The incidence of pneumonia increased with LABA-ICS initiation (HR 1.37 [95% CI 1.17-1.60]) and was similar across all eosinophil concentrations. Sensitivity analyses were consistent with these findings, but the incidence of exacerbation with LABA-ICS among the 2766 (11%) of all 24 732 patients with two or more COPD

exacerbations during the baseline year was marginally lower (HR 0.87 [95% CI 0.79-0.97]).

INTERPRETATION: In this real-world, clinical practice, observational study, initial COPD treatment with LABA-ICS inhalers was only more effective than with LAMAs in patients with high blood eosinophil concentrations (>4%) or counts (>300 cells per µL) and possibly in frequent exacerbators. Because of the increased risk of pneumonia associated with the ICS component, initiation with a LAMA should be preferred in patients with blood eosinophil concentrations of less than 4%. FUNDING: Canadian Institutes of Health Research, Canadian Foundation for Innovation.

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(18\)30368-0/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30368-0/fulltext)

Thomas, C. D., L. H. Dupree, et al. (2019). "**Evaluation of the protective effects of beta-blockers in the management of acute exacerbations of chronic obstructive pulmonary disease.**" *J Clin Pharm Ther* **44**(1): 109-114.

WHAT IS KNOWN AND OBJECTIVE: The purpose of this study was to evaluate the association between early beta-blocker continuation and major inpatient events in patients hospitalized for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). METHODS: This single centre, retrospective, investigational review board approved cohort study evaluated patients admitted for a primary diagnosis of AECOPD. Patients were evaluated based on early continuation of a beta-blocker whether a beta-blocker was initiated within 24 hours of admission and continued for at least 72 hours. Patients with AECOPD who did not receive beta-blockers were assigned to the control group. Major inpatient events were a composite outcome composed of arrhythmias, myocardial infarction (MI) and death. Safety data were collected on the incidences of bradycardia, bronchospasms and hypotension. RESULTS AND DISCUSSION: Of the 96 patients admitted for AECOPD, fifty-five patients were included in the early beta-blocker group and forty-one patients in the control group. Early beta-blocker utilization was associated with a significantly lower rate of major inpatient events compared with the control group (40% vs 80.5%;  $P < 0.001$ ). Arrhythmias were significantly less common in the early beta-blocker group (30.9% vs 65.9%;  $P = 0.001$ ); however, there were no significant differences in the rates of MI (9.1% vs 14.6%;  $P = 0.54$ ), death (0 vs 0) or safety outcomes between groups. WHAT IS NEW AND CONCLUSION: beta-blocker therapy could result in a paradigm shift in managing chronic obstructive pulmonary disease patients from a true cardiopulmonary approach. This retrospective cohort study demonstrated early beta-blocker continuation in patients admitted for an AECOPD was associated with less major inpatient events, primarily arrhythmias.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/jcpt.12767>

Thyregod, M., A. Lokke, et al. (2018). "**The impact of pulmonary rehabilitation on severe physical inactivity in patients with chronic obstructive pulmonary disease: a pilot study.**" *Int J Chron Obstruct Pulmon Dis* **13**: 3359-3365.

Introduction: In patients with COPD, severe physical inactivity (SPI, which is defined as total daily energy expenditure/resting energy expenditure; physical activity level [PAL] ratio, <1.4) is associated with increased morbidity and mortality. Pulmonary rehabilitation (PR) increases physical capacity in COPD, but the impact on SPI is unknown. In this study, we aimed at elucidating the prevalence of SPI in COPD patients attending standard PR, the impact of PR on SPI prevalence, and the relationship between SPI and time spent in moderate physical activity thus whether American College of Sports Medicine (ACSM) recommendations are clinically useful in excluding SPI in COPD. Methods: This is a prospective non-interventional pilot study on patients with COPD completing PR, consenting to wear an accelerometer (Sensewear(c)) Armband) for a week before and after completing PR to assess changes in energy expenditure, time spent in physical activity, and number of daily steps. Low level of daily physical activity was not an inclusion criterion. Results: In total, 57 patients completed the study and 31 (54%) had SPI at baseline. In patients with SPI, baseline median FEV1 was 48 (range, 28-86) % of predicted and GOLD B, n=11 (35%)/GOLD D, n=20 (65%). Surprisingly, 31 of SPI patients (97%) spent  $\geq$ 150 minutes/week in moderate physical activity. After rehabilitation, 24 (78%) did not change activity level and were

persistently SPI. We observed no differences at baseline between patient responding (n=7) vs not responding (n=24) to PR. Responders increased number of daily steps and time spent in lighter but not moderate physical activity during rehabilitation. Conclusion: In this pilot study, SPI was prevalent, and PR had limited impact. Contrain-tui-tively, most patients with SPI complied with general recommendations of weekly hours spent in moderate physical activity. Our study highlights that increasing time spent in light activity rather than improving time spent in moderate activity is important in COPD patients with chronic dyspnea.

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Titova, E., A. Christensen, et al. (2019). "**Comparison of procalcitonin, C-reactive protein, white blood cell count and clinical status in diagnosing pneumonia in patients hospitalized with acute exacerbations of COPD: A prospective observational study.**" *Chron Respir Dis* **16**: 1479972318769762.

Lower respiratory tract infection is the most common cause of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The aim of the present study was to compare the accuracy of procalcitonin (PCT), C-reactive protein (CRP) and white blood cell count (WBC) as single diagnostic tests and in combination with clinical signs and symptoms to diagnose pneumonia in patients hospitalized with AECOPD. This was a prospective, single centre observational study. Patients with spirometry-confirmed COPD who were hospitalized due to AECOPD were consecutively recruited at the hospital's Emergency Unit. Pneumonia was defined as a new pulmonary infiltrate on chest X-ray. The values of PCT, CRP and WBC were determined at admission. Receiver operating characteristic (ROC) curve analysis was used to study the accuracy of various diagnostic tests. Of the 113 included patients, 35 (31%) had pneumonia at admission. Area under the ROC curve (AUC) for PCT, CRP and WBC as a single test to distinguish between patients with and without pneumonia was 0.67 (95% CI 0.55-0.79), 0.73 (95% CI 0.63-0.84) and 0.67 (95% CI 0.55-0.79), respectively (  $p = 0.42$  for the test of difference). The AUC for a model of clinical signs and symptoms was 0.84 (95% CI 0.76-0.92). When biomarkers were added to the clinical model, the AUCs of the combined models were not significantly different from that of the clinical model alone (  $p = 0.54$ ). PCT had about the same accuracy as CRP and WBC in predicting pneumonia in patients hospitalized with AECOPD both as a single test and in combination with clinical signs and symptoms.

Towe, C. W., M. A. Nead, et al. (2019). "**Safety of Electromagnetic Navigation Bronchoscopy in Patients With COPD: Results From the NAVIGATE Study.**" *J Bronchology Interv Pulmonol* **26**(1): 33-40.

BACKGROUND: Electromagnetic navigation bronchoscopy (ENB) aids in the localization of lung lesions for biopsy and/or to guide fiducial or dye marking for stereotactic radiation or surgical localization. This study assessed ENB safety in patients with chronic obstructive pulmonary disease (COPD) and/or poor lung function. METHODS: NAVIGATE is a prospective, multicenter, observational study of ENB. This substudy analyzed the 1-month follow-up of the first 1000 enrolled subjects. COPD was determined by medical history. Pulmonary function testing (PFT) results were collected if available within 30 days of the procedure. Procedure-related complications were captured. RESULTS: The analysis included 448 subjects with COPD and 541 without COPD (COPD data missing in 11). One-month follow-up was completed in 93.3%. Subjects with COPD tended to be older, male, and have history of tobacco exposure, asthma, and recent pneumonia. Nodule size, location, and procedure time were similar between groups. There was no statistically significant difference in the procedure-related composite complication rate between groups (7.4% with COPD, 7.8% without COPD,  $P=0.90$ ). Common Terminology Criteria for Adverse Events scale grade  $\geq 2$  pneumothorax was not different between groups (2.7% with COPD, 3.7% without COPD,  $P=0.47$ ). COPD was not a significant multivariate predictor of complications. Severity of forced expiratory volume in 1 second (FEV1) or diffusing capacity of the lung for carbon monoxide impairment was not associated with increased composite procedure-related complications (ppFEV1  $P=0.66$ , ppDLCO

P=0.36). CONCLUSION: In this analysis, complication rates following ENB procedures were not increased in patients with COPD or poor pulmonary function. Because pneumothorax risk is not elevated, ENB may be the preferred method to biopsy peripheral lung lesions in patients with COPD and/or poor pulmonary function testing.

van Buul, A. R., T. S. Wildschut, et al. (2018). **"A systematic diagnostic evaluation combined with an internet-based self-management support system for patients with asthma or COPD."** *Int J Chron Obstruct Pulmon Dis* **13**: 3297-3306.

Introduction: An (inter)national systematic approach for patients with asthma COPD referred to secondary care is lacking. Therefore, a novel systematic approach was designed and tested in clinical practice. Methods: This was a retrospective observational study of data from the electronic record system of the Leiden University Medical Center. Asthma and COPD patients were included if they were evaluated with a novel systematic approach or if they had a new record for asthma or COPD and received usual care. The novel systematic approach consisted of a predefined diagnostic evaluation combined with an optional internet-based self-management support system. Diagnostic tests, final diagnosis, lifestyle advices, symptoms and individual care plans in the electronic records, number of patients referred back to primary care, and time to referral back to primary care were compared between the systematic approach and usual care groups using t-tests and chi-squared tests. Results: A total of 125 patients were included, of which 22 (21.4%) were evaluated with the systematic approach. Mean (+/-SD) age was 48.8 (+/-18.4) years and 59.2% were women. Mean (+/-SD) number of diagnostic tests was higher in the systematic approach group compared with the usual care group (7.6+/-1.0 vs 5.5+/-1.8, P<0.001). Similarly, in the systematic approach group, more lifestyle advices (81.8% vs 29.1%), symptom scores (95.5% vs 21.4%), and individual care plans (50.0% vs 7.8%) were electronically recorded (P<0.001), and more patients were referred back to primary care (81.8% vs 56.3%, P=0.03). There were no differences in the final diagnoses and time to referral back. Conclusion: Our study suggested that not all tests that were included in the systematic approach are regularly needed in the diagnostic work-up. In addition, a designated systematic approach stimulates physicians to record lifestyle advices, symptoms, and individual care plans. Thus, this approach could increase the number of patients referred back to primary care.

<https://www.dovepress.com/getfile.php?fileID=45256>

Vanfleteren, M. J., M. Koopman, et al. (2018). **"Effectiveness of Pulmonary Rehabilitation in Patients With Chronic Obstructive Pulmonary Disease With Different Degrees of Static Lung Hyperinflation."** *Arch Phys Med Rehabil* **99**(11): 2279-2286.e3.

OBJECTIVE: To evaluate the effect of pulmonary rehabilitation (PR) on exercise performance and quality of life in patients with chronic obstructive pulmonary disease (COPD) with different degrees of static lung hyperinflation (LH). DESIGN: Retrospective cohort study. SETTING: PR network. PARTICIPANTS: A cohort of 1981 patients with COPD (55% men; age: 66.8+/-9.3y; forced expiratory volume in the first second%: 50.7+/-19.5; residual volume [RV]%, 163.0+/-49.7). INTERVENTION: An interdisciplinary PR program for patients with COPD consisting of 40 sessions. MAIN OUTCOME MEASURES: Participants were stratified into 5 quintiles according to baseline RV and were evaluated on the basis of pre- and post-PR 6-minute walk distance (6MWD), constant work rate test (CWRT), and Saint George's Respiratory Questionnaire (SGRQ), among other clinical parameters. RESULTS: With increasing RV quintile, patients were younger, more frequently women, had lower forced expiratory volume in the first second%, lower body mass index and fat-free mass index, shorter 6MWD, shorter CWRT, and worse SGRQ scores (P<.01). All RV strata improved after PR in all 3 outcomes (P<.001). Nevertheless, higher, compared to lower RV categories, had lower DeltaCWRT (P<.01) but similar Delta6MWD (P=.948) and DeltaSGRQ (P=.086) after PR. CONCLUSIONS: LH in COPD is related to younger age, female sex, lower body weight, worse exercise capacity and health status, but did not prevent patients from benefitting from PR. LH, however, influences walking and cycling response after PR differently.

Vazquez Guillamet, R., O. Ursu, et al. (2018). "**Chronic obstructive pulmonary disease phenotypes using cluster analysis of electronic medical records.**" *Health Informatics J* **24**(4): 394-409.

Chronic obstructive pulmonary disease is a heterogeneous disease. In this retrospective study, we hypothesize that it is possible to identify clinically relevant phenotypes by applying clustering methods to electronic medical records. We included all the patients >40 years with a diagnosis of chronic obstructive pulmonary disease admitted to the University of New Mexico Hospital between 1 January 2011 and 1 May 2014. We collected admissions, demographics, comorbidities, severity markers and treatments. A total of 3144 patients met the inclusion criteria: 46 percent were >65 years and 52 percent were males. The median Charlson score was 2 (interquartile range: 1-4) and the most frequent comorbidities were depression (36%), congestive heart failure (25%), obesity (19%), cancer (19%) and mild liver disease (18%). Using the sphere exclusion method, nine clusters were obtained: depression-chronic obstructive pulmonary disease, coronary artery disease-chronic obstructive pulmonary disease, cerebrovascular disease-chronic obstructive pulmonary disease, malignancy-chronic obstructive pulmonary disease, advanced malignancy-chronic obstructive pulmonary disease, diabetes mellitus-chronic kidney disease-chronic obstructive pulmonary disease, young age-few comorbidities-high readmission rates-chronic obstructive pulmonary disease, atopy-chronic obstructive pulmonary disease, and advanced disease-chronic obstructive pulmonary disease. These clusters will need to be validated prospectively.

Vercammen-Grandjean, C., D. W. Schopfer, et al. (2018). "**Participation in Pulmonary Rehabilitation by Veterans Health Administration and Medicare Beneficiaries After Hospitalization for Chronic Obstructive Pulmonary Disease.**" *J Cardiopulm Rehabil Prev* **38**(6): 406-410.

**BACKGROUND:** Hospitalization with acute exacerbation of chronic obstructive pulmonary disease (COPD) is common and costly to the health care system. Pulmonary rehabilitation (PR) can improve symptom burden and morbidity associated with COPD. The use of PR among Medicare beneficiaries is poor, and the use by Veterans Health Administration (VHA) beneficiaries is unknown. We sought to determine whether participation in PR was similarly poor among eligible veterans compared with Medicare beneficiaries. **METHODS:** We performed a retrospective study using national VHA and Medicare data to determine the proportion of eligible patients who participated in PR after hospitalization for an acute exacerbation of COPD between January 2007 and December 2011. We also evaluated patient characteristics including demographic factors and comorbid medical history associated with participation. **RESULTS:** Over the 5-year study period, 485 (1.5%) of 32 856 VHA and 3199 (2.0%) of 158 137 Medicare beneficiaries hospitalized for COPD attended at least 1 session of PR. Among both VHA and Medicare beneficiaries, participation was higher in those who had had comorbid pneumonia or pulmonary hypertension and was lower in older patients. Although participation increased in both groups over time, it remained exceedingly low overall. **CONCLUSION:** Pulmonary rehabilitation is significantly underused in both the VHA and Medicare populations. Although comorbid pulmonary disease is associated with higher use, the proportion of eligible patients who participate remains extremely low.

Vested, A., I. Basinas, et al. (2019). "**A nationwide follow-up study of occupational organic dust exposure and risk of chronic obstructive pulmonary disease (COPD).**" *Occup Environ Med* **76**(2): 105-113.

**OBJECTIVES:** To study exposure-response relations between cumulative organic dust exposure and incident chronic obstructive pulmonary disease (COPD) among subjects employed in the Danish farming and wood industry. **METHODS:** We studied exposure-response relations between cumulative organic dust exposure and incident COPD (1997-2013) among individuals born during 1950-1977 in Denmark ever employed in the farming or wood industry (n=1 75 409). Industry-specific employment history (1964-2007), combined with time-dependent farming and wood industry-specific exposure matrices defined cumulative exposure. We used logistic regression analysis with discrete survival function adjusting for age, sex and calendar year. Adjustment for smoking status was explored in a subgroup of 4023 with smoking information available. **RESULTS:** Cumulative organic dust exposure was inversely associated with COPD (adjusted rate ratios (RRadj (95% CIs) of 0.90 (0.82 to 0.99), 0.76 (0.69 to 0.84) and 0.52 (0.47 to 0.58) for intermediate-low, intermediate-high and high exposure quartiles, respectively, compared with the lowest exposure quartile). Lagging exposure 10 years was not consistently suggestive of an association between cumulative exposure and COPD; RRadj (95% CI): 1.05 (0.94 to 1.16), 0.92 (0.83 to 1.02) and 0.63 (0.56 to 0.70). Additional stratification by duration of employment showed no clear association between organic dust exposure and COPD except for the longer exposed (15-40 years) where an inverse association was indicated. Subgroup analyses showed that smoking had no impact on exposure-response estimates. **CONCLUSIONS:** Our findings show no increased risk of COPD with increasing occupational exposure to organic dust in the farming or wood industry. Potential residual confounding by smoking can, however, not be ruled out.

<https://oem.bmj.com/content/oemed/76/2/105.full.pdf>

Viglino, D., A. Plazanet, et al. (2018). **"Impact of Non-alcoholic Fatty Liver Disease on long-term cardiovascular events and death in Chronic Obstructive Pulmonary Disease."** *Sci Rep* 8(1): 16559. Chronic Obstructive Pulmonary Disease (COPD) and Non-Alcoholic Fatty Liver Disease (NAFLD) both independently increase cardiovascular risk. We hypothesized that NAFLD might increase the incidence of cardiovascular disease and death in COPD patients. The relationship between NAFLD, incident cardiovascular events, and death was assessed in a prospective cohort of COPD patients with 5-year follow-up. Noninvasive algorithms combining biological parameters (FibroMax((R))) were used to evaluate steatosis, non-alcoholic steatohepatitis (NASH) and liver fibrosis. Univariate and multivariate Cox regression models were used to assess the hazard for composite outcome at the endpoint (death or cardiovascular event) for each liver pathology. In 111 COPD patients, 75% exhibited liver damage with a prevalence of steatosis, NASH and fibrosis of 41%, 37% and 61%, respectively. During 5-year follow-up, 31 experienced at least one cardiovascular event and 7 died. In univariate analysis, patients with liver fibrosis had more cardiovascular events and higher mortality (Hazard ratio [95% CI]: 2.75 [1.26; 6.03]) than those with no fibrosis; this remained significant in multivariate analysis (Hazard ratio [95% CI]: 2.94 [1.18; 7.33]). We also found that steatosis and NASH were not associated with increased cardiovascular events or mortality. To conclude, early assessment of liver damage might participate to improve cardiovascular outcomes in COPD patients.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6224555/pdf/41598\\_2018\\_Article\\_34988.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6224555/pdf/41598_2018_Article_34988.pdf)

Vishweswaraiah, S., T. A. Thimraj, et al. (2018). **"Putative Systemic Biomarkers of Biomass Smoke-Induced Chronic Obstructive Pulmonary Disease among Women in a Rural South Indian Population."** *Dis Markers* 2018: 4949175.

**Rationale:** Exposure to biomass smoke (BMS) has been implicated in chronic obstructive pulmonary disease (COPD). About 3 billion people worldwide use biomass fuel for cooking and heating. Women in rural communities of low- and lower-middle-income countries are disproportionately exposed to massive amounts of BMS during active cooking hours (4-6 h/day). Therefore, BMS exposure is considered as a risk factor for COPD in the same order of magnitude as tobacco smoke. In rural India, due to cultural reasons, women are the primary cook of the family and are mostly nonsmokers. Thus, BMS-induced COPD is predominant among rural Indian women. However, BMS-COPD remains a relatively unexplored

health problem globally. Therefore, we investigated the serum chemokine and cytokine signatures of BMS-COPD and tobacco smoke-induced COPD (TS-COPD) patients compared to their control in a rural South Indian population for this field study. Methods: Concentrations of 40 serum chemokines and cytokines were measured using a multiplexed immunoassay. The study cohort consisted of BMS-COPD (female; n = 29) and BMS-exposed subjects without COPD (BMS-CONTROL; female; n = 24). For comparison, data from TS-COPD patients (male, n = 23) and tobacco smokers without COPD (TS-CONTROL; male, n = 22) were investigated. Subjects were matched for age, sex, and biomass exposure. Tobacco consumption was slightly higher in TS-COPD subjects compared to TS-CONTROL. BMS-exposed and TS-exposed subjects (currently exposed) were from the same locality with similar dwelling habits and socioeconomic status. A validated structured questionnaire-based survey and spirometry was performed. An additional control group with no tobacco and BMS exposure (TS-BMS-CONTROL; n = 15) was included. Statistical significance was set at  $p \leq 0.01$ . Results: Serum median concentrations (pg/ml) of CCL15 [8799.35; 5977.22], CCL27 [1409.14; 1024.99], and CXCL13 [37.14; 26.03] were significantly higher in BMS-CONTROL compared to BMS-COPD subjects. Nine analytes exhibited higher concentrations in TS-CONTROL compared to TS-COPD subjects. Comparison of chemokine and cytokine concentrations among BMS-COPD versus TS-COPD and BMS-CONTROL versus TS-CONTROL subjects also revealed distinct molecular signatures. Conclusion: Our data identifies CCL27 and CXCL13 as putative, plausibly homeostatic/protective biomarkers for BMS-COPD within the investigated population that warrants validation in larger and multiple cohorts. The findings further indicate exposure-specific systemic response of chemokines and cytokines.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6282129/pdf/DM2018-4949175.pdf>

Wang, W., S. Dou, et al. (2018). **"Impact of COPD on prognosis of lung cancer: from a perspective on disease heterogeneity."** *Int J Chron Obstruct Pulmon Dis* **13**: 3767-3776.

Background: COPD is an important comorbidity of lung cancer, but the impact of COPD on the outcomes of lung cancer remains uncertain. Because both COPD and lung cancer are heterogeneous diseases, we evaluated the link between COPD phenotypes and the prognosis of different histological subtypes of lung cancer. Methods: In this retrospective study, subjects with a newly and pathologically confirmed diagnosis of lung cancer were enrolled from patients preparing for lung cancer surgery. All participants underwent pulmonary function test (PFT). The diagnosis of COPD was based on GOLD criteria. Lung cancer subtypes and COPD phenotypes were categorized by WHO classification of lung tumors and computer quantitative analysis of PFT. The HRs were estimated by Cox regression analysis. Results: Among 2,222 lung cancer patients, 32.6% coexisted with COPD. After adjustment for age, sex, body mass index (BMI), smoking status, and therapy method, COPD was significantly associated with the decreased overall survival (OS) of lung cancer (HR 1.28, 95% CI 1.05-1.57). With the increased severity of COPD, the OS of lung cancer was gradually worsened (HR 1.23, 95% CI 1.08-1.39). But surgical treatment and high BMI were independent prognostic protective factors (HR 0.46, 95% CI 0.37-0.56; HR 0.96, 95% CI 0.94-0.99). Moreover, in terms of disease heterogeneity, emphysema-predominant phenotype of COPD was an independent prognostic risk factor for squamous carcinoma (HR 2.53, 95% CI 1.49-4.30). No significant relationship between COPD phenotype and lung cancer prognosis was observed among adenocarcinoma, small cell lung cancer, large cell lung cancer, and other subtype patients. Conclusion: These findings suggest that COPD, especially emphysema-predominant phenotype, is an independent prognostic risk factor for squamous carcinoma only.

<https://www.dovepress.com/getfile.php?fileID=46323>

Wilairat, P., K. Kengkla, et al. (2019). **"Clinical outcomes of theophylline use as add-on therapy in patients with chronic obstructive pulmonary disease: A propensity score matching analysis."** *Chron Respir Dis* **16**: 1479973118815694.

To examine clinical outcomes of theophylline use in patients with chronic obstructive pulmonary disease (COPD) receiving inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABA). Electronic data from five

hospitals located in Northern Thailand between January 2011 and December 2015 were retrospectively collected. Propensity score (PS) matching (2:1 ratio) technique was used to minimize confounding factors. The primary outcome was overall exacerbations. Secondary outcomes were exacerbation not leading to hospital admission, hospitalization for exacerbation, hospitalization for pneumonia, and all-cause hospitalizations. Cox's proportional hazards models were used to estimate adjusted hazard ratio (aHR) and 95% confidence interval (CI). After PS matching, of 711 patients with COPD (mean age: 70.1 years; 74.4% male; 60.8% severe airflow obstruction), 474 theophylline users and 237 non-theophylline users were included. Mean follow-up time was 2.26 years. Theophylline significantly increased the risk of overall exacerbation (aHR: 1.48, 95% CI: 1.11-1.96;  $p = 0.008$ ) and exacerbation not leading to hospital admission (aHR: 1.47, 95% CI: 1.06-2.03;  $p = 0.020$ ). Theophylline use did not significantly increase the risk of hospitalization for exacerbation (aHR: 1.11, 95% CI: 0.79-1.58;  $p = 0.548$ ), hospitalization for pneumonia (aHR: 1.28, 95% CI: 0.89-1.84;  $p = 0.185$ ), and all-cause hospitalizations (aHR: 1.03, 95% CI: 0.80-1.33;  $p = 0.795$ ). Theophylline use as add-on therapy to ICS and LABA might be associated with an increased risk for overall exacerbation in patients with COPD. A large-scale prospective study of theophylline use investigating both safety and efficacy is warranted.

Wittbrodt, E. T., L. A. Millette, et al. (2019). **"Differences in health care outcomes between postdischarge COPD patients treated with inhaled corticosteroid/long-acting beta2-agonist via dry-powder inhalers and pressurized metered-dose inhalers."** *Int J Chron Obstruct Pulmon Dis* **14**: 101-114.

Purpose: The aim of this study was to examine real-world differences in health care resource use (HRU) and costs among COPD patients in the USA treated with a dry powder inhaler (DPI) or pressurized metered-dose inhaler (pMDI) following a COPD-related hospitalization. Methods: This retrospective analysis used the Truven MarketScan(R) databases. Eligibility criteria included 1) age  $\geq 40$  years, 2) COPD diagnosis, 3) inpatient admission with a diagnosis of COPD exacerbation, 4) inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) prescription within 10 days of hospital discharge (index date), and 5) continuous enrollment for 12 months preindex and 90 days postindex. Outcomes included pre- and postindex HRU and costs. DPI and pMDI groups were compared on postindex outcomes via multivariate models controlling for demographic and baseline characteristics. Results: The sample included 1,960 DPI and 1,086 pMDI ICS/LABA patients. During the preindex period, pMDI patients were significantly more likely to be prescribed a short-acting beta-agonist, experienced more COPD exacerbation-related hospital days, and had a greater number of pulmonologist visits compared to DPI patients ( $P < 0.05$ ), all suggestive of greater disease severity. However, multivariate models revealed that pMDI patients incurred 10% lower all-cause postindex costs (predicted mean costs [2016 US dollars]: \$2,673 vs \$2,956) and 19% lower COPD-related costs (predicted mean costs: \$138 vs \$169;  $P < 0.05$ ). Additionally, pMDI patients were 28% less likely to experience a COPD exacerbation-related hospital readmission within 60 days postdischarge compared to the DPI patients (OR: 0.72, 95% CI: 0.52-0.99,  $P < 0.05$ ). Conclusion: Despite greater COPD-related HRU and costs preceding index hospitalization, US patients using a pMDI after hospital discharge incurred significantly lower all-cause and COPD-related health care costs compared with those using a DPI, in addition to a decreased likelihood of a COPD exacerbation-related hospital readmission. Results suggest that inhaler device type may influence COPD outcomes and that COPD patients may derive greater clinical benefit from treatment delivered via pMDI vs DPI.

<https://www.dovepress.com/getfile.php?fileID=47152>

Xiong, X. F., L. L. Fan, et al. (2018). **"Effects of Tiotropium Combined with Theophylline on Stable COPD Patients of Group B, D and its Impact on Small Airway Function: A Randomized Controlled Trial."** *Adv Ther* **35**(12): 2201-2213.

INTRODUCTION: Tiotropium bromide has been widely used in clinical practice, while theophylline is another treatment option for chronic obstructive pulmonary disease (COPD). However, only a few relevant studies have investigated the long-term outcomes and efficacy of both in patients with COPD. We

evaluated the effects of tiotropium and low-dose theophylline on stable COPD patients of groups B and D. METHODS: Eligible participants (n = 170) were randomized and received either tiotropium 18 microg once daily with theophylline 100 mg twice daily (Group I) or tiotropium 18 microg once daily (Group II) for 6 months. COPD assessment test (CAT), modified Medical Research Council (mMRC) dyspnea scores and pulmonary function tests were measured before randomization and during the treatment. RESULTS: After 6 months of treatment, the CAT scores in both groups decreased significantly (11.41 +/- 3.56 and 11.08 +/- 3.05, p < 0.0001). The changes of CAT (p = 0.028) and mMRC scores (p = 0.049) between the two groups differed after 1 month of treatment. In Group I, forced expiratory flow after 25% of the FVC% predicted (MEF25% pred) was significantly improved after 3 months (4.84 +/- 8.73%, p < 0.0001) and 6 months (6.21 +/- 8.65%, p < 0.0001). There was a significant difference in small airway function tests (MEF50% pred, MEF25% pred, and MMEF% pred) between the two groups after 6 month of treatment (p = 0.003, p < 0.0001, and p = 0.021, respectively). CONCLUSIONS: Tiotropium combined with low-dose theophylline significantly improved the symptoms and general health of patients with stable COPD of groups B and D after 6 months of follow-up. Additionally, this therapy also improved the indicators of small airway function. TRIAL REGISTRATION: Chinese Clinical Trial Registry (Registry ID: ChiCTR1800019027).

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6267715/pdf/12325\\_2018\\_Article\\_831.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6267715/pdf/12325_2018_Article_831.pdf)

Yi, Y. S., W. H. Ban, et al. (2018). "**Effect of COPD on symptoms, quality of life and prognosis in patients with advanced non-small cell lung cancer.**" *BMC Cancer* **18**(1): 1053.

BACKGROUND: Many studies have reported the prevalence of chronic obstructive pulmonary disease (COPD) and its effects and prognosis in patients with lung cancer, but few have considered quality of life and survival of patients with lung cancer according to severity of airway obstruction. This study investigated the presence of COPD and the severity of airway obstruction in patients with non-small cell lung cancer (NSCLC), and analyzed how these factors affected symptoms, quality of life, and prognosis. METHODS: We retrospectively reviewed the prospective lung cancer database of the Catholic Medical Centers at the Catholic University of Korea from 2014 to 2017. We enrolled patients with advanced NSCLC and evaluated quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30. We also estimated pulmonary function and analyzed survival data. RESULTS: Of the 337 patients with advanced NSCLC, 170 (50.5%) had COPD and 167 (49.5%) did not. Significant differences were observed in symptoms between the two groups. The COPD group complained of more symptoms, such as cough, sputum, and dyspnea, than those in the non-COPD group. The distribution according to the severity of obstruction in the COPD group was as follows: Grade 1 (FEV1 >= 80%) 35 patients (20.6%), Grade 2 (50% <= FEV1 < 80%) 103 patients (60.6%), Grade 3 (30% <= FEV1 < 50%) 24 patients (14.1%), and Grade 4 (FEV1 < 30%) 8 patients (4.7%). The presence of COPD did not affect overall quality of life in patients with NSCLC, but as the airway obstruction increased, physical function decreased, and fatigue and dyspnea were more frequent. The overall median survival of the COPD group was shorter than that of the non-COPD group (median survival, 224 vs. 339 days, p = 0.035). CONCLUSIONS: In this study, a high prevalence of COPD was found among patients with advanced NSCLC, and COPD patients complained about various symptoms and had diminished quality of life in several sectors. Therefore, it is necessary to actively evaluate quality of life, lung function, and symptoms in patients with lung cancer and reflect them in the treatment and management plans of these patients.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6206922/pdf/12885\\_2018\\_Article\\_4976.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6206922/pdf/12885_2018_Article_4976.pdf)

Zaigham, S., L. Johnson, et al. (2018). "**Measures of low lung function and the prediction of incident COPD events and acute coronary events.**" *Respir Med* **144**: 68-73.

BACKGROUND: Although reduced lung function is associated with both COPD and coronary events (CE), the pattern of lung function impairment could be different for the two outcomes. We examined different measures of lung function in relation to incident COPD events and CE in a population-based cohort. METHODS: Baseline spirometry and lung clearance index (LCI) were assessed in 672 men aged 55 years.

Outcomes included incident COPD events and CE (hospitalisation or mortality). Cox regression was used to obtain HRs per 1-standard deviation (SD) decrement in baseline lung function. The Lunn-McNeil competing risks approach was used to assess if differences in risks for incident COPD events and CE were significant. RESULTS: Over 44 years follow-up there were 85 incident COPD events and 266 incident CE. Low FEV1 and FEV1/VC and high LCI showed significantly stronger relationships with COPD events than CE (adjusted HRs per 1SD decrement and p-value for equal associations: FEV1; HRCOPD: 2.11 (1.66-2.68), HRCE: 1.30 (1.13-1.49)  $p < 0.001$ , FEV1/VC; HRCOPD 1.95 (1.60-2.36), HRCE 1.11 (0.98-1.26)  $p < 0.0001$ , LCI; HRCOPD: 1.58 (1.26-1.98), HRCE: 1.14 (1.00-1.31)  $p = 0.015$ ). Low VC was significantly associated with both COPD and CE, but HRs were not significantly different between the outcomes ( $p$ -value for equal associations = 0.706). CONCLUSIONS: Low FEV1 and FEV1/VC and high LCI at baseline show significantly stronger relationships with future COPD events than CE. Low VC at baseline is similarly associated with future COPD events and CE. This indicates differences but also an important similarity in the "lung function profile" for developing incident COPD events or incident CE later in life.

[https://www.resmedjournal.com/article/S0954-6111\(18\)30313-5/fulltext](https://www.resmedjournal.com/article/S0954-6111(18)30313-5/fulltext)

Zakrisson, A. B., M. Arne, et al. (2019). "**A complex intervention of self-management for patients with COPD or CHF in primary care improved performance and satisfaction with regard to own selected activities; A longitudinal follow-up.**" *J Adv Nurs* 75(1): 175-186.

AIM: To test a self-management intervention in primary health care (PHC) for patients with chronic obstructive pulmonary disease (COPD) or chronic heart failure (CHF) on self-efficacy, symptoms, functioning, and health. BACKGROUND: Patients with COPD or CHF experience often the same symptoms such as shortness of breath, cough, lack of energy, dry mouth, numbness or tingling in hands and feet, pain and sleeping problems. DESIGN: A multicentre randomized control trial. METHOD: The trial was conducted with one intervention group (N = 73) and one control group (N = 77). The trial was performed from September 2013-September 2015 at nine PHC centres in three county councils in Sweden. At baseline patients with COPD and CHF experienced any symptom. Follow-ups were performed after 3 months and 1 year. The intervention was structured on Bandura's theory of self-efficacy in six meetings and individual action plans based on personal problems were performed and discussed. RESULTS: At baseline, there were no differences between the groups except for SF-36 social function. After 3 months, the intervention group improved performance and satisfaction with regard to own selected activities, otherwise no differences were found. CONCLUSION: When designing a program, the patient's own difficulties must be taken into consideration if person-centred care is to be established. It is feasible to include both patients with COPD and CHF in the same group in PHC. Healthcare professionals need supervision in pedagogics during intervention in self-management.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/jan.13899>

Zamarron, E., E. Prats, et al. (2019). "**Static lung hyperinflation is an independent risk factor for lung cancer in patients with chronic obstructive pulmonary disease.**" *Lung Cancer* 128: 40-46.

INTRODUCTION: Static hyperinflation, a hallmark characteristic of some patients with chronic obstructive pulmonary disease, is related to higher mortality and cardiovascular morbidity. However, information about its association with lung cancer is scarce. Our aim was to evaluate whether static hyperinflation is associated with future risk of lung cancer in COPD patients. METHODS: A cohort of 848 COPD patients recruited outside the hospital setting was monitored for an average period of 4.3 years, totaling 2858 person-years, regarding diagnosis of cancer of any origin or lung cancer. Static hyperinflation was defined by functional residual capacity measured by plethysmography greater than 120% of the predicted value. RESULTS: The incidence rates for cancer of any origin and lung cancer were 16.0 (95%CI, 15.1-17.8) and 8.7 (95%CI, 7.7-9.8) per 1000 patient-years, respectively. Among the patients with lung cancer, non-small cell lung cancer predominated (88%). In a stepwise multivariate Cox regression model, body mass index (BMI), pack-years, Charlson index, and postbronchodilator FEV1/FVC ratio were retained as independent predictors of cancer of any origin. In contrast, features associated with a future

risk of lung cancer included older age, low BMI, increased pack-years and presence of static hyperinflation (adjusted hazard ratio: 4.617, 95%CI: 1.007-21.172,  $p = 0.049$ ). CONCLUSION: In a general COPD outpatient population, static hyperinflation is an independent risk factor for the development of lung cancer, which might contribute towards justifying the excess mortality identified in COPD patients with hyperinflation.

[https://www.lungcancerjournal.info/article/S0169-5002\(18\)30709-8/fulltext](https://www.lungcancerjournal.info/article/S0169-5002(18)30709-8/fulltext)

Zhang, D. D., G. Lu, et al. (2018). "**Neural Respiratory Drive Measured Using Surface Electromyography of Diaphragm as a Physiological Biomarker to Predict Hospitalization of Acute Exacerbation of Chronic Obstructive Pulmonary Disease Patients.**" *Chin Med J (Engl)* **131**(23): 2800-2807.

Background: Neural respiratory drive (NRD) using diaphragm electromyography through an invasive transesophageal multi-electrode catheter can be used as a feasible clinical physiological parameter in patients with chronic obstructive pulmonary disease (COPD) to provide useful information on the treatment response. However, it remains unknown whether the surface diaphragm electromyogram (EMGdi) could be used to identify the deterioration of clinical symptoms and to predict the necessity of hospitalization in acute exacerbation of COPD (AECOPD) patients. Methods: COPD patients visiting the outpatient department due to acute exacerbation were enrolled in this study. All patients who were subjected to EMGdi and classical parameters such as spirometry parameters, arterial blood gas analysis, COPD assessment test (CAT) score, and the modified early warning score (MEWS) in outpatient department, would be treated effectively in the outpatient or inpatient settings according to the Global Initiative for Chronic Obstructive Lung Disease guideline. When the acute exacerbation of the patients was managed, all the examination above would be repeated. Results: We compared the relationships of admission-to-discharge changes (Delta) in the normalized value of the EMGdi, including the change of the percentage of maximal EMGdi (DeltaEMGdi%max) and the change of the ratio of minute ventilation to the percentage of maximal EMGdi (DeltaVE/EMGdi%max) with the changes of classical parameters. There was a significant positive association between DeltaEMGdi%max and DeltaCAT, DeltaPaCO<sub>2</sub>, and DeltapH. The change (Delta) of EMGdi%max was negatively correlated with DeltaPaO<sub>2</sub>/FiO<sub>2</sub> in the course of the treatment of AECOPD. Compared with the classical parameters including forced expiratory volume in 1 s, MEWS, PaO<sub>2</sub>/FiO<sub>2</sub>, the EMGdi%max (odds ratio 1.143, 95% confidence interval 1.004-1.300) has a higher sensitivity when detecting the early exacerbation and enables to predict the admission of hospital in the whole cohort. Conclusions: The changes of surface EMGdi parameters had a direct correlation with classical measures in the whole cohort of AECOPD. The measurement of NRD by surface EMGdi represents a practical physiological biomarker, which may be helpful in detecting patients who should be hospitalized timely.

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