

**COPD/Emphysema PubMed search results covering the period 10/05/2018 to 26/07/2018**

**Cohort and case-control studies**

Aaron, C. P., J. E. Schwartz, et al. (2018). **"A Longitudinal Cohort Study of Aspirin Use and Progression of Emphysema-like Lung Characteristics on CT Imaging: The MESA Lung Study."** *Chest* **154**(1): 41-50.

BACKGROUND: Platelet activation reduces pulmonary microvascular blood flow and contributes to inflammation; these factors have been implicated in the pathogenesis of COPD and emphysema. We hypothesized that regular use of aspirin, a platelet inhibitor, would be associated with a slower progression of emphysema-like lung characteristics on CT imaging and a slower decline in lung function. METHODS: The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled participants 45 to 84 years of age without clinical cardiovascular disease from 2000 to 2002. The MESA Lung Study assessed the percentage of emphysema-like lung below -950 Hounsfield units ("percent emphysema") on cardiac (2000-2007) and full-lung CT scans (2010-2012). Regular aspirin use was defined as 3 or more days per week. Mixed-effect models adjusted for demographics, anthropometric features, smoking, hypertension, angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker use, C-reactive protein levels, sphingomyelin levels, and scanner factors. RESULTS: At baseline, the 4,257 participants' mean ( $\pm$  SD) age was 61  $\pm$  10 years, 54% were ever smokers, and 22% used aspirin regularly. On average, percent emphysema increased 0.60 percentage points over 10 years (95% CI, 0.35-0.94). Progression of percent emphysema was slower among regular aspirin users compared with patients who did not use aspirin (fully adjusted model: -0.34% /10 years, 95% CI, -0.60 to -0.08;  $P = .01$ ). Results were similar in ever smokers and with doses of 81 and 300 to 325 mg and were of greater magnitude among those with airflow limitation. No association was found between aspirin use and change in lung function. CONCLUSIONS: Regular aspirin use was associated with a more than 50% reduction in the rate of emphysema progression over 10 years. Further study of aspirin and platelets in emphysema may be warranted.

Abad-Arranz, M., A. Moran-Rodriguez, et al. (2018). **"Community Assessment of COPD Health Care (COACH) study: a clinical audit on primary care performance variability in COPD care."** *BMC Med Res Methodol* **18**(1): 68.

BACKGROUND: A thorough evaluation of the adequacy of clinical practice in a designated health care setting and temporal context is key for clinical care improvement. This study aimed to perform a clinical audit of primary care to evaluate clinical care delivered to patients with COPD in routine clinical practice. METHODS: The Community Assessment of COPD Health Care (COACH) study

was an observational, multicenter, nationwide, non-interventional, retrospective, clinical audit of randomly selected primary care centers in Spain. Two different databases were built: the resources and organization database and the clinical database. From January 1, 2015 to December 31, 2016 consecutive clinical cases of COPD in each participating primary care center (PCC) were audited. For descriptive purposes, we collected data regarding the age at diagnosis of COPD and the age at audit, gender, the setting of the PCC (rural/urban), and comorbidities for each patient. Two guidelines widely and uniformly used in Spain were carefully reviewed to establish a benchmark of adequacy for the audited cases. Clinical performance was analyzed at the patient, center, and regional levels. The degree of adequacy was categorized as excellent (> 80%), good (60-80%), adequate (40-59%), inadequate (20-39%), and highly inadequate (< 20%). RESULTS: During the study 4307 cases from 63 primary care centers in 6 regions of the country were audited. Most evaluated parameters were judged to fall in the inadequate performance category. A correct diagnosis based on previous exposure plus spirometric obstruction was made in an average of 17.6% of cases, ranging from 9.8 to 23.3% depending on the region. During the audited visit, only 67 (1.6%) patients had current post-bronchodilator obstructive spirometry; 184 (4.3%) patients had current post-bronchodilator obstructive spirometry during either the audited or initial diagnostic visit. Evaluation of dyspnea was performed in 11.1% of cases. Regarding treatment, 33.6% received no maintenance inhaled therapies (ranging from 31.3% in GOLD A to 7.0% in GOLD D). The two most frequently registered items were exacerbations in the previous year (81.4%) and influenza vaccination (87.7%). CONCLUSIONS: The results of this audit revealed a large variability in clinical performance across centers, which was not fully attributable to the severity of the disease.

Abbas, A., S. Embarak, et al. (2018). **"Role of diaphragmatic rapid shallow breathing index in predicting weaning outcome in patients with acute exacerbation of COPD."** Int J Chron Obstruct Pulmon Dis 13: 1655-1661.

Background: The diaphragmatic rapid shallow breathing index (D-RSBI), which is the ratio between respiratory rate (RR) and the ultrasonographic evaluation of diaphragmatic displacement (DD), is a new and promising tool to predict weaning outcome. Its accuracy in predicting weaning failure, in ready-to-wean acute exacerbation COPD (AECOPD) patients, needs to be evaluated. Patients and methods: A prospective observational study was carried out on ready-to-wean AECOPD patients. During a T-tube spontaneous breathing trial (SBT) evaluation of the right hemidiaphragm displacement (ie, DD), M-mode ultrasonography to calculate the D-RSBI, as well as the RSBI (RR/tidal volume [VT]) were carried out simultaneously. Outcome of the weaning trial was recorded. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic accuracy of D-RSBI and RSBI. Results: A total of 50 AECOPD patients requiring mechanical ventilation for more than 48 h who were ready to perform a SBT were included. Of these, 37 (74%) were successfully liberated from mechanical ventilation. Among the 13 patients who failed the weaning trial, 8 (62%) failed the SBT and reconnected to the ventilator, 2 (15%) were reintubated within 48 h of extubation and 3 (23%) required NIV support within 48 h of extubation. The areas

under the ROC curves for D-RSBI and RSBI were 0.97 ( $p < 0.001$ ) and 0.67 ( $p < 0.06$ ), respectively. Conclusion: D-RSBI (RR/DD) is superior to the traditional RSBI (RR/VT) in predicting weaning outcome in AECOPD patients.

Acanfora, D., P. Scicchitano, et al. (2018). **"Relative lymphocyte count as an indicator of 3-year mortality in elderly people with severe COPD."** BMC Pulm Med **18**(1): 116.

**BACKGROUND:** Prognostic stratification of elderly patients with chronic obstructive pulmonary disease (COPD) is difficult due to the wide inter-individual variability in the course of the disease. No marker can exactly stratify the evolution and natural history of COPD patients. Studies have shown that leukocyte count is associated with increased risk of mortality in COPD patients. The aim of this study was to evaluate the possible role of relative lymphocyte count as a risk marker for mortality in elderly patients with COPD. **METHODS AND RESULTS:** This is a 3-year prospective study. A total of 218 patients, mean age  $75.2 \pm 7$  years, with moderate to severe COPD and free from conditions affecting lymphocyte count were enrolled. The population was divided into two groups according to the relative lymphocyte count, with a cut-off of 20%. Eighty-five patients (39%) had a relative lymphocyte count  $\leq 20\%$ . Three-year mortality rates from any cause in patients with relative lymphocyte count  $\leq$  or  $> 20\%$  were 68 and 51%, respectively ( $p = 0.0012$ ). Survival curve analysis showed higher mortality in patients with relative lymphocyte count  $\leq 20\%$  ( $p = 0.0005$ ). After adjustment for age and sex, the hazard ratio for mortality risk according to lymphocyte count was 1.79 (95% confidence interval [CI]: 1.26-2.57,  $p = 0.0013$ ), even in the analysis limited to the 171 patients without congestive heart failure (1.63; 95% CI: 1.03-2.58,  $p = 0.038$ ). **CONCLUSIONS:** Low relative lymphocyte count was associated with higher mortality in elderly patients with severe COPD.

Adwani, S. H., C. Yuan, et al. (2018). **"Variations in practice patterns and resource utilization in patients treated for chronic obstructive pulmonary disease."** J Eval Clin Pract **24**(3): 468-473.

**RATIONALE, AIMS, AND OBJECTIVES:** Several studies have looked at patient-related variables influencing hospital length of stay (LOS) in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). However, there has been increasing recognition that physician-related factors also play a significant role. This study aims to evaluate differences in practice patterns between teaching and nonteaching services and their effect on LOS in a large community hospital. **METHODS:** A retrospective study of 354 patients admitted to Florida Hospital, Orlando, with AECOPD between January 2009 and December 2011. Patients who presented with acute respiratory failure requiring mechanical ventilation were excluded. Practice patterns of interest were use of oral versus intravenous systemic steroids, use of oral versus intravenous

antibiotics, and utilization of consultations. **RESULTS:** Length of stay was significantly lower in the teaching compared with the nonteaching group (2.80 vs. 5.04 days,  $P < .001$ ). There was significantly greater use of oral steroids (85% vs. 8.9%,  $P < .001$ ), greater use of oral antibiotics (72% vs. 33%,  $P < .001$ ), and lower utilization of consults (0.3 vs. 1.4 consults per patient,  $P < .001$ ) in the teaching compared with the nonteaching group. The teaching service was independently associated with decreased LOS in a multivariable regression model. However, after adjustment for the difference in practice patterns between the 2 groups, the teaching service was no longer associated with decreased LOS. Of the practice patterns, only utilization of consults was independently associated with increased LOS. **CONCLUSIONS:** The teaching service had decreased LOS compared with the nonteaching service in patients hospitalized for AECOPD. The observed difference was completely explained by differences in practice patterns between the 2 groups. The study identifies an opportunity for more efficient and cost-effective care of AECOPD patients through streamlining of consultations, use of oral steroids in lieu of IV steroids, and antibiotic stewardship.

Al Aqqad, S. M. H., B. Tangiisuran, et al. (2017). **"Hospitalisation of multiethnic older patients with AECOPD: exploration of the occurrence of anxiety, depression and factors associated with short-term hospital readmission."** *Clin Respir J* 11(6): 960-967.

**INTRODUCTION:** The elderly, with chronic obstructive pulmonary disease (COPD), are at a higher risk of hospitalisation due to acute exacerbation of COPD (AECOPD). They also often encounter multiple co-morbidities. **OBJECTIVES:** This study was aimed to explore the occurrence of anxiety, depression and to identify the factors associated with hospital readmission among older patients after AECOPD discharge. **METHODS:** A multicentre prospective study was conducted in Malaysia (from 1st September 2012 till 31st September 2013) among older patients ( $\geq 60$  years) hospitalised for AECOPD. Anxiety and depression were assessed on discharge using previously validated questionnaires, Generalized Anxiety Disorder-7 (GAD-7) and Geriatric Depression Scale (GDS-15), respectively. Patients were followed up for a period of 3 months after discharge. **RESULTS:** A total of 81 patients with a median age of 72 years (IQR 66.40-78.00) were recruited. Anxiety was observed in 34.57% while 38.27% had depression. Both anxiety and depression were detected in 25.93% of the patients. A history of frequent AECOPD admissions was found to be associated with developing depressive symptoms, while anxiety scores were associated with severe dyspnoea. Severe depression was more commonly identified among patients aged 60-75 and in those with a history of tuberculosis. A high readmission rate (40.74%) during the 3-month period was noticed. History of frequent AECOPD admissions (OR = 2.87; 95% CI 1.05-7.85,  $P = 0.040$ ) and ischemic heart disease (IHD) (OR = 4.04; 95% CI 1.1-14.6,  $P = 0.032$ ) were identified as the factors associated with the risk of hospital readmission. **CONCLUSIONS:** Anxiety and depression were found to be relatively common among older patients with AECOPD. IHD and history of frequent COPD hospitalisation were associated with short-term readmission among the elderly.

Alma, H. J., C. de Jong, et al. (2018). **"Assessing health status over time: impact of recall period and anchor question on the minimal clinically important difference of copd health status tools."** Health Qual Life Outcomes **16**(1): 130.

**BACKGROUND:** The Minimal Clinically Important Difference (MCID) assesses what change on a measurement tool can be considered minimal clinically relevant. Although the recall period can influence questionnaire scores, it is unclear if it influences the MCID. This study is the first to examine longitudinally the impact of the recall period of an anchor question and its design on the MCID of COPD health status tools using the COPD Assessment Test (CAT), Clinical COPD Questionnaire (CCQ) and the St. George's Respiratory Questionnaire (SGRQ). **METHODS:** Moderate to very severe COPD patients without respiratory co-morbidities were recruited during 3-week Pulmonary Rehabilitation (PR). CAT, CCQ and SGRQ were completed at baseline, discharge, 3, 6, 9 and 12 months. A 15-point Global Rating of Change scale (GRC) was completed at each follow-up. A five-point GRC was used as second anchor at 12 months. Mean change scores of a subset of patients indicating a minimal improvement on each of the anchor questions were considered the MCID. The MCID estimates over different time periods were compared with one another by evaluating the degree of overlap of Confidence Intervals (CI) adjusted for dependency. **RESULTS:** In total 451 patients were included (57.9 +/- 6.6 years, 65% male, 50/39/11% GOLD II/III/IV), of which 309 completed follow-up. Baseline health status scores were 20.2 +/- 7.3 (CAT), 2.9 +/- 1.2 (CCQ) and 50.7 +/- 17.3 (SGRQ). MCID estimates for improvement ranged - 3.1 to - 1.4 for CAT, - 0.6 to - 0.3 for CCQ, and - 10.3 to - 7.6 for SGRQ. Absolute higher - though not significant - MCIDs were observed for CAT and CCQ directly after PR. Significantly absolute lower MCID estimates were observed for CAT (difference - 1.4: CI -2.3 to - 0.5) and CCQ (difference - 0.2: CI -0.3 to -0.1) using a five-point GRC. **CONCLUSIONS:** The recall period of a 15-point anchor question seemed to have limited impact on the MCID for improvement of CAT, CCQ and SGRQ during PR; although a 3-week MCID estimate directly after PR might lead to absolute higher values. However, the design of the anchor question was likely to influence the MCID of CAT and CCQ. **TRIAL REGISTRATION:** RIMTCORE trial # DRKS00004609 and #12107 (Ethik-Kommission der Bayerischen Landesärztekammer).

Alton, S. and L. Farndon (2018). **"The impact of community pharmacy-led medicines management support for people with COPD."** Br J Community Nurs **23**(6): 266-271.

Chronic obstructive pulmonary disease (COPD) is a common long-term condition involving restricted airflow, which reduces quality of life. Treatments include lifestyle changes (smoking cessation), pulmonary rehabilitation and medication with inhaled therapies. However, medication adherence is often suboptimal,

resulting in poor health outcomes. A pilot project assessed the impact of medicines management support from a community pharmacy team for people with COPD, delivered in their own homes. Individuals were given a medication review and an assessment of their inhaler technique and were followed up at 3 and 6 months. The COPD Assessment Test (CAT) score was administered before and after the intervention. A change in score of 2 or more suggests a significant difference; the average score was 19.2 at the first assessment and 16.7 at the six month follow-up. Seventeen patients had improved CAT scores, 10 patients had a reduced score and three remained unchanged. Most patients evaluated the project positively as it helped them to improve their inhaler technique. Medicines optimisation was also achieved as a person-centred approach was taken; suboptimal practice had not been picked up by health professionals previously. Community pharmacists working in integrated care teams provide invaluable support to patients with COPD. This project will be rolled out across the community team, and training on medicines management and inhaler technique provided to other health professionals involved in the care of these patients.

Andell, P., J. Sjogren, et al. (2017). **"Outcome of patients with chronic obstructive pulmonary disease and severe coronary artery disease who had a coronary artery bypass graft or a percutaneous coronary intervention."** Eur J Cardiothorac Surg **52**(5): 930-936.

**OBJECTIVES:** Patients with chronic obstructive pulmonary disease (COPD) who also have acute coronary syndromes are a high-risk population with a high mortality rate. Little is known about these patients following coronary artery bypass grafting (CABG). **METHODS:** Patients presenting with acute coronary syndromes between 2006 and 2014 with an angiogram showing 3-vessel disease or left main coronary artery involvement who were treated with CABG or percutaneous coronary intervention (PCI) only were included from the nationwide SWEDEHEART registry. Patients were stratified according to COPD status and compared with regard to outcome. The primary end-point was the 5-year mortality rate; secondary outcomes were the 30-day mortality rate and in-hospital complications after CABG. **RESULTS:** We identified 6985 patients in the population who had CABG (COPD prevalence = 8.0%) and 14 209 who had PCI only (COPD = 8.2%). Patients with COPD were older and had more comorbidities than patients without COPD. The 5-year mortality rate was nearly doubled in patients with COPD versus patients without COPD (CABG: 27.2% vs 14.5%,  $P < 0.001$ ; PCI only: 50.1% vs 29.1%,  $P < 0.001$ ). After adjusting for age, sex and comorbidities, patients with COPD in both CABG-treated [hazard ratio = 1.52 (1.25-1.86),  $P < 0.001$ ] and PCI-treated populations still had a significantly higher 5-year mortality rate. COPD was also independently associated with significantly more postoperative infections in need of antibiotics [odds ratio = 1.48 (1.07-2.04),  $P = 0.017$ ] and pneumonia [odds ratio = 2.21 (1.39-3.52),  $P = 0.001$ ]. **CONCLUSIONS:** Patients with COPD presenting with acute coronary syndromes and severe coronary artery disease are a high-risk population following CABG or PCI only, with higher risk of long-term and short-term death and postoperative

infections. Preventive measures, including careful monitoring for signs of infection and prompt antibiotic treatment when indicated, should be considered.

Ann timerapu, S., S. Goldfarb, et al. (2018). **"Development and validation of a predictive model to identify patients at risk of severe COPD exacerbations using administrative claims data."** Int J Chron Obstruct Pulmon Dis **13**: 2121-2130.

Background: Patients with COPD often experience severe exacerbations involving hospitalization, which accelerate lung function decline and reduce quality of life. This study aimed to develop and validate a predictive model to identify patients at risk of developing severe COPD exacerbations using administrative claims data, to facilitate appropriate disease management programs. Methods: A predictive model was developed using a retrospective cohort of COPD patients aged 55-89 years identified between July 1, 2010 and June 30, 2013 using Humana's claims data. The baseline period was 12 months postdiagnosis, and the prediction period covered months 12-24. Patients with and without severe exacerbations in the prediction period were compared to identify characteristics associated with severe COPD exacerbations. Models were developed using stepwise logistic regression, and a final model was chosen to optimize sensitivity, specificity, positive predictive value (PPV), and negative PV (NPV). Results: Of 45,722 patients, 5,317 had severe exacerbations in the prediction period. Patients with severe exacerbations had significantly higher comorbidity burden, use of respiratory medications, and tobacco-cessation counseling compared to those without severe exacerbations in the baseline period. The predictive model included 29 variables that were significantly associated with severe exacerbations. The strongest predictors were prior severe exacerbations and higher Deyo-Charlson comorbidity score (OR 1.50 and 1.47, respectively). The best-performing predictive model had an area under the curve of 0.77. A receiver operating characteristic cutoff of 0.4 was chosen to optimize PPV, and the model had sensitivity of 17%, specificity of 98%, PPV of 48%, and NPV of 90%. Conclusion: This study found that of every two patients identified by the predictive model to be at risk of severe exacerbation, one patient may have a severe exacerbation. Once at-risk patients are identified, appropriate maintenance medication, implementation of disease-management programs, and education may prevent future exacerbations.

Ash, S. Y., R. Harmouche, et al. (2018). **"Interstitial Features at Chest CT Enhance the Deleterious Effects of Emphysema in the COPDGene Cohort."** Radiology **288**(2): 600-609.

Purpose To determine if interstitial features at chest CT enhance the effect of emphysema on clinical disease severity in smokers without clinical pulmonary fibrosis. Materials and Methods In this retrospective cohort study, an objective

CT analysis tool was used to measure interstitial features (reticular changes, honeycombing, centrilobular nodules, linear scar, nodular changes, subpleural lines, and ground-glass opacities) and emphysema in 8266 participants in a study of chronic obstructive pulmonary disease (COPD) called COPDGene (recruited between October 2006 and January 2011). Additive differences in patients with emphysema with interstitial features and in those without interstitial features were analyzed by using t tests, multivariable linear regression, and Kaplan-Meier analysis. Multivariable linear and Cox regression were used to determine if interstitial features modified the effect of continuously measured emphysema on clinical measures of disease severity and mortality. Results Compared with individuals with emphysema alone, those with emphysema and interstitial features had a higher percentage predicted forced expiratory volume in 1 second (absolute difference, 6.4%;  $P < .001$ ), a lower percentage predicted diffusing capacity of lung for carbon monoxide (DLCO) (absolute difference, 7.4%;  $P = .034$ ), a 0.019 higher right ventricular-to-left ventricular (RVLV) volume ratio ( $P = .029$ ), a 43.2-m shorter 6-minute walk distance (6MWD) ( $P < .001$ ), a 5.9-point higher St George's Respiratory Questionnaire (SGRQ) score ( $P < .001$ ), and 82% higher mortality ( $P < .001$ ). In addition, interstitial features modified the effect of emphysema on percentage predicted DLCO, RVLV volume ratio, 6MWD, SGRQ score, and mortality ( $P$  for interaction  $< .05$  for all). Conclusion In smokers, the combined presence of interstitial features and emphysema was associated with worse clinical disease severity and higher mortality than was emphysema alone. In addition, interstitial features enhanced the deleterious effects of emphysema on clinical disease severity and mortality.

Ausin, P., J. Martinez-Llorens, et al. (2017). **"Sex differences in function and structure of the quadriceps muscle in chronic obstructive pulmonary disease patients."** *Chron Respir Dis* 14(2): 127-139.

Chronic obstructive pulmonary disease (COPD) is a complex disorder with extrapulmonary manifestations. Even though there is some knowledge regarding sex differences in the lung disease, little is known about extrapulmonary manifestations. Our aim was to analyze the specific profile of muscle dysfunction, structure, and biology in COPD women. Twenty-one women and 19 men with stable COPD as well as 15 controls were included. Nutritional status, physical activity, lung and muscle function, exercise capacity, and quality of life were assessed. In addition, blood, breath condensate, and quadriceps muscle samples were tested for inflammatory markers. Moreover, fiber phenotype, signs of damage-regeneration, and the expression of key genes linked to myogenesis and inflammation were assessed in the muscle. Inflammatory markers were increased in all body compartments but no correlation was found among them. Muscle dysfunction was present in both COPD groups but was more marked in women. The opposite occurred with the increase in the percentage of type II fibers that was lower in women despite a similar level of airway obstruction as in men. Female COPD also showed higher signs of muscle damage than COPD men who, in contrast, exhibited slightly higher signs of regeneration. We conclude that sex influences muscle phenotype and function in COPD.



Bak, S. H., S. Kim, et al. (2018). **"Quantitative computed tomography features and clinical manifestations associated with the extent of bronchiectasis in patients with moderate-to-severe COPD."** Int J Chron Obstruct Pulmon Dis 13: 1421-1431.

Background: Few studies have investigated the quantitative computed tomography (CT) features associated with the severity of bronchiectasis in COPD patients. The purpose of this study was to identify the quantitative CT features and clinical values to determine the extent of bronchiectasis in moderate-to-severe COPD patients. Methods: A total of 127 moderate-to-severe COPD patients were selected from the cohort of COPD in Dusty Areas (CODA). The study subjects were classified into three groups according to the extent of bronchiectasis on CT: no bronchiectasis, mild bronchiectasis, and moderate-to-severe bronchiectasis. The three groups were compared with respect to demographic data, symptoms, medical history, serum inflammatory markers, pulmonary function, and quantitative CT values. Results: Among 127 moderate-to-severe COPD subjects, 73 patients (57.5%) were detected to have bronchiectasis, 51 patients (40.2%) to have mild bronchiectasis, and 22 patients (17.3%) to have moderate-to-severe bronchiectasis. Compared with COPD patients without bronchiectasis, those with bronchiectasis were older and had higher frequency of prior tuberculosis, lower prevalence of bronchodilator reversibility (BDR), and more severe air trapping ( $P < 0.05$ ). Moderate-to-severe bronchiectasis patients had lower body mass index (BMI), higher frequency of prior tuberculosis, lower prevalence of BDR, worse pulmonary function, and more severe air trapping ( $P < 0.05$ ) than those in the mild bronchiectasis group. Conclusion: Moderate-to-severe bronchiectasis was associated with a history of pulmonary tuberculosis, lower BMI, severe airflow obstruction, and lower BDR in moderate-to-severe COPD patients. Quantitative analysis of CT showed that severe air trapping was associated with the extent of bronchiectasis in these patients.

Bartels, W., S. Adamson, et al. (2018). **"Emergency department management of acute exacerbations of chronic obstructive pulmonary disease: factors predicting readmission."** Int J Chron Obstruct Pulmon Dis 13: 1647-1654.

Rationale: Readmissions are common following acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and are partially responsible for increased morbidity and mortality in COPD. Numerous factors have been shown to predict readmission of patients previously admitted to hospital for AECOPD; however, factors related to readmission in patients who are triaged in emergency departments (EDs) and sent directly home are poorly understood. We postulate that patients seen in the ED for AECOPD and directly sent home have a high readmission rate, and we suspect that inadequate management and follow-up contribute to this high readmission rate. Methods: We conducted a 1-year retrospective study of all patients seen in the ED for AECOPD at an inner-city

tertiary care hospital; 30- and 90-day readmission rates for COPD and all-cause admissions to the ED and hospital were determined. Patients discharged directly home from the ED were compared with those admitted to hospital for management. Patient, treatment, and system variables that could potentially impact readmission were documented. Multivariate Poisson regression models were used to determine which factors predicted readmissions. Results: The readmission rates in the ED group (n=240) were significantly higher than that in the hospitalized group (n=271): 1) the 90-day ED readmissions (1.29 vs 0.51,  $p<0.0001$ ) and 30-day ED readmissions (0.54 vs 0.20,  $p<0.0001$ ) (ED vs hospitalized groups) were significantly higher in the ED group; 2) the time to first readmission was significantly shorter in the ED group than in the hospitalized group (24.1 $\pm$ 22 vs 31.8 $\pm$ 27.8 days;  $p<0.05$ ). Cardiovascular comorbidities ( $p<0.00001$ ), substance abuse disorder ( $p<0.001$ ), and mental illness ( $p<0.001$ ) were the strongest predictors of readmission in the ED group. Age ( $p<0.01$ ), forced expiratory volume in 1 second ( $p<0.001$ ), and cardiovascular comorbidities ( $p<0.05$ ) were the best predictors for both 30- and 90-day COPD readmission rates in the ED group. Only 50% of the ED group patients received bronchodilators, oral steroids, and antibiotics inclusively, and only 68% were referred for community follow-up. The need for oral steroids to treat AECOPD predicted future 90-day COPD readmissions in the ED group ( $p<0.003$ ). Conclusion: Patients discharged directly home from EDs have a significantly higher risk of readmission to EDs than those who are hospitalized. One possible reason for this is that COPD management is variable in EDs with <50% receiving appropriate therapy.

Bell, C. F., A. D. Coutinho, et al. (2018). **"Clinical and economic outcomes associated with the use of fluticasone propionate 250 mcg and salmeterol 50 mcg combination versus tiotropium bromide 18 mcg as initial maintenance treatment for chronic obstructive pulmonary disease in managed care."** *J Med Econ* 21(6): 629-638.

AIMS: To examine the clinical and economic outcomes associated with the use of long-acting bronchodilators for initial maintenance treatment of chronic obstructive pulmonary disease (COPD) by analyzing health insurance claims data in the US. METHODS: A retrospective, observational, matched cohort study used health insurance claims data (January 2008 to June 2013) to assess COPD-related outcomes for subjects aged  $\geq 40$  years. Subjects were assigned to a study cohort according to the first observed prescription fill for a long-acting bronchodilator (fluticasone propionate 250 mcg/salmeterol 50 mcg [FSC] or tiotropium bromide 18 mcg [TIO]). The analysis period for each subject comprised a 1-year pre-index date and 1-year post-index date. Primary outcome measure was total COPD-related costs per-patient per-year (PPPY) during the follow-up period. Secondary outcome measures included COPD-related exacerbations and the components of COPD-related costs. RESULTS: Overall, 24,040 subjects were identified; the analysis sample consisted of 19,090 subjects (9,545 per cohort) with no significant differences between cohorts. Mean COPD-related total costs PPPY were numerically lower among the FSC cohort; however, the difference was not statistically significant (\$2,224 [ $\pm$ 4,108] vs

\$2,352 [±3,721],  $p = .057$ ). There was no difference between cohorts for COPD-related medical costs ( $p = .894$ ). COPD-related pharmacy costs were significantly, yet modestly, lower in the FSC cohort compared with the TIO cohort (\$1,160 [±1,106] vs 1,275 [±1,110],  $p < .001$ ). There were no statistically significant differences in the rate or number of exacerbations between the matched cohorts. LIMITATIONS: While propensity scoring achieved balance in baseline characteristics, some residual confounding unobserved in the database may be present. CONCLUSIONS: Few clinical and economic differences between subjects initiating maintenance therapy with FSC or TIO were observed.

Bernabeu-Mora, R., L. M. Gimenez-Gimenez, et al. (2017). "**Determinants of each domain of the Short Physical Performance Battery in COPD.**" Int J Chron Obstruct Pulmon Dis **12**: 2539-2544.

BACKGROUND: The Short Physical Performance Battery (SPPB) is an assessment tool with good prognostic value in COPD. It includes the following: standing balance, 4 m gait speed test (4MGS), and the timed five-repetition sit-to-stand test (5STS). The specific differences in determinants between these three tasks have not been adequately characterized in COPD patients. We aimed to identify health-related, functional, and psychological determinants of each SPPB test. METHODS: We conducted a cross-sectional analysis of 137 patients with stable COPD. Patients performed the SPPB, quadriceps muscle strength (QMS), exercise tolerance test (6-min walk test [6MWT]), and pulmonary function; and health-related and psychological factors, physical activity, the COPD assessment test (CAT), body mass index, age, and depression were assessed. RESULTS: Separate multivariable regression models predicting the 4MGS, 5STS, and balance test results described 31%, 39.1%, and 12.1% of the variance for each test, respectively. QMS was negatively associated with all three tests. The 6MWT was negatively associated with the 4MGS and 5STS. Depression and age were positively associated with 4MGS scores, whereas CAT and age were positively associated with 5STS scores. CONCLUSION: The three SPPB tests did not provide equivalent information regarding a COPD patient's status. The 5STS was associated with health status factors, while the 4MGS was associated with psychological factors.

Bhatti, H., A. Ramdass, et al. (2017). "**Operator dependent factors implicated in failure of non-invasive positive pressure ventilation (NIPPV) for respiratory failure.**" Clin Respir J **11**(6): 901-905.

BACKGROUND: Non-invasive Positive Pressure Ventilation (NIPPV) is employed for the management of acute respiratory failure and studies have shown that it can prevent the need for endotracheal intubation, mechanical ventilation and associated complications. Given limited studies evaluating the factors, other than those related patient or underlying disease severity, that may lead to NIPPV

failure, we performed this study to gain insight into current practices in terms of utilization of NIPPV and operator dependent factors that may possibly contribute to failure of NIPPV. **METHOD:** After institutional board review approval a retrospective chart review was performed of consecutive patients who were initiated on and failed NIPPV between January 2009 and December 2009. Data was recorded regarding baseline demographics, admission diagnosis, indications for NIPPV, presence of contraindications, type of NIPPV and initial settings, ABG analysis before and after initiation, whether a titration of the settings was performed or not, operator related factors that may have contributed to failure of NIPPV and clinical outcomes. **RESULTS:** Among 1095 patients screened, 111 failed NIPPV. The mean age was 60 years with 59% males. The most frequent indication for initiating NIPPV was COPD exacerbation (N = 27) followed by pneumonia (N = 26). CPAP was used in 5(6%) patients. Median inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) setting were 10 and 5 cm of H<sub>2</sub>O respectively. Three most common reasons for failure were an inappropriate indication (33%), Progression of underlying disease (30%) and lack of titration (23%). Overall mortality was 22%. Mortality was higher when NIPPV failure was seen among patients with an inappropriate indication or an overlooked contraindication compared to those with an appropriate indication (27% vs 17%). **CONCLUSIONS:** Excluding progression of underlying disease, operator dependent factors linked to NIPPV failure are; inappropriate indication, lack of adequate titration and an overlooked contraindication. Inappropriate utilization of NIPPV in respiratory failure is associated with higher mortality.

Bourbeau, J., R. Farias, et al. (2018). **"The Quebec Respiratory Health Education Network: Integrating a model of self-management education in COPD primary care."** *Chron Respir Dis* 15(2): 103-113.

The objective of this study is to evaluate whether a chronic obstructive pulmonary disease (COPD) self-management education program with coaching of a case manager improves patient-related outcomes and leads to practice changes in primary care. COPD patients from six family medicine clinics (FMCs) participated in a 1-year educational program offered by trained case managers who focused on treatment adherence, inhaler techniques, smoking cessation, and the use of an action plan for exacerbations. Health-care utilization, health-related quality of life (HRQL), treatment adherence, inhaler technique, and COPD knowledge were assessed at each visit with validated questionnaires. We also evaluated whether the use of spirometry and the assessment of individual patient needs led to a more COPD-targeted treatment by primary care physicians, based on changes in prescriptions for COPD (medication, immunization, and written action plan). Fifty-four patients completed the follow-up visits and were included in the analysis. The number of unscheduled physician visits went from 40 the year before intervention to 17 after 1 year of educational intervention (  $p = 0.033$ ). Emergency room visits went from five to two and hospitalizations from two to three (NS). Significant improvements were observed in HRQL (  $p = 0.0001$ ), treatment adherence (  $p = 0.025$ ), adequate inhaler technique (  $p < 0.0001$ ), and COPD knowledge (  $p < 0.001$ ). Primary care physicians increased their prescriptions for long-acting bronchodilators with/without inhaled corticosteroid, flu immunizations,

and COPD action plans in the event patient had an exacerbation. The COPD self-management educational intervention in FMCs reduced unscheduled visits to the clinic and improved patients' quality of life, self-management skills, and knowledge. The program had a positive impact on COPD-related practices by primary care physicians in the FMCs.

Briend, E., G. J. Ferguson, et al. (2017). **"IL-18 associated with lung lymphoid aggregates drives IFNgamma production in severe COPD."** Respir Res **18**(1): 159.

**BACKGROUND:** Increased interferon gamma (IFNgamma) release occurs in Chronic Obstructive Pulmonary Disease (COPD) lungs. IFNgamma supports optimal viral clearance, but if dysregulated could increase lung tissue destruction. **METHODS:** The present study investigates which mediators most closely correlate with IFNgamma in sputum in stable and exacerbating disease, and seeks to shed light on the spatial requirements for innate production of IFNgamma, as reported in mouse lymph nodes, to observe whether such microenvironmental cellular organisation is relevant to IFNgamma production in COPD lung. **RESULTS:** We show tertiary follicle formation in severe disease alters the dominant mechanistic drivers of IFNgamma production, because cells producing interleukin-18, a key regulator of IFNgamma, are highly associated with such structures. Interleukin-1 family cytokines correlated with IFNgamma in COPD sputum. We observed that the primary source of IL-18 in COPD lungs was myeloid cells within lymphoid aggregates and IL-18 was increased in severe disease. IL-18 released from infected epithelium or from activated myeloid cells, was more dominant in driving IFNgamma when IL-18-producing and responder cells were in close proximity. **CONCLUSIONS:** Unlike tight regulation to control infection spread in lymphoid organs, this local interface between IL-18-expressing and responder cell is increasingly supported in lung as disease progresses, increasing its potential to increase tissue damage via IFNgamma.

Bruguera-Avila, N., A. Marin, et al. (2017). **"Effectiveness of treatment with nebulized colistin in patients with COPD."** Int J Chron Obstruct Pulmon Dis **12**: 2909-2915.

**OBJECTIVES:** To analyze whether the introduction of nebulized colistin in patients with chronic obstructive pulmonary disease (COPD) and infection with *Pseudomonas aeruginosa* (PA) is associated with a decrease of the number and duration of severe exacerbations. **MATERIALS AND METHODS:** Thirty six patients with COPD and infection with PA treated with nebulized colistin attending a day hospital during a 5-year (January 2010-December 2014) period were prospectively included. Repeated-measures t-tests were used to assess whether the introduction of colistin was associated with changes in the number of exacerbations or the length of the hospitalizations, comparing for each patient

the year prior to the introduction of colistin with the year after. RESULTS: After the introduction of colistin, the number of admissions decreased from 2.0 to 0.9 per individual year ( $P=0.0007$ ), and hospitalizations were shorter (23.3 vs 10.9 days,  $P=0.00005$ ). These results persisted when patients with and without bronchiectasis or with and without persistence of *Pseudomonas* were separately analyzed. No pre-post differences were detected in the number of exacerbations not requiring admission. CONCLUSION: Nebulized colistin seems associated with a strong decrease in the number and duration of hospitalizations due to exacerbation in patients with COPD and infection with PA. Clinical trials with a larger number of patients are needed in order to confirm these results.

Bui, D. S., C. J. Lodge, et al. (2018). "**Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life.**" *Lancet Respir Med* 6(7): 535-544.

BACKGROUND: Lifetime lung function is related to quality of life and longevity. Over the lifespan, individuals follow different lung function trajectories. Identification of these trajectories, their determinants, and outcomes is important, but no study has done this beyond the fourth decade. METHODS: We used six waves of the Tasmanian Longitudinal Health Study (TAHS) to model lung function trajectories measured at 7, 13, 18, 45, 50, and 53 years. We analysed pre-bronchodilator FEV1 z-scores at the six timepoints using group-based trajectory modelling to identify distinct subgroups of individuals whose measurements followed a similar pattern over time. We related the trajectories identified to childhood factors and risk of chronic obstructive pulmonary disease (COPD) using logistic regression, and estimated population-attributable fractions of COPD. FINDINGS: Of the 8583 participants in the original cohort, 2438 had at least two waves of lung function data at age 7 years and 53 years and comprised the study population. We identified six trajectories: early below average, accelerated decline (97 [4%] participants); persistently low (136 [6%] participants); early low, accelerated growth, normal decline (196 [8%] participants); persistently high (293 [12%] participants); below average (772 [32%] participants); and average (944 [39%] participants). The three trajectories early below average, accelerated decline; persistently low; and below average had increased risk of COPD at age 53 years compared with the average group (early below average, accelerated decline: odds ratio 35.0, 95% CI 19.5-64.0; persistently low: 9.5, 4.5-20.6; and below average: 3.7, 1.9-6.9). Early-life predictors of the three trajectories included childhood asthma, bronchitis, pneumonia, allergic rhinitis, eczema, parental asthma, and maternal smoking. Personal smoking and active adult asthma increased the impact of maternal smoking and childhood asthma, respectively, on the early below average, accelerated decline trajectory. INTERPRETATION: We identified six potential FEV1 trajectories, two of which were novel. Three trajectories contributed 75% of COPD burden and were associated with modifiable early-life exposures whose impact was aggravated by adult factors. We postulate that reducing maternal smoking, encouraging immunisation, and avoiding personal smoking, especially in those with smoking parents or low childhood lung function, might minimise COPD risk. Clinicians and patients with asthma should be made aware of the potential long-term implications of non-

optimal asthma control for lung function trajectory throughout life, and the role and benefit of optimal asthma control on improving lung function should be investigated in future intervention trials. FUNDING: National Health and Medical Research Council of Australia; European Union's Horizon 2020; The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; The Victorian, Queensland & Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline.

Bulsei, J., S. Leroy, et al. (2018). **"Cost-effectiveness of lung volume reduction coil treatment in patients with severe emphysema: results from the 2-year follow-up crossover REVOLENS study (REVOLENS-2 study)."** *Respir Res* 19(1): 84.

BACKGROUND: The REVOLENS study compared lung volume reduction coil treatment to usual care in patients with severe emphysema at 1 year, resulting in improved quality-adjusted life-year (QALY) and higher costs. Durability of the coil treatment benefit and its cost-effectiveness at 2 years are now assessed. METHODS: After one year, the REVOLENS trial's usual care group patients received coil treatment (second-line coil treatment group). Costs and QALYs were assessed in both arms at 2 years and an incremental cost-effectiveness ratio in cost per QALY gained was calculated. The uncertainty of the results was estimated by probabilistic bootstrapping. RESULTS: The average cost of coil treatment in both groups was estimated at euro24,356. The average total cost at 2 years was euro9655 higher in the first-line coil treatment group ( $p = 0.07$ ) and the difference in QALY between the two groups was 0.127 ( $p = 0.12$ ) in favor of first-line coil treatment group. The 2-year incremental cost-effectiveness ratio (ICER) was euro75,978 / QALY. The scatter plot of the probabilistic bootstrapping had 92% of the replications in the top right-hand quadrant. CONCLUSION: First-line coil treatment was more expensive but also more effective than second-line coil treatment at 2 years, with a 2-year ICER of euro75,978 / QALY. TRIAL REGISTRATION: ClinicalTrials.gov Identifier NCT01822795 .

Canonne, A. M., I. Peters, et al. (2018). **"Detection of specific bacterial agents by quantitative PCR assays in the bronchoalveolar lavage fluid of dogs with eosinophilic bronchopneumopathy vs. dogs with chronic bronchitis and healthy dogs."** *Vet J* 232: 52-56.

In humans, *Mycoplasma pneumoniae* and *Bordetella pertussis* infections are suggested to trigger or exacerbate asthma. Whether *Mycoplasma* or *Bordetella* are associated with chronic inflammatory bronchial diseases in dogs has not been investigated. The aim of this study was to assess detection rates of *Mycoplasma canis* (*M. canis*), *M. cynos* and *Bordetella bronchiseptica* (*Bb*), in dogs with eosinophilic bronchopneumopathy (EBP) and chronic bronchitis (CB), compared with healthy dogs. Specific quantitative PCR (qPCR) analysis for *M. canis*, *M.*

cynos and Bb were retrospectively performed on bronchoalveolar lavage fluid (BALF) collected from 24 dogs with EBP, 21 dogs with CB and 15 healthy dogs. Possible associations between qPCR results and age, BALF cytology or clinical severity scores (CSS) in dogs with EBP were investigated. There was no difference in *M. canis*, *M. cynos* and Bb detection rates in dogs with EBP (n=6, n=2 and n=6, respectively) and dogs with CB (n=2, n=2 and n=2, respectively) compared with control dogs (n=4, n=2 and n=2, respectively). In dogs with EBP, the proportion that were qPCR-positive for Bb was higher in dogs with higher CSS (P=0.014) and BALF from Bb-positive dogs had higher percentage of neutrophils (P<0.001). Among dogs that were qPCR-positive for Bb, moderate to high loads were only detected in dogs with EBP. *M. canis* and *M. cynos* detection was not associated with EBP or CB; higher Bb loads were only present in dogs with EBP and high CSS. A possible cause and effect relationship between Bb infection or load and EBP remains unclear and requires further investigation.

Cao, T., N. Xu, et al. (2017). **"Effects of Glutathione S-Transferase Gene Polymorphisms and Antioxidant Capacity per Unit Albumin on the Pathogenesis of Chronic Obstructive Pulmonary Disease."** Oxid Med Cell Longev **2017**: 6232397.

**OBJECTIVES:** To study the effects of GSTM1, GSTT1 gene polymorphisms, and organism antioxidant capacity and related indicators such as antioxidant capacity per unit of albumin (AC/ALB) on chronic obstructive pulmonary disease (COPD). **METHODS:** Using polymerase chain reaction technology, GSTM1 and GSTT1 gene polymorphisms were detected in 33 COPD patients and 33 healthy people. The total antioxidant capacity (TAC) found in serum was determined using the I2/KI potentiometric, KMnO4 microtitration, and H2O2 potentiometric methods. The AC/ALB was defined as the TAC divided by the serum albumin concentration. Logistic regression analysis was carried out with biochemical screening indices, which was found to be closely related with the incidence of COPD. **RESULTS:** The GSTM1 and GSTT1 gene deletion rate in the COPD group was significantly higher than that in the control group (P < 0.05). The differences in serum TAC between the COPD and control groups, GSTM1 (+) and GSTM1 (-) groups, and GSTT1 (+) and GSTT1 (-) groups were statistically significant (P < 0.001). In addition, there was a significant difference in the AC/ALB between the COPD and control groups (P < 0.05). Logistic regression analysis showed that the incidence of COPD was closely related to the AC/ALB (P < 0.05). **CONCLUSIONS:** GSTM1 and GSTT1 gene polymorphisms are closely correlated with the pathogenesis of COPD, while the AC/ALB plays a decisive role in the occurrence and development of COPD.



Cao, Y. Q., L. X. Dong, et al. (2018). "**Pulmonary Embolism in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease.**" Chin Med J (Engl) **131**(14): 1732-1737.

**Objective:** In most countries, nearly 6% of the adults are suffering from chronic obstructive pulmonary disease (COPD), which puts a huge economic burden on the society. Moreover, COPD has been considered as an independent risk factor for pulmonary embolism (PE). In this review, we summarized the existing evidence that demonstrates the associations between COPD exacerbation and PE from various aspects, including epidemiology, pathophysiological changes, risk factors, clinical features, management, and prognosis. **Data Sources:** We searched the terms "chronic obstructive pulmonary disease," "pulmonary embolism," "exacerbations," and "thromboembolic" in PubMed database and collected the results up to April 2018. The language was limited to English. **Study Selection:** We thoroughly examined the titles and abstracts of all studies that met our search strategy. The data from prospective studies, meta-analyses, retrospective studies, and recent reviews were selected for preparing this review. **Results:** The prevalence of PE in patients with COPD exacerbation varied a lot among different studies, mainly due to the variations in race, sample size, study design, research setting, and enrollment criteria. Overall, whites and African Americans showed significantly higher prevalence of PE than Asian people, and the hospitalized patients showed higher prevalence of PE compared to those who were evaluated in emergency department. PE is easily overlooked in patients with COPD exacerbation due to the similar clinical symptoms. However, several factors have been identified to contribute to the increased risk of PE during COPD exacerbation. Obesity and lower limb asymmetry were described as independent predictors for PE. Moreover, due to the high risk of PE, thromboprophylaxis has been used as an important treatment for hospitalized patients with COPD exacerbation. **Conclusions:** According to the previous studies, COPD patients with PE experienced an increased risk of death and prolonged length of hospital stay. Therefore, the thromboembolic risk in patients with acute exacerbation of COPD, especially in the hospitalized patients, should carefully be evaluated.

Carr, L. L., S. Jacobson, et al. (2018). "**Features of COPD as Predictors of Lung Cancer.**" Chest **153**(6): 1326-1335.

**BACKGROUND:** Lung cancer is a leading cause of death and hospitalization for patients with COPD. A detailed understanding of which clinical features of COPD increase risk is needed. **METHODS:** We performed a nested case-control study of Genetic Epidemiology of COPD (COPDGene) Study subjects with and without lung cancer, age 45 to 80 years, who smoked at least 10-pack years to identify clinical and imaging features of smokers, with and without COPD, that are associated with an increased risk of lung cancer. The baseline evaluation included spirometry, high-resolution chest CT scanning, and respiratory questionnaires. New lung cancer diagnoses were identified over 8 years of longitudinal follow-up. Cases of lung cancer were matched 1:4 with control subjects for age, race, sex, and smoking history. Multiple logistic regression analyses were used to determine features predictive of lung cancer. **RESULTS:**

Features associated with a future risk of lung cancer included decreased FEV1/FVC (OR, 1.28 per 10% decrease [95% CI, 1.12-1.46]), visual severity of emphysema (OR, 2.31, none-trace vs mild-advanced [95% CI, 1.41-3.86]), and respiratory exacerbations prior to study entry (OR, 1.39 per increased events [0, 1, and  $\geq 2$ ] [95% CI, 1.04-1.85]). Respiratory exacerbations were also associated with small-cell lung cancer histology (OR, 3.57 [95% CI, 1.47-10]). CONCLUSIONS: The degree of COPD severity, including airflow obstruction, visual emphysema, and respiratory exacerbations, was independently predictive of lung cancer. These risk factors should be further studied as inclusion and exclusion criteria for the survival benefit of lung cancer screening. Studies are needed to determine if reduction in respiratory exacerbations among smokers can reduce the risk of lung cancer.

Chalise, S. N., H. T. Shaheen, et al. (2016). **"Pulmonary Rehabilitation: A Retrospective Study in Eastern North Carolina."** N C Med J 77(5): 314-8.

BACKGROUND: Pulmonary rehabilitation (PR) is an evidence-based measure to benefit chronic obstructive pulmonary disease (COPD) patients. Many patients have benefitted from our robust university hospital-based PR program. We have objectively assessed the benefit of our PR program for COPD patients in Eastern North Carolina. METHODS: We used retrospective chart review to collect data from all the patients who completed PR from January 1, 2012 through December 31, 2013. Data collection included quality-of-life scores using short-form 36 (SF-36) and 6-minute walk distance (6MWD) to measure exercise capacity before and after PR. We also collected data on COPD exacerbation frequency 1 year before and 1 year after PR. The data were analyzed using the statistical software Statistical Package for the Social Sciences version 22.0. RESULTS: We analyzed data from 51 patients with 4 categories of COPD: mild (n = 2), moderate (n = 12), severe (n = 23), and very severe (n = 14). The PR program resulted in improvement in 6MWD of an average of 263.8 feet (P < .01) and a decrease in COPD exacerbation frequency by 0.3 events per year (P < .05). There were mixed results for quality-of-life scores. LIMITATIONS: Our study was conducted at 1 center and thus involved a single COPD patient population with limited sample size. We did not follow patients long term to see whether the benefits were sustained. CONCLUSIONS: Our PR program resulted in a positive impact on exercise capacity, COPD exacerbation rate, and some aspects of quality of life.

Chen, J. Z., I. M. Katz, et al. (2017). **"Comparison of pulsed versus continuous oxygen delivery using realistic adult nasal airway replicas."** Int J Chron Obstruct Pulmon Dis 12: 2559-2571.

BACKGROUND: Portable oxygen concentrators (POCs) typically include pulse flow (PF) modes to conserve oxygen. The primary aims of this study were to develop

a predictive in vitro model for inhaled oxygen delivery using a set of realistic airway replicas, and to compare PF for a commercial POC with steady flow (SF) from a compressed oxygen cylinder. **METHODS:** Experiments were carried out using a stationary compressed oxygen cylinder, a POC, and 15 adult nasal airway replicas based on airway geometries derived from medical images. Oxygen delivery via nasal cannula was tested at PF settings of 2.0 and 6.0, and SF rates of 2.0 and 6.0 L/min. A test lung simulated three breathing patterns representative of a chronic obstructive pulmonary disease patient at rest, during exercise, and while asleep. Volume-averaged fraction of inhaled oxygen (FiO<sub>2</sub>) was calculated by analyzing oxygen concentrations sampled at the exit of each replica and inhalation flow rates over time. POC pulse volumes were also measured using a commercial O<sub>2</sub> conserver test system to attempt to predict FiO<sub>2</sub> for PF. **RESULTS:** Relative volume-averaged FiO<sub>2</sub> using PF ranged from 68% to 94% of SF values, increasing with breathing frequency and tidal volume. Three of 15 replicas failed to trigger the POC when used with the sleep breathing pattern at the 2.0 setting, and four of 15 replicas failed to trigger at the 6.0 setting. FiO<sub>2</sub> values estimated from POC pulse characteristics followed similar trends but were lower than those derived from airway replica experiments. **CONCLUSION:** For the POC tested, PF delivered similar, though consistently lower, volume-averaged FiO<sub>2</sub> than SF rates equivalent to nominal PF settings. Assessment of PF oxygen delivery using POC pulse characteristics alone may be insufficient; testing using airway replicas is useful in identifying possible cases of failure and may provide a better assessment of FiO<sub>2</sub>.

Chiba, S., K. Tsuchiya, et al. (2017). "**Interstitial changes in asthma-COPD overlap syndrome.**" *Clin Respir J* 11(6): 1024-1031.

**INTRODUCTION:** Asthma-COPD overlap syndrome (ACOS) is the widely recognized syndrome of asthma and COPD coexisting together. Cigarette smoking is a known risk factor for ACOS and is reported to be associated with interstitial lung diseases (ILDs). Subclinical ILDs have been frequently detected in smokers' lungs by radiological and pathological examinations. This finding raises the possibility that unrecognized mild interstitial changes take place in lungs with ACOS. **OBJECTIVES:** We sought to determine whether interstitial changes were present in the lungs of patients with ACOS and to characterize the clinical features of ACOS with interstitial changes. **METHODS:** Thirty patients with ACOS were enrolled in the study (26 men and 4 women, mean age 70.1 years). Interstitial changes in the lungs were estimated by high-resolution computed tomography (HRCT). Clinical findings and airway wall thickness on HRCT were assessed retrospectively and compared between ACOS patients with and without interstitial changes. **RESULTS:** Interstitial changes were found in seven patients (23.3%) with ACOS who had HRCT. The age and smoking amount were significantly higher in ACOS with interstitial changes than in ACOS without interstitial changes. ACOS with interstitial changes tended to have a higher rate of fungal sensitisation. Multivariate analysis showed pack-years were significantly related to the presence of interstitial changes. Airway walls assessed by HRCT were significantly thicker in ACOS with interstitial changes than in ACOS without interstitial changes. **CONCLUSIONS:** The ACOS patients with interstitial changes

were heavier smokers and had thicker airway walls on HRCT compared to the ACOS patients without interstitial changes.

Chung, W. S. and C. L. Lin (2018). "**Acute respiratory events in patients with bronchiectasis-COPD overlap syndrome: A population-based cohort study.**" Respir Med **140**: 6-10.

BACKGROUND: The clinical phenotypes of chronic obstructive pulmonary disease (COPD) are related to various outcomes. We investigated the risk of acute respiratory events in patients with bronchiectasis-COPD overlap syndrome (BCOS) in Taiwan. METHODS: We included 3955 patients who received diagnoses of COPD and bronchiectasis from 2000 to 2007 from the Taiwan Longitudinal Health Insurance Database in the BCOS cohort. In the comparison cohort, we included patients with COPD but without bronchiectasis at a ratio of 4:1, frequency matched by age, sex, and index year with each patient with BCOS. We followed both cohorts for 5 years to investigate the incidence and risk of acute respiratory events in the BCOS cohort relative to the comparison cohort, the incidence rate ratios (IRRs) and corresponding 95% confidence intervals (CIs) were determined using Poisson regression models. RESULTS: The BCOS cohort experienced more episodes of acute respiratory events than did the comparison cohort (16.4 vs 5.52 per 100 person-y). After adjustment for potential covariates, the BCOS cohort had a 2.20-fold higher risk of pneumonia (adjusted IRR=2.20, 95% CI=2.06-2.34), a 3.88-fold higher risk of acute exacerbation (adjusted IRR=3.88, 95% CI=3.64-4.13), a 1.74-fold higher risk of acute respiratory failure (adjusted IRR=1.74, 95% CI=1.47-2.06), and a 1.99-fold higher risk of cardiopulmonary arrest (adjusted IRR=1.99, 95% CI=1.81-2.20) than did the comparison cohort. CONCLUSION: The patients with BCOS had a higher risk of acute respiratory events than did COPD patients without bronchiectasis.

Citgez, E., M. Zuur-Telgen, et al. (2018). "**Stable-State Midrange Proadrenomedullin Is Associated With Severe Exacerbations in COPD.**" Chest **154**(1): 51-57.

BACKGROUND: Elevated levels of midrange proadrenomedullin (MR-proADM) are associated with worse outcome in different diseases, including COPD. The association of stable-state MR-proADM with severe acute exacerbations of COPD (AECOPDs) requiring hospitalization, or with community-acquired pneumonia (CAP) in patients with COPD, has not been studied yet. The aim of this study was to evaluate the association of stable-state MR-proADM with severe AECOPD and CAP in patients with COPD. METHODS: This study pooled data of 1,285 patients from the Cohort of Mortality and Inflammation in COPD (COMIC) and PRedicting Outcome using systemic Markers In Severe Exacerbations of Chronic Obstructive Pulmonary Disease (PROMISE-COPD) cohort studies. Time until first severe AECOPD was compared between patients with high ( $\geq 0.87$  nmol/L) or low ( $< 0.87$  nmol/L) levels of plasma MR-proADM

in stable state as previously defined. For time until first CAP, only COMIC data (n = 795) were available. **RESULTS:** Patients with COPD with high-level stable-state MR-proADM have a significantly higher risk for severe AECOPD compared with those with low-level MR-proADM with a corrected hazard ratio (HR) of 1.30 (95% CI, 1.01-1.68). Patients with high-level stable-state MR-proADM had a significantly higher risk for CAP compared with patients with COPD with low-level MR-proADM in univariate analysis (HR, 1.93; 95% CI, 1.24-3.01), but after correction for age, lung function, and previous AECOPD, the association was no longer significant (corrected HR, 1.10; 95% CI, 0.68-1.80). **CONCLUSIONS:** Stable-state high-level MR-proADM in patients with COPD is associated with severe AECOPD but not with CAP.

Criner, G. J., M. Dreher, et al. (2018). **"COPD Home Oxygen Therapy and Home Mechanical Ventilation: Improving Admission-Free Survival in Persistent Hypercapnic COPD."** *Chest* **153**(6): 1499-1500.

As seen in this CME online activity (available at <http://journal.cme.chestnet.org/copd-hot-hmv>), acute exacerbations of COPD are associated with significant levels of morbidity and mortality. Acute noninvasive ventilation has been demonstrated its clinical efficacy and cost-effectiveness in reducing intubation rate and mortality and in patients with acute decompensated hypercapnic exacerbations of COPD. However, those patients with evidence of chronic hypercapnic respiratory failure have worse long-term outcomes compared with patients who have only transient hypercapnia during the acute phase returning to eucapnia in the recovery stage. Indeed, there are limited options available to improve the clinical outcome in these COPD patients with persistent hypercapnia. The Home Oxygen Therapy-Home Mechanical Ventilation (HOT-HMV) trial investigated admission-free survival in patients with persistent hypercapnia following a life-threatening exacerbation requiring acute noninvasive ventilation. Phenotyping patients to ensure chronic hypercapnia enriched the trial population to identify those patients at highest risk of readmission or death following an exacerbation. The addition of home noninvasive ventilation to home oxygen therapy in patients with persistent hypercapnia led to improved admission-free survival. The noninvasive ventilation was titrated to overnight measures of transcutaneous CO<sub>2</sub> to achieve control of nocturnal hypoventilation, which improved daytime chronic respiratory failure. Home noninvasive ventilation is a complex intervention requiring a multidisciplinary team and long-term patient follow-up to maximize the clinical benefit to the patient.

Crisafulli, E., M. Guerrero, et al. (2018). **"Impact of bronchiectasis on outcomes of hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease: A propensity matched analysis."** *Sci Rep* **8**(1): 9236.

The coexistence of both Chronic Obstructive Pulmonary Disease (COPD) and bronchiectasis (BE) define an emerging phenotype with a worse prognosis; however, data about these patients do not consider baseline characteristics as confounders. We evaluate the impact of BE on outcomes of hospitalized patients with acute exacerbation of COPD (AECOPD). We prospectively considered AECOPD patients, analysed using a propensity score matching (PSM) method. The outcomes included length of hospital stay, use of non-invasive and invasive mechanical ventilation, intensive care unit admission, and mortality up to 3-years. Out of the 449 patients enrolled, 160 had associated BE. AECOPD with BE were older, had lower body mass index and greater functional impairment and severity of symptoms than AECOPD without BE. After PSM, 91 patients were considered for each group and no significant differences were found for all baseline characteristics. In full cohort, the cumulative mortality rate, the survival time, the Kaplan-Meier survival curves and the risk of death were worse in AECOPD with BE in the follow-up of 6-months, 1-year and 3-years. After PSM, data on mortality were similar between AECOPD with and without BE. In conclusion, in AECOPD patients the presence of BE does not influence mortality in a long-term follow-up.

de Miguel-Diez, J., A. Lopez-de-Andres, et al. (2017). **"Impact of COPD on outcomes in hospitalized patients with community-acquired pneumonia: Analysis of the Spanish national hospital discharge database (2004-2013)."** Eur J Intern Med **43**: 69-76.

AIM: To examine trends in incidence and outcomes of community-acquired pneumonia (CAP) hospitalizations among patients with or without COPD in Spain (2004-2013). METHODS: We used national hospital discharge data to select all hospital admissions for CAP. Incidence was calculated overall and according to the presence or absence of COPD. RESULTS: We identified 901,136 hospital admissions for CAP (32.25% with COPD). Incidence of hospitalizations of CAP increased significantly over time among patients with and without COPD, but it was higher among people with COPD for all years analyzed. *S. pneumoniae* decreased over time for both groups. Time trend analyses showed significant decreases in mortality during admission for CAP for patients with and without COPD. Factor independently associated with higher mortality in both groups included: male sex, older age, higher comorbidity, isolation of *S. aureus* or *P. aeruginosa*, use of mechanical ventilation, and readmission. The presence of COPD was associated with a lower in-hospital mortality (IHM) (OR: 0.58, 95%CI 0.57-0.59). CONCLUSIONS: The incidence of hospitalizations for CAP increased over time in patients with and without COPD, being higher in the COPD population for all years analyzed. IHM decreased over time in both groups. There were no differences in mortality between COPD and non-COPD patients.

Dursunoglu, N., D. Dursunoglu, et al. (2017). **"Severity of coronary atherosclerosis in patients with COPD."** Clin Respir J 11(6): 751-756.

**BACKGROUND AND AIMS:** Chronic obstructive pulmonary disease (COPD) has many comorbidities such as coronary artery disease (CAD) and stroke. Chronic low-grade systemic inflammation and oxidative stress play a significant role in CAD and COPD. We analysed that impact of COPD on intensity and severity of coronary artery lesions on the angiogram in the groups of patients with COPD according to the Global Initiative for Obstructive Lung Disease (GOLD) grades updated in 2015. **METHODS:** The study included 102 COPD patients and 80 randomly selected subjects without any pulmonary disease who underwent coronary angiography. According to the GOLD grade for COPD, patients were divided into four groups: A, B, C and D. The severity and extent of CAD were determined using the Gensini score. **RESULTS:** There were no significant between-group differences in age, body mass index, smoking history, plasma lipids levels, frequency of hypertension, diabetes and CAD. The mean Gensini score in patients with COPD was significantly higher than those without (respectively, 25.7 +/- 32.9 vs 17.5 +/- 24.8,  $P = 0.01$ ). While Gensini score was the highest level in the patient group D (64.9 +/- 34.9), it was the lowest level in the patient group A (10.2 +/- 19.4,  $P = 0.0001$ ). The Gensini scores increased in accordance with increases in the GOLD grades. We observed that COPD was independently predictive for Gensini score after a multi-variate logistic regression analysis (odds ratio 1.374; 95% confidence interval 1.672-9.232;  $P = 0.001$ ). **CONCLUSION:** Severity and intensity of coronary atherosclerosis increases in accordance with increases in the GOLD grades for COPD.

Edriss, H., K. Selvan, et al. (2017). **"Glucose Levels in Patients With Acute Respiratory Failure Requiring Mechanical Ventilation."** J Intensive Care Med 32(10): 578-584.

**BACKGROUND:** Recent studies suggest that patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) frequently develop hyperglycemia, which has been linked to adverse outcomes. **METHODS:** We retrospectively collected information about patient demographics, admission diagnosis, comorbidities, use of insulin, and glucose levels and related tests in 174 patients who required mechanical ventilation for acute respiratory failure. **RESULTS:** These patients had a mean age of 57.8 +/- 16.8 years, a mean Acute Physiology and Chronic Health Evaluation (APACHE II) score of 13.8 +/- 6.1, and an overall mortality of 32.2%. The mean number of ventilator days was 7.5 +/- 7.1. The mean highest glucose level was 239.3 +/- 88.9 mg/dL in patients with COPD ( $n = 41$ ) and 259.1 +/- 131.7 mg/dL in patients without COPD ( $n = 133$ ). Patients with diabetes had higher glucose levels than patients without this diagnosis ( $P < .05$ ). Patients receiving corticosteroids did not have increased glucose levels ( $P > .05$ ). The mortality rate was higher in patients with glucose levels  $>140$  mg/dL than in patients below 140 mg/dL (35.1% vs 10.5%,  $P < .05$  unadjusted analysis). **CONCLUSION:** In this study, hyperglycemia occurred in 89% of the patients with acute respiratory failure requiring mechanical ventilation. The most important risk factor for this was a premorbid diagnosis of diabetes.

Ekstrom, M., Z. Ahmadi, et al. (2017). **"A nationwide structure for valid long-term oxygen therapy: 29-year prospective data in Sweden."** Int J Chron Obstruct Pulmon Dis **12**: 3159-3169.

Background: Long-term oxygen therapy (LTOT) improves prognosis in COPD with severe hypoxemia. However, adherence to criteria for eligibility and quality of LTOT is often insufficient and varies between countries. The aim of this study was to evaluate a national structure for prescription and management of LTOT over three decades in Sweden. Methods: The study was a prospective, population-based study of 23,909 patients on LTOT from 1987 to 2015 in the Swedish National Register of Respiratory Failure (Swedevox). We assessed the prevalence, incidence, and structure of LTOT; completeness of registration in Swedevox; and validity of prescription and management of LTOT in Sweden according to seven published quality indicators. Results: LTOT was prescribed by 48 respiratory or medicine units and managed mainly by specialized oxygen nurses. Swedevox had a stable completeness of 85% of patients starting LTOT since 1987. The national incidence of LTOT increased from 3.9 to 14.7/100,000 inhabitants over the time period. In 2015, 2,596 patients had ongoing therapeutic LTOT in the registry, a national prevalence of 31.6/100,000. Adherence to prescription recommendations and fulfillment of quality criteria was stable or improved over time. Of patients starting LTOT in 2015, 88% had severe hypoxemia (partial pressure of arterial oxygen [PaO<sub>2</sub>] <7.4 kPa) and 97% had any degree of hypoxemia (PaO<sub>2</sub> <8.0 kPa); 98% were prescribed oxygen ≥15 hours/day or more; 76% had both stationary and mobile oxygen equipment; 75% had a mean PaO<sub>2</sub> >8.0 kPa breathing oxygen; and 98% were non-smokers. Conclusion: We present a structure for prescription, management, and follow-up of LTOT. The national registry effectively monitored adherence to prescription recommendations and most likely contributed to improved quality of care.

Estirado, C., A. Ceccato, et al. (2018). **"Microorganisms resistant to conventional antimicrobials in acute exacerbations of chronic obstructive pulmonary disease."** Respir Res **19**(1): 119.

BACKGROUND: Antimicrobial treatment for acute exacerbations of chronic obstructive pulmonary disease (AECOPD) remains controversial. In some cases AECOPD are caused by microorganisms that are resistant to treatments recommended by guidelines. Our aims were: 1) identify the risk factors associated with infection by microorganisms resistant to conventional treatment (MRCT), 2) Compare the clinical characteristics and outcomes of patients with AECOPD resulting from MRCT against those with AECOPD from other causes. METHODS: We prospective analysed a cohort of patients admitted with severe AECOPD (2009 to 2015) who were assigned to three groups: patients with MRCT (those patients with germs resistant to antibiotics recommended in guidelines), patients with microorganisms sensitive to conventional antimicrobial treatment (MSCT), and



patients with negative microbiology results who had not previously received antibiotics. Multinomial logistic regression analyses were used to examine the associations between microbial aetiology groups and risk factors. The association between LOS and risk factors was also tested in simple and multiple analyses, and similar inclusion criteria were applied for the linear regression analysis. RESULTS: Of the 451 patients admitted, 195 patients (43%) were included. Respiratory cultures were positive in 86(44%) and negative in 109(56%). MRCT were isolated in 34 cases (40%) and MSCT in 52 (60%). Patients with MRCT had more AECOPD in the previous year, received more antibiotic treatment in the previous three months, had more severe disease, higher dyspnoea and a positive respiratory culture in the previous year (mainly for *Pseudomonas aeruginosa*). The following conditions were independent factors for MRCT isolation: non-current smoker (odds ratio [OR] 4.19 [95% confidence interval [CI] 1.29-13.67],  $p = 0.017$ ),  $\geq 2$  AECOPD or  $\geq 1$  admission for AECOPD in the previous year (OR 4.13 [95% CI 1.52-11.17],  $p = 0.005$ ), C-reactive protein  $< 5$  mg/dL; (OR 3.58 [95% CI 1.41-9.07],  $p = 0.007$ ). Mortality rates were comparable at 30-days, one year and 3 years; however, patients in the MRCT group had longer hospital stays. CONCLUSION: In conclusion, there are risk factors for resistant germs in AECOPD; however, the presence of these germs does not increase mortality. Patients with isolation of MRCT had longer length of stay.

Faerk, G., Y. Colak, et al. (2018). **"Low concentrations of 25-hydroxyvitamin D and long-term prognosis of COPD: a prospective cohort study."** *Eur J Epidemiol* **33**(6): 567-577.

Role and importance of vitamin D deficiency in long-term prognosis of chronic obstructive pulmonary disease (COPD) still remains undetermined. We tested the hypothesis that among individuals with COPD, those with low concentrations of 25-hydroxyvitamin D have a poorer prognosis compared to those with normal concentrations. We studied 35,153 individuals from the general population aged 20-100 years with 25-hydroxyvitamin D measurements and spirometry, the Copenhagen City Heart Study [median follow-up 21 years (range 13 days-36 years)] and the Copenhagen General Population Study [7.1 years (3 days-13 years)]. Spirometric COPD ( $n = 5178$ ; 15% of all) was defined as forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC)  $< 0.70$  in individuals without asthma and clinical COPD ( $n = 2033$ ; 6%) as FEV1/FVC  $< 0.70$  and FEV1  $< 80\%$  of predicted in ever-smokers aged  $> 40$  years without asthma and with cumulative tobacco consumption  $\geq 10$  pack-years. In spirometric COPD, median age at death in years was 70.2 (95% confidence interval [CI] 64.4-71.2) for individuals with 25-hydroxyvitamin D  $< 12.5$  nmol/L and 80.3 (74.4-83.4) for those with  $\geq 50$  nmol/L. In clinical COPD, corresponding values were 69.0 (63.3-70.9) and 76.2 (73.8-78.0). In spirometric COPD, multivariable adjusted hazard ratios for individuals with 25-hydroxyvitamin D  $< 12.5$  nmol/L versus those with  $\geq 50$  nmol/L were 1.35 (95% CI 1.09-1.67) for all-cause mortality, 1.63 (1.00-2.64) for respiratory mortality, 1.14 (0.76-1.70) for cardiovascular mortality, 1.37 (0.90-2.06) for cancer mortality, and 1.61 (1.04-2.49) for other mortality. In clinical COPD, corresponding values were 1.39 (1.07-1.82), 1.57 (0.91-2.72),

0.88 (0.51-1.53), 1.63 (0.99-2.67), and 2.00 (1.12-3.56). Low concentrations of 25-hydroxyvitamin D were associated with an increased risk of death in individuals with COPD. No clear pattern of association could be observed for cause of death; however, there may be an increased risk of respiratory, cancer, and other mortality. It is likely that low concentrations of 25-hydroxyvitamin D is a marker of poor health in COPD.

Fahndrich, S., F. Biertz, et al. (2017). **"Cardiovascular risk in patients with alpha-1-antitrypsin deficiency."** Respir Res **18**(1): 171.

BACKGROUND: Alpha-1-antitrypsin deficiency (AATD) is a rare inherited condition caused by mutations of the SERPINA1 gene that is associated with the development of a COPD like lung disease. The comorbidities in patients with AATD-related lung diseases are not well defined. The aim of this study was to analyze the clinical phenotype of AATD patients within the German COPD cohort study COSYCONET ("COPD and SYstemic consequences-COMorbidities NETwork") cohort focusing on the distribution of comorbidities. METHOD AND RESULTS: The data from 2645 COSYCONET patients, including 139 AATD patients (110 with and 29 without augmentation therapy), were analyzed by descriptive statistics and regression analyses. We found significantly lower prevalence of cardiovascular comorbidities in AATD patients as compared to non-AATD COPD patients. After correction for age, pack years, body mass index, and sex, the differences were still significant for coronary artery disease ( $p = 0.002$ ) and the prevalence of peripheral artery disease as determined by an ankle-brachial-index  $\leq 0.9$  ( $p = 0.035$ ). Also the distribution of other comorbidities such as bronchiectasis differed between AATD and non-deficient COPD. CONCLUSION: AATD is associated with a lower prevalence of cardiovascular disease, the underlying mechanisms need further investigation.

Feng, J. F., G. R. Ding, et al. (2018). **"Efficacy of budesonide/formoterol and tiotropium combination for the treatment of Chinese patients with chronic obstructive pulmonary disease."** Medicine (Baltimore) **97**(22): e10841.

This study investigated the efficacy and safety of budesonide/formoterol (B/F) and tiotropium combination in the management of chronic obstructive pulmonary disease (COPD) in Chinese patients. Between January 2015 and November 2017, 113 eligible Chinese patients with COPD were included and divided into an intervention group and a control group. Sixty-three patients in the intervention group underwent B/F combined tiotropium, while 50 patients in the control group received tiotropium alone. The primary outcome was severity of dyspnea on exertion (DOE), measured by the 6-minute walk test (6MWT) scale. The secondary outcomes included lung function, measured by the forced expiratory volume in 1 second (FEV1), quality of life, measured by the St. George's Respiratory Questionnaire (SGRQ), and adverse events. All outcomes were

measured at the end of 12-week treatment. B/F and tiotropium combination showed greater efficacy in DOE ( $P < .01$ ), lung function ( $P < .01$ ), and quality of life ( $P < .01$ ), compared with tiotropium alone at the end of 12-week treatment. In addition, adverse events in both groups were similar and tolerable. The findings suggest that B/F and tiotropium combination can be used as an effective treatment in Chinese patients with COPD.

Feng, Z., T. Wang, et al. (2017). **"Efficacy of Various Scoring Systems for Predicting the 28-Day Survival Rate among Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease Requiring Emergency Intensive Care."** *Can Respir J* 2017: 3063510.

We aimed to investigate the efficacy of four severity-of-disease scoring systems in predicting the 28-day survival rate among patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) requiring emergency care. Clinical data of patients with AECOPD who required emergency care were recorded over 2 years. APACHE II, SAPS II, SOFA, and MEDS scores were calculated from severity-of-disease indicators recorded at admission and compared between patients who died within 28 days of admission (death group; 46 patients) and those who did not (survival group; 336 patients). Compared to the survival group, the death group had a significantly higher GCS score, frequency of comorbidities including hypertension and heart failure, and age ( $P < 0.05$  for all). With all four systems, scores of age, gender, renal inadequacy, hypertension, coronary heart disease, heart failure, arrhythmia, anemia, fracture leading to bedridden status, tumor, and the GCS were significantly higher in the death group than the survival group. The prediction efficacy of the APACHE II and SAPS II scores was 88.4%. The survival rates did not differ significantly between APACHE II and SAPS II ( $P = 1.519$ ). Our results may guide triage for early identification of critically ill patients with AECOPD in the emergency department.

Fiorelli, A., R. Scaramuzzi, et al. (2017). **"Comparison of plethysmographic and helium dilution lung volumes in patients with a giant emphysematous bulla as selection criteria for endobronchial valve implant."** *Eur J Cardiothorac Surg* 52(3): 534-542.

**OBJECTIVES:** To assess whether the difference in lung volume measured with plethysmography and with the helium dilution technique could differentiate an open from a closed bulla in patients with a giant emphysematous bulla and could be used as a selection criterion for the positioning of an endobronchial valve. **METHODS:** We reviewed the data of 27 consecutive patients with a giant emphysematous bulla undergoing treatment with an endobronchial valve. In addition to standard functional and radiological examinations, total lung capacity and residual volume were measured with the plethysmographic and helium

dilution technique. We divided the patients into 2 groups, the collapse or the no-collapse group, depending on whether the bulla collapsed or not after the valves were put in position. We statistically evaluated the intergroup differences in lung volume and outcome. **RESULTS:** In the no-collapse group ( $n = 6$ ), the baseline plethysmographic values were significantly higher than the helium dilution volumes, including total lung capacity ( $188 \pm 14$  vs  $145 \pm 13$ ,  $P = 0.0007$ ) and residual volume ( $156 \pm 156$  vs  $115 \pm 15$ ,  $P = 0.001$ ). In the collapse group, there was no significant difference in lung volumes measured with the 2 methods. A difference in total lung capacity of  $\leq 13\%$  and in residual volume of  $\leq 25\%$  measured with the 2 methods predicted the collapse of the bulla with a success rate of 83% and 84%, respectively. Only the collapse group showed significant improvement in functional data. **CONCLUSIONS:** Similar values in lung volumes measured with the 2 methods support the hypothesis that the bulla communicates with the airway (open bulla) and thus is likely to collapse when the endobronchial valve is implanted. Further studies are needed to validate our model.

Fisher, J. A., R. C. Puett, et al. (2016). **"Particulate matter exposures and adult-onset asthma and COPD in the Nurses' Health Study."** *Eur Respir J* **48**(3): 921-4.

Fisk, M., J. Cheriyan, et al. (2018). **"Vascular inflammation and aortic stiffness: potential mechanisms of increased vascular risk in chronic obstructive pulmonary disease."** *Respir Res* **19**(1): 100.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is a complex inflammatory condition in which an important extra-pulmonary manifestation is cardiovascular disease. We hypothesized that COPD patients would have increased aortic inflammation and stiffness, as candidate mechanisms mediating increased cardiovascular risk, compared to two negative control groups: healthy never-smokers and smokers without COPD. We also studied patients with COPD due to alpha-1 antitrypsin deficiency (alpha1ATD) as a comparator lung disease group. **METHODS:** Participants underwent (18)F-Fluorodeoxyglucose (FDG) positron emission tomography imaging to quantify aortic inflammation as the tissue-to-blood-ratio (TBR) of FDG uptake. Aortic stiffness was measured by carotid-femoral aortic pulse wave velocity (aPWV). **RESULTS:** Eighty-five usual COPD (COPD due to smoking), 12 alpha1ATD-COPD patients and 12 each smokers and never-smokers were studied. There was no difference in pack years smoked between COPD patients and smokers ( $45 \pm 25$  vs  $37 \pm 19$ ,  $p = 0.36$ ), but alpha1ATD patients smoked significantly less ( $19 \pm 11$ ,  $p < 0.001$  for both). By design, spirometry measures were lower in COPD and alpha1ATD-COPD patients compared to smokers and never-smokers. Aortic inflammation and stiffness were increased in COPD (TBR:  $1.90 \pm 0.38$ , aPWV:  $9.9 \pm 2.6$

m/s) and alpha1ATD patients (TBR: 1.94 +/- 0.43, aPWV: 9.5 +/- 1.8 m/s) compared with smokers (TBR: 1.74 +/- 0.30, aPWV: 7.8 +/- 1.8 m/s,  $p < 0.05$  all) and never-smokers (TBR: 1.71 +/- 0.34, aPWV: 7.9 +/- 1.7 m/s,  $p \leq 0.05$  all). **CONCLUSIONS:** In this cross-sectional prospective study, novel findings were that both usual COPD and alpha1ATD-COPD patients have increased aortic inflammation and stiffness compared to smoking and never-smoking controls, regardless of smoking history. These findings suggest that the presence of COPD lung disease per se may be associated with adverse aortic wall changes, and aortic inflammation and stiffening are potential mechanisms mediating increased vascular risk observed in COPD patients.

Fujimoto, Y., Y. Oki, et al. (2017). **"Usefulness of the desaturation-distance ratio from the six-minute walk test for patients with COPD."** Int J Chron Obstruct Pulmon Dis **12**: 2669-2675.

**PURPOSE:** A straightforward, noninvasive method is needed to assess emphysema and pulmonary hypertension (PH) in COPD patients. The desaturation-distance ratio (DDR) is an index derived from the distance traveled and level of desaturation during a six-minute walk test (6MWT); it has previously been shown to be associated with percentage of forced expiratory volume in the first second of expiration (%FEV1.0) and percentage of diffusion capacity of the lung for carbon monoxide (%DLCO). The aim of this study was to examine the associations between DDR and emphysema and PH. **PATIENTS AND METHODS:** We collected the following data for 74 stable COPD outpatients: lung function tests (%FEV1.0 and %DLCO), 6MWT distance and desaturation, and area of emphysema on computed tomography (percentage of low attenuation area). Enlargement of the pulmonary artery (PA) was assessed by the ratio of the diameter of the PA to that of the aorta (PA:A ratio) as an index of PH. DDR was calculated by the distance traveled and the degree of desaturation reached during a 6MWT. The relationships between study outcomes were assessed with Spearman's rank-correlation analysis. Receiver operating characteristic (ROC) curves were used to determine the threshold values with the optimum cutoff points for predicting severe or very severe airway obstruction, pulmonary diffusing capacity disorder, moderate or severe emphysema, and enlargement of the PA. **RESULTS:** DDR correlated significantly with %FEV1.0, %DLCO, %LAA, and PA:A ratio. DDR showed high accuracy (area under the ROC curve  $>0.7$ ) for predicting severe or very severe airway obstruction, pulmonary diffusing capacity disorder, moderate or severe emphysema, and enlargement of the PA. **CONCLUSION:** The results suggest that DDR is a good index of emphysema and PH in COPD patients. The 6MWT is widely used to assess COPD, and DDR could help with the early diagnosis of COPD.

Gao, J., W. Zhou, et al. (2017). **"Sputum cell count: biomarkers in the differentiation of asthma, COPD and asthma-COPD overlap."** Int J Chron Obstruct Pulmon Dis **12**: 2703-2710.

**INTRODUCTION:** Cell count in induced sputum is a noninvasive biomarker to assess airway inflammation phenotypes. Accordingly, sputum cell counts are extensively used in the treatment of asthma and COPD. Nevertheless, the clinical application of sputum cell counts in patients with asthma-COPD overlap (ACO) remains elusive. The aim of this study was to investigate sputum cell counts in patients with ACO which are different from those in patients with asthma and COPD and also to examine the relationship between sputum cell counts in bronchial reversibility and bronchial hyperresponsiveness (BHR). **PATIENTS AND METHODS:** A total of 374 patients participated in the study, including 142 patients with asthma, 160 patients with COPD and 72 patients with ACO. All patients underwent the following tests on the same day: pulmonary function test (PFT), BHR test or bronchodilator reversibility test and inducing sputum. They were classified into the asthma group, COPD group or ACO group based on a clinical history, PFT values and BHR test or bronchodilator reversibility test. **RESULTS:** The three groups had different PFT values ( $p < 0.001$ ) except for forced vital capacity (FVC) between the asthma and ACO groups ( $p = 0.378$ ). The sputum levels of eosinophil% were decreased in patients with COPD when compared with those in patients with asthma and ACO ( $p < 0.001$  and  $p < 0.001$ , respectively). There was a difference in sputum neutrophil% and macrophage% counts among the three groups ( $p < 0.001$  and  $p < 0.001$ , respectively); there was no difference in sputum eosinophil% counts between patients with ACO and asthma ( $p = 0.668$ ) and there was no difference in the percentage of induced sputum cells between the stage of airway obstruction and the stage of BHR. **CONCLUSION:** The clinical relevance of this study provides evidence that sputum cell counts as an inflammatory biomarker could carry some information to distinguish ACO, asthma and COPD, and these biomarkers need more studies to provide diagnostic value in the differentiation between ACO, asthma and COPD.

Garcia, I. F. F., C. T. Tiuganji, et al. (2017). **"Systemic effects of chronic obstructive pulmonary disease in young-old adults' life-space mobility."** Int J Chron Obstruct Pulmon Dis **12**: 2777-2785.

**PURPOSE:** The objective was to assess whether dyspnea, peripheral muscle strength and the level of physical activity are correlated with life-space mobility of older adults with COPD. **PATIENTS AND METHODS:** Sixty patients over 60 years of age (40 in the COPD group and 20 in the control group) were included. All patients were evaluated for lung function (spirometry), life-space mobility (University of Alabama at Birmingham Study of Aging Life-Space Assessment), dyspnea severity (Modified Dyspnea Index), peripheral muscle strength (handgrip dynamometer), level of physical activity and number of daily steps (accelerometry). Groups were compared using unpaired t-test. Pearson's correlation was used to test the association between variables. **RESULTS:** Life-space mobility ( $60.41 \pm 16.93$  vs  $71.07 \pm 16.28$  points), dyspnea (8 [7-9] vs 11 [10-11] points), peripheral muscle strength ( $75.16 \pm 14.89$  vs  $75.50 \pm 15.13$  mmHg), number of daily steps ( $4,865.4 \pm 2,193.3$  vs  $6,146.8 \pm 2,376.4$  steps),

and time spent in moderate to vigorous activity (197.27+/-146.47 vs 280.05+/-168.95 minutes) were lower among COPD group compared to control group (p<0.05). The difference was associated with the lower mobility of COPD group in the neighborhood. **CONCLUSION:** Life-space mobility is decreased in young-old adults with COPD, especially at the neighborhood level. This impairment is associated to higher dyspnea, peripheral muscle weakness and the reduced level of physical activity.

Garcia-Lucio, J., V. I. Peinado, et al. (2018). **"Imbalance between endothelial damage and repair capacity in chronic obstructive pulmonary disease."** PLoS One **13**(4): e0195724.

**BACKGROUND:** Circulating endothelial microparticles (EMPs) and progenitor cells (PCs) are biological markers of endothelial function and endogenous repair capacity. The study was aimed to investigate whether COPD patients have an imbalance between EMPs to PCs compared to controls and to evaluate the effect of cigarette smoke on these circulating markers. **METHODS:** Circulating EMPs and PCs were determined by flow cytometry in 27 nonsmokers, 20 smokers and 61 COPD patients with moderate to severe airflow obstruction. We compared total EMPs (CD31+CD42b-), apoptotic if they co-expressed Annexin-V+ or activated if they co-expressed CD62E+, circulating PCs (CD34+CD133+CD45+) and the EMPs/PCs ratio between groups. **RESULTS:** COPD patients presented increased levels of total and apoptotic circulating EMPs, and an increased EMPs/PCs ratio, compared with nonsmokers. Women had less circulating PCs than men through all groups and those with COPD showed lower levels of PCs than both control groups. In smokers, circulating EMPs and PCs did not differ from nonsmokers, being the EMPs/PCs ratio in an intermediate position between COPD and nonsmokers. **CONCLUSIONS:** We conclude that COPD patients present an imbalance between endothelial damage and repair capacity that might explain the frequent concurrence of cardiovascular disorders. Factors related to the disease itself and gender, rather than cigarette smoking, may account for this imbalance.

Gawlitza, J., H. Haubenreisser, et al. (2018). **"Finding the right spot: Where to measure airway parameters in patients with COPD."** Eur J Radiol **104**: 87-93.

**PURPOSE:** The importance of spirometry for management of COPD was reduced in the 2017 revision of the GOLD report. CT derived airway measurements show strong correlations with lung function tests and symptoms. However, these correlations are specific to the airway localization, and currently there is no evidence for the ideal spot. Therefore, the aim of this prospective study was to systematically correlate CT derived airway measurements with extensive lung function testing. **METHODS AND MATERIALS:** 65 patients with diagnosed COPD underwent body plethysmography, impulse oscillometry and dose optimized qCT

examination (Somatom Force, Healthineers, Germany) in inspiration and expiration. Eight airway parameters (e.g. outer diameter, maximal wall thickness) were acquired for both scans in every lobe for the third to fifth generation bronchus and correlated with the lung function tests. RESULTS: The most significant correlations between airway parameters were found for the third generation bronchus of the upper left lobe during expiration (25 out of 48 correlation pairs, mean  $r=-0.39$ ) and for the third generation bronchus of the upper right lobe during inspiration (9 out of 48 correlation pairs, mean  $r=-0.25$ ). No significant correlations were for example found for the upper right lobe in expiration. CONCLUSION: Correlations between airway parameters and lung function tests vary widely between lobes, bronchus generations and breathing states. Our work suggests that the third generation bronchus of the upper left lobe in expiration could be the preferred localization for airway quantification in future studies.

Gershon, A. S., J. Hwee, et al. (2016). **"Factors associated with undiagnosed and overdiagnosed COPD."** Eur Respir J **48**(2): 561-4.

Gershon, A. S., D. Thiruchelvam, et al. (2018). **"Health Services Burden of Undiagnosed and Overdiagnosed COPD."** Chest **153**(6): 1336-1346.

BACKGROUND: Misdiagnosis of COPD is common. The goal of this study was to quantify the health services burden of undiagnosed and overdiagnosed COPD in a real-world, North American population. METHODS: A population-based cohort study was conducted. Presence of COPD using spirometry was ascertained in randomly selected adults aged  $\geq 40$  years from Ontario, Canada, who participated in the Canadian Obstructive Lung Disease study. The presence of physician-diagnosed COPD was ascertained for the same subjects by using linked health administrative data. Participants were then categorized into four groups: correctly diagnosed, undiagnosed, overdiagnosed, and no COPD according to either criteria. Age- and sex-standardized rates of hospitalizations, ED visits, and ambulatory care visits in each group were determined and compared. RESULTS: Of 1,403 participants, 13.7% had undiagnosed COPD, 5.1% were overdiagnosed, and 3.7% had correctly diagnosed COPD. Subjects with overdiagnosed COPD had significantly higher rates of hospitalizations, ED visits, and ambulatory care visits, and subjects with moderate to severe undiagnosed COPD had higher rates of hospitalizations, than subjects in the non-COPD population. CONCLUSIONS: Undiagnosed and overdiagnosed COPD contribute to significant health care burden. Given that misdiagnosed COPD was fivefold more common than correctly diagnosed COPD, these findings point to a substantial misdiagnosis-associated burden of disease that might be prevented, at least in part, with a correct diagnosis.



Godinas, L., J. L. Corhay, et al. (2017). **"Increased production of TGF-beta1 from sputum cells of COPD: Relationship with airway obstruction."** Cytokine **99**: 1-8.

Chronic obstructive pulmonary disease (COPD) is a chronic airway disease characterized by a profound airway remodelling that leads to airway obstruction. A role for transforming growth factor-beta1 (TGF-beta1) has been proposed in airway remodelling of COPD. Regarding the TGF-beta1 production at local level, the results seemed to be controversial. In this study, an original model of sputum cell culture thought to maintain important cells interactions, was used. We investigated the production of TGF-beta1 from sputum cell culture in 33 COPD encompassing the whole severity spectrum and compared the results with those found in 39 healthy controls. Sputum was induced by inhalation of saline, the cellular fraction cultured for 24 h and the spontaneous production of total TGF-beta1 was assessed by ELISA. Using, a TGF-beta1 reporter cell assay, we also compared the levels of active and total TGF-beta1 in the sputum cell culture supernatants of COPD and controls. Moreover, as a combination of tumor necrosis factor-alpha (TNF-alpha) and TGF-beta1 have been shown to have a cumulative impact on the severity of airflow limitation in COPD, the TNF-alpha release was also measured in a representative subgroup of patients. Our results indicated that the use of sputum cell culture was a reliable and reproducible method to assess TGF-beta1 production at airway level. Sputum cells from COPD produced greater amount of total TGF-beta1 than those of healthy controls ( $p < 0.001$ ). This result was confirmed using the cell reporter assay which also showed a higher level of active TGF-beta1 in the COPD group compared to controls. In addition, total TGF-beta1 production was increased according to GOLD stage and was inversely related to FEV1/FVC ratio ( $p < 0.05$ ). By contrast, the production of this growth factor was not correlated with the functional markers of emphysema nor with demographic characteristics such as age, BMI or smoking status. Interestingly, the production of total TGF-beta1 was inversely related to that of TNF-alpha ( $r = -0.53$ ,  $p < 0.05$ ) which was decreased in COPD. In summary, COPD patients displayed a raised production of total and active TGF-beta1 from their airway cells. Total TGF-beta1 correlates with the severity of airway obstruction without evidence of a link with emphysema. .

Godtfredsen, N. S., D. V. Jorgensen, et al. (2018). **"Soluble urokinase plasminogen activator receptor predicts mortality in exacerbated COPD."** Respir Res **19**(1): 97.

BACKGROUND: The inflammatory biomarker soluble urokinase plasminogen activator receptor (suPAR) is elevated in severe acute and chronic medical conditions and has been associated with short-term mortality. The role of suPAR in predicting risk of death following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has never been studied. We hypothesized that increased

suPAR is an independent predictor of short-term mortality in patients admitted to hospital with COPD or acute respiratory failure. **METHODS:** This retrospective cohort study from a university hospital in the Capital Region of Denmark included 2838 acutely admitted medical patients with COPD as primary (AECOPD) or secondary diagnosis, who had plasma suPAR measured at the time of admission between November 18th, 2013 to September 30th, 2015 and followed until December 31st, 2015. Primary outcomes were 30- and 90-days all-cause mortality. Association of suPAR and mortality was investigated by Cox regression analyses adjusted for age, sex, CRP values and Charlson comorbidity index. **RESULTS:** For patients with AECOPD or underlying COPD, median suPAR levels were significantly higher among patients who died within 30 days compared with those who survived (5.7 ng/ml (IQR 3.8-8.1) vs. 3.6 ng/ml (2.7-5.1),  $P < 0.0001$ ). Increasing suPAR levels independently predicted 30-day mortality in patients with COPD with a hazard ratio of 2.0 (95% CI 1.7-2.4) but not respiratory failure. **CONCLUSIONS:** In this large group of acutely admitted patients with COPD, elevated suPAR levels were associated with increased risk of mortality. The study supports the value of suPAR as a marker of poor prognosis.

Golpe, R., I. Martin-Robles, et al. (2017). **"Prevalence of Major Comorbidities in Chronic Obstructive Pulmonary Disease Caused by Biomass Smoke or Tobacco."** Respiration **94**(1): 38-44.

**BACKGROUND:** Comorbidities are very common in chronic obstructive pulmonary disease (COPD), contributing to the overall severity of the disease. The relative prevalence of comorbidities in COPD caused by biomass smoke (B-COPD), compared with COPD related to tobacco (T-COPD), is not well known. **OBJECTIVES:** To establish if both types of COPD are associated with a different risk for several major comorbidities. **METHOD:** The prevalence of comorbidities was compared in 863 subjects with B-COPD ( $n = 179$ , 20.7%) or T-COPD ( $n = 684$ , 79.2%). Multivariate analysis was carried out to explore the independent relationship between comorbidities and type of exposure. **RESULTS:** Three comorbidities were more frequent in T-COPD than in B-COPD: ischemic heart disease (11.5 vs. 5.0%, respectively,  $p = 0.01$ ), peripheral vascular disease (9.2 vs. 2.7%,  $p = 0.006$ ), and peptic ulcer disease (4.8% vs. 0,  $p = 0.005$ ). After correcting for potential confounding variables, the risk of ischemic heart disease was lower in B-COPD than in T-COPD (OR: 0.33, 95% CI: 0.16-0.69,  $p = 0.003$ ). **CONCLUSIONS:** The prevalence of ischemic heart disease is significantly lower in B-COPD than in T-COPD, suggesting a different systemic effect of both types of smoke in COPD patients.

Goto, T., M. K. Faridi, et al. (2018). **"Time-varying Readmission Diagnoses During 30 Days After Hospitalization for COPD Exacerbation."** *Med Care* **56**(8): 673-678.

**OBJECTIVE:** To investigate the longitudinal changes in principal readmission diagnoses within 30 days after hospitalization for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). **STUDY SETTING:** Medicare claims data, 2010-2012. **STUDY DESIGN:** Retrospective cohort study. **DATA COLLECTION METHODS:** We identified AECOPD hospitalizations aged 65 years and above, and examined the principal 30-day readmission diagnoses (respiratory related, cardiac related, and other conditions). We also constructed Joinpoint regression models to test whether patients with each of the 3 major readmission conditions had a unique temporal pattern of readmission during the 30-day period. **PRINCIPAL FINDINGS:** Among 76,697 index hospitalizations with AECOPD, 14,090 (18.4%) were readmitted within 30 days. Respiratory-related conditions accounted for 55% of readmissions. The proportion of respiratory-related conditions as the readmission diagnosis decreased from postdischarge day 1 to day 8 (4.0% decrease), and then increased thereafter (13.2% increase;  $P=0.06$ ). Cardiac-related conditions had a similar nonlinear trend with an inflection point at day 6 ( $P=0.02$ ), with a subsequent downward trend from day 22 ( $P=0.01$ ). By contrast, the other conditions increased from day 1 to day 6 (15.0% increase), and then significantly decreased (28.8% decrease;  $P=0.04$ ). **CONCLUSIONS:** The proportions of principal discharge diagnosis of readmission changed significantly at around postdischarge day 7. Our findings advance research into identification of the underlying mechanisms and development of targeted interventions to prevent readmissions.

Grote, L., D. Sommermeyer, et al. (2017). **"REM Sleep Imposes a Vascular Load in COPD Patients Independent of Sleep Apnea."** *Copd* **14**(6): 565-572.

Arterial stiffness, a marker for cardiovascular risk, is increased in patients with Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA). The specific influence of both on arterial stiffness during sleep is unknown. Nocturnal arterial stiffness (Pulse Propagation Time (PPT) of the finger pulse wave) was calculated in 142 individuals evaluated for sleep apnea: 27 COPD patients (64.7  $\pm$  11y, 31.2  $\pm$  8 kg/m<sup>2</sup>), 72 patients with cardiovascular disease (CVD group, 58.7  $\pm$  13y, 33.6  $\pm$  6 kg/m<sup>2</sup>) and 43 healthy controls (HC group 49.3  $\pm$  12y, 27.6  $\pm$  3 kg/m<sup>2</sup>). Sleep stage related PPT changes were assessed in a subsample of COPD patients and matched controls ( $n = 12/12$ ). Arterial stiffness during sleep was increased in COPD patients (i.e. shortened PPT) compared to healthy controls (158.2  $\pm$  31 vs. 173.2  $\pm$  38 ms,  $p = 0.075$ ) and to patients with CVD (161.4  $\pm$  41 ms). Arterial stiffening was particular strong during REM sleep (145.9  $\pm$  28 vs. 172.4  $\pm$  43 ms, COPD vs. HC,  $p = 0.003$ ). In COPD, time SaO<sub>2</sub> < 90% was associated with reduced arterial stiffness (Beta +1.7 ms (1.1-2.3)/10 min,  $p < 0.001$ ). Sleep apnea did not affect PPT. In COPD, but not in matched controls, arterial stiffness increased from wakefulness to REM-sleep (DeltaPPT-8.9  $\pm$  10% in COPD and 3.7  $\pm$  12% in matched controls,  $p = 0.021$ ). Moreover, REM-sleep related arterial stiffening was correlated with elevated daytime blood pressure ( $r = -0.92$ ,  $p < 0.001$ ) and

increased myocardial oxygen consumption ( $r = -0.88$ ,  $p < 0.01$ ). Hypoxia and REM sleep modulate arterial stiffness. In contrast to healthy controls, REM sleep imposes a vascular load in COPD patients independent of sleep apnea indices, intermittent and sustained hypoxia. The link between REM-sleep, vascular stiffness and daytime cardiovascular function suggests that REM-sleep plays a role for increased cardiovascular morbidity of COPD patients.

Gungor, S., F. Kargin, et al. (2018). **"Severity of acidosis affects long-term survival in COPD patients with hypoxemia after intensive care unit discharge."** Int J Chron Obstruct Pulmon Dis **13**: 1495-1506.

**Background:** Patients admitted to the intensive care unit (ICU) with acute respiratory failure (ARF) due to COPD have high mortality and morbidity. Acidosis has several harmful effects on hemodynamics and metabolism, and the current knowledge regarding the relationship between respiratory acidosis severity on the short- and long-term survival of COPD patients is limited. We hypothesized that COPD patients with severe acidosis would have a poorer short- and long-term prognosis compared with COPD patients with mild-to-moderate acidosis. **Patients and methods:** This retrospective observational cohort study was conducted in a level III respiratory ICU of a tertiary teaching hospital for chest diseases between December 1, 2013, and December 30, 2014. Subject characteristics, comorbidities, ICU parameters, duration of mechanical ventilation, length of ICU stay, ICU mortality, use of domiciliary noninvasive mechanical ventilation (NIMV) and long-term oxygen therapy (LTOT), and short- and long-term mortality were recorded. Patients were grouped according to their arterial blood gas (ABG) values during ICU admission: severe acidotic ( $\text{pH} \leq 7.20$ ) and mild-to-moderate acidotic ( $\text{pH} 7.21-7.35$ ). These groups were compared with the recorded data. The mortality predictors were analyzed by logistic regression test in the ICU and the Cox regression test for long-term mortality predictors. **Results:** During the study period, a total of 312 COPD patients admitted to the ICU with ARF, 69 (72.5% male) in the severe acidosis group and 243 (79% male) in the mild-to-moderate acidosis group, were enrolled. Group demographics, comorbidities, duration of mechanical ventilation, and length of ICU stay were similar in the two groups. The severe acidosis group had a significantly higher rate of NIMV failure (60.7% vs 40%) in the ICU. Mild-to-moderate acidotic COPD patients using LTOT had longer survival after ICU discharge than those without LTOT. On the other hand, severely acidotic COPD patients without LTOT showed shorter survival than those with LTOT. Kaplan-Meier cumulative survival analysis showed that the 28-day and 1-, 2-, and 3-year mortality rates were 12.2%, 36.2%, 52.6%, 63.3%, respectively ( $p=0.09$ ). The Cox regression analyses showed that older age,  $\text{PaO}_2/\text{FiO}_2 < 300$  mmHg, and body mass index  $\leq 20$  kg/m<sup>2</sup> was associated with mortality of all patients after 3 years. **Conclusion:** Severely acidotic COPD patients had a poorer short- and long-term prognosis compared with mild-to-moderate acidotic COPD patients if acute and chronic hypoxemia was predominant.

Guo, Y., C. Hong, et al. (2018). **"Diagnostic value of fractional exhaled nitric oxide for asthma-chronic obstructive pulmonary disease overlap syndrome."** Medicine (Baltimore) **97**(23): e10857.

To examine the difference in the fractional exhaled nitric oxide (FeNO) between chronic obstructive pulmonary disease (COPD) patients with asthma-COPD overlap syndrome (ACOS) and patients with Non-ACOS COPD (Non-ACOS) and to investigate the correlation between FeNO levels and the differential cell counts of eosinophils in induced sputum, in order to explore the diagnostic value of FeNO in ACOS. A prospective, case-control study was performed on 53 cases of ACOS group and 53 cases of Non-ACOS group in the Respiratory Medicine Outpatient of Zhangzhou Municipal TCM Hospital, Affiliated to Fujian University of Traditional Chinese Medicine. The FeNO levels and induced sputum cell counts were determined and the correlation between FeNO levels and eosinophile percentage was analyzed by Pearson linear correlation analysis. The FeNO levels in patients with ACOS (37[24.5-53.0]) ppb were significantly higher than those of patients with Non-ACOS (20 [15.5-24.5] ppb) ( $P < .01$ ). Also, the percentage of eosinophils in induced sputum in the ACOS group (5.70 [1.50-17.62]%) were significantly higher than those of the Non-ACOS group (0.50 [0.00-1.00]%) ( $P < .01$ ). FeNO in both groups correlated positively with the percentage of eosinophils in induced sputum ( $P < .01$ ), with a correlation coefficient  $r$  of 0.521. The area under the receiver operating curve of FeNO for the diagnosis of ACOS phenotype was 0.815 ( $P < .01$ ), the sensitivity and specificity reach highest when the cut off value was 25.50 ppb. The FeNO in patients from the ACOS group were significantly higher than those in Non-ACOS group and were moderately correlated with the percentage of eosinophils in induced sputum. The results indicated that FeNO may be used as a diagnostic index for ACOS, in addition to the induced sputum.

Hahn, B., M. Hull, et al. (2018). **"Rates of escalation to triple COPD therapy among incident users of LAMA and LAMA/LABA."** Respir Med **139**: 65-71.

**BACKGROUND:** Improved outcomes have been reported for patients with chronic obstructive pulmonary disease (COPD) receiving combination long-acting muscarinic antagonist/long-acting beta2-agonist (LAMA/LABA) therapy compared with LAMA monotherapy. However, little is known about the relative characteristics of these patients and their rates of escalation to triple therapy (TT, combining a LAMA, LABA, and inhaled corticosteroid). This study aimed to characterize patients initiating treatment with the LAMA tiotropium (TIO) and the fixed-dose LAMA/LABA combination therapy umeclidinium/vilanterol (UMEC/VI), and to compare rates of escalation to TT between patients receiving these therapies. **METHODS:** Retrospective study of patients with COPD enrolled in a US health insurance plan during 2013-2015 and newly initiated on TIO or UMEC/VI. Patients were  $\geq 40$  years of age at index (date of therapy initiation) with continuous enrollment for 12 months pre-index and  $\geq 30$  days post-index. LAMA users were propensity score matched 1:1 to LAMA/LABA users, with TT

initiation rates reported by cohort using pharmacy claims. RESULTS: 35,357 patients initiating on TIO and 2407 patients initiating on UMEC/VI were identified. After propensity score matching, the rate of TT initiation was significantly higher in new TIO users (n=1320) than in new UMEC/VI users (n=1320) (0.92 vs 0.49 per 100 months of exposure, respectively;  $p<0.001$ ). Relative to the UMEC/VI cohort, the TIO cohort had an 87% higher risk of TT initiation (hazard ratio: 1.87; 95% confidence interval: 1.4-2.5;  $p=0.001$ ). CONCLUSIONS: Patients receiving UMEC/VI progressed to TT more slowly, and were at lower risk of progressing to TT, than patients receiving TIO.

Halding, A. G., E. I. Aarsheim, et al. (2018). **"COPD transitions in health and self-management: service users' experiences from everyday life."** Int J Chron Obstruct Pulmon Dis **13**: 2075-2088.

Purpose: To explore how persons living with COPD experience transitions related to health, self-management, and follow-up from the healthcare services. Patients and methods: This study is part of a participatory research project. Six males and five females living with COPD, with a COPD assessment test score of 21-29, participated; all the participants were living at home. Data were collected in qualitative research interviews and analyzed using qualitative content analysis highlighting the participants' experiences. Results: The findings showed two main themes: "The struggle to keep going" and "The need for continuity and competent facilitation". The participants reported complex health transitions, with changes in roles and function, demanding exacerbations and critical events, and challenges with learning needed self-management. They expressed a great need for and had great benefit from, education, rehabilitation, and follow-up in their management of everyday life. Not all received offers in line with current guidelines. Conclusion: In-depth knowledge of patients' experienced COPD transitions offers clinicians guidance for the timing and quality of follow-up services. Life with COPD entails challenging transitions in health and self-management. Good rehabilitation and follow-up from the healthcare services are needed throughout the disease trajectory. Participation in self-management education and rehabilitation that include psychosocial aspects may facilitate health-enhancing transitions and improve self-management skills. Experienced lack of competence and flexibility among healthcare providers hinders trust and collaboration. Access to stable and competent follow-up in the primary health services may facilitate cohesive services and collaborative self-management.

Hamada, S., S. Tatsumi, et al. (2017). **"Radiographic Evidence of Sinonasal Inflammation in Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome: An Underrecognized Association."** J Allergy Clin Immunol Pract **5**(6): 1657-1662.

**BACKGROUND:** Sinonasal inflammation on both clinical examinations and imaging significantly impacts both asthma and chronic obstructive pulmonary disease (COPD). **OBJECTIVE:** The objective of this study was to examine the association between sinonasal inflammation and asthma-COPD overlap syndrome (ACOS). **METHODS:** A total of 112 patients with a ratio of forced expiratory volume in 1 s to forced vital capacity of less than 70% were enrolled. COPD, asthma, and ACOS were clinically diagnosed according to the 2014 Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease guidelines. Sinonasal inflammatory condition was evaluated using sinus computed tomography, and its severity was assessed according to the Lund-Mackay staging (LMS) system. Ethmoid sinus-dominant shadow was defined as the presence of greater LMS scores for the anterior and posterior ethmoid sinuses than for the maxillary sinus. **RESULTS:** COPD, asthma, and ACOS were diagnosed in 55 (49.1%), 39 (34.8%), and 18 patients (16.1%), respectively. The frequency of radiographic evidence of sinonasal inflammation in patients with COPD, asthma, ACOS was 60.0%, 94.9%, and 72.2%, respectively. Patients with ACOS and COPD had only mild radiographic evidence of sinonasal inflammation (LMS score, 1-7), whereas moderate (LMS score, 8-11) and severe (LMS score,  $\geq 12$ ) radiographic evidence of sinonasal inflammation were detected only in patients with asthma. Furthermore, the frequency of ethmoid sinus-dominant shadow was significantly higher in patients with asthma than in those with COPD and ACOS. **CONCLUSIONS:** Radiographic evidence of sinonasal inflammation was a common comorbidity in ACOS. Future studies are required to examine the role of sinonasal inflammation in ACOS.

Hambleton, K., C. M. Connolly, et al. (2017). **"Comparison of the peripheral blood eosinophil count using near-patient testing and standard automated laboratory measurement in healthy, asthmatic and COPD subjects."** Int J Chron Obstruct Pulmon Dis **12**: 2771-2775.

Near-patient testing (NPT) allows clinical decisions to be made in a rapid and convenient manner and is often cost effective. In COPD the peripheral blood eosinophil count has been demonstrated to have utility in providing prognostic information and predicting response to treatment during an acute exacerbation. For this potential to be achieved having a reliable NPT of blood eosinophil count would be extremely useful. Therefore, we investigated the use of the HemoCue((R)) WBC Diff System and evaluated its sensitivity and specificity in healthy, asthmatic and COPD subjects. This method requires a simple skin prick of blood and was compared to standard venepuncture laboratory analysis. The HemoCue((R)) WBC Diff System measured the peripheral blood eosinophil count in healthy, asthma and COPD subjects with very close correlation to the eosinophil count as measured by standard venepuncture. The correlations were unaffected by disease status. This method for the measurement of the peripheral blood eosinophil count has the potential to provide rapid near-patient results and thus influence the speed of management decisions in the treatment of airway diseases.

Harrison, A., B. Borg, et al. (2017). **"Inappropriate inhaled corticosteroid prescribing in chronic obstructive pulmonary disease patients."** Intern Med J **47**(11): 1310-1313.

The Australian National Chronic Obstructive Pulmonary Disease (COPD) guidelines recommend that inhaled corticosteroids (ICS) be reserved for patients with a post-bronchodilator forced expiratory volume in 1 s (FEV1 ) less than 50% predicted and those who experience  $\geq 2$  exacerbations in 12 months. In total, 707 COPD patients were identified from the lung function test database at our tertiary hospital; 52.4% of patients with a post-bronchodilator FEV1  $\geq 50\%$  were prescribed an ICS. Significant discordance exists between guideline recommendations and inhaler prescription.

Hassan, M. M., M. T. Hussein, et al. (2018). **"Is insufficient pulmonary air support the cause of dysphonia in chronic obstructive pulmonary disease?"** Auris Nasus Larynx **45**(4): 807-814.

**OBJECTIVE:** Optimal pulmonary air support is essential pre-requisite for efficient phonation. The objective is to correlate pulmonary and vocal functions in chronic obstructive pulmonary disease (COPD) to find out whether the reduced pulmonary function per se could induce dysphonia. **METHODS:** In this prospective case-control study, sixty subjects with stable COPD underwent evaluation of pulmonary and vocal functions. The pulmonary functions measured include {Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio, peak expiratory flow (PEF), maximum mid-expiratory flow (MMEF)}. The vocal functions were {jitter, shimmer, noise-to-harmonic ratio, pitch perturbation quotient, amplitude perturbation quotient, maximum phonation time (MPT), sound pressure level, phonatory efficiency, resistance and power. A control group (n=35) underwent the same measurements. These functions were compared between subjects and controls. Also, correlation of the vocal and pulmonary functions was conducted. **RESULTS:** Thirty five (58.3%) of COPD subjects have dysphonia. The pulmonary functions were lower in all COPD group than in the control group ( $P < 0.001$  for all parameters). Also, the FVC, FEV1, PEF and MMEF % of predicted values were significantly lower in subjects with dysphonia (n=35) than those without dysphonia (n=25) with P values 0.0018,  $< 0.001$ , 0.0011 and 0.0026 respectively. In addition, the MPT in all subjects showed positive correlations to the 5 pulmonary functions ( $P = 0.004$  for FEV1/FVC ratio and  $P < 0.001$  for the rest). Also, the phonatory efficiency showed significant positive correlations with the pulmonary functions FVC, FEV1, PEF and MMEF ( $P = 0.001$ , 0.001, 0.002 and 0.001 respectively). Unlike efficiency, the phonatory resistance revealed significant negative correlations with these pulmonary functions in the same order ( $P = 0.001$ , 0.003, 0.002, 0.001 respectively). **CONCLUSION:** Dysphonia is a common comorbidity with COPD which attributed to multifactorial etiologies. The lower the pulmonary function in COPD patients is the more likely to have dysphonia. Decreased pulmonary



function was associated with reduced MPT and phonatory efficiency but with increased phonatory resistance. The reduced pulmonary functions in COPD can be the underlying cause of the altered vocal function and dysphonia. Great part of this dysphonia is functional, and hence, can be corrected by voice therapy in compensated subjects. Further researches are needed to evaluate the efficacy of voice therapy in these patients.

Herigstad, M., O. K. Faull, et al. (2017). **"Treating breathlessness via the brain: changes in brain activity over a course of pulmonary rehabilitation."** Eur Respir J **50**(3) Breathlessness in chronic obstructive pulmonary disease (COPD) is often discordant with airway pathophysiology ("over-perception"). Pulmonary rehabilitation profoundly affects breathlessness, without influencing lung function. Learned associations influence brain mechanisms of sensory perception. We hypothesised that improvements in breathlessness with pulmonary rehabilitation may be explained by changing neural representations of learned associations. In 31 patients with COPD, we tested how pulmonary rehabilitation altered the relationship between brain activity during a breathlessness-related word-cue task (using functional magnetic resonance imaging), and clinical and psychological measures of breathlessness. Changes in ratings of breathlessness word cues positively correlated with changes in activity in the insula and anterior cingulate cortex. Changes in ratings of breathlessness-anxiety negatively correlated with activations in attention regulation and motor networks. Baseline activity in the insula, anterior cingulate cortex and prefrontal cortex correlated with improvements in breathlessness and breathlessness-anxiety. Pulmonary rehabilitation is associated with altered neural responses related to learned breathlessness associations, which can ultimately influence breathlessness perception. These findings highlight the importance of targeting learned associations within treatments for COPD, demonstrating how neuroimaging may contribute to patient stratification and more successful personalised therapy.

Hong, S., E. C. Park, et al. (2018). **"Effect of pre existing respiratory conditions on survival of lung cancer patients: A nationwide population-based cohort study."** Asia Pac J Clin Oncol **14**(2): e71-e80.

**BACKGROUND:** Common diseases with potential to increase the risk of death from lung cancer have so far not been studied in large populations. **METHODS:** We did a population-based retrospective cohort study using nationwide health insurance claims data from 2005 to 2012 in Korea including 205 403 lung cancer patients. Multivariate-adjusted hazard ratios (aHRs) of lung cancer mortality by presence, time intervals with lung cancer diagnosis and combinations of pre-existing chronic obstructive pulmonary disease (COPD), pneumonia, asthma and tuberculosis were calculated using the Cox-proportional hazards model. **RESULTS:** The total number of person-years of follow-up was 397 780 and

60.2% of patients died (mean survival 23.2 months after lung cancer diagnosis). Lung cancer patients with previous respiratory disease had increased aHR for mortality (COPD, hazard ratio [HR] = 1.32, CI 1.29-1.35; pneumonia, HR = 1.14, CI 1.08-1.19; and asthma, HR = 1.11, CI 1.06-1.16). Risks were positively associated with longer duration of pre-existing disease diagnosis; cases with >5 years since diagnosis compared to <2 years: COPD, HR = 2.91, CI 2.82-3.00; pneumonia, HR = 1.67, CI 1.51-1.85; asthma, HR = 1.56, CI 1.45-1.68; and tuberculosis, HR = 2.03, CI 1.90-2.17. Furthermore, elevated HRs of death were found among patients with multiple pre-existing co-morbidities. **CONCLUSION:** Hazards of death from lung cancer are significantly increased in cases with pre-existing lung disease, and worse with longer durations, and with multiple combinations before cancer diagnosis. Patients and physicians should be aware of these meaningful risk/prognostic factors for lung cancer when identifying high-risk patient groups.

Huang, Y. C. and M. C. Yang (2017). **"Associations between occupational inhalation risks and FeNO levels in airway obstruction patients: results from the National Health and Nutrition Examination Survey, 2007-2012."** Int J Chron Obstruct Pulmon Dis **12**: 3085-3093.

**Purpose:** To investigate associations between occupational inhalation risks and fractional exhaled nitric oxide (FeNO) levels in patients with chronic obstructive pulmonary disease (COPD). **Patients and methods:** Data of 16,486 subjects who had undergone spirometry with pre-bronchodilator and post-bronchodilator lung function assessment were retrieved from the National Health and Nutrition Examination Survey, 2007-2012 database. After excluding 2,638 subjects with missing spirometry values, data of 13,336 subjects were included for analysis. Factors associated with occupational inhalation, FeNO levels and COPD were analyzed using logistic regression analysis. **Results:** COPD was associated with occupational exposures to mineral dusts, organic dusts, exhaust fumes, other fumes, and second-hand smoking ( $P < 0.05$ ). Long-term exposure to these occupational hazards carried significantly higher risk for subjects with COPD than for controls (crude odds ratios [ORs]: mineral dusts: 2.364, organic dusts: 2.427, exhaust fumes: 2.728, other fumes: 2.144). In subgroup analysis, COPD correlated positively with long-term exposures to organic dusts and exhaust fumes in subjects with FeNO  $\leq 50$  ppb (ORs 1.361 and 1.314, respectively); conversely, COPD correlated negatively with intermediate to long-term exposures to organic dusts and exhaust fumes in those with FeNO  $> 50$  ppb (ORs 0.058 and 0.210, respectively). **Conclusion:** Occupational exposures to airborne pollutants carries higher risk of COPD than non-exposure and the risk is higher the longer the duration of exposure. Exposure-response relationships are inconsistent in subjects with suspected asthmatic airway inflammation (FeNO  $\geq 50$  ppb). More careful risk assessment is needed in occupational inhalation exposure, since COPD with asthmatic airway inflammation, or asthma-COPD overlapping syndrome, may have the distinguishing features of both COPD and asthma.

Hyldgaard, C., E. Bendstrup, et al. (2018). **"Increased mortality among patients with rheumatoid arthritis and COPD: A population-based study."** Respir Med **140**: 101-107.

**OBJECTIVES:** Only few studies have addressed the prognostic impact of chronic obstructive pulmonary disease (COPD) among patients with rheumatoid arthritis (RA), although both diseases are frequent and smoking is a shared risk factor. The objectives of the present study were to investigate the burden of COPD among RA patients and the subsequent mortality. **METHODS:** We included patients who had a first-time diagnosis of RA in the Danish National Patient Registry between 2004 and 2016. RA patients with COPD were identified and matched with RA patients without COPD for year of birth, gender, and age at RA diagnosis. Mortality risks were assessed using Kaplan-Meier mortality curves. Adjusted hazard rate ratios (aHRRs) for death were estimated using Cox regression models. **RESULTS:** The study population included 31,333 individuals with RA. 3254 of those (10.4%) had a diagnosis of COPD and were matched to 9706 RA patients without COPD. The mortality risks in RA patients with COPD and RA patients without COPD were 4.5% and 1.5% within 2-6 months (aHRR=3.0, CI 2.3-3.9), and 59.3% and 39.8% within 0.5-10 years (aHRR=2.1, CI 1.9-2.1). **CONCLUSION:** Mortality was significantly increased among RA patients with COPD. The relative mortality risk remained significantly increased throughout the course of follow up.

Jacob, J., B. J. Bartholmai, et al. (2018). **"Likelihood of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and emphysema."** Respirology **23**(6): 593-599.

**BACKGROUND AND OBJECTIVE:** This study evaluated whether patients with combined pulmonary fibrosis and emphysema (CPFE) have an increased likelihood of pulmonary hypertension (PHT) when compared with idiopathic pulmonary fibrosis (IPF) patients without emphysema. **METHODS:** Two consecutive IPF populations having undergone transthoracic echocardiography were examined (n = 223 and n = 162). Emphysema and interstitial lung disease (ILD) extent were quantified visually; ILD extent was also quantified by a software tool, CALIPER. Echocardiographic criteria categorized PHT risk. **RESULTS:** The prevalence of an increased PHT likelihood was 29% and 31% in each CPFE cohort. Survival at 12 months was 60% across both CPFE cohorts with no significantly worsened outcome identified when compared with IPF patients without emphysema. Using logistic regression models in both cohorts, total computed tomography (CT) disease extent (ILD and emphysema) predicted the likelihood of PHT. After adjustment for total disease extent, CPFE had no stronger association with PHT likelihood than IPF patients without emphysema. **CONCLUSION:** Our findings indicate that the reported association between CPFE and PHT is explained by the summed baseline CT extents of ILD and emphysema. Once baseline severity is taken into account, CPFE is not

selectively associated with a malignant microvascular phenotype, when compared with IPF patients without emphysema.

Jarenback, L., E. Tufvesson, et al. (2018). **"The Efficiency Index (EFFi), based on volumetric capnography, may allow for simple diagnosis and grading of COPD."** Int J Chron Obstruct Pulmon Dis **13**: 2033-2039.

Background: Spirometry, the main tool for diagnosis and follow-up of COPD, incompletely describes the disease. Based on volumetric capnography (VCap), an index was developed for the diagnosis and grading of COPD, aimed as a complement or alternative to spirometry. Methods: Nine non-smokers, 10 smokers/former smokers without COPD and 54 smokers/former smokers with COPD were included in the study. Multiple breath washout of N<sub>2</sub> and VCap were studied with Exhalyzer D during tidal breathing. VCap was based on signals for flow rate and CO<sub>2</sub> and was recorded during one breath preceding N<sub>2</sub> washout. Efficiency Index (EFFi) is the quotient between exhaled CO<sub>2</sub> volume and the hypothetical CO<sub>2</sub> volume exhaled from a completely homogeneous lung over a volume interval equal to 15% of predicted total lung capacity. Results: EFFi increased with increased Global initiative for chronic Obstructive Lung Disease (GOLD) stage and the majority of subjects in GOLD 2 and all subjects in GOLD 3 and 4 could be diagnosed as having COPD using the lower 95% confidence interval of the healthy group. EFFi also correlated with N<sub>2</sub> washout ( $r=-0.73$ ;  $p<0.001$ ), forced expiratory volume in 1 second ( $r=0.70$ ;  $p<0.001$ ) and diffusion capacity for carbon oxide ( $r=0.69$ ;  $p<0.001$ ). Conclusion: EFFi measures efficiency of tidal CO<sub>2</sub> elimination that is limited by inhomogeneity of peripheral lung function. EFFi allows diagnosis and grading of COPD and, together with FEV<sub>1</sub>, may explain limitation of physical performance. EFFi offers a simple, effortless and cost-effective complement to spirometry and might serve as an alternative in certain situations.

Jareno-Esteban, J. J., M. A. Munoz-Lucas, et al. (2017). **"Study of 5 Volatile Organic Compounds in Exhaled Breath in Chronic Obstructive Pulmonary Disease."** Arch Bronconeumol **53**(5): 251-256.

INTRODUCTION: A major risk factor for chronic obstructive pulmonary disease (COPD) is tobacco smoke, which generates oxidative stress in airways, resulting in the production of volatile organic compounds (VOC). The purpose of this study was to identify VOCs in exhaled breath and to determine their possible use as disease biomarkers. METHOD: Exhaled breath from 100 healthy volunteers, divided into 3 groups (never smokers, former smokers and active smokers) and exhaled breath from 57 COPD patients were analyzed. Samples were collected using BioVOC((R)) devices and transferred to universal desorption tubes. Compounds were analyzed by thermal desorption, gas chromatography and mass spectrometry. VOCs analyzed were linear aldehydes and carboxylic acids.

**RESULTS:** The COPD group and healthy controls (never smokers and former smokers) showed statistically significant differences in hexanal concentrations, and never smokers and the COPD group showed statistically significant differences in nonanal concentrations. **CONCLUSIONS:** Hexanal discriminates between COPD patients and healthy non-smoking controls. Nonanal discriminates between smokers and former smokers (with and without COPD) and never smokers.

Jeong, M., H. K. Kang, et al. (2017). **"Hand grip strength in patients with chronic obstructive pulmonary disease."** Int J Chron Obstruct Pulmon Dis **12**: 2385-2390.

**PURPOSE:** Hand grip strength (HGS) is a simple way of predicting the risk of cardiovascular disease and all-cause mortality in the general population. However, the practical significance of grip strength in patients with COPD is uncertain. The aim of this study was to compare HGS between subjects with and without COPD and to evaluate its clinical relevance in patients with COPD by using a national survey. **METHODS:** Data were collected from the Korean National Health and Nutrition Examination Survey. The study included 421 adults with COPD and 2,542 controls who completed questionnaires, spirometry, and a HGS test. HGS was compared between subjects with and without COPD, and the association between grip strength, lung function, and quality of life (QoL) was evaluated. **RESULTS:** The mean HGS was 33.3 $\pm$ 9.1 kg in the COPD group and 29.9 $\pm$ 9.5 kg in the non-COPD group; adjusted HGS was 30.9 $\pm$ 0.33 kg and 30.9 $\pm$ 0.11 kg, respectively ( $P=0.99$ ). HGS was not related to forced vital capacity ( $\beta=0.04$ ,  $P=0.70$ ) or forced expiratory volume in 1 second ( $\beta=0.11$ ,  $P=0.24$ ) in multivariable analysis. HGS was independently associated with the EQ-5D index, but the relationship was stronger in the COPD group ( $\beta=0.30$ ,  $P<0.001$ ) than in the non-COPD group ( $\beta=0.21$ ,  $P<0.001$ ). The results were similar for each component of the EQ-5D, including mobility ( $\beta=-0.25$ ,  $P<0.001$ ), daily activity ( $\beta=-0.19$ ,  $P=0.01$ ), pain/discomfort ( $\beta=-0.32$ ,  $P<0.001$ ), and anxiety/depression ( $\beta=-0.16$ ,  $P=0.01$ ). **CONCLUSION:** HGS was not different between subjects with and without COPD, but was associated with QoL - including mobility, daily activity, pain/discomfort, and anxiety/depression - in patients with COPD. The HGS test could be used as a marker of QoL in patients with COPD and could assist risk stratification in clinical practice.

Joly, P., A. Lachaux, et al. (2017). **"SERPINA1 and MAN1B1 polymorphisms are not linked to severe liver disease in a French cohort of alpha-1 antitrypsin deficiency children."** Liver Int **37**(11): 1608-1611.

**BACKGROUND & AIMS:** Fifteen to twenty percent of alpha-1 antitrypsin deficiency patients (A1ATD) have a severe liver outcome (portal hypertension - PHT) during

childhood. Since they all share the same ZZSERPINA1 genotype and that environmental factors such as alcohol cannot be advanced, the presence of modifier genes is now well recognized. SNPs located on the SERPINA1 and MAN1B1 genes have already been tested in very few studies with contradictory or not replicated results. METHODS: Our genotype-phenotype correlation study, performed on 92 ZZ children, aimed at determining once and for all if SERPINA1 and MAN1B1 polymorphisms may be implied in the onset of PHT. To do so, we also performed for the first time a complete haplotype reconstruction for data analysis. RESULTS: The two genetic associations with severe liver disease that had been suspected previously (one SNP for SERPINA1 and another for MAN1B1) were not confirmed in our cohort. Moreover, the haplotype analysis identified only one major genetic background for the SERPINA1 Z-allele, allowing us to exclude the presence of a frequent modifier SNP within. For MAN1B1, four major haplotypes were identified but the prevalence of PHT did not significantly differ between them. CONCLUSION: We conclude that genetic polymorphisms in these two genes probably do not influence the onset of severe liver disease in A1ATD.

Jorgensen, M., J. Mainz, et al. (2018). **"Quality of care and clinical outcomes of chronic obstructive pulmonary disease in patients with schizophrenia. A Danish nationwide study."** *Int J Qual Health Care* **30**(5): 351-357.

Objective: To examine the association between schizophrenia and the quality of care and clinical outcomes of chronic obstructive pulmonary disease (COPD). Design: A Danish nationwide population-based cohort study using comprehensive information from Danish registries between 2008 and 2013. Setting: Public Danish hospitals. Participants: 72 692 COPD patients with hospital contacts including 621 with schizophrenia. Intervention: COPD care. Main Outcome Measures: The quality of COPD care was defined as meeting guideline-recommended process performance measures of care. Potential predictors of COPD care among patients with schizophrenia included patient- (sex, age, alcohol or drug abuse, Global Assessment of Functioning score, duration of schizophrenia), provider- (quality of schizophrenia care), and system-related factors (contact-volume defined as hospital department and clinics' annual average contact volume of COPD patients). Clinical outcomes included 30-day all-cause readmission and 30-day all-cause mortality risk following an admission for exacerbation of COPD. Results: Compared to COPD patients without schizophrenia, COPD patients with schizophrenia had a lower chance of receiving treatment with long-acting muscarinic antagonists (LAMA) or long-acting beta2-agonists (LABA) (Relative risk (RR) 0.92, 95% CI: 0.87-0.98). Female sex was associated with a higher chance of receiving LAMA/LABA treatment among COPD patients with schizophrenia. COPD patients with schizophrenia had a higher risk of 30-day mortality (adjusted odds ratio (OR) 1.27, 95% CI: 1.01-1.59) but not a higher risk of readmission compared with COPD patients without schizophrenia. Conclusions: COPD patients with schizophrenia had a slightly lower chance of receiving LAMA/LABA treatment, but a substantially increased risk of death following admission for an exacerbation compared with patients without schizophrenia.

Kahnert, K., P. Alter, et al. (2018). **"Uric acid, lung function, physical capacity and exacerbation frequency in patients with COPD: a multi-dimensional approach."** *Respir Res* **19**(1): 110.

**BACKGROUND:** Recent investigations showed single associations between uric acid levels, functional parameters, exacerbations and mortality in COPD patients. The aim of this study was to describe the role of uric acid within the network of multiple relationships between function, exacerbation and comorbidities. **METHODS:** We used baseline data from the German COPD cohort COSYCONET which were evaluated by standard multiple regression analyses as well as path analysis to quantify the network of relations between parameters, particularly uric acid. **RESULTS:** Data from 1966 patients were analyzed. Uric acid was significantly associated with reduced FEV1, reduced 6-MWD, higher burden of exacerbations (GOLD criteria) and cardiovascular comorbidities, in addition to risk factors such as BMI and packyears. These associations remained significant after taking into account their multiple interdependences. Compared to uric acid levels the diagnosis of hyperuricemia and its medication played a minor role. **CONCLUSION:** Within the limits of a cross-sectional approach, our results strongly suggest that uric acid is a biomarker of high impact in COPD and plays a genuine role for relevant outcomes such as physical capacity and exacerbations. These findings suggest that more attention should be paid to uric acid in the evaluation of COPD disease status.

Kania, A., R. Krenke, et al. (2018). **"Distribution and characteristics of COPD phenotypes - results from the Polish sub-cohort of the POPE study."** *Int J Chron Obstruct Pulmon Dis* **13**: 1613-1621.

**Background:** This study aimed to examine the distribution of predefined phenotypes, demographic data, clinical outcomes, and treatment of patients who were included in the Polish cohort of the Phenotypes of COPD in Central and Eastern Europe (POPE) study. **Patients and methods:** This was a sub-analysis of the data from the Polish cohort of the POPE study, an international, multicenter, observational cross-sectional survey of COPD patients in Central and Eastern European countries. The study included patients aged >40 years, with a confirmed diagnosis of COPD, and absence of exacerbation for at least 4 weeks before study inclusion. A total of seven Polish centers participated in the study. **Results:** Among the 430 Polish COPD patients enrolled in the study, 61.6% were non-exacerbators (NON-AE), 25.3% were frequent exacerbators with chronic bronchitis (AE CB), 7.9% were frequent exacerbators without chronic bronchitis (AE NON-CB), and 5.1% met the definition of asthma-COPD overlap syndrome (ACOS). There were statistically significant differences among these phenotypes in terms of symptom load, lung function, comorbidities, and treatment. Patients with the AE CB phenotype were most symptomatic with worse lung function, and

more frequently reported anxiety and depression. Patients with the ACOS phenotype were significantly younger and were diagnosed with COPD earlier than those with other COPD phenotypes; those with the ACOS phenotype were also more often atopic and obese. Conclusion: There is significant heterogeneity among COPD patients in the Polish population in terms of phenotype and clinical outcome. The non-exacerbator phenotype is observed most frequently in Poland, while the frequent exacerbator with chronic bronchitis phenotype is the most symptomatic.

Kardos, P., I. Mokros, et al. (2018). **"Health status in patients with COPD treated with roflumilast: two large noninterventional real-life studies: DINO and DACOTA."** Int J Chron Obstruct Pulmon Dis **13**: 1455-1468.

Purpose: DINO and DACOTA were prospective, noninterventional studies assessing the health status and quality of life of patients with COPD newly treated with roflumilast 500 mug once-daily add-on therapy. Patients and methods: Patients were evaluated over 6 months. Clinical COPD questionnaire (CCQ) and COPD assessment test (CAT) scores were recorded at baseline and after 3 and 6 months. In DACOTA, post-bronchodilator FEV1 was recorded at each time point. Results: Of 5,462 and 3,645 patients recruited into DINO and DACOTA, respectively, 3,274 patients in DINO and 916 patients in DACOTA completed the 6-month visit. Almost all patients had severe or very severe airway obstruction; mean baseline CCQ total score was 3.9 in DINO and 3.7 in DACOTA. Overall, 33.8% of patients in DACOTA and 30.6% in DINO discontinued treatment prematurely. Significant and clinically relevant improvements in CCQ total scores were observed in both studies (mean change from baseline of 1.36 in DINO and 0.91 in DACOTA at Month 6 [all  $P < 0.001$ ]). Changes in CAT total score from baseline to Month 6 indicated that the average clinical impact of COPD was reduced from a severe (score: 21-30) to a moderate (score: 11-20) impairment. In DACOTA, mean change in post-bronchodilator FEV1 was 202 mL ( $P < 0.001$ ). Diarrhea, nausea, and weight decrease were the most frequently reported adverse drug reactions. Conclusion: In real-life clinical practice, roflumilast treatment as an add-on therapy is associated with clinically relevant improvements in health status and quality of life.

Kelly, A. M., A. Holdgate, et al. (2018). **"Epidemiology, treatment, disposition and outcome of patients with acute exacerbation of COPD presenting to emergency departments in Australia and South East Asia: An AANZDEM study."** Respirology **23**(7): 681-686.

BACKGROUND AND OBJECTIVE: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common presentation to emergency departments (ED) but data regarding its epidemiology and outcomes are scarce. We describe the epidemiology, clinical features, treatment and outcome of



patients treated for AECOPD in ED. **METHODS:** This was a planned sub-study of patients with an ED diagnosis of AECOPD identified in the Asia, Australia and New Zealand Dyspnoea in Emergency Departments (AANZDEM) study. The AANZDEM was a prospective, interrupted time series cohort study conducted in 46 ED in Australia, New Zealand, Singapore, Hong Kong and Malaysia over three 72-h periods in May, August and October 2014. Primary outcomes were patient epidemiology, clinical features, treatment and outcomes (hospital length of stay (LOS) and mortality). **RESULTS:** Forty-six ED participated. There were 415 patients with an ED primary diagnosis of AECOPD (13.6% of the overall cohort; 95% CI: 12.5-14.9%). Median age was 73 years, 60% males and 65% arrived by ambulance. Ninety-one percent had an existing COPD diagnosis. Eighty percent of patients received inhaled bronchodilators, 66% received systemic corticosteroids and 57% of those with pH < 7.30 were treated with non-invasive ventilation (NIV). Seventy-eight percent of patients were admitted to hospital, 7% to an intensive care unit. In-hospital mortality was 4% and median LOS was 4 days (95% CI: 2-7). **CONCLUSION:** Patients treated in ED for AECOPD commonly arrive by ambulance, have a high admission rate and significant in-hospital mortality. Compliance with evidence-based treatments in ED is suboptimal affording an opportunity to improve care and potentially outcomes.

Khare, P., A. Talwar, et al. (2016). **"Vascular Responses to Post Occlusive Reactive Hyperemia and Systemic Inflammation in Overlap Syndrome of Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea."** Indian J Physiol Pharmacol **60**(2): 155-166.

**BACKGROUND:** Post-occlusive reactive hyperemia (RH) is impaired in Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA). The aim of the present study was to examine systemic vascular response and endothelial function in patients of Overlap Syndrome (OS) of COPD and OSA and also to investigate whether OS has any additional effect on endothelial dysfunction when compared to dysfunction caused by COPD alone. **METHODS:** 31 COPD patients and 13 healthy controls participated in the study. Overnight Polysomnogra was done to classify the patients into COPD only group (Apnea-Hypopnea Index <5) (n=15) and OS group (AHI >5) (n=16). Peripheral pulse waveform changes during reactive hyperemia were assessed using digital Photoplethysmography (PPG) technique in which pulse wave amplitude (PWA), Maximum slope of upstroke and Pulse Transit Time (PTT) were measured. C - reactive protein was assessed as marker of inflammation by ELISA. **RESULTS:** Maximum percentage changes in PWA during RH were significantly lower in the both COPD group [20.34(12.02-34.07)] (p<0.001) and Overlap Syndrome group [10.96(6.21-21.49)] (p<0.0001) as compared to Controls [49.79(46.03-65.32)], whereas amplitude responses were not significantly different in the COPD and OS group (p>0.05). Maximum percentage change in slope of upstroke showed similar responses in the three groups. CRP levels (mg/l) were raised in COPD [11.60(1.75-15.00)] (p<0.001) and OS group [12.52(5.28- 15.70)](p<0.0001) as compared to controls [0.59(0.58-0.91)]. Maximum percentage change in amplitude negatively correlated with serum CRP levels in COPD group (r=-0.557,

p=0.03) and in OS group (r=-0.552, p= 0.02). FEV1% predicted positively correlated with maximum percentage change in amplitude in OS group (r=0.579, p=0.018). No correlation of AHI was found with any of the vascular function parameter in Overlap group. **CONCLUSION:** The patients with Overlap Syndrome have systemic inflammation and impaired reactive hyperaemia response. However, no additive effect of OSA was observed on impaired RH in patients with co-existing COPD.

Khauri, S., E. Abston, et al. (2017). **"Incomplete fissures are associated with increased alveolar ventilation via spiracles in severe emphysema."** Interact Cardiovasc Thorac Surg **25**(6): 851-855.

**OBJECTIVES:** In emphysema, air can flow preferentially via collateral pathways, which can connect an entire lung when incomplete fissures are present. Spiracles are openings through the chest wall into the lung parenchyma. We previously observed increased alveolar ventilation (VA) in subjects with severe emphysema, when spiracles occurred during lung transplant operations. In this study, we set out to identify a computed tomography (CT) imaging phenotype associated with improved VA via spiracles in severe emphysema. **METHODS:** We retrospectively reviewed 4 patients with severe emphysema who exhaled  $\geq 75\%$  of the inhaled tidal volume via transpleural spiracles during a lung transplant operation. We used quantitative image analysis via VIDA VISION CT software to describe emphysema severity and distribution and fissure integrity from pretransplant CT scans of the chest. We analysed partial pressure of carbon dioxide and calculated estimates of VA at baseline and during spiracle ventilation. **RESULTS:** All 4 subjects demonstrated severe hyperinflation (total lung capacity 148  $\pm$  24% predicted, residual volume 296  $\pm$  79% predicted). On CT imaging, severe emphysema was present, with an average 38.7  $\pm$  9% (range 28-50%) of lung parenchyma showing low-attenuation areas of  $\leq$  950 Hounsfield units or less. Lung fissure integrity analysis demonstrated evidence of incomplete fissures (average detectable fissure integrity 67  $\pm$  19%, range 40  $\pm$  11-90  $\pm$  10%). During spiracle ventilation on unchanged ventilator settings, there was a significant reduction in partial pressure of carbon dioxide (61  $\pm$  4-35  $\pm$  4 mmHg,  $P < 0.001$ ) and increase in estimated VA (2.1  $\pm$  0.5-3.8  $\pm$  0.8 l/min,  $P < 0.001$ ). **CONCLUSIONS:** Incomplete lung fissures on quantitative CT analysis seem to be a key image phenotype associated with substantial improvements in VA during transpleural ventilation via spiracles in severe emphysema.

Kim, W. J., V. Gupta, et al. (2018). **"Identification of chronic obstructive pulmonary disease subgroups in 13 Asian cities."** Int J Tuberc Lung Dis **22**(7): 820-826.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition that can differ in its clinical manifestation, structural changes and response to treatment. **OBJECTIVE:** To identify subgroups of COPD with distinct

phenotypes, evaluate the distribution of phenotypes in four related regions and calculate the 1-year change in lung function and quality of life according to subgroup. **METHODS:** Using clinical characteristics, we performed factor analysis and hierarchical cluster analysis in a cohort of 1676 COPD patients from 13 Asian cities. We compared the 1-year change in forced expiratory volume in one second (FEV1), modified Medical Research Council dyspnoea scale score, St George's Respiratory Questionnaire (SGRQ) score and exacerbations according to subgroup derived from cluster analysis. **RESULTS:** Factor analysis revealed that body mass index, Charlson comorbidity index, SGRQ total score and FEV1 were principal factors. Using these four factors, cluster analysis identified three distinct subgroups with differing disease severity and symptoms. Among the three subgroups, patients in subgroup 2 (severe disease and more symptoms) had the most frequent exacerbations, most rapid FEV1 decline and greatest decline in SGRQ total score. **CONCLUSION:** Three subgroups with differing severities and symptoms were identified in Asian COPD subjects.

Kistenev, Y. V., A. V. Borisov, et al. (2017). **"Exhaled air analysis using wideband wave number tuning range infrared laser photoacoustic spectroscopy."** J Biomed Opt **22**(1): 17002.

The infrared laser photoacoustic spectroscopy (LPAS) and the pattern-recognition-based approach for noninvasive express diagnostics of pulmonary diseases on the basis of absorption spectra analysis of the patient's exhaled air are presented. The study involved lung cancer patients ( N = 9 ), patients with chronic obstructive pulmonary disease ( N = 12 ), and a control group of healthy, nonsmoking volunteers ( N = 11 ). The analysis of the measured absorption spectra was based at first on reduction of the dimension of the feature space using principal component analysis; thereafter, the dichotomous classification was carried out using the support vector machine. The gas chromatography-mass spectrometry method (GC-MS) was used as the reference. The estimated mean value of the sensitivity of exhaled air sample analysis by the LPAS in dichotomous classification was not less than 90% and specificity was not less than 69%; the analogous results of analysis by GC-MS were 68% and 60%, respectively. Also, the approach to differential diagnostics based on the set of SVM classifiers usage is presented.

Konecny, T., K. R. Somers, et al. (2018). **"Chronic obstructive pulmonary disease as a risk factor for ventricular arrhythmias independent of left ventricular function."** Heart Rhythm **15**(6): 832-838.

**BACKGROUND:** The association between chronic obstructive pulmonary disease (COPD) and sudden cardiac death has not been fully elucidated. **OBJECTIVE:** The purpose of this study was to investigate whether decreased left ventricular ejection fraction (LVEF) can explain the increased rate of ventricular tachycardia

(VT) in COPD. **METHODS:** This retrospective study included consecutive adult patients who underwent pulmonary function testing (PFT), Holter monitoring, and transthoracic echocardiography. COPD was correlated with the frequency of VT in a multivariate analysis that adjusted for known confounders including LVEF. Long-term all-cause mortality of patients with COPD and VT was examined. **RESULTS:** Of the 6351 patients included in this study (age 66 +/- 15 years; 48% woman; 92% Caucasian, LVEF 59% +/- 12%), 2800 (44%) had PFT indicative of COPD. VT was nearly twice as likely to occur during Holter monitoring in COPD patients (13% vs 23%;  $P < .001$ ), and the severity of COPD correlated with the risk of VT (21% vs 28% vs 37% for mild-moderate, severe, and very severe COPD;  $P < .001$ ). COPD and VT remained independently associated ( $P < .001$ ) even after adjusting for LVEF, demographics, and comorbidities (age, sex, body mass index, hypertension, chronic kidney disease, coronary artery disease, cancer history, diabetes mellitus). COPD was associated with all-cause mortality independently of LVEF ( $P < .001$ ). **CONCLUSION:** COPD patients are at higher risk for VT and mortality. This may not be fully attributed to the confounding effect of systolic heart failure measured by LVEF. Further studies are needed to explore the mechanistic interactions between VT and COPD in order to determine whether antiarrhythmic strategies would apply especially to patients with severe COPD.

Koo, H. K., S. W. Park, et al. (2018). "**Chronic cough as a novel phenotype of chronic obstructive pulmonary disease.**" Int J Chron Obstruct Pulmon Dis **13**: 1793-1801.

**Background and purpose:** Chronic cough can be a dominant symptom of chronic obstructive pulmonary disease (COPD), although its clinical impact remains unclear. The aim of our study was to identify phenotypic differences according to the presence of chronic cough or sputum and evaluate the impact of chronic cough on the risk of acute exacerbation of COPD (AECOPD). **Methods:** In a nationwide COPD cohort including 1,613 COPD patients, patients with chronic cough only, those with sputum only, those with chronic bronchitis (CB), and those without cough and sputum were compared with regard to dyspnea, lung function, quality of life (QoL), and risk of AECOPD. **Results:** The rates of chronic cough, chronic sputum, and both were 23.4%, 32.4%, and 18.2%, respectively. Compared with patients without chronic cough, those with chronic cough exhibited a lower forced expiratory volume in 1 second (% predicted) and diffusing capacity of the lungs for carbon monoxide (% predicted), more frequent AECOPD, more severe dyspnea, and worse QoL. Pulmonary function, dyspnea severity, and QoL worsened in the following order: without cough or sputum, with sputum only, with cough only, and with CB. Multivariate analyses revealed chronic cough as an independent risk factor for a lower lung function, more severe dyspnea, and a poor QoL. Moreover, the risk of future AECOPD was significantly associated with chronic cough (odds ratio 1.56, 95% CI 1.08-2.24), but not with chronic sputum. **Conclusion:** Our results suggest that chronic cough should be considered as an important phenotype during the determination of high-risk groups of COPD patients.

Kovacik, A., P. C. Bell, et al. (2018). **"Impact of delayed prescription fill on readmission rates for chronic obstructive pulmonary disease and heart failure."** J Am Pharm Assoc (2003) **58**(4s): S41-s45.

**OBJECTIVES:** In an effort to reduce reimbursement penalty from the Centers for Medicare & Medicaid Services, hospitals have looked to evaluate the effectiveness of existing programs as well as adopt innovative practices to reduce 30-day readmission rates. The objective of this study was to evaluate the impact of delaying prescription fill on 30-day readmission rates for patients with heart failure (HF) and chronic obstructive pulmonary disease (COPD). Identifying an association between delaying prescription fill and readmission rate would validate programs that provide patients with their medications before discharge. **METHODS:** A retrospective chart review was performed for all patients admitted to Henry County Medical Center with an HF or COPD exacerbation from January to October 2016. Outpatient pharmacies were contacted for each patient to determine time of prescription fill. Time of fill was compared with time of discharge, and patients were separated into 2 subgroups: those who filled within 48 hours of discharge and those who filled after 48 hours. The primary outcome was 30-day readmission rate, and a secondary end point was to identify patient characteristics associated with delayed prescription fills. **RESULTS:** A total of 104 patients were included in the study. COPD patients experienced a lower readmission rate when delaying prescription fill at least 48 hours ( $P = 0.23$ ). HF patients experienced a higher readmission rate when delaying prescription fill at least 48 hours ( $P = 0.48$ ). No baseline characteristics were associated with a significantly higher rate of delaying prescription fill. **CONCLUSION:** Delaying discharge prescription fills resulted in a nonsignificant increase in the rate of HF readmission but did not increase the rate of readmission for COPD. Rate of delaying prescription fill was not statistically greater for any of the baseline characteristics.

Labaki, W. W., M. Xia, et al. (2018). **"NT-proBNP in stable COPD and future exacerbation risk: Analysis of the SPIROMICS cohort."** Respir Med **140**: 87-93.

**BACKGROUND:** High N-terminal pro-brain natriuretic peptide (NT-proBNP) during COPD exacerbations is associated with worse clinical outcomes. The prognostic value of NT-proBNP measured during clinical stability has not been well characterized. **METHODS:** We studied SPIROMICS participants 40-80 years of age with COPD GOLD spirometric stages 1-4. The association between baseline NT-proBNP and incident COPD exacerbations within one year of follow-up was tested using zero-inflated Poisson regression models adjusted for age, gender, race, body mass index, current smoking status, smoking history, FEV1 percent predicted, COPD Assessment Test score, exacerbation history, total lung capacity on chest CT and cardiovascular disease (any of coronary artery

disease, myocardial infarction or congestive heart failure). RESULTS: Among 1051 participants (mean age 66.1 years, 41.4% women), mean NT-proBNP was 608.9pg/ml. Subjects in GOLD stage D had the highest mean NT-proBNP. After one year of follow-up, 268 participants experienced one or more COPD exacerbations. One standard deviation increase in baseline NT-proBNP was associated with a 13% increase in the risk of incident exacerbations (incident risk ratio 1.13; 95% CI 1.06-1.19;  $p < 0.0001$ ). This association was maintained in participants with and without cardiovascular disease. CONCLUSION: Baseline NT-proBNP in COPD is an independent predictor of respiratory exacerbations, even in individuals without overt cardiac disease. The impact of detection and treatment of early cardiovascular dysfunction on COPD exacerbation frequency warrants further investigation.

Labarca, G., A. Bustamante, et al. (2017). **"The boundaries of mild chronic obstructive pulmonary disease (COPD): design of the searching clinical COPD onset (SOON) study."** *BMJ Open* 7(8): e015731.

INTRODUCTION: Clinical onset of chronic obstructive pulmonary disease (COPD) is the point at which the disease is first identifiable by physicians. It is a poorly defined stage which seems to include both mild spirometric and non-spirometric disease, and could be described as early grade COPD, for practical purposes. While dyspnoea; chronic bronchitis and CT imaging evidence of emphysema and airway disease may be present very early, the lone significance of dyspnoea, the most relevant symptom in COPD in identifying these individuals, has been scarcely assessed. The Searching Clinical COPD Onset (SOON) Study was designed primarily to detect clinical, physiological and structural differences between dyspnoeic and non-dyspnoeic individuals with early grade COPD. It is hypothesised that presence of dyspnoea in early disease may identify a subtype of individuals with reduced exercise capacity, notwithstanding of their spirometry results. In addition, dyspnoeic individuals will share worse quality of life, lower physical activity, greater lung hyperinflation greater emphysema and airway thickness and reduced peripheral muscle mass than their non-dyspnoeic counterpart. METHODS AND ANALYSIS: SOON is a monocentric study, with a cross sectional design aimed at obtaining representative samples of current or ex-smoker-adults aged  $\geq 45$  and  $\leq 80$  years. Two hundred and forty participants will be enrolled into four strata, according to normal spirometry or mild spirometric obstruction and presence or not of dyspnoea modified Medical Research Council score  $\geq 1$ . The primary outcome will be the difference between dyspnoeic and non-dyspnoeic individuals on the 6-min walk test performance, regardless of their spirometry results. To account for the confounding effect of heart failure on dyspnoea, stress echocardiography will be also performed. Secondary outcomes will include clinical (quality of life, physical activity), physiological (exercise testing) and structural characteristics (emphysema, airway disease and peripheral muscle mass by CT imaging). ETHICS AND DISSEMINATION: The Institutional Ethics Committee from Pontificia Universidad Catolica de Chile has approved the study protocol and signed informed consent will be obtained from all participants. The findings of the trial will be disseminated through relevant peer-reviewed journals and

international conference presentations. TRIAL REGISTRATION NUMBER: NCT03026439.

Lee, D. W., H. J. Jin, et al. (2017). **"Presence of sarcopenia in asthma-COPD overlap syndrome may be a risk factor for decreased bone-mineral density, unlike asthma: Korean National Health and Nutrition Examination Survey (KNHANES) IV and V (2008-2011)."** *Int J Chron Obstruct Pulmon Dis* **12**: 2355-2362.

**BACKGROUND:** Sarcopenia and decreased bone-mineral density (BMD) are common in elderly people, and are major comorbidities of obstructive airway disease (OAD). However, the relationship between sarcopenia and BMD in each OAD phenotype, especially asthma-COPD overlap syndrome (ACOS), is not yet clear. We aimed to evaluate differences in BMD according to the presence of sarcopenia in each OAD phenotype. **MATERIALS AND METHODS:** Among the research subjects in KNHANES IV and V (2008-2011), 5,562 were  $\geq 50$  years old and underwent qualified spirometry and dual-energy X-ray absorptiometry. A total of 947 subjects were included in the study: 89 had asthma, 748 COPD, and 110 ACOS. **RESULTS:** In the COPD and ACOS phenotypes, T-scores were lower in the sarcopenia group than the nonsarcopenia group. Prevalence rates of osteopenia and osteoporosis were higher in the sarcopenia group than the nonsarcopenia group. ( $P < 0.001$  and  $P = 0.017$ , respectively). The sarcopenia group had higher risks of developing osteopenia, osteoporosis, and low BMD than the nonsarcopenia group in the ACOS phenotype (OR 6.620, 95% CI 1.129-38.828 [ $P = 0.036$ ], OR 9.611, 95% CI 1.133-81.544 [ $P = 0.038$ ], and OR 6.935, 95% CI 1.194-40.272 [ $P = 0.031$ ], respectively). However, in the asthma phenotype, the sarcopenia group showed no increased risk compared with the nonsarcopenia group. **CONCLUSION:** In the ACOS phenotype, individuals with sarcopenia had a higher prevalence rate and higher risks of osteopenia and osteoporosis than those without sarcopenia among all OAD phenotypes.

Lee, H., Y. Hong, et al. (2018). **"Inflammatory biomarkers and radiologic measurements in never-smokers with COPD: A cross-sectional study from the CODA cohort."** *Chron Respir Dis* **15**(2): 138-145.

Various biomarkers have emerged as potential surrogates to represent various subgroups of chronic obstructive pulmonary disease (COPD), which manifest with different phenotypes. However, the biomarkers representing never-smokers with COPD have not yet been well elucidated. The aim of this study was to evaluate the associations of certain serum and radiological biomarkers with the presence of COPD in never-smokers. To explore the associations of serum and radiological biomarkers with the presence of COPD in never-smokers, we conducted a cross-sectional patient cohort study composed of never-smokers from the COPD in Dusty Areas (CODA) cohort, consisting of subjects living in

dusty areas near cement plants in South Korea. Of the 131 never-smokers in the cohort, 77 (58.8%) had COPD. There were no significant differences in the number of subjects with high levels of inflammatory biomarkers (>90th percentile of never-smokers without COPD), including white blood cell count, total bilirubin, interleukin (IL)-6, IL-8, and C-reactive protein, or radiologic measurements (including emphysema index and mean wall area percentage) between never-smokers with COPD and those without COPD. However, the number of subjects with high uric acid was significantly higher in never-smokers with COPD than never-smokers without COPD (31.2% (24/77) vs. 11.1% (6/54);  $p = 0.013$ ). In addition, multivariate analysis revealed that high uric acid was significantly associated with the presence of COPD in never-smokers (adjusted relative risk: 1.63; 95% confidence interval: 1.21, 2.18;  $p = 0.001$ ). Our study suggests that high serum levels of uric acid might be a potential biomarker for assessing the presence of COPD in never-smokers.

Lee, S. H., S. J. Kim, et al. (2017). **"Hand grip strength and chronic obstructive pulmonary disease in Korea: an analysis in KNHANES VI."** Int J Chron Obstruct Pulmon Dis **12**: 2313-2321.

**BACKGROUND:** Muscle mass is known to be associated with mortality in elderly adults. Because hand grip strength (HGS) is known as a simple assessment tool for muscular strength, many researchers have studied the association between HGS and disease. However, empirical evidence for the relationship between chronic obstructive pulmonary disease (COPD) and HGS is still controversial. The aim of this study was to evaluate the association between COPD and HGS, using Korean population data. **METHODS:** This was a population-based cross-sectional study. Data were obtained from the sixth Korean National Health and Nutrition Examination Survey, which was conducted from 2013 to 2015. To reduce the effects of HGS-related factors and potential confounding factors, propensity score matching was used to match subjects with and without COPD. **RESULTS:** Among 14,930 subjects, 832 were enrolled in each group (non-COPD and COPD) after propensity score matching. COPD subjects did not have lower HGS than non-COPD subjects (non-COPD vs COPD, male,  $38.0 \pm 7.0$  vs  $38.9 \pm 7.0$  kg,  $P=0.044$ , female,  $23.8 \pm 4.6$  vs  $24.2 \pm 4.9$  kg,  $P=0.342$ ). Lung function was classified by Global Initiative for Chronic Obstructive Lung Disease stages and was not significantly associated with HGS. For male COPD subjects, there was a significant correlation between HGS and the EuroQol Five-Dimension Questionnaire (EQ5D) utility score index, which is an indicator of quality of life that adjusts for age and body mass index ( $r=0.201$ ,  $P<0.001$ ). The correlation was absent for female subjects ( $r=0.098$ ,  $P=0.170$ ). **CONCLUSION:** COPD subjects did not have lower HGS than non-COPD subjects. HGS did not associate with lung function. However, the HGS of male COPD subjects was positively associated with EQ5D utility score index, an indicator of quality of life. HGS may be helpful as an additional method to the evaluation of quality of life in male COPD patients.



Lee, S. R., W. T. Kim, et al. (2018). **"Association between the length of the MUC8-minisatellite 5 region and susceptibility to chronic obstructive pulmonary disease (COPD)."** *Genes Genomics* **40**(1): 123-127.

In asthma and chronic obstructive pulmonary disease (COPD), mucins display disease-related alterations caused by airway mucus obstruction. MUC5AC, MUC5B and MUC8 are known as the major secretory mucins in human airway epithelial cells. Analysis of mucin genes has identified the presence of several features with a variable number of tandem repeats (VNTR; minisatellites) in the central region of each mucin. In our previous study, six minisatellites in the region of the MUC8 gene were identified, and the MUC8-MS5 minisatellite showed the highest heterozygosity among them. In this study, we evaluated the relationship between MUC8-MS5 and susceptibility to asthma and COPD. A case-control study was performed with 229 controls, 123 COPD cases and 77 asthma cases. A significant association (OR 3.96) between short alleles (2/2 repeats) and the occurrence of COPD was observed [95% confidence interval (CI) 1.32-11.88;  $p = 0.008$ ]. Hence, the increased frequency of 2/2 homo-short alleles were also found in asthma cases (3.11; CI 0.88-11.05;  $p = 0.066$ ), though this association was not statistically significant. These results revealed a genetic association between MUC8 and COPD, and that the specific short minisatellite alleles (2/2) of MUC8-MS5 may be a risk factor for COPD.

Leong, P., A. Tran, et al. (2017). **"Expiratory central airway collapse in stable COPD and during exacerbations."** *Respir Res* **18**(1): 163.

**BACKGROUND:** Tracheal obstruction resulting from expiratory tracheal deformation has been associated with respiratory symptoms and severe airway exacerbations. In chronic obstructive pulmonary disease (COPD), acute exacerbations (AECOPD) create large intrathoracic pressure swings which may increase tracheal deformation. Excessive central airway collapse (ECAC) may be diagnosed when the tracheal area on expiration is less than 50% of that on inspiration. The prevalence of ECAC in AECOPD and its temporal course have not been systematically studied. **METHODS:** We prospectively recruited healthy volunteers ( $n = 53$ ), stable outpatients with COPD ( $n = 40$ ) and patients with hospitalised acute exacerbations of COPD (AECOPD,  $n = 64$ ). 17 of the AECOPD group returned for repeat evaluation when clinically well at 6-12 weeks. All subjects underwent dynamic 320-slice computed tomography of the larynx and trachea during tidal breathing, enabling quantitation of tracheal area and dimensions (mean  $\pm$  SD). **RESULTS:** No healthy individuals had ECAC. The prevalence of ECAC in stable COPD and AECOPD was 35% and 39% respectively. Mean tracheal collapse did not differ between stable COPD (57.5  $\pm$  19.8%), AECOPD (53.8  $\pm$  19.3%) and in the subset who returned when convalescent (54.9  $\pm$  17.2%). AECOPD patients with and without ECAC had similar clinical characteristics. **CONCLUSIONS:** Tracheal collapse in both stable and AECOPD is considerably more prevalent than in healthy individuals. ECAC warrants assessment as part of comprehensive COPD evaluation and

management. Further studies should evaluate the aetiology of ECAC and whether it predisposes to exacerbations.

Li, Y., J. Feng, et al. (2018). **"Assessment of a Domiciliary Integrated Pulmonary Rehabilitation Program for Patients with a History of Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Retrospective 12-Month Observational Study."** *Med Sci Monit* **24**: 5054-5063.

**BACKGROUND** Integrated pulmonary rehabilitation (PR) in chronic obstructive pulmonary disease (COPD) may prevent acute exacerbations of COPD (AECOPD). The aim of this study was to evaluate the effectiveness, before and 12 months after, the use of an integrated PR program in patients discharged from hospital for AECOPD. **MATERIAL AND METHODS** A retrospective observational clinical study included patients diagnosed with COPD who participated in a domiciliary integrated PR program that included a weekly phone interview supervised by a respiratory team. A six-minute walk test (6MWT), COPD assessment test (CAT), and the modified Medical Research Council scale (mMRC) were evaluated every three months. **RESULTS** Of the 303 eligible patients, 267 patients (88.1%), with a mean age of 64.9 $\pm$ 8.7 years, a mean FEV1 percentage predicted of 48.8 $\pm$ 12.9%, successfully completed the 12-month study program and achieved a significant improvement in their clinical performance with a significantly reduced frequency of episodes of EACOPD (3.1 $\pm$ 1.7 vs. 2.0 $\pm$ 1.4) ( $p$ <0.001), a significant reduction in emergency department visits (2.5 $\pm$ 1.5 vs. 1.2 $\pm$ 1.1) ( $p$ <0.001), and significantly reduced episodes of hospitalization (2.0 $\pm$ 1.2 vs. 1.4 $\pm$ 1.2) ( $p$ <0.001). Significant patient benefits were found during the 12-month study, on CAT, mMRC, and patient well-being when compared with the end of the study after 12 months ( $p$ <0.001). **CONCLUSIONS** A multidisciplinary integrated PR program maintained a significant clinical improvement, in patients with COPD by reducing episodes of AECOPD, CAT, mMRC, emergency hospital admissions, and improved patient well-being, for the duration of the program.

Liao, K. M. and C. Y. Chen (2017). **"Incidence and risk factors of atrial fibrillation in Asian COPD patients."** *Int J Chron Obstruct Pulmon Dis* **12**: 2523-2530.

**OBJECTIVE:** To investigate the incidence and risk factors of atrial fibrillation (AF) in Asian chronic obstructive pulmonary disease (COPD) patients. **PATIENTS AND METHODS:** We selected a study population older than 40 years with a COPD diagnosis and who had used at least one inhaled bronchodilator medication between 1998 and 2012. The date of the index COPD diagnosis was defined as the index date. We excluded patients with a history of AF, significant mitral valve disease, disorders of the thyroid gland, or ischemic heart disease before the index date. We followed all patients from the index date to the day of AF occurrence, the day of death, or the date of December 31, 2013. The baseline of

comorbidities was identified before the index date. Comorbidities included hypertension, diabetes mellitus, end-stage renal disease, congenital heart failure, stroke, peripheral arterial occlusive disease, and malignancy. RESULTS: We included 6,208 COPD patients and 12,409 patients without COPD. The incidence of AF was higher in COPD patients than in those without COPD. The adjusted hazard ratio (HR) for AF among those with COPD was 2.23 with a 95% confidence interval (CI) of 1.98-2.51 compared to those without COPD. After multiple analyses, patients with hypertension (HR 1.43 [95% CI =1.26-1.62]) or heart failure (HR 2.36 [95% CI =1.81-3.08]) were found to have a significantly higher incidence of AF than those without these conditions. CONCLUSION: It is important for physicians to monitor, prevent, and provide early intervention for AF in COPD patients with hypertension or heart failure.

Liao, K. M., Y. C. Chen, et al. (2018). **"Trends in intensive care unit admissions of COPD patients from 2003 to 2013 in Taiwan."** Int J Chron Obstruct Pulmon Dis **13**: 2007-2012.

Objective: The objective of this study was to investigate the trends in COPD patients admitted to the intensive care unit (ICU) in Taiwan from 2003 to 2013. Patients and methods: A retrospective study was conducted to analyze the available data in the National Health Insurance Research Database compiled by the Taiwan Department of Health. We selected patients admitted to the ICU nationwide from 2003 to 2013. Patients older than 40 years with a diagnosis of COPD were enrolled. The ICU admission date was used as the index date. Baseline comorbidities existing before the index date were identified. The comorbidities of interest included diabetes, hypertension, diabetes mellitus, coronary artery disease, stroke, dyslipidemia, cancer, and end-stage renal disease. Results: The number of COPD patients in the ICU increased from 12,384 in 2003 to 13,308 in 2013 ( $P<0.0001$ ). The mean age of patients and SD was 76.66 $\pm$ 9.48 and 78.32 $\pm$ 10.59 in 2003 and 2013, respectively. The percentage of COPD patients aged  $\geq 70$  years in the ICU decreased markedly. COPD patients per 10,000 ICU patients decreased for both males and females. The length of ICU stays, and in-hospital mortality increased from 21.58 to 23.14 days and 14.97% to 30.98% from 2003 to 2013, respectively. Conclusion: The number of COPD patients admitted to the ICU in Taiwan increased over the 11-year study period. Increased mean patient age, length of ICU stays, hospital mortality, and comorbidities were observed. The use of a nationwide population-based database allowed for a sufficient sample size, generalizability, and statistical power to analyze COPD patients admitted to the ICU in Taiwan.

Lim, J. U., J. H. Lee, et al. (2018). **"Alternative definitions of chronic bronchitis and their correlation with CT parameters."** Int J Chron Obstruct Pulmon Dis **13**: 1893-1899.

Introduction: Phenotyping of chronic bronchitis (CB) using COPD assessment tool (CAT) scores and St George's Respiratory Questionnaire (SGRQ) has rarely been attempted. The present study defined CB using CAT 1 and 2 scores and the questions on the severity of cough and sputum from the SGRQ. Furthermore, the predictability of CT parameters was also assessed for each CB definition. Materials and methods: Patients enrolled in the Korean Obstructive Lung Disease study from June 2005 to October 2015 were evaluated for this study. The patients were spirometrically diagnosed with COPD and had a smoking history of >10 pack-years. Volumetric CT scans were performed for each patient upon enrollment in the cohort. Two definitions of CB using CAT 1/2 scores and SGRQ questions were used to phenotype CB among the study patients. Receiver operating characteristic curve analysis was performed to estimate the predictability of CT parameters for the CB phenotypes. Results: Using CAT 1/2 scores, 57 of 279 (20.4%) patients had CB, and 178 of 573 (31.1%) had CB when the SGRQ questions were used to phenotype it. Total CAT and SGRQ scores were significantly higher in the CB group than those in the non-CB group for both definitions of CB. Forced expiratory volume in 1 second was lower for both CAT-defined and SGRQ-defined CB than that in the non-CB group. Mean wall thickness was significantly higher for both CB groups than in the non-CB group. Expiratory lung volume was higher and mean lung density was significantly lower for the SGRQ-defined CB group than non-CB group. Conclusion: The 2 CB definitions using CAT scores and the SGRQ questions correlated with associated CT airway parameters. SGRQ-defined CB better reflected the accompaniment of small airway obstruction when compared with CAT-defined CB.

Liu, S., Y. Zhou, et al. (2018). **"Clinical impact of the lower limit of normal of FEV1/FVC on detecting chronic obstructive pulmonary disease: A follow-up study based on cross-sectional data."** *Respir Med* **139**: 27-33.

BACKGROUND: Criteria of obstruction that establish a diagnosis of COPD have been debated in recent years. We carried out a follow-up study to assess the impact of the new LLN reference equation for Chinese on detecting COPD compared with the traditional 0.7fixed criteria. METHODS: We examined the prevalence and characteristics of airflow limitation for a non-child population using post-bronchodilator airflow with both age-dependent predicted lower limit of the normal value and fixed-ratio spirometric criterion. Questionnaires and spirometry were completed for all eligible subjects during the baseline examination. Participants with inconsistent diagnosis according to the two criteria, normal participants (controls) and COPD patients in stages I or II, were invited to take a cardiopulmonary exercise testing (CPET) examination and follow up for 2-4 years. RESULTS: A total of 5448 (mean age 50.51+/-13.2yr) study subjects with acceptable spirometry and complete questionnaire data were included in our final analyses. COPD detection based on LLN was consistent with the GOLD 0.7 fixed-ratio in general, as 51 subjects (0.9%) were underdiagnosed, and 61 subjects (1.1%) were overdiagnosed when using LLN as the reference diagnostic criterion. The underdiagnosed subjects were younger, had more symptoms, more exposure to biofuels and worse FEV1 than the normal group; they also

demonstrated a damaged cardiopulmonary reserve capacity and significant FEV1 decline. Except for being older, the overdiagnosed subjects differed little from the normal group. CONCLUSIONS: Individual-dependent LLN appears to better reveal impacts on detecting airflow limitation. Participants underdiagnosed by GOLD criterion should be paid more attention. CLINICAL TRIAL REGISTRATION: ChiCTR-ECS-13004110.

Luczak-Wozniak, K., M. Dabrowska, et al. (2018). **"Mishandling of pMDI and DPI inhalers in asthma and COPD - Repetitive and non-repetitive errors."** Pulm Pharmacol Ther **51**: 65-72.

BACKGROUND: Pharmacological treatment of asthma and chronic obstructive pulmonary disease (COPD) is based mainly on inhaled medications. There is a continuous need to examine and train patients in their inhalation technique. The objective of the presented study is to determine whether the errors which patients made during inhalations are repetitive, and therefore easier to eradicate, or rather accidental, hence require more attention and effort from the health care professionals. METHODS: It was a prospective, cohort study which included adults with asthma or COPD, who have used at least one inhaler daily on a regular basis. Inhalation technique was evaluated twice in a six months interval basing on a list of the most common errors in the inhalation technique. There was no training of inhalation skills between visits. RESULTS: There were 92 patients (46 asthmatics, 46 with COPD; median age 66 years, median duration of the disease 10 years) included into the analysis. 92% of patients made at least one error during their inhalation. Among pMDI users the most common device mishandlings were: no or too short breath-holding after inhalation (60% of the patients during the first visit; 50% during the 2nd), too rapid and too forceful inhalation (52%; 61%) and lack of exhalation before the use of the medicine (48%; 43%). Among the DPI users, the most numerous errors were: no or too short (less than 3s) breath-holding after inhalation (62%; 55%) and slow and not forceful enough inhalation (38%; 36%). When comparing the mishandlings in the inhalation technique conducted during the first and second visit the majority of the errors conducted by the patients were repetitive. However, some errors such as too early termination of inhalation ( $p=0.016$ ), inhalation through the nose during actuation ( $p=0.002$ ) among pMDI users and lack of expiration before inhalation ( $p=0.027$ ) among DPI users, were non-permanent. CONCLUSIONS: Improper inhalation technique is very common and the majority of errors made in inhalation technique are repetitive. This emphasizes the role of an ongoing verification and training of a proper inhalation technique in all patients that are regularly treated with inhalers.

Magadzire, B. P., T. Mathole, et al. (2017). **"Reasons for missed appointments linked to a public-sector intervention targeting patients with stable chronic**

**conditions in South Africa: results from in-depth interviews and a retrospective review of medical records." *BMC Fam Pract* 18(1): 82.**

**BACKGROUND:** Missed appointments serve as a key indicator for adherence to therapy and as such, identifying patient reasons for this inconsistency could assist in developing programmes to improve health outcomes. In this article, we explore the reasons for missed appointments linked to a centralised dispensing system in South Africa. This system dispenses pre-packed, patient-specific medication parcels for clinically stable patients to health facilities. However, at least 8%-12% of about 300,000 parcels are not collected each month. This article aims to establish whether missed appointments for collection of medicine parcels are indicative of loss-to-follow-up and also to characterise the patient and health system factors linked to missed appointments. **METHODS:** We applied an exploratory mixed-methods design in two overlapping research phases. This involved in-depth interviews to yield healthcare practitioners' and patients' experiences and medical record reviews. Data collection was conducted during the period 2014-2015. Qualitative data were analysed through a hybrid process of inductive and deductive thematic analysis which integrated data-driven and theory-driven codes. Data from medical records (N = 89) were analysed in MS excel using both descriptive statistics and textual descriptions. **RESULTS:** Review of medical records suggests that the majority of patients (67%) who missed original appointments later presented voluntarily to obtain medicines. This could indicate a temporal effect of some barriers. The remaining 33% revealed a range of CDU implementation issues resulting from, among others, erroneous classification of patients as defaulters. Interviews with patients revealed the following reasons for missed appointments: temporary migration, forgetting appointments, work commitments and temporary switch to private care. Most healthcare practitioners confirmed these barriers to collection but perceived that some were beyond the scope of health services. In addition, healthcare practitioners also identified a lack of patient responsibility, under-utilisation of medicines and use of plural healthcare sources (e.g. traditional healers) as contributing to missed appointments. **CONCLUSION:** We suggest developing a patient care model reflecting the local context, attention to improving CDU's implementation processes and strengthening information systems in order to improve patient monitoring. This model presents lessons for other low-and-middle income countries with increasing need for dispensing of medicines for chronic illnesses.

Makinson, A., M. Hayot, et al. (2018). "**HIV is associated with airway obstruction: a matched controlled study.**" *Aids* 32(2): 227-232.

**OBJECTIVE:** To explore whether airway obstruction is associated with HIV in a cohort of HIV-infected and uninfected smokers. **METHODS:** People living with HIV (PLWHIV) participated in the ANRS EP48 HIV CHEST study, an early lung cancer diagnosis study with low-dose chest tomography. HIV-uninfected study participants were from the CONSTANCES cohort. Inclusion criteria were an age greater than 40 years, a smoking history of at least 20 pack-years, and for PLWHIV, a CD4 T-lymphocyte nadir less than 350/mul and last CD4 cell count more than 100 cells/mul. Two randomly selected HIV-uninfected study

participants were matched by age and sex with one PLWHIV. Prebronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio was the primary outcome, and association of FEV1/FVC ratio less than 0.70 and FEV1 less than 80% of the theoretical value, as a proxy of chronic obstructive pulmonary disease, the secondary outcome. RESULTS: In total, 351 PLWHIV and 702 HIV-uninfected study participants were included. Median age was 50 years, and 17% of study participants were women. Plasma HIV RNA was less than 50 copies/ml in 89% of PLWHIV, with a median CD4 cell count of 573 cells/mul. HIV (beta -2.19), age (per 10 years increase; beta -2.81), tobacco use (per 5 pack-years increase; beta -0.34), and hepatitis C virus serology (beta-2.50) were negatively associated with FEV1/FVC. HIV [odds ratio (OR: 1.72)], age (per 10 years increase; OR 1.77), and tobacco use (per 5 pack-years increase; OR 1.11) were significantly associated with the secondary outcome. CONCLUSION: Our study found a significant association of airway obstruction with HIV status in smokers aged more than 40 years with previous immunodeficiency.

Maltais, F., R. Buhl, et al. (2018). "**beta-Blockers in COPD: A Cohort Study From the TONADO Research Program.**" *Chest* **153**(6): 1315-1325.

BACKGROUND: Cardiovascular disease is a frequent comorbidity in patients with COPD. Many physicians, particularly pulmonologists, are reluctant to use beta-adrenoceptor blocking agents (beta-blockers) in patients with COPD, despite their proven effectiveness in preventing cardiovascular events. METHODS: The large (5,162 patients) phase III TONADO 1 and 2 studies assessed lung function and patient-reported outcomes in patients with moderate to very severe COPD receiving long-acting bronchodilator treatment across 1 year. This post hoc analysis characterized lung-function changes, patient-reported outcomes, and safety in the subgroup of patients receiving beta-blockers in the studies. RESULTS: In total, 557 of 5,162 patients (11%) received beta-blockers at baseline. Postbronchodilator FEV1 at baseline was higher in the beta-blocker group (1.470 L) compared with that in the no beta-blocker group (1.362 L). As expected, patients receiving beta-blockers had a more frequent history of cardiovascular comorbidities and medications. Lung function improved from baseline in patients with or those without beta-blocker treatment, and no relevant between-group differences were observed in trough FEV1 or trough FVC at 24 or 52 weeks. No relevant differences were observed for St. George's Respiratory Questionnaire results and Transition Dyspnea Index in patients with beta-blockers compared with those in patients without. Safety findings were comparable between groups. CONCLUSIONS: Lung function, overall respiratory status, and safety of tiotropium/olodaterol were not influenced by baseline beta-blocker treatment in patients with moderate to very severe COPD. Results from this large patient cohort support the cautious and appropriate use of beta-blockers in patients with COPD and cardiovascular comorbidity. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01431274 and No. NCT01431287; URL: [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

Medina-Mirapeix, F., R. Bernabeu-Mora, et al. (2018). **"Patterns and predictors of exhaustion episodes in patients with stable COPD: A longitudinal study."** *Int J Clin Pract* **72**(5): e13068.

**BACKGROUND AND OBJECTIVE:** Exhaustion is the perception of low energy. Little is known about how exhaustion persists, remits or reappears over time in patients with chronic obstructive pulmonary disease (COPD) or how to predict these events. We determined the likelihood of transitions between states of exhaustion and no exhaustion among patients with stable COPD followed up for 2 years. We investigated combinations of potential factors for their abilities to predict new-onset exhaustion episodes. **METHODS:** We prospectively included 137 patients with stable COPD (mean age, 66.9 years  $\pm$  8.3). Exhaustion states were measured at baseline and 1 and 2 years later. Exhaustion was defined as an answer of "most of the time" or "a moderate amount of time" to 1 of 2 questions: "How often have you found it hard to get going?" and "How often does everything seem to require effort?" We evaluated demographic, non-respiratory and respiratory variables as potential predictors. The likelihoods of new episodes and recovery were calculated. Predictors were evaluated with generalised estimating equations. **RESULTS:** At baseline, 27 patients (19.7%) displayed exhaustion. Of the 110 patients without exhaustion at baseline, 17 (15.5%) displayed exhaustion at least once during the follow-up period. During the study period, a total of 204 annual transitions displaying no exhaustion at the beginning were identified. Of them, 10.3% transitioned to exhaustion in the next year. The likelihood of recovery after exhaustion was 50%. Independent predictors of new-onset exhaustion episodes within the following year were: the COPD assessment test score (odds ratio [OR] = 1.10; 95% confidence interval [CI] 1.01-1.21), depression (OR = 6.89; 95% CI: 1.00-47.41) and female gender (OR = 6.88; 95% CI: 1.83-25.73). **CONCLUSIONS:** Patients in stable COPD with high CAT scores and depression were most likely to experience new-onset exhaustion episodes. Thus, exhaustion might be predicted by a combination of psychological factors and respiratory health status. Nevertheless, exhaustion is dynamic in COPD; half of patients recover from exhaustion.

Meier-Schroers, M., A. M. Sprinkart, et al. (2018). **"Quantitative and Qualitative Assessment of Pulmonary Emphysema with T2-Weighted PROPELLER MRI in a High-Risk Population Compared to Low-Dose CT."** *Rofo* **190**(8): 733-739.

**PURPOSE:** To determine the suitability of T2-weighted PROPELLER MRI for the assessment of pulmonary emphysema. **MATERIALS AND METHODS:** 60 participants in a lung cancer screening program (30 subjects with pulmonary emphysema, and 30 control subjects without emphysema) were included for this retrospective study. All subjects were examined with low-dose CT (LDCT) and MRI within the screening program. The use of a T2-weighted PROPELLER sequence for the assessment of emphysema was analyzed and correlated with



the results of LDCT. The presence and the extent of pulmonary emphysema were first assessed qualitatively using a three-point score, and then quantitatively with a semi-automated software program to obtain emphysema indices.

**RESULTS:** All 30 cases with pulmonary emphysema were accurately detected by MRI. There were 3 cases with emphysema according to MRI without emphysematous changes on LDCT (false-positive results). The qualitative scores as well as the emphysema indices were significantly higher in the emphysema group compared to the control group for MRI and LDCT ( $p < 0.001$ ). Both the scores and the indices correlated significantly between MRI and LDCT (qualitative score of severity:  $r = 0.912/p < 0.001$  in the emphysema group and  $r = 0.668/p < 0.001$  in the control group; emphysema index:  $r = 0.960/p < 0.001$  in the emphysema group and  $r = 0.746/p < 0.001$  in the control group).

**CONCLUSION:** The presence and the extent of pulmonary emphysema may be assessed qualitatively and quantitatively by T2-weighted PROPELLER MRI with very good correlation to LDCT. **KEY POINTS:** . T2-weighted PROPELLER MRI may be suitable for the assessment of pulmonary emphysema.. . There was significant correlation between MRI and LDCT regarding qualitative scores and quantitative emphysema indices in our study with correlation coefficients for different subgroups ranging from  $r = 0.668$  to  $r = 0.960$ .. . T2-weighted PROPELLER MRI may have the potential to be used for follow-up examinations in patients with severe emphysema to avoid radiation exposure of repeated CTs.. **CITATION FORMAT:** . Meier-Schroers M, Sprinkart AM, Becker M et al. Quantitative and Qualitative Assessment of Pulmonary Emphysema with T2-Weighted PROPELLER MRI in a High-Risk Population Compared to Low-Dose CT. *Fortschr Rontgenstr* 2018; 190: 733 - 739.

Mendy, A., E. Forno, et al. (2018). "**Blood biomarkers as predictors of long-term mortality in COPD.**" *Clin Respir J* 12(5): 1891-1899.

**BACKGROUND:** Blood biomarkers are easily accessible and might reflect chronic obstructive pulmonary disease (COPD) activity. **AIM:** The aim of this study was to determine whether a panel of blood biomarkers [C-reactive protein (CRP), neutrophils, eosinophils, albumin and vitamin D] could predict mortality in COPD. **METHODS:** We analyzed data from 431 COPD participants to the 2007-2010 National Health and Nutrition Examination Surveys who were followed for a median time of 36 months. COPD was defined as post-bronchodilator forced expiratory volume in 1 second (FEV1) and forced vital capacity ratio  $< 0.70$ . Weibull survival analysis adjusted for covariates was performed to calculate the risk of mortality associated with the biomarkers, and C-statistics was used to assess their added predictive value. **RESULTS:** During follow-up, 38 of the 431 participants died. Participants with high CRP, eosinophil count  $< 2\%$ , hypoalbuminemia and hypovitaminosis D had worse baseline FEV1 and subsequently higher mortality compared to controls. In adjusted analysis, increasing CRP [hazard ratio (HR): 4.45, 95% CI: 1.91-10.37] and neutrophil count (HR: 1.07, 95% CI: 1.03-1.11) as well as decreasing eosinophil count (HR: 7.03, 95% CI: 2.05-24.01) were associated with an increased risk of mortality. The addition of CRP with eosinophil and/or neutrophil count significantly improved a base model for the prediction of mortality which included age,

gender, race/ethnicity, body mass index, smoking, poverty income ratio, asthma, diabetes, hypertension and history of stroke or myocardial infarction.

CONCLUSION: High CRP and neutrophils as well as low eosinophils are predictive of poor COPD prognosis. They also add significant value to prediction models of mortality in COPD.

Michaeloudes, C., C. H. Kuo, et al. (2017). "**Metabolic re-patterning in COPD airway smooth muscle cells.**" Eur Respir J **50**(5) Chronic obstructive pulmonary disease (COPD) airways are characterised by thickening of airway smooth muscle, partly due to airway smooth muscle cell (ASMC) hyperplasia. Metabolic reprogramming involving increased glycolysis and glutamine catabolism supports the biosynthetic and redox balance required for cellular growth. We examined whether COPD ASMCs show a distinct metabolic phenotype that may contribute to increased growth. We performed an exploratory intracellular metabolic profile analysis of ASMCs from healthy nonsmokers, healthy smokers and COPD patients, under unstimulated or growth conditions of transforming growth factor (TGF)-beta and fetal bovine serum (FBS). COPD ASMCs showed impaired energy balance and accumulation of the glycolytic product lactate, glutamine, fatty acids and amino acids compared to controls in unstimulated and growth conditions. Fatty acid oxidation capacity was reduced under unstimulated conditions. TGF-beta/FBS-stimulated COPD ASMCs showed restoration of fatty acid oxidation capacity, upregulation of the pentose phosphate pathway product ribose-5-phosphate and of nucleotide biosynthesis intermediates, and increased levels of the glutamine catabolite glutamate. In addition, TGF-beta/FBS-stimulated COPD ASMCs showed a higher reduced-to-oxidised glutathione ratio and lower mitochondrial oxidant levels. Inhibition of glycolysis and glutamine depletion attenuated TGF-beta/FBS-stimulated growth of COPD ASMCs. Changes in glycolysis, glutamine and fatty acid metabolism may lead to increased biosynthesis and redox balance, supporting COPD ASMC growth.

Millares, L., S. Marti, et al. (2017). "**Specific IgA against Pseudomonas aeruginosa in severe COPD.**" Int J Chron Obstruct Pulmon Dis **12**: 2807-2811.

BACKGROUND: The bronchial mucosa is protected by a specialized immune system focused on the prevention of colonization and infection by potentially pathogenic microorganisms (PPMs). Immunoglobulin A (IgA) is the principal antibody involved in this mechanism. A defective immune barrier may facilitate the recurrent presence of PPMs in COPD. PURPOSE: The aim of this study was to determine IgA-mediated bronchial specific immune responses against Pseudomonas aeruginosa in stable patients with severe disease. METHODS: COPD patients with good-quality sputum samples obtained during stability were included and classified according to the presence or absence of chronic bronchial colonization by P. aeruginosa. Levels of specific IgA for P. aeruginosa

in sputum were determined by ELISA and expressed as ratios, using the pooled level of 10 healthy subjects as reference (optical density 450 patient/control). RESULTS: Thirty-six stable COPD patients were included, 15 of whom had chronic colonization by *P. aeruginosa*. Levels of specific IgA against *P. aeruginosa* in stable non-colonized patients were lower than those in healthy subjects (IgA ratio: median = 0.15 [interquartile range {IQR} 0.05-0.36]). Colonized patients had higher levels, (1.56 [IQR 0.59-2.79]) ( $p < 0.001$ , Mann-Whitney U test), with figures equivalent but not exceeding the reference value. CONCLUSION: IgA-based immune response against *P. aeruginosa* was low in severe COPD patients. Levels of specific IgA against this microorganism were higher in colonized patients, but did not attain clear-cut levels above the reference. An impaired local response against *P. aeruginosa* may favor chronic colonization and recurrent infections in severe COPD.

Muller, J., H. J. Lim, et al. (2017). **"Influence of fissure integrity on quantitative CT and emphysema distribution in emphysema-type COPD using a dedicated COPD software."** Eur J Radiol **95**: 293-299.

OBJECTIVES: Fissure integrity (FI) plays a key role in selecting patients for interventional emphysema therapy. We investigated its interference with automated lobar segmentation in quantitative computed tomography (CT) and emphysema distribution. METHODS: CT was available for 50 patients with chronic obstructive pulmonary disease (COPD). Lobe segmentation was performed fully automated by software and corrected manually. FI was evaluated visually using a %-scale. The influence of FI on emphysema ratio (ER=percentage of lung volume with density values  $< -950$  HU), mean lung density (MLD), emphysema and total volume of adjacent lobes was analyzed. Lobe-based results were compared with respect to FI. RESULTS: Differences in ER in adjacent lobes for complete vs. incomplete fissures were 12.4% for the right horizontal, 0.2% and 3% for the right oblique and 4.4% for the left oblique fissure (all  $p > 0.05$ ). Results for emphysema comparing automated vs. manually corrected segmentation exceeded clinically acceptable values, but were not significantly affected by FI ( $p > 0.05$ ). The widest limits of agreement for ER and MLD were noted in the right middle lobe ([-14, 17.4%], [-22.4, 32.4 Hounsfield Units]). CONCLUSIONS: Automated lobe segmentation and emphysema distribution are not significantly affected by FI. Manual correction of automated lobar segmentation is still recommended in severe emphysema.

Nagar, S., J. Patel, et al. (2018). **"Characteristics and health care resource use of subjects with COPD in the year before initiating LAMA monotherapy or LAMA+LABA combination therapy: A U.S. database study."** Manag Care **27**(5): 40-47.

**PURPOSE:** To characterize subjects with chronic obstructive pulmonary disease (COPD) newly initiated on long-acting muscarinic antagonists (LAMA) or dual LAMA/long-acting beta2-adrenergic agonist (LABA) therapy. **DESIGN:** This pilot/preliminary analysis was a retrospective crosssectional study of subjects with COPD from the Optum Impact National Managed Care Benchmark Database. **METHODOLOGY:** Subjects with at least one LAMA prescription in the index period (July 2008-June 2009) were included and stratified by treatment. Data were collected in the year before the index date and included comorbidities, medication use, COPD-related costs, health care resource use, and exacerbations. **RESULTS:** Of 5,311 eligible subjects, 2,057 initiated LAMA therapy (LAMA cohort) and 191 initiated LAMA+LABA therapy (LAMA+LABA cohort). The Charlson comorbidity index was slightly lower in the LAMA+LABA cohort than the LAMA cohort (mean $\pm$ -SD: 0.63 $\pm$ -1.13 vs. 0.66 $\pm$ -1.28), but the number of prescriptions was higher (mean $\pm$ -SD: 42.9 $\pm$ -23.2 vs. 30.5 $\pm$ -27.2). The LAMA+LABA cohort had higher short-acting inhaled beta2 agonist (56.0% vs. 35.7%), oral corticosteroid (37.7% vs. 32.6%), and home oxygen therapy use (14.1% vs. 3.2%) than the LAMA cohort. Total medical costs were greater in the LAMA+LABA cohort than the LAMA cohort (mean $\pm$ -SD: \$3,320.40 $\pm$ -4085.9 vs. \$1,226.20 $\pm$ -3602.9), although emergency department (\$11.00 $\pm$ -66.8 vs. \$30.70 $\pm$ -259.2) and outpatient visit (\$39.60 $\pm$ -163.1 vs. \$41.70 $\pm$ -424.3) costs were lower. Resource use and exacerbation incidence were similar between cohorts. **CONCLUSION:** In this first look, subjects with COPD initiating LAMA or LAMA+LABA therapy exhibited different clinical and resource use characteristics in the year before treatment. Subjects receiving LAMA+LABA were older, with higher COPD co-medication use, more prescriptions, and associated higher pharmacy costs compared with subjects initiating LAMA. These differences may reflect a higher severity of COPD in those starting LABA+LAMA treatment.

Nagaraj, C., C. Tabeling, et al. (2017). **"Hypoxic vascular response and ventilation/perfusion matching in end-stage COPD may depend on p22phox."** *Eur Respir J* **50**(1) Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease in which the amount of emphysema and airway disease may be very different between individuals, even in end-stage disease. Emphysema formation may be linked to the involvement of the small pulmonary vessels. The NAPDH oxidase (Nox) family is emerging as a key disease-related factor in vascular diseases, but currently its role in hypoxia-induced pulmonary remodelling in COPD remains unclear. Here we investigate the role of p22phox, a regulatory subunit of Nox, in COPD lungs, hypoxic pulmonary vasoconstriction (HPV), hypoxia-induced pulmonary vascular remodelling and pulmonary hypertension. In COPD, compared to control lungs, p22phox expression was significantly reduced. The expression was correlated positively with mean pulmonary arterial pressure and oxygenation index and negatively with the diffusing capacity of the lung for carbon monoxide ( $p < 0.02$ ). This suggests a role of p22phox in ventilation/perfusion ratio matching, vascular remodelling and loss of perfused lung area. In p22phox(-/-) mice, HPV was significantly impaired. In the chronic hypoxic setting, lack of p22phox was associated with improved right ventricular function and decreased pulmonary vascular remodelling. p22phox-

dependent Nox plays an important role in the COPD phenotype, by its action on phase II HPV and chronic vascular remodelling.

Noell, G., B. G. Cosio, et al. (2017). **"Multi-level differential network analysis of COPD exacerbations."** *Eur Respir J* **50**(3) Patients with chronic obstructive pulmonary disease (COPD) often suffer episodes of exacerbation (ECOPD) that impact negatively the course of their disease. ECOPD are heterogeneous events of unclear pathobiology and non-specific diagnosis. Network analysis is a novel research approach that can help unravelling complex biological systems. We hypothesised that the comparison of multi-level (i.e., clinical, physiological, biological, imaging and microbiological) correlation networks determined during ECOPD and convalescence can yield novel patho-biologic information. In this proof-of-concept study we included 86 patients hospitalised because of ECOPD in a multicentre study in Spain. Patients were extensively characterised both during the first 72 h of hospitalisation and during clinical stability, at least 3 months after hospital discharge. We found that 1) episodes of ECOPD are characterised by disruption of the network correlation observed during convalescence; and 2) a panel of biomarkers that include increased levels of dyspnoea, circulating neutrophils and C-reactive protein (CRP) has a high predictive value for ECOPD diagnosis (AUC 0.97). We conclude that ECOPD 1) are characterised by disruption of network homeokinesis that exists during convalescence; and 2) can be identified objectively by using a panel of three biomarkers (dyspnoea, circulating neutrophils and CRP levels) frequently determined in clinical practice.

Obeidat, M., X. Li, et al. (2017). **"Surfactant protein D is a causal risk factor for COPD: results of Mendelian randomisation."** *Eur Respir J* **50**(5) Surfactant protein D (SP-D) is produced primarily in the lung and is involved in regulating pulmonary surfactants, lipid homeostasis and innate immunity. Circulating SP-D levels in blood are associated with chronic obstructive pulmonary disease (COPD), although causality remains elusive. In 4061 subjects with COPD, we identified genetic variants associated with serum SP-D levels. We then determined whether these variants affected lung tissue gene expression in 1037 individuals. A Mendelian randomisation framework was then applied, whereby serum SP-D-associated variants were tested for association with COPD risk in 11 157 cases and 36 699 controls and with 11 years decline of lung function in the 4061 individuals. Three regions on chromosomes 6 (human leukocyte antigen region), 10 (SFTPD gene) and 16 (ATP2C2 gene) were associated with serum SP-D levels at genome-wide significance. In Mendelian randomisation analyses, variants associated with increased serum SP-D levels decreased the risk of COPD (estimate -0.19,  $p=6.46 \times 10^{-03}$ ) and slowed the lung function decline (estimate=0.0038,  $p=7.68 \times 10^{-3}$ ). Leveraging genetic variation effect on protein,

lung gene expression and disease phenotypes provided novel insights into SP-D biology and established a causal link between increased SP-D levels and protection against COPD risk and progression. SP-D represents a very promising biomarker and therapeutic target for COPD.

Occhipinti, M., M. Paoletti, et al. (2018). **"Emphysematous and Nonemphysematous Gas Trapping in Chronic Obstructive Pulmonary Disease: Quantitative CT Findings and Pulmonary Function."** *Radiology* **287**(2): 683-692.

**Purpose** To identify a prevalent computed tomography (CT) subtype in patients with chronic obstructive pulmonary disease (COPD) by separating emphysematous from nonemphysematous contributions to total gas trapping and to attempt to predict and grade the emphysematous gas trapping by using clinical and functional data. **Materials and Methods** Two-hundred and two consecutive eligible patients (159 men and 43 women; mean age, 70 years [age range, 41-85 years]) were prospectively studied. Pulmonary function and CT data were acquired by pulmonologists and radiologists. Noncontrast agent-enhanced thoracic CT scans were acquired at full inspiration and expiration, and were quantitatively analyzed by using two software programs. CT parameters were set as follows: 120 kVp; 200 mAs; rotation time, 0.5 second; pitch, 1.1; section thickness, 0.75 mm; and reconstruction kernels, b31f and b70f. Gas trapping obtained by difference of inspiratory and expiratory CT density thresholds (percentage area with CT attenuation values less than -950 HU at inspiration and percentage area with CT attenuation values less than -856 HU at expiration) was compared with that obtained by coregistration analysis. A logistic regression model on the basis of anthropometric and functional data was cross-validated and trained to classify patients with COPD according to the relative contribution of emphysema to total gas trapping, as assessed at CT. **Results** Gas trapping obtained by difference of inspiratory and expiratory CT density thresholds was highly correlated ( $r = 0.99$ ) with that obtained by coregistration analysis. Four groups of patients were distinguished according to the prevalent CT subtype: prevalent emphysematous gas trapping, prevalent functional gas trapping, mixed severe, and mixed mild. The predictive model included predicted forced expiratory volume in 1 second/vital capacity, percentage of predicted forced expiratory volume in 1 second, percentage of diffusing capacity for carbon monoxide, and body mass index as emphysema regressors at CT, with 81% overall accuracy in classifying patients according to its extent. **Conclusion** The relative contribution of emphysematous and nonemphysematous gas trapping obtained by coregistration of inspiratory and expiratory CT scanning can be determined accurately by difference of CT inspiratory and expiratory density thresholds. CT extent of emphysema can be predicted with accuracy suitable for clinical purposes by pulmonary function data and body mass index. ((c)) RSNA, 2018 Online supplemental material is available for this article.

Oh, J. Y., Y. S. Lee, et al. (2018). **"Increased urinary l-histidine in patients with asthma-COPD overlap: a pilot study."** Int J Chron Obstruct Pulmon Dis **13**: 1809-1818.

Purpose: Asthma-COPD overlap (ACO) is heterogeneous in nature and requires a unified diagnostic approach. We investigated the urinary levels of l-histidine, a precursor of histamine related to inflammatory responses, as a new candidate biomarker for diagnosing this condition. Patients and methods: We performed a prospective multicenter cohort study with retrospective analysis of 107 patients, who were divided into three groups: asthma, COPD, and ACO, according to the Spanish guidelines algorithm. Urinary l-histidine levels were measured using liquid chromatography-mass spectrometry. High-resolution metabolomic analysis, coupled with liquid chromatography-mass spectrometry and followed by multivariate statistical analysis, was performed on urine samples to discriminate between the metabolic profiles of the groups. Results: Urinary l-histidine levels were significantly higher in patients with ACO than in those with asthma or COPD, but the subgroups of ACO, classified according to disease origin, did not differ significantly. High urinary l-histidine level was a significant factor for the diagnosis of ACO even after adjusting for age, sex, and smoking amount. Among patients with airflow obstruction, the urinary l-histidine levels were elevated in patients with a documented history of asthma before the age of 40 years or bronchodilator responsiveness  $\geq 400$  mL; bronchodilator responsiveness  $\geq 200$  mL of forced expiratory volume in 1 second and exceeding baseline values by 12% on two or more visits; blood eosinophil count  $\geq 300$  cells/mm<sup>3</sup>; and frequent exacerbations ( $P < 0.05$ ). Conclusion: Urinary l-histidine could be a potential biomarker for ACO, regardless of the diversity of diagnostic definitions used.

Papłinska-Goryca, M., R. Rubinsztajn, et al. (2017). **"The association between serological features of chronic Chlamydia pneumoniae infection and markers of systemic inflammation and nutrition in COPD patients."** Scand J Clin Lab Invest **77**(8): 644-650.

INTRODUCTION: Chlamydia pneumoniae is an obligatory human pathogen involved in lower and upper airway infections, including pneumonia, bronchitis. Asymptomatic C. pneumoniae carriage is also relatively common. The association of C. pneumoniae infections with the chronic obstructive pulmonary disease (COPD) course is unclear. OBJECTIVES: The aim of the study was to investigate the association between chronic C. pneumoniae infection and clinical features of COPD, markers of inflammation and metabolic dysfunction. PATIENTS AND METHODS: The study included 59 patients with stable COPD who had no, or had  $\geq 2$  acute exacerbations during last year. The level of IgA and IgG antibody against C. pneumoniae, IL-6, IL-8, resistin, insulin, adiponectin and acyl ghrelin was measured in serum by enzyme-linked immunosorbent assay (ELISA). RESULTS: No differences in clinical and functional data were observed between COPD patients without serological features of C. pneumoniae infection and chronic C. pneumoniae infection. The level of anti C. pneumoniae IgA significantly correlated with IL-8, IL-6, resistin concentration in group of

frequent exacerbators. IgG level correlated negatively with acetyl ghrelin and body mass index (BMI) in patients without frequent exacerbations, in contrast to frequent COPD exacerbation group where significant correlations between IgG level and BMI was demonstrated. Serum IL-6 correlated positively with resistin and insulin and negatively with adiponectin in group of patients with serological features of chronic C. pneumoniae infection only. **CONCLUSIONS:** Our study showed that chronic C. pneumoniae infection does not influence the clinical course of COPD in the both study groups. Chronic C. pneumoniae infections might be associated with a distinct COPD phenotype that affects metabolic dysfunction.

Park, S. C., Y. S. Kim, et al. (2018). **"Hemoglobin and mortality in patients with COPD: a nationwide population-based cohort study."** Int J Chron Obstruct Pulmon Dis **13**: 1599-1605.

**Purpose:** Previous studies have reported that anemia increased mortality in patients with COPD. However, it is unclear whether anemia is associated with increased COPD mortality in the general population. The purpose of our study is to identify whether anemia is related to long-term mortality in COPD using a large population-based database. **Patients and methods:** Using the National Health Insurance Service-Health Screening Cohort, we identified COPD patients with available hemoglobin level. We analyzed mortality among patients with COPD from 2003 to 2013 according to hemoglobin level. **Results:** A total of 7,114 patients with COPD were identified. Mean age was 65.0 $\pm$ 9.3 years, and 62.9% were male. Anemia was present in 469 patients (6.6%). The overall mortality rate was 46.5% in anemia and 32.1% in non-anemia groups ( $p < 0.001$ ). The hazard ratio of anemia for mortality was 1.31 (95% CI, 1.11-1.54). Among patients with anemia, the hemoglobin level correlated well with mortality. **Conclusion:** Anemia was associated with increased long-term mortality of COPD, and even mild anemia was related to a significantly increased risk.

Parkin, L., D. Barson, et al. (2018). **"Patterns of use of long-acting bronchodilators in patients with COPD: A nationwide follow-up study of new users in New Zealand."** Respirology **23**(6): 583-592.

**BACKGROUND AND OBJECTIVE:** While several studies have found that prescribing practices do not conform to chronic obstructive pulmonary disease (COPD) treatment guidelines, none have examined longitudinal patterns of use of long-acting beta2 -agonist (LABA) and long-acting muscarinic antagonist (LAMA) therapy across an entire country. We undertook a nationwide follow-up study to describe treatment patterns in new users of long-acting bronchodilators. **METHODS:** National health and pharmaceutical dispensing data were used to identify patients aged  $\geq 45$  years who initiated LABA and/or LAMA therapy for COPD between 1 February 2006 and 31 December 2013. Dispensings of



LABAs, LAMAs and inhaled corticosteroids (ICSs) were aggregated into episodes of use of therapeutic regimens. Kaplan-Meier curves, sunburst plots and sequence index plots were generated to summarize, respectively, the duration of the first regimen, the sequences in which unique regimens were used and the patterns of use and non-use during follow-up. **RESULTS:** The study cohort included 83 435 patients with 290 400 person-years of follow-up. The most commonly initiated regimen was a LABA with an ICS. ICS use was inconsistent with international guidelines: over- and under-treatment occurred in patients with infrequent and frequent exacerbations, respectively, and ICS monotherapy was common. The median duration of the first regimen was 46 days. Many patients used multiple regimens over time and periods of non-use were common. **CONCLUSION:** In this nationwide study, patterns of use of LABAs, LAMAs and ICSs were complex and often did not comply with treatment guidelines. Further work is required to address the discrepancy between guidelines and prescribing practices.

Parlewar, R. and R. Shaikh (2016). "**Evaluation of Latencies and Interpeak Latencies of BAEP Waves in COPD Patients.**" Indian J Physiol Pharmacol **60**(2): 128-136.

The present study is carried out to assess brainstem auditory evoked potentials in patients of COPD and to evaluate effects of COPD on it before any clinical signs and symptoms of auditory impairment appear. This early diagnosis will help in maintaining a better quality of life in patients of COPD. Study includes 100 individuals divided in two groups, study group (n=50) and controls (n=50). Study group consist of COPD patients those had duration of COPD for more than 5 years with stable course of disease. Latency of wave 1, I-II, IV, V were prolonged in cases compared to controls in right ear and left ear. The difference is statistically significant (p value <0.05). Right ear interpeak latencies of I-II, III-V and I-V were increased with statistical significance among cases compared to controls (p value <0.05). In left ear, interpeak latencies of I-II and I-V were statistically more (p value <0.05) in case group compared to control group. The subclinical BAEP impairment in patients of COPD was due to the severity of airflow obstruction which causes chronic hypoxemia. The progressive chronic hypoxemia leads to development of tissue hypoxia and decreases the cerebral Perfusion; also it slows the nerve conduction in auditory pathway which causes prolongation of latency.

Perikleous, P., A. Sharkey, et al. (2017). "**Long-term survival and symptomatic relief in lower lobe lung volume reduction surgery.**" Eur J Cardiothorac Surg **52**(5): 982-988.

**OBJECTIVES:** Lung volume reduction surgery (LVRS) has been demonstrated to provide symptomatic relief and improve lung function in patients with end-stage

emphysema. The National Emphysema Treatment Trial specifically noted functional benefits in patients with predominantly upper lobe emphysema and demonstrated improvement in quality-of-life parameters, in patients with non-upper lobe emphysema and a low-baseline exercise capacity. We aimed to investigate whether physiological and health status benefits correlated with lower lobe LVRS. **METHODS:** A retrospective analysis was performed from our prospectively collected patient database. A total of 36 patients with severe, non-upper lobe predominant emphysema underwent lower lobe LVRS in our institution, over a 20-year period. The assessments consisted of measurements of body mass index, pulmonary function tests and health-related quality of life using the Short Form 36-item questionnaires. **RESULTS:** Forced expiratory volume in 1 s was seen to improve 3 months [coefficient of time = 1.55 (0.88, 2.21);  $P < 0.0001$ ] after the procedure, maintained until the first 6 months [0.48 (0.12, 0.85);  $P = 0.010$ ], decline over the second half of the first year and gradually return to preoperative levels after 2 years, while residual volume to total lung capacity (%) ratio was seen to follow a similar pattern with significant decrease from baseline after 3 months [coefficient of time = -1.76 (-2.75, -0.76);  $P = 0.001$ ] and 6 months [-1.05 (-1.51, -0.59);  $P < 0.0001$ ]. Quality-of-life improvements were mainly noted in physical components. **CONCLUSIONS:** Contrary to a widely held misconception following the National Emphysema Treatment Trial that lower lobe lung volume reduction does not offer significant benefits to patients with non-upper lobe predominant emphysema, we feel justified in offering lower lobe LVRS in these patients when they meet the same selection criteria as upper lobe LVRS.

Politis, A., V. Ioannidis, et al. (2018). **"Effects of varenicline therapy in combination with advanced behavioral support on smoking cessation and quality of life in inpatients with acute exacerbation of COPD, bronchial asthma, or community-acquired pneumonia: A prospective, open-label, preference-based, 52-week, follow-up trial."** *Chron Respir Dis* 15(2): 146-156.

Quitting smoking is the most important element in the therapeutic management of chronic respiratory diseases. Combining pharmacotherapy with behavioral support increases smoking cessation success rates. In addition, hospitalized smokers have increased motivation to quit. We investigated the efficacy on smoking cessation, of varenicline in combination with behavioral support, in smokers hospitalized due to (a) acute exacerbation of chronic obstructive pulmonary disease (COPD), or (b) bronchial asthma attack, or (c) community-acquired pneumonia (CAP). The method used is prospective, open-label, preference-based, parallel group, 52-week trial. Patients chose the smoking cessation intervention they preferred: a standard regimen of varenicline combined with post-discharge advanced behavioral support (group A) or one private consultation session during hospitalization (group B). Follow-up phone calls were scheduled in weeks 1, 2, and 4 and months 3, 6, and 9. The final hospital visit was performed in week 52. Primary outcome was success rate defined as the percentage (%) of smoking abstinence at week 52 and secondary outcomes were (a) changes in quality of life (QoL) indicated by the scores on the Short Form 36 (SF36) questionnaire and (b) predictors of smoking abstinence

investigated with multiple binary logistic regression. One hundred one patients were enrolled, 44 (43.6%) in group A and 57 (56.4%) in group B. Respective abstinence rates were 54.5% and 15.8% at week 12 and 52.3% and 14.0% at week 52. Scores on SF36 were statistically significantly increased in both groups. Predictors of smoking abstinence were varenicline (odds ratio (OR) 7.29; 95% confidence interval (CI) 2.15, 24.77;  $p = 0.001$ ), age (OR 1.07; 95%CI 1.00, 1.15;  $p = 0.042$ ), Fagerstrom score (OR 0.37; 95%CI 0.20, 0.68;  $p = 0.001$ ), SF36 domains "vitality" (OR 1.12; 95%CI 1.04, 1.21;  $p = 0.003$ ), and "social functioning" (OR 0.95; 95%CI 0.90, 1.00;  $p = 0.041$ ). Varenicline in combination with behavioral support resulted in high abstinence rates inpatients hospitalized for exacerbation of COPD, asthma attack, or CAP, and improved QoL.

Pothirat, C., T. Pothirat, et al. (2017). **"Risk Factors of Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease Among Patients Regularly Managed by Pulmonologists."** *J Med Assoc Thai* **100**(2): 142-8.

Objective: The present study intended to determine the risk factors of severe exacerbation in chronic obstructive pulmonary disease patients even though managed by pulmonologists on a regular basis. Material and Method: A retrospective case-controlled study was conducted at the chest clinic, Maharaj Nakorn Chiang Mai Hospital from 1st August 2009 to 31st July 2010. The clinical relevant data for acute exacerbation (age, sex, co-morbidity, severity of COPD, COPD medication, annual influenza vaccination, compliance with inhaled drug use, chest radiographic abnormality, and long-term oxygen therapy) were compared between severe AECOPD and stable COPD patients by logistic regression analysis. Results: Out of 137 COPD patients, 17 (12.4%) had severe AECOPD with 29 episodes (21.2%). Six risk factors were identified, two modifiable and four non-modifiable. The two modifiable risk factors were annual influenza non-vaccination (odds ratio [OR] 27.79; 95% confidence interval [CI], 2.29-337.66,  $p$ -value = 0.01) and improper use of inhaled devices (OR 9.94, 95%CI 1.07-92.54,  $p$ -value = 0.04). The four non-modifiable risk factors were age <60 yrs (OR, 10.67; 95%CI, 1.92-59.31,  $p$ -value = 0.01), hypertension (OR, 4.03; 95%CI, 1.05-15.44,  $p$ -value = 0.04), enlarged pulmonary trunk as demonstrated by chest radiograph (OR, 8.61; 95%CI, 1.49-49.85,  $p$ -value = 0.02), and long-term oxygen therapy (OR, 7.09; 95%CI, 1.36-37.00,  $p$ -value = 0.02). Conclusion: Six risk factors of severe AECOPD among patients whom were provided regularly managed by pulmonologists were identified; two of them, annual influenza non-vaccination and improper use of inhaled devices, could be potentially modified.

Quint, J. K., E. Moore, et al. (2018). **"Recruitment of patients with Chronic Obstructive Pulmonary Disease (COPD) from the Clinical Practice Research Datalink (CPRD) for research."** *NPJ Prim Care Respir Med* **28**(1): 21.

Databases of electronic health records (EHR) are not only a valuable source of data for health research but have also recently been used as a medium through which potential study participants can be screened, located and approached to take part in research. The aim was to assess whether it is feasible and practical to screen, locate and approach patients to take part in research through the Clinical Practice Research Datalink (CPRD). This is a cohort study in primary care. The CPRD anonymised EHR database was searched to screen patients with Chronic Obstructive Pulmonary Disease (COPD) to take part in a research study. The potential participants were contacted via their General Practitioner (GP) who confirmed their eligibility. Eighty two practices across Greater London were invited to the study. Twenty-six (31.7%) practices consented to participate resulting in a pre-screened list of 988 patients. Of these, 632 (63.7%) were confirmed as eligible following the GP review. Two hundred twenty seven (36%) response forms were received by the study team; 79 (34.8%) responded 'yes' (i.e., they wanted to be contacted by the research assistant for more information and to talk about enrolling in the study), and 148 (65.2%) declined participation. This study has shown that it is possible to use EHR databases such as CPRD to screen, locate and recruit participants for research. This method provides access to a cohort of patients while minimising input needed by GPs and allows researchers to examine healthcare usage and disease burden in more detail and in real-life settings.

Raherison, C., E. H. Ouaalaya, et al. (2018). **"Comorbidities and COPD severity in a clinic-based cohort."** *BMC Pulm Med* **18**(1): 117.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality around the world. The aim of our study was to determine the association between specific comorbidities and COPD severity. **METHODS:** Pulmonologists included patients with COPD using a web-site questionnaire. Diagnosis of COPD was made using spirometry post-bronchodilator FEV1/FVC < 70%. The questionnaire included the following domains: demographic criteria, clinical symptoms, functional tests, comorbidities and therapeutic management. COPD severity was classified according to GOLD 2011. First we performed a principal component analysis and a non-hierarchical cluster analysis to describe the cluster of comorbidities. **RESULTS:** One thousand, five hundred and eighty-four patients were included in the cohort during the first 2 years. The distribution of COPD severity was: 27.4% in group A, 24.7% in group B, 11.2% in group C, and 36.6% in group D. The mean age was 66.5 (sd: 11), with 35% of women. Management of COPD differed according to the comorbidities, with the same level of severity. Only 28.4% of patients had no comorbidities associated with COPD. The proportion of patients with two comorbidities was significantly higher ( $p < 0.001$ ) in GOLD B (50.4%) and D patients (53.1%) than in GOLD A (35.4%) and GOLD C ones (34.3%). The cluster analysis showed five phenotypes of comorbidities: cluster 1 included cardiac profile; cluster 2 included less comorbidities; cluster 3 included metabolic syndrome, apnea and anxiety-depression; cluster 4 included denutrition and osteoporosis and cluster 5 included bronchiectasis. The clusters were mostly significantly associated with symptomatic patients i.e. GOLD B and GOLD D.

**CONCLUSIONS:** This study in a large real-life cohort shows that multimorbidity is common in patients with COPD.

Raparelli, V., D. Pastori, et al. (2018). "**Major adverse cardiovascular events in non-valvular atrial fibrillation with chronic obstructive pulmonary disease: the ARAPACIS study.**" Intern Emerg Med **13**(5): 651-660.

Chronic obstructive pulmonary disease (COPD) increases the risk of mortality in non-valvular atrial fibrillation (NVAF) patients. Data on the relationship of COPD to major cardiovascular events (MACE) in AF have not been defined. The aim of the study is to assess the predictive value of COPD on incident MACE in NVAF patients over a 3-year follow-up. In the Atrial Fibrillation Registry for Ankle-Brachial Index Prevalence Assessment-Collaborative Italian Study (ARAPACIS) cohort, we evaluate the impact of COPD on the following clinical endpoints: MACE (including vascular death, fatal/non-fatal MI and stroke/TIA), cardiovascular (CV) death and all-cause mortality. Among 2027 NVAF patients, patients with COPD (9%) are more commonly male, elderly and at higher thromboembolic risk. During a median 36.0 months follow-up, 186 patients experienced MACE: vascular death (n = 72), MI (n = 57), stroke/TIA (n = 57). All major outcomes (including stroke/TIA, MI, vascular death, and all-cause death) are centrally adjudicated. Kaplan-Meier curves show that NVAF patients with COPD are at higher risk for MACE (p < 0.001), CV death (p < 0.001) and all-cause death (p < 0.001). On Cox proportional hazard analysis, COPD is an independent predictor of MACE (Hazard ratio [HR] 1.77, 95% Confidence Intervals [CI] 1.20-2.61; p = 0.004), CV death (HR 2.73, 95% CI 1.76-4.23; p < 0.0001) and all-cause death (HR 2.16, 95% CI 1.48-3.16; p < 0.0001). COPD is an independent predictor of MACE, CV death and all-cause death during a long-term follow-up of NVAF patients.

Reiger, G., R. Zwick, et al. (2018). "**Phenotypes of COPD in an Austrian population : National data from the POPE study.**" Wien Klin Wochenschr **130**(11-12): 382-389.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) represents a major global health problem; however, there are no data regarding clinical phenotypes of these patients in Austria. **METHODS:** This was an analysis from the Austrian cohort of the cross-sectional Phenotypes of COPD in Central and Eastern Europe (POPE) study, which was offered to patients with stable COPD in a real-life setting. Patients were recruited at 5 different outpatient facilities in 3 different provinces in Austria. All consecutive patients aged  $\geq 40$  years with a diagnosis of COPD confirmed by a post-bronchodilator forced expired volume in 1 s/forced vital capacity (FEV1/FVC) ratio  $< 0.7$  during a stable state ( $\geq 4$  weeks without exacerbation or worsening of any relevant comorbidities) were considered eligible. The primary aim of this study was to assess the prevalence of

phenotypes according to predefined criteria. Secondary aims included analyses of differences in patient characteristics, symptom load, comorbidities, and pharmacological treatment. **RESULTS:** Among 283 patients fulfilling the inclusion criteria, 49.5% were considered non-exacerbators, 21.6% were classified as exacerbators with chronic bronchitis, 21.2% exacerbators without chronic bronchitis, and 7.8% were patients with an asthma-COPD overlap. Exacerbators had significantly higher prevalence of symptoms, lower lung function and exercise capacity, and a higher prevalence of comorbidities, such as heart failure and depression, compared with the other patient phenotypes. A large majority of patients with stable COPD in this cohort received inhaled triple therapy, irrespective of exacerbation history. **CONCLUSIONS:** There were significant differences in COPD outcome measures between predefined phenotypes of COPD in this study. The majority of patients with stable COPD in this Austrian population were not treated according to current COPD guidelines. While non-exacerbators appear to have been overtreated, patients with an asthma-COPD overlap appear to have been undertreated.

Rinne, S. T., A. R. Elwy, et al. (2017). **"Implementation of guideline-based therapy for chronic obstructive pulmonary disease: Differences between men and women veterans."** *Chron Respir Dis* 14(4): 385-391.

Chronic obstructive pulmonary disease (COPD) is common among both men and women, and guidelines recommend the same therapy for both sexes. While previous studies have identified gender differences in other chronic disease management, few studies have examined how implementation of COPD guidelines differs between men and women. We performed a cross-sectional study of veterans admitted to Veterans Affairs (VA) hospitals for COPD during October 1, 2008, to September 30, 2011. We collected information on baseline COPD medications during the 6 months prior to hospitalization and categorized therapies as "appropriate" or "inappropriate" based on current guidelines. We used multivariable logistic regression to examine the differences in COPD medications between men and women, after controlling for baseline patient characteristics. We also examined the differences in hospital outcomes, including length of stay and hospital readmission. We identified 33,558 veterans, including 1149 women and 32,409 men who were admitted to 130 VA hospitals. Women were significantly less likely to have received inhaler therapies prior to admission, with lower rates of short-acting beta agonists, short-acting muscarinic antagonists, long-acting beta agonists, and long-acting muscarinic antagonists compared to men. Women also received fewer appropriate inhaler combinations (odds ratio [OR] = 0.83, 95% confidence interval [CI] 0.74-0.93) and more inappropriate combinations (OR = 1.33, 95% CI 1.17-1.51). Women and men were prescribed similar rates of inhaled steroid and oral steroids. Hospital outcomes were also similar between the two groups. These findings highlight a potential gender disparity in appropriate outpatient COPD therapy. Improving the quality of care for patients with COPD should include equitable implementation of guideline-based COPD management.

Robinson, K., E. Lucas, et al. (2018). "**Living with chronic obstructive pulmonary disease: The stories of frequent attenders to the Emergency Department.**" J Clin Nurs **27**(1-2): 48-56.

**AIMS AND OBJECTIVES:** To explore the experiences of chronic obstructive pulmonary disease (COPD) amongst individuals who have a high frequency of presentations to the Emergency Department and their carers. **BACKGROUND:** Patients with COPD are amongst the most frequent attenders in the Emergency Department despite the chronic nature of their condition. Good self-management has previously been identified as a key to maintaining health and reducing COPD exacerbations. There has been limited investigation of those with COPD who frequently attend the Emergency Department. **DESIGN:** Descriptive qualitative phase of a mixed methods study. **METHODS:** Individuals who had attended an Emergency Department within a single health district at least three times in the previous year for COPD were invited to participate in semistructured face-to-face interviews. A total of 19 individuals consented to participate, of whom 12 were male. Half of the interviews included both those with COPD and carers. Data were audio-recorded and transcribed, before being analysed using thematic analysis. **RESULTS:** Five main themes emerged from the data, namely (i) a sense of grief, loss and guilt, yet hope for the future; (ii) the impact on carers; (iii) the end point of self-management; (iv) the healthcare experience; and (v) the primary care experience. **CONCLUSION:** The experience of individuals with COPD who frequently present to the Emergency Department and their carers highlights the complexity of living with this disease. Providing effective intervention to manage exacerbation requires an understanding of the issues that are faced by patients and their carers. Clear systems and skills for sharing information are essential to decrease avoidable use of the Emergency Department.

Runggaldier, D., T. Minami, et al. (2018). "**Acute COPD exacerbation presenting with pronounced intrabullous haemorrhage and haemoptysis.**" BMJ Case Rep **2018A** 54-year-old man with history of chronic obstructive pulmonary disease (COPD) presented with subacute onset of chest pain, shortness of breath, productive cough with haemoptysis and night sweats. There were no fever or recent weight loss reported. The chest radiograph showed right upper lobe bullae with adjacent opacification and an emphysematous lung. Due to worsening haemoptysis and persistent chest pain, CT of the chest with contrast was performed, which revealed moderate to severe emphysema and numerous blood-filled bullae. Cardiac work-up for chest pain was negative for myocardial ischaemia and for aortic dissection. Further infectious work-ups for mycobacterial and invasive fungal infection were negative. The patient was treated for acute COPD exacerbation and responded well to the antibiotics with the resolution of haemoptysis. Follow-up CT of the chest revealed the gradual resolution of the haemorrhage, while the patient remained asymptomatic.

Sandelin, M., S. Mindus, et al. (2018). **"Factors associated with lung cancer in COPD patients."** Int J Chron Obstruct Pulmon Dis **13**: 1833-1839.

Background: The risk of dying of lung cancer is up to eightfold higher in patients with COPD than in age- and gender-matched controls. The aim of this study was to investigate the factors associated with lung cancer in a large cohort of COPD patients from primary care centers. Methods: To analyze whether age, gender, socioeconomic factors, comorbidity, and medication affect the risk of lung cancer in COPD, we used a COPD cohort of primary care patients. Data from primary care medical records and mandatory Swedish national registers were collected and linked in this population-based, retrospective observational registry study (NCT01146392). Results: Of the total cohort, 19,894 patients were included in the study. Five hundred and ninety-four lung cancer cases were diagnosed, corresponding to 3.0% of the studied population. In a multivariate analysis, the risk of lung cancer was lower if the COPD patients had a concurrent asthma diagnosis (HR: 0.54, CI: 0.41-0.71), while the risk of lung cancer increased with increasing age. A decreased lung cancer risk was observed in an exposure-dependent manner in patients who were prescribed inhaled corticosteroids (HR: 0.52, CI: 0.37-0.73), while the opposite was found for the use of acetylsalicylic acid (HR: 1.58, CI: 1.15-2.16). Conclusion: In this large population-based cohort, a concurrent asthma diagnosis and use of inhaled corticosteroids were independently related to decreased risk of lung cancer in COPD patients, while the use of acetylsalicylic acid was associated with an increased risk. The findings of the present study should be seen as hypothesis generating and need to be confirmed in prospective studies.

Santurtun, A., D. F. Rasilla, et al. (2017). **"Relationship Between Chronic Obstructive Pulmonary Disease and Air Pollutants Depending on the Origin and Trajectory of Air Masses in the North of Spain."** Arch Bronconeumol **53**(11): 616-621.

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is a common respiratory condition and one of the leading causes of death. Our aim was to analyze the association between emergency room visits due to this disease and meteorological variables and atmospheric contaminant levels in Santander, depending on the origin and trajectory of air masses. METHODS: Data from emergency room visits at Hospital Marques de Valdecilla were collected on a daily basis during an 8-year period. Data on concentrations of the main atmospheric pollutants and meteorological variables were also recorded. Retrotrajectories leading to Santander at a height of 1,500 meters above sea level were then calculated. Finally, a correlation model was produced to evaluate the effect of the contaminants on emergency visits due to COPD. RESULTS: There is a direct association between PM 10 levels and the number



of visits to the emergency room due to COPD. For every 10 $\mu$ g/m<sup>3</sup> increase in pollutant levels, emergency visits increase by 3.34% ( $p=0.00005$ ), and this effect is enhanced in individuals over 74 years of age. This effect is heightened when PM<sub>10</sub> levels depend on air masses from the South and when air recirculation occurs. There is no association between other pollutants and the number of visits to the emergency room. **CONCLUSIONS:** Exposure to high levels of PM<sub>10</sub> causes exacerbations in COPD patients. By studying the atmospheric circulation pattern, we can predict whether PM<sub>10</sub> levels will be inappropriately high, and we can also obtain information about the particle components.

Schafer, M., V. O. Kheyfets, et al. (2018). **"Reduced shear stress and associated aortic deformation in the thoracic aorta of patients with chronic obstructive pulmonary disease."** *J Vasc Surg* 68(1): 246-253.

**OBJECTIVE:** Central aortic stiffness and chronic obstructive pulmonary disease (COPD) are associated with increased incidence of devastating aortopathies. However, the exact mechanism leading to elevated aortic stiffness in patients with COPD is unknown. The purpose of this study was to quantify flow and shear hemodynamic indices, known markers of vascular remodeling, in the thoracic aorta of patients with mild to moderate COPD ( $n = 16$ ) and to compare these results with an age-matched control group ( $n = 10$ ). **METHODS:** Four-dimensional flow magnetic resonance imaging has been applied to measure hemodynamic wall shear stress (WSS) at four specific planes along the ascending aorta, aortic arch, and proximal descending aorta for all subjects. Peak systolic WSS and time-averaged WSS, which respectively reflect magnitude and temporal shear variability, were calculated at standardized planes. Aortic deformation was measured by means of relative area change (RAC) at the midlevel of the ascending and descending aorta. **RESULTS:** Compared with controls, patients with COPD had significantly reduced RAC in the mid ascending aorta (9% vs 18%;  $P < .0001$ ) and descending aorta (15% vs 19%;  $P = .0206$ ). Peak systolic WSS in COPD patients was significantly reduced in all considered planes, with the most dramatic difference occurring in the descending aorta (0.46 vs 0.86 N/m<sup>2</sup>;  $P < .0001$ ). Peak systolic WSS and time-averaged WSS were both significantly correlated with aortic RAC at each evaluated plane. **CONCLUSIONS:** Reduced flow shear metrics assessed at specific aortic regions correlated with RAC, a marker of aortic stiffness. Reduced hemodynamic WSS may then contribute to central aortic stiffening and perpetuate the risk for development of severe aortopathy.

Schaper-Magalhaes, F., J. F. Pinho, et al. (2017). **"Positive end-expiratory pressure attenuates hemodynamic effects induced by an overload of inspiratory muscles in patients with COPD."** *Int J Chron Obstruct Pulmon Dis* 12: 2943-2954.

**BACKGROUND:** Inspiratory muscle training (IMT) using a Threshold((R)) device is commonly used to improve the strength and endurance of inspiratory muscles. However, the effect of IMT, alone or with positive end-expiratory pressure (PEEP), on hemodynamic parameters in patients with chronic obstructive pulmonary disease (COPD) remains unknown. **OBJECTIVE:** To assess the effects of an overload of inspiratory muscles using IMT fixed at 30% of the maximal inspiratory pressure (MIP), and IMT associated with 5 cmH<sub>2</sub>O of PEEP (IMT + PEEP), on the echocardiographic parameters in healthy subjects and patients with COPD. **METHODS:** Twenty patients with COPD (forced expiratory volume in 1 second 53.19 $\pm$ 24.71 pred%) and 15 age-matched healthy volunteers were evaluated using spirometry, MIP, the COPD assessment test (CAT), and the modified Medical Research Council (mMRC) dyspnea scale. The E- (fast-filling phase) and A- (atrial contraction phase) waves were evaluated at the tricuspid and mitral valves during inspiration and expiration in the following sequence: at basal conditions, using IMT, and using IMT + PEEP. **RESULTS:** Patients with COPD had reduced MIPs versus the control group. Ten patients had CAT scores <10 and 12 patients had mMRC scores <2. E-wave values at the mitral valve were significantly decreased with IMT during the inspiratory phase in both groups. These effects were normalized with IMT + PEEP. During the expiratory phase, use of IMT + PEEP normalized the reduction in E-wave values in the COPD group. During inspiration at the tricuspid valve, reduction in E-wave values during IMT was normalized by IMT + PEEP in COPD group. During the expiratory phase, the value of the E-waves was significantly reduced with overload of the inspiratory muscles in both groups, and these effects were normalized with IMT + PEEP. A-waves did not change under any conditions. **CONCLUSION:** Acute hemodynamic effects induced by overloading of the inspiratory muscles were attenuated and/or reversed by the addition of PEEP in COPD patients.

Schildcrout, J. S., E. F. Schisterman, et al. (2018). "**Outcome-related, Auxiliary Variable Sampling Designs for Longitudinal Binary Data.**" Epidemiology 29(1): 58-66.

**BACKGROUND:** Epidemiologists have long used case-control and related study designs to enhance variability of response and information available to estimate exposure-disease associations. Less has been done for longitudinal data. **METHODS:** We discuss an epidemiological study design and analysis approach for longitudinal binary response data. We seek to gain statistical efficiency by oversampling relatively informative subjects for inclusion into the sample. In this methodological demonstration, we develop this concept by sampling repeatedly from an existing cohort study to estimate the relationship of chronic obstructive pulmonary disease to past-year smoking in a panel of baseline smokers. To account for oversampling, we describe a sequential offsetted regressions approach for valid inferences in this setting. **RESULTS:** Targeted sampling can lead to increased statistical efficiency when combined with sequential offsetted regressions. Efficiency gains are degraded with increased prevalence of the disease response variable, with decreased association between the sampling variable and the response, and with other design and analysis parameters,

providing guidance to those wishing to use these types of designs in the future.  
CONCLUSIONS: These designs hold promise for efficient use of resources in longitudinal cohort studies.

Schildcrout, J. S., E. F. Schisterman, et al. (2018). **"Extending the Case-Control Design to Longitudinal Data: Stratified Sampling Based on Repeated Binary Outcomes."** *Epidemiology* 29(1): 67-75.

We detail study design options that generalize case-control sampling when longitudinal outcome data are already collected as part of a primary cohort study, but new exposure data must be retrospectively processed for a secondary analysis. Furthermore, we assume that cost will limit the size of the subsample that can be evaluated. We describe a novel class of stratified outcome-dependent sampling designs for longitudinal binary response data where distinct strata are created for subjects who never, sometimes, and always experienced the event of interest during longitudinal follow-up. Individual designs within this class are differentiated by the stratum-specific sampling probabilities. We show for parameters associated with time-varying exposures, subjects who experience the event/outcome at some but not at all of the follow-up times (i.e., those who exhibit response variation) are highly informative. If the time-varying exposure varies exclusively within individuals (i.e., intraclass correlation coefficient is 0), then sampling all subjects with response variability can yield highly precise parameter estimates even when compared with an analysis of the original cohort. The flexibility of the designs and analysis procedures also permits estimation of parameters that correspond to time-fixed covariates, and we show that with an imputation-based estimation procedure, baseline covariate associations can be estimated with very high precision irrespective of the design. We demonstrate features of the designs and analysis procedures via a plasmode simulation using data from the Lung Health Study.

Schneiderman, A. I., D. D. Dougherty, et al. (2017). **"Diagnosing Chronic Obstructive Pulmonary Disease Among Afghanistan and Iraq Veterans: Veterans Affairs Concordance With Clinical Guidelines for Spirometry Administration."** *Mil Med* 182(9): e1993-e2000.

BACKGROUND: Early diagnosis and treatment of chronic obstructive pulmonary disease (COPD) can slow disease progression. The Department of Veterans Affairs (VA)/Department of Defense Clinical Practice Guidelines (CPG), established to improve patient outcomes, recommend the use of spirometry in the COPD diagnostic process. The aims of this study were to assess VA health care providers' performance related to CPG-recommended spirometry administration in the evaluation of newly diagnosed COPD among veterans, determine the patient characteristics that may influence the adherence rate, and compare VA concordance rates to those of other health plans. METHODS:

Administrative health care data related to Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) veterans was used to identify newly diagnosed COPD cases and the proportion of cases receiving spirometry. Cases were defined as veterans who had their first medical encounter with a coded diagnosis of COPD  $\geq 6$  months after their initial VA health care evaluation. The relationship between prediagnostic and comorbid conditions and the administration of CPG-concordant spirometry was examined using regression analyses. FINDINGS: Among the 923,646 OEF/OIF/OND veterans receiving VA health care between January 2002 and December 2014, 32,076 (3%) had a coded diagnosis of COPD. Among those, 22,156 (69%) were identified as newly diagnosed COPD cases; only 6,827 (31%) had CPG-concordant spirometry. Concordant spirometry was more likely to occur in veterans aged  $\geq 40$ . A pre-existing tobacco use disorder marginally changed the concordance rate. DISCUSSION: VA provider adherence to CPG-concordant spirometry would decrease the prevalence of false-positive COPD cases and lead to more targeted disease treatment. Future research should focus on such cases by assessing the association between COPD diagnosis and bronchodilator responsiveness.

Seetee, S., S. Terathongkum, et al. (2016). **"Effect of Pulmonary Rehabilitation Program with Meditation on Perceived Self-Efficacy, Pulmonary Rehabilitation Behavior, Exercise Tolerance, and Dyspnea in Patients with Chronic Obstructive Pulmonary Disease."** *J Med Assoc Thai* **99**(7): 828-8.

Objective: This quasi-experimental research using a single-group repeated measure design was conducted to assess the effect of a pulmonary rehabilitation program with meditation on perceived self-efficacy, pulmonary rehabilitation behavior, exercise tolerance, and dyspnea in patients with chronic obstructive pulmonary disease (COPD). Material and Method: Thirty-three COPD patients followed-up at the Outpatient Department at Wangpong District Hospital, Petchaboon Province were included into this study. All participants received the Pulmonary Rehabilitation Program (PRP) adjunct with meditation for eight weeks. The data were collected by using a Perceived Self-efficacy for Pulmonary Rehabilitation Questionnaire, a Pulmonary Rehabilitation Behaviors Questionnaire, an Exercise Tolerance Test, and a Perceived Dyspnea Questionnaire and other cardio-pulmonary parameters (PR, BP, RR, and oxygen saturation) at the baseline, at the fourth week, and at the eighth week of visits. The data were analyzed by using descriptive statistics, a repeated measure ANOVA, and Bonferroni's correction. Results: At the eighth week, the participants had a significant higher average of perceived self-efficacy, pulmonary rehabilitation behaviors and exercise tolerance ( $p$ -value  $< 0.001$ ), and lower average perceived of dyspnea than at the baseline and at the fourth week ( $p$ -value  $< 0.05$ ). The PR, BP, RR, and oxygen saturation were significantly improved between pre and post pulmonary rehabilitation with adjuncts meditation in baseline, 4 and 8 weeks of visits ( $p$ -value  $< 0.001$ ). The most effective improvement was most related to respiratory domain (RR and oxygen saturation). These effects established early in 4 weeks and strongly improved after 8 weeks and showed statistically significant when compared of 8 weeks of visit with baseline (pre-measurement of RR;  $p$ -value  $< 0.001$ , 0.0326, and  $< 0.001$ , and post-measurement after adjuncts meditation

program; p-value = 0.206, 0.0139, and <0.001, respectively). For cardiovascular domain, PR, and SBP were seemed to improve and compensate well when comparing 8-week visit to baseline (p-value = 0.005 and 0.0032, respectively). PR was decreased after continuing adjuncts meditation compared to baseline state (p-value = 0.0004). Conclusion: The mediation adjuncts with routine pulmonary rehabilitation program demonstrated improving of average of perceived self-efficacy meditation, behaviors, exercise tolerance, and cardio-pulmonary parameters (RR and oxygen saturation). It was promising and should be recommended and applied to COPD patients to restore the pulmonary function, reducing perceived of dyspnea symptom, increasing exercise endurance, activity daily life, and quality of life of patients.

Shen, J. J., E. Ko, et al. (2018). **"Life-Sustaining Procedures, Palliative Care Consultation, and Do-Not Resuscitate Status in Dying Patients With COPD in US Hospitals: 2010-2014."** *J Palliat Care* **33**(3): 159-166.

AIM: Little is known regarding the extent to which dying patients with chronic obstructive pulmonary disease (COPD) receive life-sustaining procedures and palliative care in US hospitals. We examined temporal trends and the impact of palliative care on the use of life-sustaining procedures in this population. MATERIALS AND METHODS: A retrospective nationwide cohort analysis was performed using weighted National Inpatient Sample (NIS) data obtained from 2010 to 2014. Decedents  $\geq 18$  years of age at the time of death and with a principal diagnosis of COPD were included. We examined the receipt of life-sustaining procedures, defined as 1 ventilation (intubation, mechanical ventilation, and noninvasive ventilation), 2 vasopressor use (infusion and intravascular monitoring), 3 nutrition (enteral and parenteral infusion of concentrated nutrition), 4 dialysis, and 5 cardiopulmonary resuscitation as well as palliative care consultation and do not resuscitate (DNR). We used compound annual growth rates (CAGRs) and the Rao-Scott correction of the chi<sup>2</sup> statistic to determine the statistical significance of temporal trends of life-sustaining procedures, palliative care utilization, and DNR status. RESULTS: Among 37 312 324 hospitalizations, 38 425 patients were examined. The CAGRs of life-sustaining procedures were 6.61% and -9.73% among patients who underwent multiple procedures and patients who did not undergo any procedure, respectively (both  $P < .001$ ). The CAGRs of palliative consultation and DNR were 5.25% and 36.62%, respectively (both  $P < .001$ ). CONCLUSIONS: Among adults with COPD dying in US hospitals between 2010 and 2014, the utilization of life-sustaining procedures, palliative care, and DNR status increased.

Shi, F., C. Qiu, et al. (2018). **"Comparison of Fractional Exhaled Nitric Oxide in Elderly Patients with Asthma-chronic Obstructive Pulmonary Disease**

**Overlap and Other Airway Inflammatory Diseases." *Iran J Allergy Asthma Immunol* 17(3): 232-239.**

The exact role of fractional exhaled nitric oxide (FeNO) in older patients with chronic inflammatory diseases including asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) remains unclear. This study aimed to investigate the differences in FeNO levels of elderly patients with ACO, asthma, COPD, and chronic cough. We conducted a retrospective study analysing the data of stable outpatients from Pulmonary Department of the Second Clinical College, Jinan University. All participants (Age $\geq$ 55 years) were divided into the ACO group (n=19), asthma group (n=16), COPD group (n=25), and chronic cough group (n=22). The clinical data such as peripheral eosinophil counts, serum high sensitivity C-reactive protein (hs-CRP), FeNO, and spirometry was collected, and the correlations between FeNO levels and systemic markers or spirometric indices were analyzed. Patients with ACO and asthma had significantly elevated FeNO levels (37.7 $\pm$ 16.5, and 36.3 $\pm$ 17.7 ppb) compared with COPD, and chronic cough patients (21.9 $\pm$ 10.3, and 16.1 $\pm$ 8.8 ppb). The FeNO levels were negatively associated with forced expiratory volume in 1 second (FEV<sub>1</sub>, p=0.003), FEV<sub>1</sub>% predicted (p=0.012), and FEV<sub>1</sub>/forced vital capacity (FVC, p=0.002) in all groups. However, there were no significant correlation between FeNO levels and FVC, peripheral eosinophil counts, or serum hs-CRP (p>0.05). Elderly patients with ACO have higher levels of FeNO, when compared with patients with COPD or chronic cough. These findings suggest that FeNO measurement may provide an important implication for the etiological diagnosis of ACO in the elderly patients.

Shin, S. H., H. Y. Park, et al. (2018). **"Serial blood eosinophils and clinical outcome in patients with chronic obstructive pulmonary disease."** *Respir Res* 19(1): 134.

**BACKGROUND:** Blood eosinophils have been suggested as a potential biomarker in chronic obstructive pulmonary disease (COPD), and their stability over time has been investigated in a few studies. However, the association between the stability of blood eosinophils and long-term clinical outcomes in COPD patients has yet to be fully elucidated. This study aimed to evaluate the stability of blood eosinophils and its association with clinical outcomes in COPD patients. **METHODS:** In total, 299 COPD patients from the Korean Obstructive Lung Disease cohort with at least two blood eosinophil measurements were included. Patients were stratified according to a cut-off of 300 cells/ $\mu$ L, and the association between eosinophil changes and all-cause mortality was analysed. The annual decline in forced expiratory volume in 1 s (FEV<sub>1</sub>), serial changes in St George's Respiratory Questionnaire score (SGRQ), and exacerbations during follow-up were compared among eosinophil groups. **RESULTS:** Patients were stratified into three groups according to the blood eosinophil cut-off: persistently < 300 cells/ $\mu$ L (PL; n = 175), variable (V; n = 68), and persistently  $\geq$ 300 cells/ $\mu$ L (PH; n = 56). There were no significant differences in baseline characteristics (age, sex, smoking, body mass index, use of inhaled corticosteroids, exacerbations in the previous year, FEV<sub>1</sub> (L or % predicted), or emphysema score) among the groups. During a median follow-up of 6.0 years,

the PH group had a better survival rate than the PL group (adjusted mortality rate ratio, 0.29; 95% confidence interval, 0.09-0.97;  $P = 0.045$ ). The PH group also showed improved symptoms and impact domains of SGRQ score compared to the PL group. No difference was found in annual FEV1 decline or exacerbations during follow-up among the groups. **CONCLUSIONS:** Patients with persistently high blood eosinophils had a better survival rate than those with persistently low blood eosinophils. Serial follow-up of blood eosinophils could help to predict outcomes in COPD patients.

Smith, B. M., H. Traboulsi, et al. (2018). **"Human airway branch variation and chronic obstructive pulmonary disease."** Proc Natl Acad Sci U S A **115**(5): E974-e981.

Susceptibility to chronic obstructive pulmonary disease (COPD) beyond cigarette smoking is incompletely understood, although several genetic variants associated with COPD are known to regulate airway branch development. We demonstrate that in vivo central airway branch variants are present in 26.5% of the general population, are unchanged over 10 y, and exhibit strong familial aggregation. The most common airway branch variant is associated with COPD in two cohorts ( $n = 5,054$ ), with greater central airway bifurcation density, and with emphysema throughout the lung. The second most common airway branch variant is associated with COPD among smokers, with narrower airway lumens in all lobes, and with genetic polymorphisms within the FGF10 gene. We conclude that central airway branch variation, readily detected by computed tomography, is a biomarker of widely altered lung structure with a genetic basis and represents a COPD susceptibility factor.

Spero, K., G. Bayasi, et al. (2017). **"Overdiagnosis of COPD in hospitalized patients."** Int J Chron Obstruct Pulmon Dis **12**: 2417-2423.

**BACKGROUND:** The diagnosis of chronic obstructive pulmonary disease (COPD) is usually made based on history and physical exam alone. Symptoms of dyspnea, cough, and wheeze are nonspecific and attributable to a variety of diseases. Confirmatory testing to verify the airflow obstruction is available but rarely used, which may result in substantial misdiagnoses of COPD. The aim of this study is to evaluate the use of confirmatory testing and assess the accuracy of the diagnosis. **METHODS:** From January 2011 through December 2013, 6,018 patients with COPD as a principal or leading diagnosis were admitted at a community teaching hospital. Of those, only 504 (8.4%) patients had spirometry performed during hospitalization. The studies were reviewed by two board-certified pulmonologists to verify presence of persistent airflow obstruction. Charts of these patients were then examined to determine if the spirometry results had changed the diagnosis or the treatment plan for these patients. **RESULTS:** Spirometry confirmed the diagnosis of COPD in 270 patients (69.2%)

treated as COPD during their hospitalization. Restrictive lung disease was found to be present in 104 patients (26.6%) and normal in 16 patients (4.2%). Factors predictive of airflow obstruction included smoking status and higher pack-year history. Negative predictive factors included higher body mass index (BMI) and other medical comorbidities. These patients were significantly more likely to be misdiagnosed and mistreated as COPD. **CONCLUSION:** Up to a third of patients diagnosed and treated as COPD in the hospital may be inaccurately diagnosed as COPD based on confirmatory spirometry testing. Factors contributing to the inaccuracy of diagnosis include less smoking history, high BMI, and associated comorbidities.

Spielmanns, M., T. Boeselt, et al. (2018). **"Effect of Pulmonary Rehabilitation on Inspiratory Capacity During 6-min Walk Test in Patients With COPD: A PROSPECTIVE CONTROLLED STUDY."** J Cardiopulm Rehabil Prev **38**(4): 264-268.

**PURPOSE:** Purpose of this study was to analyze the impact of a pulmonary rehabilitation (PR) program on the measured inspiratory capacity (IC) in patients with chronic obstructive pulmonary disease (COPD) while performing a 6-min walk test (6MWT). **METHODS:** Before and after PR, IC was measured by spirometry both at the beginning and at the end of the 6MWT for 15 patients with COPD in the PR group (PRG) and compared with a similar calisthenics training group (CTG; n = 15). In addition, the COPD Assessment Test (CAT), St George's Respiratory Questionnaire (SGRQ), and other lung function tests were recorded and compared. **RESULTS:** Both groups were not significantly different at baseline. Compared with the CTG, the PRG achieved a significant increase in the delta of IC measured during the 6MWT ( $0.5 \pm 0.2$  L [PRG] vs  $-0.2 \pm 0.2$  L [CTG],  $P = .001$ ). Significant differences were found for the 6MWT walking distance (PRG:  $99 \pm 36$  m vs CTG:  $5 \pm 25$  m,  $P = .001$ ). No significant increase in dyspnea while performing the 6MWT was found in either group. The differences in the CAT score and the SGRQ Global score were significant only for the PRG in intragroup comparisons, whereas the intergroup comparison showed no significant differences. Except for residual volume, no significant changes in all parameters of the static lung function tests were observed in either group. **CONCLUSION:** Participation in a PR may lead to a significant and clinically relevant increase in IC and the walking distance. Additional research is necessary to define the effects of this increase in IC on exercise capacity.

Sultana, A., D. Torres, et al. (2017). **"Special indications for Opioid Free Anaesthesia and Analgesia, patient and procedure related: Including obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, opioid addiction and cancer surgery."** Best Pract Res Clin Anaesthesiol **31**(4): 547-560.



Opioid-free anaesthesia (OFA) is a technique where no intraoperative systemic, neuraxial or intracavitary opioid is administered with the anaesthetic. Opioid-free analgesia similarly avoids opioids in the perioperative period. There are many compelling reasons to avoid opioids in the surgical population. A number of case reports and, increasingly, prospective studies from all over the world support its benefits, especially in the morbidly obese population with or without sleep apnoea. A derivative technique is opioid sparing, where the same techniques are used but some opioid use is allowed. This chapter is a review of the current knowledge regarding opioid-free or low-dose opioid anaesthetic and analgesic techniques for the following special populations: obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, acute/chronic opioid addiction and cancer surgery. Practical aspects include sympatholysis, analgesia and Minimum Alveolar Concentration (MAC) reduction with dexmedetomidine; analgesia with low-dose ketamine and co-anaesthesia; and sympatholysis with intravenous lignocaine. Non-opioid adjuvants such as NSAIDs, paracetamol, magnesium, local anaesthetic infiltration and high-dose steroids are added in the perioperative period to further achieve co-analgesia. Loco-regional anaesthesia and analgesia are also maximised. It remains to be seen whether OFA and early postoperative analgesia, which similarly avoids opioids, can prevent the development of hyperalgesia and persistent postoperative pain syndromes.

Sun, L., Y. Chen, et al. (2017). **"Changes in definition lead to changes in the clinical characteristics across COPD categories according to GOLD 2017: a national cross-sectional survey in China."** Int J Chron Obstruct Pulmon Dis **12**: 3095-3102.

Purpose: To investigate how the changes of definition in assessment of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stratification 2017 lead to changes of chronic obstructive pulmonary disease (COPD) patient clinical characteristics across categories in China. Patients and methods: COPD patients from 11 medical centers in China were stratified into old and new groups A-D twice according to the GOLD 2011 and 2017 comprehensive assessment. Demography and clinical characteristics were compared between old and new groups A-D. Results: In 1,532 COPD patients, the distribution from group A to D was 330 (21.5%), 132 (8.6%), 411 (26.8%), 659 (43.0%) and 557 (36.4%), 405 (26.4%), 184 (12.0%), 386 (25.2%), respectively according to GOLD 2011 and 2017. 46.7% (500/1,070) patients in high-risk groups were regrouped to low-risk groups. Compared to the old groups A and B, the new groups A and B had a higher proportion of males, lower body mass index, higher modified Medical Research Council (mMRC) grade, poor pulmonary function, more patients with chronic bronchitis, and fewer patients with coronary heart disease and hypertension disease. Compared to the old groups C and D, the new groups C and D had older patients, fewer men, better pulmonary functions, frequent acute exacerbations in the previous year, and more patients with chronic bronchitis, coronary heart disease, or diabetes mellitus. The new group D had more patients with stroke than the old group D. Conclusion: In China, GOLD 2017 shifted the overall COPD comprehensive assessments distribution to more low-risk groups.

The new high-risk groups had more characteristics associated with high risk of acute exacerbation and mortality. Some of the changes in demography and clinical characteristics of the new low-risk groups were associated with high risk of acute exacerbation and/or mortality.

Tangedal, S., M. Aanerud, et al. (2017). "**Comparing microbiota profiles in induced and spontaneous sputum samples in COPD patients.**" *Respir Res* **18**(1): 164.

**BACKGROUND:** Induced and spontaneous sputum are used to evaluate the airways microbiota. Whether the sputum types can be used interchangeably in microbiota research is unknown. Our aim was to compare microbiota in induced and spontaneous sputum from COPD patients sampled during the same consultation. **METHODS:** COPD patients from Bergen, Norway, were followed between 2006/2010, examined during the stable state and exacerbations. 30 patients delivered 36 sample pairs. DNA was extracted by enzymatic and mechanical lysis methods. The V3-V4 region of the 16S rRNA gene was PCR-amplified and prepared for paired-end sequencing. Illumina Miseq System was used for sequencing, and Quantitative Insights Into Microbial Ecology (QIIME) and Stata were used for bioinformatics and statistical analyses. **RESULTS:** Approximately 4 million sequences were sorted into 1004 different OTUs and further assigned to 106 different taxa. Pair-wise comparison of both taxonomic composition and beta-diversity revealed significant differences in one or both parameters in 1/3 of sample pairs. Alpha-diversity did not differ. Comparing abundances for each taxa identified, showed statistically significant differences between the mean abundances in induced versus spontaneous samples for 15 taxa when disease state was considered. This included potential pathogens like *Haemophilus* and *Moraxella*. **CONCLUSION:** When studying microbiota in sputum samples one should take into consideration how samples are collected and avoid the usage of both induced and spontaneous sputum in the same study.

Toledo-Pons, N., G. Noell, et al. (2018). "**Bone marrow characterization in COPD: a multi-level network analysis.**" *Respir Res* **19**(1): 118.

**BACKGROUND:** Bone marrow (BM) produces hematopoietic and progenitor cells that contribute to distant organ inflammation and repair. Chronic obstructive pulmonary disease (COPD) is characterized by defective lung repair. Yet, BM composition has not been previously characterized in COPD patients. **METHODS:** In this prospective and controlled study, BM was obtained by sternum fine-needle aspiration in 35 COPD patients and 25 healthy controls (10 smokers and 15 never-smokers). BM cell count and immunophenotype were determined by microscopy and flow cytometry, respectively. Circulating inflammatory (C-reactive protein, IL-6, IL-8) and repair markers (HGF, IGF, TGF-beta, VEGF) were quantified by ELISA. Results were integrated by multi-level network correlation analysis. **RESULTS:** We found that: (1) there were no major

significant pair wise differences between COPD patients and controls in the BM structural characteristics; (2) multi-level network analysis including patients and controls identifies a relation between immunity, repair and lung function not previously described, that remains in the COPD network but is absent in controls; and (3) this novel network identifies eosinophils as a potential mediator relating immunity and repair, particularly in patients with emphysema. **CONCLUSIONS:** Overall, these results suggest that BM is activated in COPD with impaired repair capacity in patients with more emphysema and/or higher circulating eosinophils.

Travassos, A., A. Rodrigues, et al. (2017). **"Fat-free mass depletion in patients with COPD in Brazil: development of a new cutoff point and its relation with mortality and extrapulmonary manifestations."** Eur J Clin Nutr **71**(11): 1285-1290.

**BACKGROUND/OBJECTIVES:** None of the cutoff points for fat-free mass index (FFMI) were tested for the Brazilian population, and it is unknown whether the available ones are able to discriminate extrapulmonary disease manifestations. This cross-sectional study aims to develop and validate a cutoff point for FFM depletion based on Brazilian patients with chronic obstructive pulmonary disease (COPD) and to verify its association and of previously published cutoffs with extrapulmonary manifestations. **SUBJECTS/METHODS:** A new cutoff point was obtained from the best FFMI value for discrimination of preserved exercise capacity in a sample of patients (n=57). The discriminative capacity was assessed in another sample (n=96). The new cutoff point and other previously published ones were tested to discriminate low exercise capacity, physical inactivity, sedentary lifestyle and low quality of life. A receiver operation characteristics curve with area under the curve (AUC) value was plotted and each cutoff points' discriminative capacity was calculated. Cox regression and Kaplan-Meier method assessed the association between the cutoff points and mortality. **RESULTS:** The new cutoff points for FFMI were 14.65 kg/m<sup>2</sup> for women (AUC=0.744; sensitivity (Se)=0.88; specificity (Sp)=0.60) and 20.35 kg/m<sup>2</sup> for men (AUC=0.565; Se=0.36; Sp=0.81). The new cutoffs were the best to discriminate poor exercise capacity assessed by walked distance in % predicted and quality of life. Only the new cutoff point was associated with mortality (HR=2.123; 95% CI: 1.03-4.33, P=0.039, log rank P=0.035). **CONCLUSIONS:** Only the new cutoff point was associated with all-cause mortality, and it had the highest discriminating capacity for exercise capacity and quality of life in Brazilian patients with COPD.

Tural Onur, S., S. Emet, et al. (2018). **"T wave peak-to-end interval in COPD."** Int J Chron Obstruct Pulmon Dis **13**: 2157-2162.

**Introduction:** The interval from the peak to the end of the electrocardiographic (ECG) T wave (Tp-Te) can estimate cardiovascular mortality and ventricular

tachyarrhythmias. Objectives: In this study, we aimed to define a new ECG parameter in patients with COPD. Methods: This was a cross-sectional observational study that included COPD patients who were diagnosed previously and followed up in the outpatient clinic. All data of the patients' demographic features, history, spirometry, and electrocardiographs were analyzed. Results: We enrolled 134 patients with COPD and 40 healthy volunteers as controls in our study. Patients already known to be having COPD who were under follow-up for their COPD and diagnosed as having COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were included. Men comprised 82.8% of the COPD group and 73.2% of controls. The mean age in the COPD and control group was 60.2 $\pm$ 9.4 and 58.2 $\pm$ 6.7 years, respectively. There was no significant difference between the groups for age or sex ( $p=0.207$ ,  $p=0.267$ , respectively). There were 46 (34.3%) patients in group A, 23 (17.2%) patients in group B, 26 (19.4%) patients in group C, and 46 (29.1%) patients in group D as COPD group. There was a significant increase in Tp-Te results in all precordial leads in the COPD group compared with the control group ( $p<0.05$ ). Precordial V4 lead has the most extensive area under the curve (0.831; sensitivity 76.5%, specificity 89.6%). Conclusion: We present strong evidence that Tp-Te intervals were increased in patients with COPD, which suggests that there may be an association between COPD and ventricular arrhythmias and cardiac morbidity.

Uchida, Y., T. Tsugawa, et al. (2017). **"Exclusion of emphysematous lung from dose-volume estimates of risk improves prediction of radiation pneumonitis."** *Radiat Oncol* 12(1): 160.

**BACKGROUND:** The risk factors for radiation pneumonitis (RP) in patients with chronic obstructive pulmonary disease (COPD) are unclear. Mean lung dose (MLD) and percentage of irradiated lung volume are common predictors of RP, but the most accurate dosimetric parameter has not been established. We hypothesized that the total lung volume irradiated without emphysema would influence the onset of RP. **METHODS:** We retrospectively evaluated 100 patients who received radiotherapy for lung cancer. RP was graded according to the Common Terminology Criteria for Adverse Events (version 4.03). We quantified low attenuation volume (LAV) using quantitative computed tomography analysis. The association between RP and traditional dosimetric parameters including MLD, volume of the lung receiving a dose of  $\geq 2$  Gy,  $\geq 5$  Gy,  $\geq 10$  Gy,  $\geq 20$  Gy, and  $\geq 30$  Gy, and counterpart measurements of the lung without LAV, were analyzed by logistic regression. We compared each dosimetric parameter for RP using multiple predictive performance measures including area under the receiver operating characteristic curve (AUC) and integrated discrimination improvement (IDI). **RESULTS:** Of 100 patients, RP of Grades 1, 2, 3, 4, and 5 was diagnosed in 24, 12, 13, 1, and 1 patients, respectively. Compared with traditional dosimetric parameters, counterpart measurements without LAV improved risk prediction of symptomatic RP. The ratio of the lung without LAV receiving  $\geq 30$  Gy to the total lung volume without LAV most accurately predicted symptomatic RP (AUC, 0.894; IDI, 0.064). **CONCLUSION:** Irradiated

lung volume without LAV predicted RP more accurately than traditional dosimetric parameters.

Ugurlu, E., E. Kilic-Toprak, et al. (2017). **"Impaired Hemorheology in Exacerbations of COPD."** Can Respir J **2017**: 1286263.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation. Cardiovascular-related comorbidities are established to contribute to morbidity and mortality especially during exacerbations. The aim of the current study was to determine alterations in hemorheology (erythrocyte aggregation, deformability) in newly diagnosed COPD patients and their response to medical treatment and to compare with values of COPD patients with exacerbations. **MATERIALS AND METHODS:** The study comprised 13 COPD patients, 12 controls, and 16 COPD patients with exacerbations. The severity of COPD was determined according to Global Initiative for Chronic Obstructive Lung Disease guidelines. Red blood cell (RBC) deformability and aggregation were measured by an ektacytometer. **RESULTS:** RBC deformability of COPD patients with exacerbations was decreased compared to the other groups. Erythrocyte aggregation and plasma fibrinogen of COPD patients determined during exacerbations were higher than control. **CONCLUSION:** Decreased RBC deformability and increased aggregation associated with exacerbations of COPD may serve as unfavorable mechanisms to worsen oxygenation and thus clinical symptoms of the patient. Treatment modalities that modify rheological parameters might be beneficial.

Valipour, A., S. Asadi, et al. (2018). **"Long-term safety of bilateral targeted lung denervation in patients with COPD."** Int J Chron Obstruct Pulmon Dis **13**: 2163-2172.

**Background:** Targeted lung denervation (TLD) is a novel bronchoscopic therapy for COPD which ablates parasympathetic pulmonary nerves running along the outside of the two main bronchi with the intent of inducing permanent bronchodilation. The goal of this study was to evaluate the feasibility and long-term safety of bilateral TLD during a single procedure. **Patients and methods:** This prospective, multicenter study evaluated 15 patients with moderate-to-severe COPD (forced expiratory volume in 1 s [FEV1] 30%-60%) who underwent bilateral TLD treatment following baseline assessment without bronchodilators. The primary safety end point was freedom from documented and sustained worsening of COPD directly attributable to TLD up to 1 year. Secondary end points included technical feasibility, change in pulmonary function tests, exercise capacity, and health-related quality of life. Follow-up continued up to 3 years for subjects who reconsented for longer-term follow-up. **Results:** A total of 15 patients (47% male, age 63.2 $\pm$ 4.0 years) underwent TLD with a total procedure time of 89 $\pm$ 16 min, and the total fluoroscopy time was 2.5 $\pm$ 2.7 min. Primary

safety end point of freedom from worsening of COPD was 100%. There were no procedural complications reported. Results of lung function analysis and exercise capacity demonstrated similar beneficial effects of TLD without bronchodilators, when compared with long-acting anticholinergic therapy at 30 days, 180 days, 365 days, 2 years, and 3 years post-TLD. Five of the 12 serious adverse events that were reported through 3 years of follow-up were respiratory related with no events being related to TLD therapy. Conclusion: TLD delivered to both lungs in a single procedure is feasible and safe with few respiratory-related adverse events through 3 years.

van Dort, M. J., P. Geusens, et al. (2018). **"High Imminent Vertebral Fracture Risk in Subjects With COPD With a Prevalent or Incident Vertebral Fracture."** J Bone Miner Res **33**(7): 1233-1241.

Subjects with chronic obstructive pulmonary disease (COPD) have an increased risk of vertebral fractures (VFs); however, VF incidence is largely unknown. Therefore, the aim of our study was to determine the incidence of new and/or worsening VF in subjects with COPD. Smokers and subjects with COPD (GOLD II-IV) from the ECLIPSE study with complete set of chest CT scans (baseline and 1- and 3-year follow-up) to evaluate vertebrae T1 down to L1 were included. If a VF was diagnosed on the last scan, detailed VF assessment of the previous scans was performed. VFs were scored according to the method of Genant as mild, moderate, or severe. Main outcome measure was the cumulative incidence of new and/or worsening VF at subject level, within 1 and 3 years. Of 1239 subjects (mean age 61 years, 757 males [61%], 999 subjects with COPD), 253 (20.5%) had  $\geq 1$  prevalent VF. The cumulative incidence of VFs was 10.1% within 1 year and 24.0% within 3 years. After adjustment for age, sex, body mass index (BMI), pack-years, and smoking status, prevalence and incidence were similar between smokers and COPD GOLD stages. Within 1 year, 29.2% of the subjects with a prevalent VF had an incident VF, compared with 5.1% in absence of prevalent VF (hazard ratio [HR] = 5.1; 95% confidence interval [CI] 3.6-7.4) and 58.5% versus 15.0% within 3 years (HR = 3.6; 95% CI 2.9-4.6). The incidence of VF was higher with increasing number and severity of prevalent VFs. Among subjects having an incident VF within the first year, 57.3% had a subsequent VF within the next 2 years. In this study, more than half of the smokers and subjects with COPD with a prevalent VF or an incident VF within the first year sustained a subsequent VF within 3 years. The 3-year risk was even higher in the presence of multiple or severe prevalent VFs. (c) 2018 The Authors. Journal of Bone and Mineral Research Published by Wiley Periodicals Inc.

Van Oekelen, O., K. Vermeersch, et al. (2018). **"Significance of prolonged QTc in acute exacerbations of COPD requiring hospitalization."** Int J Chron Obstruct Pulmon Dis **13**: 1937-1947.

Background: A prolonged QT interval is associated with increased risk of Torsade de Pointes and cardiovascular death. The prevalence and clinical relevance of QT prolongation in acute exacerbations of COPD (AECOPD), with high risk for cardiac morbidity and mortality, is currently unclear. Methods: A dual cross-sectional study strategy was therefore designed. A retrospective study evaluated 140 patients with an AECOPD requiring hospitalization, half of which had prolonged QTc on the admission ECG. Univariate and multivariate analyses were conducted to determine associated factors; Kaplan-Meier and Cox regression analyses to assess prognostic significance. A prospective study evaluated 180 pulmonary patients with acute respiratory problems requiring hospitalization, to determine whether a prolonged QTc at admission represents an AECOPD-specific finding and to investigate the change in QTc-duration during hospitalization. Results: Retrospectively, hypokalemia, cardiac troponin T and conductance abnormalities on ECG were significantly and independently associated with QTc prolongation. A prolonged QTc was associated with increased all-cause mortality (HR 2.698 (95% CI 1.032-7.055),  $p=0.043$ ), however, this association was no longer significant when corrected for age, FEV1 and cardiac troponin T. Prospectively, QTc prolongation was observed in 1/3 of the patients diagnosed with either an AECOPD, lung cancer, pulmonary infection or miscellaneous acute pulmonary disease, and was not more prevalent in AECOPD. The QTc-duration decreased significantly during hospitalization in patients with and without COPD. Conclusion: A prolonged QTc is a marker of underlying cardiovascular disease during an AECOPD. It is not COPD-specific, but a common finding during the acute phase of a pulmonary disease requiring urgent hospital admission.

Vedel-Krogh, S., B. G. Nordestgaard, et al. (2018). **"Blood eosinophil count and risk of pneumonia hospitalisations in individuals with COPD."** *Eur Respir J* 51(5) Blood eosinophil count in chronic obstructive pulmonary disease (COPD) is associated with higher exacerbation rate and favourable response to corticosteroids; however, frequent exacerbations and use of inhaled corticosteroids could elevate pneumonia risk. We tested the hypothesis that high blood eosinophil counts are associated with high risk of pneumonia in individuals with severe COPD from the general population. We included 7180 individuals with COPD from the Copenhagen General Population Study, including 643 with forced expiratory volume in 1 s (FEV1) <50% predicted between 2003 and 2011. All primary discharge diagnoses of pneumonia during follow-up were recorded. Among individuals with COPD and FEV1 <50% pred, the multivariable adjusted incidence rate ratio was 2.17 (95% CI 1.31-3.58) for pneumonia comparing individuals with blood eosinophil counts  $\geq 0.34 \times 10^9$  cells.L(-1) versus  $< 0.34 \times 10^9$  cells.L(-1). In individuals with clinical COPD, defined by recent exacerbation,  $\geq 10$  pack-years of smoking and FEV1 <70% pred, the corresponding risk was 4.52 (2.11-9.72). Risk of pneumonia did not differ by blood eosinophil count in individuals with COPD and FEV1  $\geq 50\%$  pred. In individuals with COPD and FEV1 <50% pred, blood eosinophil count  $\geq 0.34 \times 10^9$  cells.L(-1) was associated with high risk of hospitalisation due to pneumonia.

Verhamme, F. M., L. J. M. Seys, et al. (2017). "**Elevated GDF-15 contributes to pulmonary inflammation upon cigarette smoke exposure.**" Mucosal Immunol **10**(6): 1400-1411.

The molecular mechanisms underlying the pathogenesis of chronic obstructive pulmonary disease (COPD) are still unclear, however signaling pathways associated with lung development, such as the transforming growth factor (TGF)-beta superfamily, could be implicated in COPD. Growth differentiation factor (GDF)-15, a member of the TGF-beta superfamily, is involved in inflammation, mucus secretion, and cachexia. We analyzed the pulmonary expression of GDF-15 in smokers and patients with COPD, in cigarette smoke (CS)-exposed cultures of primary human bronchial epithelial cells (pHBECs), and in CS-exposed mice. Next, we exposed GDF-15 KO and control mice to air or CS and evaluated pulmonary inflammation. GDF-15 levels were higher in sputum supernatant and lung tissue of patients with COPD and smokers without COPD compared with never smokers. Immunohistochemistry revealed GDF-15 staining in the airway epithelium. Increased expression and secretion of GDF-15 was confirmed in vitro in CS-exposed pHBECs compared with air-exposed pHBECs. Similarly, GDF-15 levels were increased in lungs of CS-exposed mice. Importantly, GDF-15 deficiency attenuated the CS-induced pulmonary inflammation. These results suggest that increased GDF-15-as observed in lungs of smokers and patients with COPD-contributes to CS-induced pulmonary inflammation.

Villalobos, N., R. Davidson, et al. (2017). "**External Validation of the COMorbidity Test.**" Copd **14**(5): 513-517.

The COMorbidity TEST (COTE) is a Chronic Obstructive Pulmonary Disease (COPD)-specific co-morbidity score created to predict mortality. Before its wide application at the University of New Mexico we intended to validate it. The study was conducted at the University of New Mexico Hospital (UNMH) in Albuquerque, NM, USA, a tertiary academic hospital. Consecutive patients with the clinical diagnosis of COPD were identified using the hospital's medical records system and included if they were older than 40 years, had smoked at least 20 pack-years and their post bronchodilator forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) was <0.7 without an alternative diagnosis. The data collected included demographics, co-morbidities as described in the COTE, COPD-specific therapies, spirometry results and mortality. Of 317 patients 51.4% were male, average age was 65.6 +/- 9.6 years and the mean post-bronchodilator FEV1 percent predicted (FEV1%) was 52.9 +/- 16.9%. 31 (9.8%) patients were on triple long-acting bronchodilator inhaler therapy, 88 (27.8%) on two long-acting bronchodilators and 163 (51.4%) on at least one long-acting bronchodilator. The median follow-up was 3.5 years (IQR =



1.9-6.9). Fifty four patients died by the end of the follow-up period and their median COTE of 4 (IQR = 1-8) was significantly higher than for the survivors with COTE = 1 (IQR = 0-6;  $p = 0.002$ ). In univariable analyses COTE was positively associated while FEV1%, body mass index (BMI) and gender were negatively associated with all-cause mortality. In multivariable analysis BMI, FEV1% and COTE remained independent predictors for mortality. The COTE is an independent predictor of mortality for COPD patients at UNMH.

Vishweswaraiah, S., L. George, et al. (2018). **"A candidate gene identification strategy utilizing mouse to human big-data mining: "3R-tenet" in COPD genetic research."** *Respir Res* **19**(1): 92.

**BACKGROUND:** Early life impairments leading to lower lung function by adulthood are considered as risk factors for chronic obstructive pulmonary disease (COPD). Recently, we compared the lung transcriptomic profile between two mouse strains with extreme total lung capacities to identify plausible pulmonary function determining genes using microarray analysis (GSE80078). Advancement of high-throughput techniques like deep sequencing (eg. RNA-seq) and microarray have resulted in an explosion of genomic data in the online public repositories which however remains under-exploited. Strategic curation of publicly available genomic data with a mouse-human translational approach can effectively implement "3R- Tenet" by reducing screening experiments with animals and performing mechanistic studies using physiologically relevant in vitro model systems. Therefore, we sought to analyze the association of functional variations within human orthologs of mouse lung function candidate genes in a publicly available COPD lung RNA-seq data-set. **METHODS:** Association of missense single nucleotide polymorphisms, insertions, deletions, and splice junction variants were analyzed for susceptibility to COPD using RNA-seq data of a Korean population (GSE57148). Expression of the associated genes were studied using the Gene Paint (mouse embryo) and Human Protein Atlas (normal adult human lung) databases. The genes were also assessed for replication of the associations and expression in COPD-/mouse cigarette smoke exposed lung tissues using other datasets. **RESULTS:** Significant association ( $p < 0.05$ ) of variations in 20 genes to higher COPD susceptibility have been detected within the investigated cohort. Association of HJURP, MCRS1 and TLR8 are novel in relation to COPD. The associated ADAM19 and KIT loci have been reported earlier. The remaining 15 genes have also been previously associated to COPD. Differential transcript expression levels of the associated genes in COPD- and/ or mouse emphysematous lung tissues have been detected. **CONCLUSION:** Our findings suggest strategic mouse-human datamining approaches can identify novel COPD candidate genes using existing datasets in the online repositories. The candidates can be further evaluated for mechanistic role through in vitro studies using appropriate primary cells/cell lines. Functional studies can be limited to transgenic animal models of only well supported candidate genes. This approach will lead to a significant reduction of animal experimentation in respiratory research.

Wan, E. S., A. Kantorowski, et al. (2018). **"Self-reported task-oriented physical activity: A comparison with objective daily step count in COPD."** Respir Med **140**: 63-70.

**BACKGROUND:** Low physical activity (PA) is associated with adverse health outcomes independent of airflow limitation in COPD. Self-reported assessments are often limited to global estimates of PA and may not be directly translatable to patients' goals and motivations. We developed a task-oriented PA checklist and examined its performance relative to pedometer-assessed daily step count in two COPD cohorts. **METHODS:** Task-oriented daily physical activity (DPA) was assessed in two COPD cohorts using either interviewer-administered recall questionnaire (DPA-R, Cohort 1, n=109) or a self-administered diary-format daily checklist (DPA-C, Cohort 2, n=175). Daily step count was measured in both cohorts using the Omron HJ-720 ITC pedometer. Univariate associations between individual DPA items and [a] cross-sectional and [b] longitudinal change (Cohort 1) in daily step count were assessed using a Pearson's correlation. Composite scores comprised of individual DPA items with univariate association p-values <0.1 were tested for association with daily step count using multivariate models. **RESULTS:** Tasks associated with average daily step count in both cohorts included putting on shoes, showering, washing hair, walking for exercise, the frequency of walks >10min, and walking on an incline (Pearson's rho range=0.14-0.43). A composite score of these 6 DPA items demonstrated significant associations with baseline average daily step count in both cohorts (rho=0.5 & 0.47, Cohorts 1 & 2, respectively) and longitudinal change in daily step count (rho=0.46, Cohort 1). **CONCLUSIONS:** Self-reported task-oriented assessments complement direct monitoring and have potential clinical utility in exercise counseling to increase PA among COPD patients. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT01772082.

Wang, Y., Q. Zhou, et al. (2018). **"The effects of CXCL10 polymorphisms on COPD susceptibility."** Mol Genet Genomics **293**(3): 649-655.

The polymorphisms of cytokine genes has been reported to modulate the individual's susceptibility to environmental stimuli in COPD development. C-X-C motif chemokine 10 (CXCL10) mediates recruitment inflammatory cells such as monocytes. Therefore, it may play a key role in COPD. Here, a case-control study was conducted to evaluate the association between CXCL10 tag-SNPs and COPD risk. Four tag-SNPs including rs4256246, rs4508917, rs56061981, and rs56316945 were identified based on the linkage disequilibrium (LD) analysis in 30 healthy controls. The associations between these four tag-SNPs and COPD risk were further evaluated in 480 COPD cases and 488 controls. We found that the "T" allele of rs56061981 was significantly associated with reducing risk of COPD, while "G" allele of rs56316945 was significantly associated with increasing risk of COPD. SNP rs56316945 was significantly associated with increasing risk of COPD under different models except recessive model after

adjusting the sex, age, pack year, and biomass. SNP rs56061981 was significantly associated with decreasing COPD risk under different models except recessive model after adjusting the sex, age, pack year, and biomass. Stratified analysis of smoking status and biomass with SNPs supported rs56061981 may interact with biomass and smoking thus modulate COPD susceptibility and rs56216945 was apparently associated with the severity of pulmonary function of COPD patients. This study suggests that rs56061981 and rs56216945 in CXCL10 gene promoter contribute COPD susceptibility.

Weir-McCall, J. R., P. S. Liu-Shiu-Cheong, et al. (2018). **"Pulmonary arterial stiffening in COPD and its implications for right ventricular remodelling."** Eur Radiol **28**(8): 3464-3472.

**BACKGROUND:** Pulmonary pulse wave velocity (PWV) allows the non-invasive measurement of pulmonary arterial stiffening, but has not previously been assessed in COPD. The aim of the current study was to assess PWV in COPD and its association with right ventricular (RV) remodelling. **METHODS:** Fifty-eight participants with COPD underwent pulmonary function tests, 6-min walk test and cardiac MRI, while 21 healthy controls (HCs) underwent cardiac MRI. Thirty-two COPD patients underwent a follow-up MRI to assess for longitudinal changes in RV metrics. Cardiac MRI was used to quantify RV mass, volumes and PWV. Differences in continuous variables between the COPD and HC groups was tested using an independent t-test, and associations between PWV and right ventricular parameters was examined using Pearson's correlation coefficient. **RESULTS:** Those with COPD had reduced pulsatility (COPD (mean $\pm$ SD):24.88 $\pm$ 8.84% vs. HC:30.55 $\pm$ 11.28%,  $p=0.021$ ), pulmonary acceleration time (COPD:104.0 $\pm$ 22.9ms vs. HC: 128.1 $\pm$ 32.2ms,  $p<0.001$ ), higher PWV (COPD:2.62 $\pm$ 1.29ms<sup>-1</sup> vs. HC:1.78 $\pm$ 0.72ms<sup>-1</sup>,  $p=0.001$ ), lower RV end diastolic volume (COPD:53.6 $\pm$ 11.1ml vs. HC:59.9 $\pm$ 13.0ml,  $p=0.037$ ) and RV stroke volume (COPD:31.9 $\pm$ 6.9ml/m<sup>2</sup> vs. HC:37.1 $\pm$ 6.2ml/m<sup>2</sup>,  $p=0.003$ ) with no difference in mass ( $p=0.53$ ). PWV was not associated with right ventricular parameters. **CONCLUSIONS:** While pulmonary vascular remodelling is present in COPD, cardiac remodelling favours reduced filling rather than increased afterload. Treatment of obstructive lung disease may have greater effect on cardiac function than treatment of pulmonary vascular disease in most COPD patients **KEY POINTS:** \* Pulmonary pulse wave velocity (PWV) is elevated in COPD. \* Pulmonary PWV is not associated with right ventricular remodelling. \* Right ventricular remodelling is more in keeping with that of reduced filling.

Worth, H., R. Buhl, et al. (2017). **"GOLD 2017 treatment pathways in 'real life': An analysis of the DACCORD observational study."** Respir Med **131**: 77-84.

**INTRODUCTION:** The 2017 update to the Global Initiative for Obstructive Lung Disease (GOLD) strategy document includes recommendations for treatment

intensification or step-down in chronic obstructive pulmonary disease (COPD), although recognises that limited supporting information is available. DACCORD is an ongoing observational, non-interventional study, recruiting patients following COPD maintenance treatment change or initiation, a subset of whom were receiving a long-acting beta2-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) fixed-dose combination (FDC) on entry. Since there were no requirements in terms of prior medication (and no washout before commencing LABA/LAMA FDC), this provides an opportunity to generate 'real world' data to test the GOLD 2017 recommendations. METHODS: To reduce heterogeneity, the current analyses include patients receiving indacaterol/glycopyrronium at baseline, and who, prior to the study, were receiving no COPD maintenance medication ('none'), LABA or LAMA monotherapy ('mono'), LABA plus inhaled corticosteroid (ICS; 'LABA/ICS'), or triple therapy ('triple'). At the baseline visit, data collected included: demographic and disease characteristics; COPD Assessment Test (CAT); and exacerbations in the 6 months prior to entry. At 3, 6, 9 and 12 months data on exacerbations were collected, with CAT recorded at 3 and 12 months. RESULTS: A total of 2724 patients were included in the baseline analyses: 795, 954, 598 and 377 in the 'none', 'mono', 'LABA/ICS' and 'triple' subgroups, respectively. There were no clinically relevant differences in baseline demographics between the four groups. In terms of disease characteristics, the 'triple' group had the highest proportion of patients with a disease duration of more than 1 year since diagnosis and with severe/very severe airflow limitation, but a similar percentage of non-exacerbators compared to the 'none' group. Over the 1-year follow-up, the majority of patients in all four subgroups did not exacerbate (exacerbation rates 0.16, 0.19, 0.21, and 0.26 in the 'none', 'mono', 'LABA/ICS' and 'triple' groups, respectively). At 12 months, 61.4%, 65.0%, 71.0% and 52.4% of patients had a clinically relevant improvement in CAT score. CONCLUSIONS: Overall, the results support the GOLD recommendations in suggesting that a switch from a mono-bronchodilator or LABA plus ICS to LABA/LAMA FDC is a valid treatment option for patients with COPD. The results also validate the use of a LABA/LAMA FDC as initial maintenance treatment for COPD, and provide first 'real world' evidence to support the newly added 'step down' recommendation (from triple to LABA/LAMA FDC).

Wu, M., N. M. Woodrick, et al. (2017). **"Developing a Virtual Teach-To-Goal() Inhaler Technique Learning Module: A Mixed Methods Approach."** J Allergy Clin Immunol Pract 5(6): 1728-1736.

BACKGROUND: Most hospitalized patients with asthma or chronic obstructive pulmonary disease misuse respiratory inhalers. An in-person educational strategy, teach-to-goal (TTG), improves inpatients' inhaler technique. OBJECTIVE: To develop an effective, portable education intervention that remains accessible to hospitalized patients postdischarge for reinforcement of proper inhaler technique. METHODS: A mixed methods approach at an urban academic hospital was used to iteratively develop, modify, and test a virtual teach-to-goal() (V-TTG()) educational intervention using patient end-user feedback. A survey examined access and willingness to use technology for self-

management education. Focus groups evaluated patients' feedback on access, functionality, and quality of V-TTG(). RESULTS: Forty-eight participants completed the survey, with most reporting having Internet access; 77% used the Internet at home and 82% used the Internet at least once every few weeks. More than 80% reported that they were somewhat or very likely to use V-TTG() to gain skills to improve their health. Most participants reported smartphone access (73%); half owned laptop computers (52%). Participants with asthma versus chronic obstructive pulmonary disease were more likely to own a smartphone, have a data plan, and have daily Internet use ( $P < .05$ ). Nine focus groups ( $n = 25$ ) identified themes for each domain: access-platform and delivery, Internet access, and technological literacy; functionality-usefulness, content, and teaching strategy; and quality-clarity, ease of use, length, and likability. CONCLUSIONS: V-TTG() is a promising educational tool for improving patients' inhaler technique, iteratively developed and refined with patient input. Patients in our urban, academic hospital overwhelmingly reported access to platforms and willingness to use V-TTG() for health education.

Xu, Y., T. Yamashiro, et al. (2017). "**Hyperinflated lungs compress the heart during expiration in COPD patients: a new finding on dynamic-ventilation computed tomography.**" Int J Chron Obstruct Pulmon Dis **12**: 3123-3131.

Purpose: The aims of this study were to evaluate dynamic changes in heart size during the respiratory cycle using four-dimensional computed tomography (CT) and to understand the relationship of these changes to airflow limitation in smokers. Materials and methods: A total of 31 smokers, including 13 with COPD, underwent four-dimensional dynamic-ventilation CT during regular breathing. CT data were continuously reconstructed every 0.5 s, including maximum cross-sectional area (CSA) of the heart and mean lung density (MLD). Concordance between the cardiac CSA and MLD time curves was expressed by cross-correlation coefficients. The CT-based cardiothoracic ratio at inspiration and expiration was also calculated. Comparisons of the CT indices between COPD patients and non-COPD smokers were made using the Mann-Whitney test. Spearman rank correlation analysis was used to evaluate associations between CT indices and the forced expiratory volume in 1 s (FEV1.0) relative to the forced vital capacity (FVC). Results: Cardiac CSA at both inspiration and expiration was significantly smaller in COPD patients than in non-COPD smokers ( $P < 0.05$ ). The cross-correlation coefficient between cardiac CSA and MLD during expiration significantly correlated with FEV1.0/FVC ( $\rho = 0.63$ ,  $P < 0.001$ ), suggesting that heart size decreases during expiration in COPD patients. The change in the cardiothoracic ratio between inspiration and expiration frames was significantly smaller in COPD patients than in non-COPD smokers ( $P < 0.01$ ). Conclusion: Patients with COPD have smaller heart size on dynamic-ventilation CT than non-COPD smokers and have abnormal cardiac compression during expiration.

Yakubek, G. A., G. L. Curtis, et al. (2018). **"Chronic Obstructive Pulmonary Disease Is Associated With Short-Term Complications Following Total Knee Arthroplasty."** *J Arthroplasty* **33**(8): 2623-2626.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is a major global health issue and a leading cause of morbidity and mortality. Patients with COPD are at increased risk of complications following surgery. The purpose of this study is to evaluate the postoperative total knee arthroplasty (TKA) outcomes in these patients in comparison to a non-COPD matching cohort. Specifically, we asked the following questions: (1) "Is COPD associated with adverse perioperative outcomes?" and (2) "Does COPD increase the risk of short-term complications following TKA?" **METHODS:** The American College of Surgeons National Surgical Quality Improvement Program database was used to identify 111,168 patients who underwent TKA between 2008 and 2014. A total of 3975 patients with COPD were identified. Both COPD and non-COPD cohorts were compared in terms of the following outcomes: hospital length of stay, discharge disposition, and 30-day postoperative complications. **RESULTS:** COPD was a predictor for a prolonged length of stay and a discharge to an extended care facility ( $P < .001$ ). They were at significantly increased risk of any complication including increased mortality, pneumonia, reintubation, use of a mechanical ventilator for >48 hours, cardiac arrest, progressive renal insufficiency, deep infection, return to operating room, and a readmission within 30 days postoperatively. **CONCLUSION:** Patients with COPD are more likely to experience postoperative complications following TKA when compared to non-COPD patients. Pulmonary evaluation and optimization are crucial to minimize adverse events from occurring in this difficult-to-treat population.

Yan, Y., L. Liu, et al. (2018). **"Evaluation and Exploration on the Effect of the Management of Chronic Obstructive Pulmonary Disease in Rural Areas through an Internet-Based Network Consulting Room."** *Med Princ Pract* **27**(3): 222-226.

**OBJECTIVE:** This study aims to improve the management quality of chronic obstructive pulmonary disease (COPD) in rural areas. **METHODS:** Two hundred forty discharged COPD patients were divided into an intervention group and a control group. In the intervention group, 120 patients established contact with doctors through the network consulting room, i.e., the doctor's mobile platform, and were managed through video, voice, and text by the doctors, kept close contact with the doctors after discharge (education, consultation), and received electronic prescriptions, and drugs were sent to the patients' door by online retailers. The patients in the control group were managed in the traditional manner. One year later, the predicted forced expiratory volume in 1 s (FEV1)%, FEV1/forced vital capacity (FVC), and CAT scores and the number of rehospitalized patients were compared between these 2 groups. **RESULTS:** After 1 year of follow-up, the predicted FEV1% and the FEV1/FVC ratio were significantly higher in the intervention group than in the control group ( $p < 0.05$ ). CAT scores were lower for patients in the intervention group than for those in the control group after 1 year of follow-up ( $p < 0.05$ ). After 1 year of follow-up, 22 (18.33%) patients were

rehospitalized in the intervention group and 58 (48.33%) patients were rehospitalized in the control group ( $p < 0.05$ ). **CONCLUSION:** Doctors can improve the quality of life of patients with COPD and reduce the number of rehospitalizations through use of the network consulting room.

Yang, X., B. Huo, et al. (2017). **"Imbalance between Subpopulations of Regulatory T Cells in Patients with Acute Exacerbation of COPD."** *Copd* **14**(6): 618-625.

Human regulatory T cells (Tregs) have been reported to be not significantly different in the peripheral blood of patients with chronic obstructive pulmonary disease (COPD) and healthy controls. Recent research has identified some new markers for Tregs and indicated that Tregs are composed of distinct subpopulations. The aim of the study was to describe the changing patterns of circulating Treg subpopulations in patients with acute exacerbation of COPD (AECOPD) and healthy controls, and to explore their potential roles in AECOPD pathogenesis. Blood samples were obtained from 30 never-smokers with normal lung function and 30 patients with COPD before and after they had an exacerbation. The proportions of Treg subpopulations were evaluated using flow cytometry. In the peripheral blood, decreased proportions of CD4(+)CD25(+)CD127(low) Tregs, CD4(+)CD25(+)CD45RA(+) Tregs, and CD4(+)CD25(+)CD62L(+) Tregs and an increased proportion of CD4(+)CD25(+)CD45RO(+) Tregs were found in patients with stable COPD compared with non-smokers with normal lung function. The patients showed further changes in Treg subpopulations when they had an AECOPD, with an overall decrease in a suppressive subset, indicating that the immune negative regulatory population of Tregs did not play an effective role. Immune homeostasis favored inflammation, and a negative correlation between the circulating tumor necrosis factor-alpha and the proportions of CD4(+)CD25(+)CD62L(+) cells ( $r = -0.698$ ,  $p < 0.05$ ) in patients with AECOPD was found. The imbalance between the suppressive subsets and the proinflammatory subset of Tregs and the decline of Treg subpopulations with immunosuppressive activity may play important roles in AECOPD progression.

Ye, X., M. Wang, et al. (2017). **"Echo intensity of the rectus femoris in stable COPD patients."** *Int J Chron Obstruct Pulmon Dis* **12**: 3007-3015.

**OBJECTIVE:** The aim of this study was to investigate whether echo intensity of the rectus femoris when measured using ultrasound can distinguish muscles affected by COPD compared with healthy non-COPD affected muscles and whether the severity of ultrasonic abnormalities was associated with health-related quality of life (HRQoL). **METHODS:** Echo intensity, areas of the rectus femoris, and the thickness of quadriceps muscles were measured using ultrasound in 50 COPD outpatients and 21 age-matched non-COPD controls. The results of the 8-Item Short-Form Health Survey and the functional assessment of chronic illness therapy fatigue scales were used to evaluate HRQoL. **RESULTS:** There was a

significantly higher echo intensity of the rectus femoris in all stages of COPD patients than in age-matched non-COPD subjects; the quadriceps muscle thickness and cross-sectional area of the rectus femoris significantly decreased in COPD GOLD III-IV only. Furthermore, in our stable COPD patients, echo intensity of the rectus femoris was associated with HRQoL independently. CONCLUSION: Quantitative ultrasound distinguishes healthy muscles from those affected by COPD grade I-IV, and quality and quantity of muscles are associated with HRQoL and forced expiratory volume in 1 second. Ultrasonic echo intensity of the rectus femoris may be a useful instrument for assessing disease severity and monitoring the changes of skeletal muscle resulting from disease progression or clinical intervention in patients with COPD.

Yun, J. H., A. Lamb, et al. (2018). "**Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease.**" J Allergy Clin Immunol **141**(6): 2037-2047.e10.

BACKGROUND: Eosinophilic airway inflammation in patients with chronic obstructive pulmonary disease (COPD) is associated with exacerbations and responsiveness to steroids, suggesting potential shared mechanisms with eosinophilic asthma. However, there is no consistent blood eosinophil count that has been used to define the increased exacerbation risk. OBJECTIVE: We sought to investigate blood eosinophil counts associated with exacerbation risk in patients with COPD. METHODS: Blood eosinophil counts and exacerbation risk were analyzed in patients with moderate-to-severe COPD by using 2 independent studies of former and current smokers with longitudinal data. The Genetic Epidemiology of COPD (COPDGene) study was analyzed for discovery (n = 1,553), and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study was analyzed for validation (n = 1,895). A subset of the ECLIPSE study subjects were used to assess the stability of blood eosinophil counts over time. RESULTS: COPD exacerbation risk increased with higher eosinophil counts. An eosinophil count threshold of 300 cells/ $\mu$ L or greater showed adjusted incidence rate ratios for exacerbations of 1.32 in the COPDGene study (95% CI, 1.10-1.63). The cutoff of 300 cells/ $\mu$ L or greater was validated for prospective risk of exacerbation in the ECLIPSE study, with adjusted incidence rate ratios of 1.22 (95% CI, 1.06-1.41) using 3-year follow-up data. Stratified analysis confirmed that the increased exacerbation risk associated with an eosinophil count of 300 cells/ $\mu$ L or greater was driven by subjects with a history of frequent exacerbations in both the COPDGene and ECLIPSE studies. CONCLUSIONS: Patients with moderate-to-severe COPD and blood eosinophil counts of 300 cells/ $\mu$ L or greater had an increased risk exacerbations in the COPDGene study, which was prospectively validated in the ECLIPSE study.



Zhai, T., S. Li, et al. (2018). **"Potential Micronutrients and Phytochemicals against the Pathogenesis of Chronic Obstructive Pulmonary Disease and Lung Cancer."** *Nutrients* **10**(7) Lung cancer and chronic obstructive pulmonary disease have shared etiology, including key etiological changes (e.g., DNA damage and epigenetics change) and lung function impairment. Focusing on those shared targets may help in the prevention of both. Certain micronutrients (vitamins and minerals) and phytochemicals (carotenoids and phenols) have potent antioxidant or methyl-donating properties and thus have received considerable interest. We reviewed recent papers probing into the potential of nutrients with respect to lung function preservation and prevention of lung cancer risk, and suggest several hypothetical intervention patterns. Intakes of vitamins (i.e., A, C, D, E, B12), carotenoids, flavonoids, curcumins, resveratrol, magnesium, and omega-3 fatty acids all show protective effects against lung function loss, some mainly by improving average lung function and others through reducing decline rate. Dietary interventions early in life may help lung function reserve over the lifespan. Protective nutrient interventions among smokers are likely to mitigate the effects of cigarettes on lung health. We also discuss their underlying mechanisms and some possible causes for the inconsistent results in observational studies and supplementation trials. The role of the lung microbiome on lung health and its potential utility in identifying protective nutrients are discussed as well. More prospective cohorts and well-designed clinical trials are needed to promote the transition of individualized nutrient interventions into health policy.

Zhang, H., J. Xie, et al. (2018). **"Lung morphometry using hyperpolarized (129) Xe multi-b diffusion MRI with compressed sensing in healthy subjects and patients with COPD."** *Med Phys* **45**(7): 3097-3108.

**PURPOSE:** To demonstrate the feasibility of compressed sensing (CS) to accelerate the acquisition of hyperpolarized (HP) (129) Xe multi-b diffusion MRI for quantitative assessments of lung microstructural morphometry. **METHODS:** Six healthy subjects and six chronic obstructive pulmonary disease (COPD) subjects underwent HP (129) Xe multi-b diffusion MRI ( $b = 0, 10, 20, 30, \text{ and } 40 \text{ s/cm}^2$ ). First, a fully sampled (FS) acquisition of HP (129) Xe multi-b diffusion MRI was conducted in one healthy subject. The acquired FS dataset was retrospectively undersampled in the phase encoding direction, and an optimal twofold undersampled pattern was then obtained by minimizing mean absolute error (MAE) between retrospective CS (rCS) and FS MR images. Next, the FS and CS acquisitions during separate breath holds were performed on five healthy subjects (including the above one). Additionally, the FS and CS synchronous acquisitions during a single breath hold were performed on the sixth healthy subject and one COPD subject. However, only CS acquisitions were conducted in the rest of the five COPD subjects. Finally, all the acquired FS, rCS and CS MR images were used to obtain morphometric parameters, including acinar duct radius ( $R$ ), acinar lumen radius ( $r$ ), alveolar sleeve depth ( $h$ ), mean linear intercept ( $L_m$ ), and surface-to-volume ratio (SVR). The Wilcoxon signed-rank test and the Bland-Altman plot were employed to assess the fidelity of the CS reconstruction. Moreover, the t-test was used to demonstrate the effectiveness of the multi-b diffusion MRI with CS in clinical applications. **RESULTS:** The

retrospective results demonstrated that there was no statistically significant difference between rCS and FS measurements using the Wilcoxon signed-rank test ( $P > 0.05$ ). Good agreement between measurements obtained with the CS and FS acquisitions during separate breath holds was demonstrated in Bland-Altman plots of slice differences. Specifically, the mean biases of the R, r, h, Lm, and SVR between the CS and FS acquisitions were 1.0%, 2.6%, -0.03%, 1.5%, and -5.5%, respectively. Good agreement between measurements with the CS and FS acquisitions was also observed during the single breath-hold experiments. Furthermore, there were significant differences between the morphometric parameters for the healthy and COPD subjects ( $P < 0.05$ ).

**CONCLUSIONS:** Our study has shown that HP (129) Xe multi-b diffusion MRI with CS could be beneficial in lung microstructural assessments by acquiring less data while maintaining the consistent results with the FS acquisitions.

Zhang, Y., J. Qiu, et al. (2018). **"Genetic variants in FAM13A and IREB2 are associated with the susceptibility to COPD in a Chinese rural population: a case-control study."** Int J Chron Obstruct Pulmon Dis **13**: 1735-1745.

**Background:** Genome-wide association studies identified several genomic regions associated with the risk of chronic obstructive pulmonary disease (COPD), including the 4q22 and 15q25 regions. These regions contain the FAM13A and IREB2 genes, which have been associated with COPD but data are lacking for Chinese patients. The objective of the study was to identify new genetic variants in the FAM13A and IREB2 associated with COPD in Northwestern China.

**Methods:** This was a case-control study performed in the Ningxia Hui Autonomous Region between January 2014 and December 2016. Patients were grouped as COPD and controls based on FEV1/FVC<70%. Seven tag single-nucleotide polymorphisms (SNPs) in the FAM13A and IREB2 genes were genotyped using the Agena MassARRAY platform. Logistic regression was used to determine the association between SNPs and COPD risk.

**Results:** rs17014601 in FAM13A was significantly associated with COPD in the additive (odds ratio [OR]=1.36, 95% confidence interval [CI]: 1.11-1.67,  $P=0.003$ ), heterozygote (OR=1.76, 95% CI: 1.33-2.32,  $P=0.0001$ ), and dominant (OR=1.67, 95% CI: 1.28-2.18,  $P=0.0001$ ) models. Stratified analyses indicated that the risk was higher in never smokers. rs16969858 in IREB2 was significantly associated with COPD but in the univariate analysis only, and the multivariate analysis did not show any association.

**Conclusion:** The results suggest that the new variant rs17014601 in the FAM13A gene was significantly associated with COPD risk in a Chinese rural population. Additional studies are required to confirm the role of this variant in COPD development and progression.

Zheng, Z., Z. Wu, et al. (2016). **"Silent aspiration in patients with exacerbation of COPD."** Eur Respir J **48**(2): 570-3.

Zinellu, A., E. Sotgiu, et al. (2017). "**Blood global DNA methylation is decreased in non-severe chronic obstructive pulmonary disease (COPD) patients.**" Pulm Pharmacol Ther **46**: 11-15.

BACKGROUND: Alterations in global DNA methylation have been associated with oxidative stress (OS). Since chronic obstructive pulmonary disease (COPD) is characterized by increased oxidative stress we aimed to evaluate the levels of global DNA methylation in this patient group. METHODS: We assessed methylcytosine (mCyt) levels in DNA from blood collected in 43 COPD patients (29 with mild and 14 with moderate disease) and 43 age- and sex-matched healthy controls. RESULTS: DNA methylation was significantly lower in COPD patients vs. controls ( $4.20 \pm 0.18\%$  mCyt vs.  $4.29 \pm 0.18\%$  mCyt,  $p = 0.02$ ). Furthermore, DNA methylation in COPD patients with moderate disease was significantly lower than that in patients with mild disease ( $4.14 \pm 0.15\%$  mCyt vs.  $4.23 \pm 0.19\%$  mCyt,  $p < 0.05$ ). Univariate logistic regression analysis showed that lower DNA methylation levels were associated with presence of COPD (crude OR = 0.06, 95% CI 0.00 to 0.67,  $p = 0.023$ ). This relationship remained significant after adjusting for several confounders (OR 0.03, 95% CI 0.00 to 0.67;  $p = 0.028$ ). Receiver operating characteristics (ROC) curve analysis demonstrated the area under the curve of mCyt was 0.646, with 46.6% sensitivity and 79.1% specificity for presence of COPD. CONCLUSIONS: There were no significant correlations between methylation and OS indices. The presence and severity of COPD is associated with progressively lower DNA methylation in blood. However, this epigenetic alteration seems independent of oxidative stress.