Predicting the occurrence and outcomes of exacerbations of COPD

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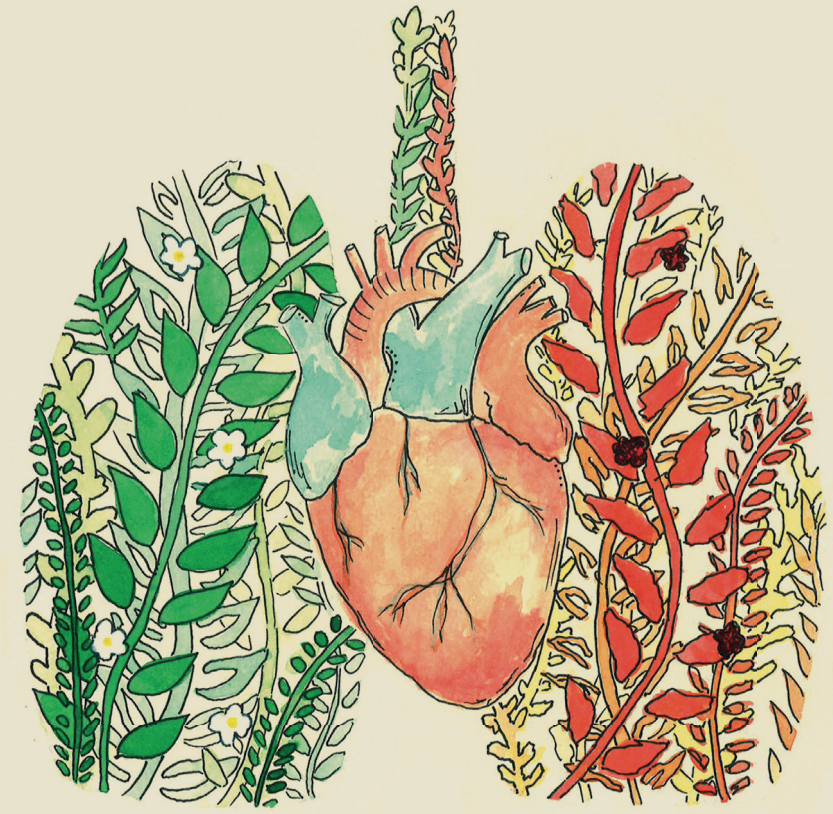

Kiki Waeijen-Smit

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CHAPTER 1

General introduction

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Unmet needs in the management of exacerbations of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms, including dyspnea, cough and/or sputum production, due to abnormalities of the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema), that cause persistent, often progressive, airflow obstruction.[1] Its main risk factor is cigarette smoking but environmental or occupational pollutions, prematurity, childhood infections and genetic susceptibility may also contribute to the development of COPD.[2] Exposure to these risk factors is commonly associated with an enhanced inflammatory response in the lungs, and structural changes of the small airways and lung parenchyma.[3-7] These changes persist even after smoking cessation due to largely unknown mechanisms, although perturbation of the lung microbiota is suggested to play a role.[8] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends pulmonary function testing when considering a diagnosis of COPD in individuals presenting with respiratory symptoms, a history of recurrent lower respiratory tract infections, and/or a history of exposure to risk factors of the disease.[1] Goals of initial COPD assessment include establishing the severity of airflow obstruction, the impact of the disease on the patient's overall health status, and the risk of future events including exacerbations of COPD (ECOPD) and hospital admissions.

According to the World Health Organization (WHO), COPD is currently the third leading cause of death worldwide[9], and is associated with a high disease and economic burden.[10] In 2016, the disease claimed 3 million lives around the globe, of which 300.000 deaths in Europe.[11] The direct healthcare costs of COPD are estimated to be €38.6 billion in Europe, excluding indirect costs such as COPD-related reduced workplace- and home productivity.[1] Globally, ECOPD are responsible for the greatest proportion of COPD-related healthcare costs.[1, 12] In the Netherlands, COPD accounted for an estimated total healthcare expenditure of 753 million euros in 2019, constituting 0.8% of the overall healthcare expenditure, and 22.8% of the total expenditure on respiratory diseases. Hospital care consumed 249 million euros (33%) of this expenditure, whereas primary care accounted for 178 million euros (24%).[13] Continued exposure to risk factors, as well as the aging population are expected to contribute to an increased global COPD burden in the coming years.[1] By 2050, the number of COPD cases is estimated to increase by 23%, affecting 600 million individuals globally.[14] With a projected rise

of 14.6%, the highest projected increase in prevalence among European countries is expected in the Netherlands.[15]

Over the years it has become evident that the disease cannot be fully captured by the severity of airflow limitation, and that the structural and inflammatory manifestations associated with COPD may extend beyond the lungs.[16] As such, extra-pulmonary manifestations including fatigue[17] and deconditioning[18] are also common. Moreover, concomitant chronic diseases, including cardiovascular disease, osteoporosis, and anxiety and depression are frequently seen in patients with COPD.[19-22] Indeed, individuals with COPD are two to three times more likely to develop cardiovascular diseases than individuals without COPD[23], and the prevalence of osteoporosis in COPD is 32.5% versus 11.4% in healthy age-matched controls.[24] Comorbidities can directly impact the burden and prognosis of COPD, *vice versa* COPD may adversely affect the outcomes of other disorders.[1, 16] For instance, for every 10% reduction in the forced expiratory volume in the first second (FEV_1) the risk of cardiovascular death increases by 28%.[25] Conversely, the presence of concomitant arrhythmia in COPD poses a significant detrimental impact on outcomes including hospital stay, hospitalization charges and in-hospital mortality.[26] COPD and concomitant chronic diseases can be causally related either via shared risk factors such as physical inactivity and cigarette smoking, or by pharmacological cross-effects (e.g. non-cardio-selective β-blockers worsening lung function through bronchoconstriction, or frequent use of oral corticosteroids increasing the risk of osteoporosis).[1, 16] Given that most (97.7%) patients with COPD have at least one comorbidity[22], proactive diagnosis and integrated disease management are essential to optimize clinical outcomes.[27]

Exacerbations of COPD

Whilst perceived respiratory symptoms are naturally fluctuating by day, week or season[28, 29], patients with COPD may experience a sudden deterioration in respiratory health, called exacerbations of COPD (ECOPD).[1] Such events are traditionally defined as an acute worsening of respiratory symptoms that extend beyond normal day-to-day variations, and necessitate a change in regular medication.[30] ECOPD are typically associated with increased airway inflammation, mucus production, increased sputum volume and purulence, cough and wheeze, marked gas trapping and hyperinflation.[5, 31] These changes contribute to increased

dyspnea, the key symptom of an ECOPD.[1] Since the traditional definition of ECOPD was rather subjective, did not include a link with pathogenesis, and lacked a framework of timing, a novel definition of ECOPD was recently proposed by a panel of international COPD experts.[32] This new definition states that ECOPD are characterized by dyspnea and/or cough and sputum that worsens over ≤14 days, that may be accompanied by tachypnea and/or tachycardia, often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways. Stepping away from relying solely on a worsening of respiratory symptoms, this updated definition was an important step towards a more objective diagnosis of these complex events[32], and has been integrated in GOLD since 2023.[33]

To date, GOLD classifies ECOPD treated with short acting bronchodilators as mild, ECOPD treated with antibiotics and/or oral corticosteroids as moderate, and ECOPD requiring hospital admission as severe.[1] Hospital management of severe ECOPD may include, in addition to the previously mentioned pharmacotherapies, respiratory support such as oxygen therapy and (non)invasive ventilation. As such, the severity of ECOPD is established *post hoc* based on the healthcare resource used to treat the event. Given the differences between healthcare systems and practitioners, the availability and access to healthcare, and patient specific traits such as self-management skills, this *post hoc* grading system is highly subjective. Hence, according to the novel Rome proposal, ECOPD severity should be determined by objectively measured clinical variables including dyspnea (visual analogue scale value ≥5), oxygen saturation (SaO_2 <92%, and/or change >3%), respiratory rate (≥24 breaths/min), heart rate (≥95 bpm), serum C-reactive protein (CRP) (≥10 mg/L), and in selected cases, arterial blood gases ($PaCO_2$ >45 mmHg and pH <7.35).[32] Using these parameters, ECOPD are classified as mild by default, as moderate when three out of five parameters exceed the respective threshold values, and as severe when arterial blood gas values additionally indicate the presence of hypercapnia and respiratory acidosis. Using these criteria, studies have shown that only up to a third of hospitalized patients meets the criteria of a severe ECOPD.[34-37]

The risk of ECOPD is related to the severity of airflow limitation: approximately 40% of patients with moderate COPD experiences at least one ECOPD per year. This percentage increases with an additional 10% respectively as the disease progresses to severe, or very severe.[38] Moreover, a substantial number of patients experiences frequent ECOPD, defined as two or

more annual ECOPD.[1, 38] Whilst the annual ECOPD rate may be highly variable for an individual patient[39], for more than a decade the strongest single determinant of frequent ECOPD remains a history of ECOPD.[38] Accordingly, GOLD classifies patients with a history of two or more moderate ECOPD, and/or one or more hospitalizations in the preceding year as being at high risk of ECOPD.[1] However, these cutoffs lack validation to date. Importantly, many patients experience difficulties with the recognition of an ECOPD.[40, 41] Studies have shown that mild, unreported ECOPD are 2.5 times more frequent than those resulting in healthcare contact.[42, 43] While both reported and unreported ECOPD have an impact on health status, ECOPD that do result in seeking healthcare, particularly those necessitating visits to the emergency department and hospital admission, are associated with a more severe prognosis.[44] Indeed, 10% of patients dies in hospital, whilst another 26% dies within one year after ECOPD-related hospitalization[45, 46], although in literature great heterogeneity exists in mortality rates between studies and countries.

Annually, around 26,000 hospital admissions for ECOPD are recorded in the Netherlands.[47] Hospital managed ECOPD are the main contributor to global COPD-related healthcare expenses[48], and can be up to 60 times more expensive than those managed in primary care.[49] Furthermore, once experiencing an ECOPD-related hospitalization, the risk of successive severe events increases: more than a third of patients surviving ECOPD-related hospitalization are readmitted to the hospital for another ECOPD within 90 days.[50] To illustrate, in the Netherlands, half of the 200,000 annual ECOPD-related hospitalization days can be attributed to readmissions.[51] However, it should be noted that not all readmissions may concern ECOPD: studies have shown that only half of the reasons for hospital readmission in COPD are driven by respiratory-related diseases.[52] A systematic review identified comorbidities, previous ECOPD and hospitalization, and increased length of stay as significant risk factors for 30- and 90-day all-cause hospital readmission.[53] Nevertheless, the personalized prediction of outcomes such as hospital readmission remains challenging in clinical practice. The PEARL (previous admissions, extended medical research council dyspnea score, age, right-sided heart failure and left-sided heart failure), CORE (COPD readmission, based on eosinophil count, lung function, triple inhaler therapy, previous hospitalization and neuromuscular disease) and CORE+ (also including out of hospital NIV use and comorbidities) scores rank among the most accurate readmission prediction scores currently available.[54, 55]

It is well recognized that ECOPD are heterogeneous events with respect to etiology and inflammatory profiles.[31, 38, 56] Most ECOPD have an infectious origin and are triggered by respiratory bacterial- and/or viral infections.[57-59] Eosinophilic inflammation provides another common trigger of ECOPD.[56, 60] In addition, a 'pauci-inflammatory' cluster of ECOPD has been identified, characterized by limited inflammatory changes and a largely unknown pathophysiology.[56] To date, the susceptibility of an individual patient to exacerbate remains largely unknown and timely prediction of these events in individual patients remains unsuccessful. The non-COPD specific nature of ECOPD symptoms adds to its complexity and heterogeneity. It is estimated that 15 to 19% of all ECOPD are in fact exacerbation-like events triggered by differential acute conditions such as pulmonary embolism, pneumonia or heart failure.[61, 62] As such, excluding differential diagnoses plays a central role in ECOPD diagnosis[1], and has important clinical consequences. Indeed, as mentioned, patients with COPD often have (multiple) comorbidities, which can both mimic and aggravate symptoms and outcomes of ECOPD.[62, 63] Hence, COPD may be considered the pulmonary component of multimorbidity. The relation between ECOPD and cardiovascular events has received a particular interest over the past few years since studies have shown that ECOPD present an independent risk factor for subsequent cardiovascular events.[64-71] The association between COPD and cardiovascular diseases may be explained by shared risk factors such as older age, cigarette smoking and physical inactivity.[23] The exact mechanisms linking these conditions during more acute settings are, however, still largely unclear. Future studies exploring the causal pathways involved are indicated to provide hints for therapeutic targets.

The respiratory microbiome

The respiratory microbiome, i.e. the complete set of genes, metabolites and microbes found in the lungs, is increasingly suggested to play a pivotal role in the pathogenesis of COPD as well as the onset of ECOPD and comorbidities.[57, 72-74] Conversely, factors such as severity of airflow limitation, ECOPD, inflammation and COPD-related medications including antibiotics, corticosteroids and β2-agonists may affect the composition of the respiratory microbiome through local microenvironmental changes including the type and presence of immune cells, pH, mucus, nutrient and oxygen levels.[72, 75] Compared to healthy individuals, the lung microbiota of patients with COPD is less diverse and is characterized by the abundance of specific bacterial phyla such as Proteobacteria[72, 76] and Firmicutes[58, 77], and immune cell

infiltration and inflammation which contributes to increased airflow obstruction.[72] These alterations may further increase during ECOPD (Figure 1).

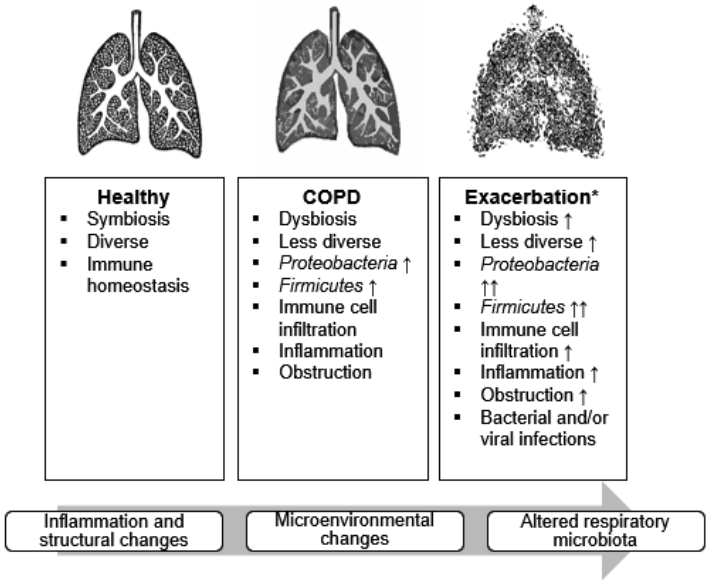

Fig. 1 Common lung microbial characteristics of healthy individuals, and patients with COPD at stable disease state and during ECOPD. **Not every ECOPD is characterized by these factors*

Indeed, patients with COPD with a Proteobacteria predominant microbiota at stable disease state were previously shown to exhibit less microbial diversity, and were more prone to suffer from future ECOPD and viral infections.[57] Furthermore, dysbiosis of the microbiota was shown to be associated with a greater symptom burden and increased ECOPD severity.[78] Indeed, important outcomes of ECOPD such as length of hospital stay and mortality have been linked to microbial diversity.[79, 80] However, not every ECOPD is characterized by microbial dysbiosis.[78] Moreover, some patients with COPD do not exacerbate although potential pathogenic bacteria do reside their microbiota. The mechanisms or factors responsible for this beneficial phenotype are currently still unknown. Although, accumulating evidence suggests that the balance between distinct microbial populations determines distinct host immune responses, and different disease phenotypes.[72, 75, 78, 80-82]

Taken together, the lung microbiota regulates immune responses and the susceptibility to infections and ECOPD. Whether the changes in microbial composition are the cause or rather the consequence of inflammation and ECOPD, remains unclear. Moreover, its clinical relevance is yet to be established. As techniques to investigate the lung microbiota become more available, future studies need to explore their application in the clinical management of ECOPD.

Exacerbation prevention strategies

ECOPD play a pivotal role in the progressive decline in lung function[83], reduced health status[84], low physical activity[85] and increased mortality risk[44] in COPD. Furthermore, each ECOPD increases the risk of further ECOPD.[86] Inherently, the prevention of ECOPD is one of the major aims in the management of COPD.[1] Since smoking is a major risk factor for ECOPD and hospitalizations, smoking cessation is essential in their prevention.[87] Other non-pharmacologic ECOPD prevention strategies include enhancing physical activity[88], pulmonary rehabilitation[89] and self-management education.[90] Vaccination, i.e. Influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pneumococcal, pertussis, varicella zoster and respiratory syncytial virus (RSV) vaccination, is furthermore indicated to reduce the risk of infection-related ECOPD.[91, 92] The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the novel coronavirus SARS-CoV-2[93], significantly affected morbidity and mortality in individuals around the world, particularly elderly individuals with underlying illnesses.[94, 95] Besides hypertension, cardiovascular disease and diabetes, COPD has been identified as an independent risk factor for severe illness or death[94, 95], although a low prevalence of COPD in COVID-19 cases has been observed.[96] Despite the previously established association between coronaviruses and ECOPD[97, 98], a global 50% reduction in the number of ECOPD-related hospitalizations has been observed during the COVID-19 pandemic.[99] This decline has been attributed to a reduction in respiratory viral infections other than SARS-CoV-2[99] due to the implementation of COVID-19-related infection prevention and control (IPC) measures including social distancing, mask wearing and lockdowns.[100] Indeed, historically low activity of influenza and other respiratory viruses such as RSV were observed during the COVID-19 pandemic.[101] Conversely, these measures indirectly improved pollutant emissions and environmental air quality, other well-known triggers of ECOPD.[1] Nevertheless, in response to this significant reduction in ECOPD, GOLD recommends shielding measures, on top of

established (non)pharmacological measures, for patients with COPD at high-risk of ECOPD during high-risk seasons.[1] An alternative explanation for the observed global reduction in ECOPD-related hospitalizations could, however, be the avoidance of healthcare by patients due to fear of contracting a SARS-CoV-2 infection. This would question the effectiveness of such prevention strategies. As such, studies unraveling the direct impact of IPC measures for the prevention of (the different types of) ECOPD are needed to provide policymakers and guideline developers with informed strategies for preventing ECOPD. Noteworthy, although the diagnosis of COVID-19 or an ECOPD may be complicated by the close resemblance of symptoms, and although the diagnosis of COVID-19 does not exclude a coexisting ECOPD, a SARS-CoV-2 infection causes distinct pathophysiological changes, and once a COVID-19 infection is confirmed in a patient with COPD, treatment of COVID-19 should be conducted regardless of the presence of COPD.[1, 102, 103]

Besides the afore mentioned non-pharmacologic strategies, different maintenance pharmacotherapies exist to reduce symptoms as well as the frequency and severity of ECOPD.[1] Depending on the patient's treatable traits, treatments differing in their mechanism and duration of action, route of delivery, inhaler types, or combination treatments may be prescribed.[1] Common medications are bronchodilators (i.e. β2-agonists), anticholinergics (i.e. muscarinic antagonists), anti-inflammatory drugs (i.e. inhaled corticosteroids, oral glucocorticosteroids and prophylactic antimicrobials), phosphodiesterase-4 inhibitors and mucolytic agents.[1, 31, 60] Despite the available (non)pharmacological therapies, a significant proportion of patients continues to experience (recurrent) ECOPD. This stresses the urgent need for strengthened and improved ECOPD prevention strategies.

Exacerbation biomarkers

In order to improve the prevention of ECOPD, and to reduce the negative impact of these events in individual patients, early and accurate diagnosis followed by timely initiation of treatment are warranted. Indeed, adequate recognition of symptoms and early treatment are associated with a faster recovery, reduced risk of hospitalization and better health-related quality of life.[77] At present, biomarkers to predict ECOPD form an important unmet need in the management of COPD, as they might provide a helpful tool for clinicians to improve early diagnosis, and steer treatment decisions. According to the National Institutes of Health,

biomarkers are defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention'.[104] Biomarkers of ECOPD may furthermore increase our understanding of the underlying ECOPD etiology, and steer the characterization of the severity and different endotypes of these events.[58] Several potential ECOPD biomarkers have previously been studied. Biomarkers of inflammation such as CRP, leukocyte count, interleukin (IL) 6 and 8, TNF-α, cardiac markers including brain natriuretic peptide, and markers involved in collagen formation such as matrix metalloproteinase-9 are often elevated during ECOPD, but are not specific for, and predictive of, ECOPD.[56, 58, 62, 104-109] Recently, a combination of elevated CRP, neutrophils and dyspnea revealed to discriminate best between the stable disease state and ECOPD.[58] In contrast, although established clinical features were predictive of ECOPD, biomarkers identified in blood did not add significantly to the prediction of ECOPD in two large COPD cohort studies.[107] Rather, enlargement of the pulmonary artery diameter was associated with a three-fold increased exacerbation risk.[110]

A biological pathway that merits further consideration in the context of ECOPD and ECOPD biomarkers, is airway remodeling. Airway remodeling refers to the structural and mechanical changes to the lungs that occur with aging or upon injury.[3] A pivotal element of airway remodeling is degradation of the interstitial extracellular matrix (ECM).[3, 4] Research has shown that ECM composition and turnover are altered in patients with (E)COPD.[111-113] Indeed, an accelerated turnover of ECM components can be observed during ECOPD, leading to increased fragmentation, and thus increased levels of circulating ECM components such as collagen and hyaluronic acid (HA).[112, 114, 115] Since ECM integrity is essential for physiological lung function[3], this may explain why lung function does not recover post-ECOPD in some patients[116], leading to all associated worse clinical outcomes.[117] In this light, monitoring ECM markers, such as HA, might be pertinent in the context of ECOPD. Nevertheless, it remains unknown how this relates to individuals without COPD, and whether systemic concentrations of such markers rise in the period leading up to an ECOPD. A potential disease specific and predictive role thus remains to be elucidated.

It is evident that multifactorial influences, e.g. demographics, pulmonary physiology, comorbidities and microbial profile, play a role in a patient's susceptibility to future ECOPD[60,

[61] and these must be taken into account while searching for ECOPD biomarkers. Furthermore, future studies should focus on a broad(er) time window to assess whether biomarkers could already be detected when the ECOPD is triggered and well before the patient presents with a worsening of respiratory symptoms.

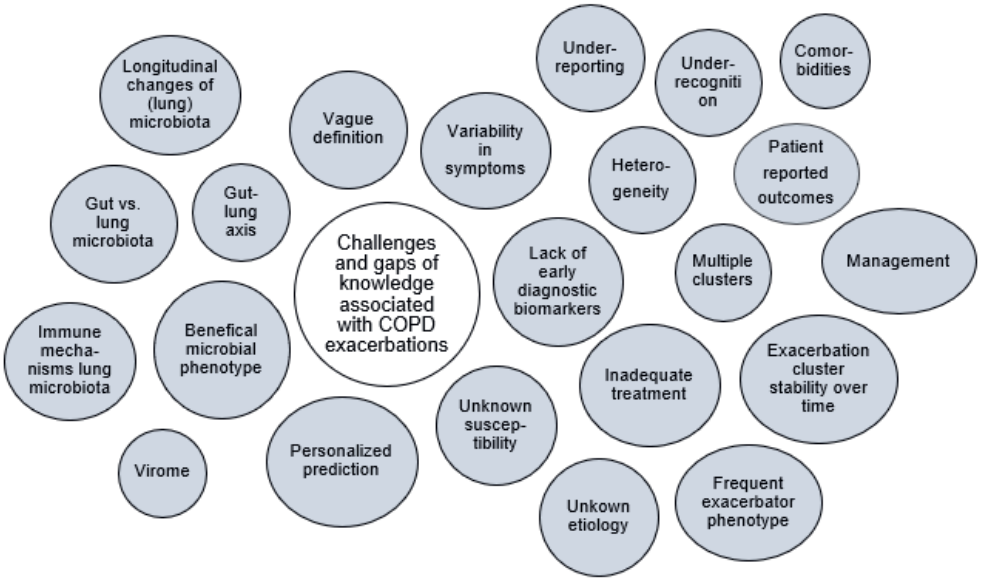

Fig. 2 Current challenges and knowledge gaps associated with ECOPD

Aims of this thesis

ECOPD are complex and heterogeneous events with a central role in the burden and progressive course of COPD. As outlined in this chapter and as summarized in Figure 2, many knowledge gaps, challenges and unmet needs exist in the management of ECOPD. Important challenges include, but are not limited to, the lack of personalized prediction and prevention strategies regarding the occurrence and outcomes of ECOPD, the intricate interplay between ECOPD and comorbidities, as well as the absence of early and accurate diagnostic ECOPD biomarkers. A better understanding of the occurrence, determinants and outcomes of ECOPD is essential to improve the personalized prediction and prevention of these events in individual patients. Therefore, the central aims of this thesis were to predict the occurrence and outcomes of ECOPD.

Specifically, this thesis aims:

- To provide more precise estimates of global in-hospital and post-discharge mortality, and hospital readmission rates following COPD exacerbation-related hospitalization, and to evaluate determinants of these prognostic outcomes.
- To study all-cause hospital admission trajectories of patients with COPD following their first ever exacerbation-related hospitalization.
- To assess whether the current ECOPD history categories by GOLD are valid for accurate risk status assessment in COPD.
- To compare levels of systemic HA and its metabolic regulators between patients with clinically stable COPD and (non)smoking controls.
- To assess the impact of the COVID-19-related IPC measures on the occurrence of ECOPD in a real-life inpatient pulmonary rehabilitation setting.

Thesis outline

Chapters 2-3 outline the outcomes of exacerbation-related hospitalizations. **Chapter 2** presents the results of an individual patient data meta-analysis to study global estimates of mortality and hospital readmission rates following COPD exacerbation-related hospitalization. This chapter underlines the poor prognosis and high heterogeneity of ECOPD. Moreover, routinely available predictive determinants of mortality and hospital readmission are discussed. **Chapter 3** reports the all-cause hospital admission trajectories of patients with COPD following their first ever exacerbation-related hospitalization, using data from the Danish national patient registry. Furthermore, differences between short- and long-term admissions, and frequently and less-frequently admitted patients are discussed. **Chapters 4-6** outline (predictors of) the occurrence of ECOPD. **Chapter 4** discusses the current ECOPD history categories by GOLD in relation to future ECOPD and all-cause mortality using data from the German prospective, observational, multi-center COSYCONET cohort study. **Chapter 5** reports whether, and to what extent, systemic HA and its metabolic regulators differ between patients with clinically stable COPD and (non)smoking controls from the Dutch single-center, longitudinal, observational ICE-Age study. Moreover, the associations between HA and ECOPD frequency, airway-related hospitalizations, systemic inflammation and cardiovascular risk are discussed. **Chapter 6** describes the impact of the COVID-19-related IPC measures on the occurrence of ECOPD in patents with COPD admitted for an eight-week inpatient pulmonary

rehabilitation program at Ciro (Horn, the Netherlands). At last, **Chapter 7** puts the results of this thesis in perspective, and offers directions for future research.

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CHAPTER 2

Global mortality and readmission rates following COPD exacerbation-related hospitalization: a meta-analysis of 65945 individual patients

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Abstract

Background: Exacerbations of COPD (ECOPD) have a major impact on patients and healthcare systems across the world. Precise estimates of the global burden of ECOPD on mortality and hospital readmission are needed to inform policy makers and aid preventive strategies to mitigate this burden.

Aims: To explore global in-hospital mortality, post-discharge mortality and hospital readmission rates after ECOPD-related hospitalization using an individual patient data meta-analysis (IPDMA) design.

Methods: A systematic review was performed identifying studies that reported in-hospital mortality, post-discharge mortality and hospital readmission rates following ECOPD-related hospitalization. Data analyses were conducted using a one-stage random-effects meta-analysis model. This study was conducted and reported in accordance with the PRISMA-IPD statement.

Results: Data of 65945 individual patients with COPD were analyzed. The pooled in-hospital mortality rate was 6.2%, pooled 30-, 90- and 365-day post-discharge mortality rates were 2.0%, 6.4% and 12.2% respectively, and pooled 30-, 90- and 365-day hospital readmission rates were 11.8%, 26.5% and 38.2% respectively, with noticeable variability between studies and countries. Strongest predictors of mortality and hospital readmission included non-invasive mechanical ventilation, and a history of ≥2 ECOPD-related hospitalizations <12 months.

Conclusions: This IPDMA stresses the poor outcomes and high heterogeneity of ECOPD-related hospitalization across the world. Whilst global standardization of the management and follow-up of ECOPD-related hospitalization should be at the heart of future implementation research, policy makers should focus on reimbursing evidence-based therapies that decrease (recurrent) ECOPD.

Background

Exacerbations of chronic obstructive pulmonary disease (ECOPD) exert deleterious effects on patients and health care systems[1], and significantly increase resource utilization and health care costs around the world.[2] Each ECOPD may contribute to an accelerated decline in lung function, lower-limb muscle function, physical activity, and health-related quality of life.[3-5] Specifically, severe ECOPD, i.e. exacerbations necessitating hospitalization[6], are important drivers of disease deterioration and are associated with a poor prognosis and an increased risk of successive events.[7-10] ECOPD are common. Recent results from the IMPACT trial revealed an annual ECOPD rate of 0.91, 1.07 and 1.21 in patients with a history of ECOPD on triple therapy (inhaled glucocorticoids, long-acting β2-agonists [LABA] and long-acting muscarinic antagonists [LAMA]), and dual therapy with inhaled glucocorticoids and LABA, or LAMA and LABA, respectively.[11]

During the past 20 years numerous studies have addressed the rates and determinants of in-hospital mortality, post-discharge mortality and hospital readmission for subsequent ECOPD.[8-10, 12-21] However, great heterogeneity exists between studies, hindering our understanding of the true, global burden of ECOPD on health care systems. In-hospital mortality rates ranging between 2.5%[13] and 11.5%[22], 1-year post-discharge mortality rates ranging between 9.8%[23] and 23%[10], and hospital readmission rates ranging between 6.7%[24] and 35.1%[25] have been reported, with noticeable variability between countries. Mortality and hospital readmission are important outcomes of ECOPD that drive healthcare utilization and, in some countries, allocation of COPD related healthcare budgets. Older age, male sex, and worse Global initiative for chronic obstructive lung disease (GOLD) grade have frequently been identified as predictors of mortality[26]. Likewise, previous ECOPD and hospitalizations, higher symptom burden at hospital discharge, reduced lung function and increased length of hospital stay are known risk factors for hospital readmission.[27] Such determinants have not been studied on a global level however.

Providing precise estimates of the outcomes of severe ECOPD and their determinants is important to value the true burden of such events, and to strengthen preventive measures. Moreover, predictors of in-hospital and post-discharge mortality and hospital readmission

have not been addressed in an individual patient data meta-analysis (IPDMA). Therefore, the current IPDMA aimed to (1) provide more precise estimates on in-hospital and post-discharge mortality and readmission rates after a severe ECOPD, and (2) to evaluate determinants of in-hospital and post-discharge mortality, as well as hospital readmission.

Methods

This study was conducted and reported in accordance with the PRISMA-IPD statement for reporting systematic reviews and meta-analyses of individual patient data.[28] The protocol of the current IPDMA is not registered on a recognized database such as PROSPERO. As of October 2019, submission of protocols of systematic reviews require that data extraction had not yet been commenced. Since data extraction had already commenced at the time of registration, the current protocol could not be included in PROSPERO.

Search strategy

Online databases PubMed, Embase (OVID), and Web Of Science were searched for studies reporting mortality during and/or after hospitalization for ECOPD, and/or subsequent ECOPD hospital readmission (Online Supplement). The search was conducted from database inception until March 31, 2021. The search strategy was limited to full text and English articles, and articles based on studies involving human subjects only. Furthermore, given the global efforts to standardize COPD guidelines in the late 1990s, and the subsequent establishment of the first GOLD report in 2001[29], studies had to be conducted after the year 2000. Titles, abstracts and full-texts of the search results were evaluated by three independent reviewers (MC, SK, KWS). Agreements upon inclusion were made in consensus with a fourth independent person (MAS).

Study selection

Eligible studies needed to be conducted in (1) patients with COPD aged ≥18 years, (2) patients hospitalized for ECOPD, and (3) needed to report death, survival and/or hospital readmission rates. Corresponding authors of eligible studies were contacted and asked about their willingness to participate.

Outcomes

The initial hospital admission for an ECOPD was defined as the index event. Main outcomes of interest were: in-hospital mortality (yes/no), post-discharge mortality (yes/no), and hospital readmission (yes/no) after the index event. Secondary outcomes included length of hospital stay (days) during the index event, and follow-up time (days) after hospital discharge from the index event (either as exact number of days, or the set study follow-up time) to study time till event (post-discharge mortality and hospital readmission).

Data extraction and harmonization

Original individual patient data was extracted in an anonymized and secured manner. To be able to participate, datasets needed to include at least the following variables: age (years), sex (male/female), in-hospital mortality (yes/no), and/or death during follow-up after the index event (yes/no), and/or hospital readmission for a subsequent ECOPD during follow-up after the index event (yes/no).

Additionally, variables such as total number of ECOPD and hospitalizations <12 months prior to the index event (0, 1, ≥2), non-invasive mechanical ventilation (NIMV) during the index event (yes/no), invasive mechanical ventilation (IMV) during the index event, stay at an intensive care unit (ICU) during the index event (yes/no), total in-hospital stay (days) during the index event, ethnicity (European, African, Asian), modified Medical Research Council (mMRC) dyspnea grades (i.e. 0-4) during the index event and forced expiratory volume in 1 second (FEV_1) % predicted were included based on availability. If available, FEV_1 needed to be assessed in the year prior to the index event at a clinically stable state. GOLD classification for airflow limitation grades (I-IV) was extracted from FEV_1. Data were checked for incorrect and missing values, and screened for duplicates. Data queries were resolved by consulting the corresponding author.

Statistical analyses

Data analyses were conducted using a one-stage meta-analysis model[30]; all individual patient records were combined to compose three data subsets based on the availability of the three distinct outcomes of interest in-hospital mortality, post-discharge mortality and hospital readmission. Stratified (per study and country) and pooled analyses were conducted incorporating random-effects to enable borrowing of information across studies.[31] The

Shapiro-Wilk test was used to test for normality. Baseline characteristics were presented as frequencies and percentages for categorical variables, and as means ± standard deviation (SD) or median ± inter quartile range (IQR) as appropriate for continuous variables. The independent samples T-test and Mann-Whitney U test were used to compare continuous data. The relationship between categorical variables was assessed using the Chi-squared test. Median survival was presented as median ± IQR and in-hospital mortality as % of patients dying during index hospitalization.

To determine predictors of mortality and readmission a Cox proportional hazard regression for univariate and multivariate age- and sex-adjusted analyses was performed for the different baseline characteristics (i.e. FEV_1, ethnicity, GOLD grade, ECOPD and hospitalization history, mMRC, use of NIMV or IMV and ICU stay). Effect estimates were presented as hazard rates (HR) with their associated 95% confidence interval (CI). Kaplan-Meier survival analyses were conducted to assess median time to post-discharge mortality and hospital readmission defined by the number of days between discharge from the index event and death or hospital readmission respectively. Patient data were censored if the event did not occur until the end of follow-up, or if the patient was lost to follow-up. Cox proportional hazard regressions and Kaplan-Meier survival analyses were performed taking follow-up time into account: only cases with an exact follow-up time till the event (i.e. exact number of days) were included in the analyses. Statistical analyses were conducted using IBM SPSS Statistics 25.0 (IBM Corp. Armonk, NY, USA). *A priori*, *p*-values ≤0.05 were considered statistically significant. Graphs were created in GraphPad Prism 9.3.1. (GraphPad Software, La Jolla, CA, USA).

Role of the funding source

The current study was co-funded by the PPP Allowance made available by Health~Holland, Top Sector Life Sciences & Health (LSHI19003) and ZonMWAQ10 (ERACoSysMed grant #90030355). The funding source had no involvement in the study design, the collection, analysis, and interpretation of data, the writing of the report, nor in the decision to submit the paper for publication.

Results

The manual electronic database search identified 1,400 potentially relevant records. After screening, 321 studies were eligible for inclusion and contacted for sharing of IPD. In total, 47 authors shared data of 65,945 individual patients (Figure S1) from 30 different countries (Figure 1). Further details of the participating studies and the (stratified) sample sizes of the three data subsets are presented in the Online Supplement (Table S1 and Table S2).

Fig 1. Countries included in the current IPDMA. *NB: countries included in the IPDMA with IPD of n<90 (i.e. Mexico, Colombia, United States and Slovakia) are not colored.*

In-hospital mortality

Results for in-hospital mortality were available for 62,022 patients from 35 studies.[17, 32-62] Baseline characteristics of the pooled data subset are displayed in the Online Supplement (Table S3). Briefly, the median age was 74 years, and 59% of the patients were male. Most patients had moderate to severe airflow limitation and experienced two or more ECOPD in the year before the index event. In total, 3,868 (6.2%, 95% CI 6.0-6.4) patients died during the index event. Non-survivors were less often male, were older, had a lower FEV_1, experienced more hospitalizations in the year before index admission, spent more days in-hospital, experienced more dyspnea during hospitalization, and were more likely to receive (N)IMV or

to be admitted to the ICU. Length of hospital stay was available in 1,364 of the 3,868 non-surviving patients. Median length of stay was 7 days (IQR 3-16). Most patients (15.0%) died on the first day of admission, half of the deaths (50.2%) occurred within one week of hospitalization, and 5.1% died after ≥40 days of hospitalization (Figure 2).

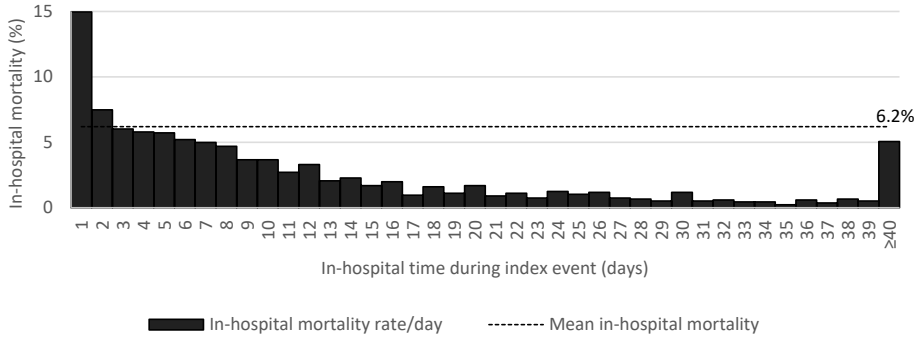

Fig 2. In-hospital mortality rates (%) by day for a severe ECOPD (n=1,346).

In-hospital mortality rates and median length of hospital stay stratified by study are provided in the Online Supplement (Figure S2). In-hospital mortality rates stratified by country are shown in Figure 3. The lowest stratified in-hospital mortality rates were observed in China (1.0%, n=191), whereas the highest stratified in-hospital mortality rates were observed in Turkey (11.8%, n=1,421).

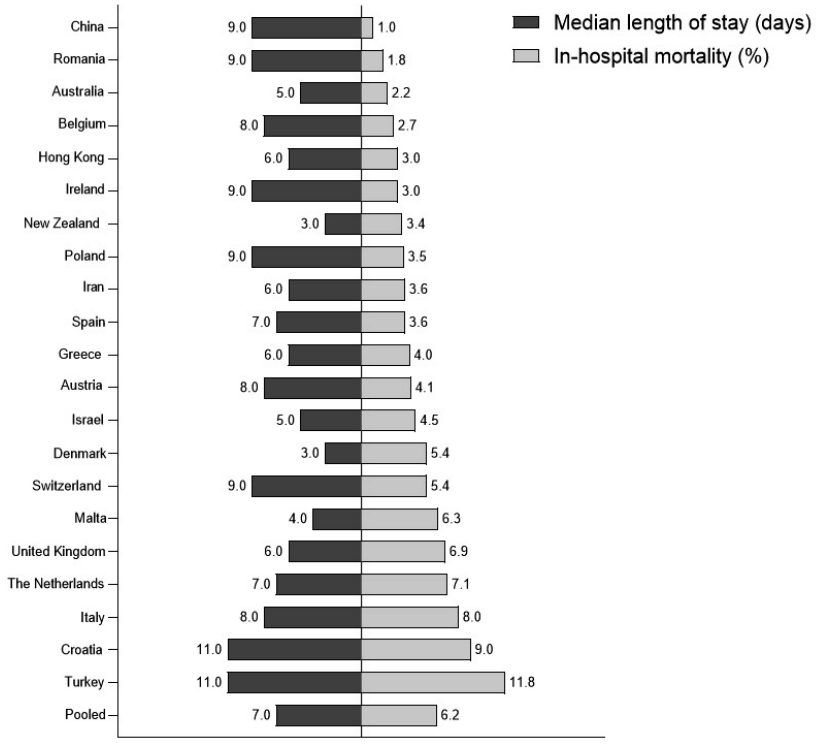

Fig 3. Pooled and stratified median length of hospital stay (left) and in-hospital mortality rates (right) during the index event per country. Relative percentages are displayed. China n=191 (0.3%), Romania n=718 (1.2%), Australia n=90 (0.1%), Belgium n=814 (1.3%), Hong Kong n=401 (0.6%), Ireland n=237 (0.4%), New Zealand n=1,126 (1.8%), Poland n=734 (1.2%), Iran n=507 (0.8%), Spain n=8,859 (14.3%), Greece n=1,133 (1.8%), Austria n=822 (1.3%), Israel n=67 (0.1%), Denmark n=405 (0.7%), Switzerland n=295 (0.5%), Malta n=112 (0.2%), United Kingdom n=35,707 (57.6%), The Netherlands n=662 (1.1%), Italy n=7,234 (11.7%), Croatia n=445 (0.7%), Turkey n=1,421 (2.3%).

Multivariate analyses showed that older age, use of (N)IMV and ICU admission were significantly associated with a higher odds of in-hospital mortality, whereas male sex and European ethnicity were significantly associated with a lower odds of in-hospital mortality (Figure 4 and Table S4).

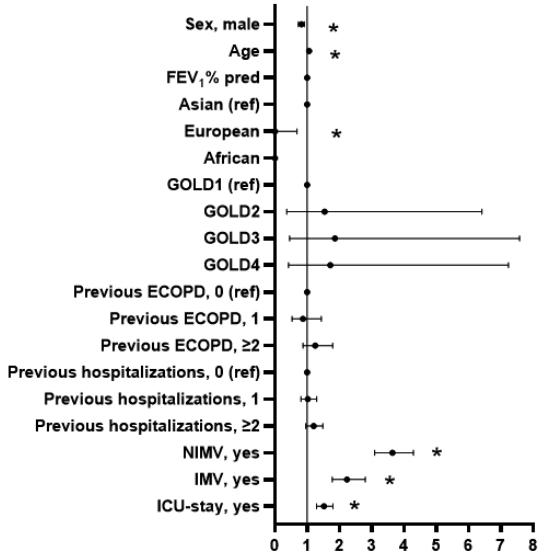

Fig 4. Forest plot displaying Cox proportional hazard ratios for in-hospital mortality in the pooled data subset. * p<0.05. Details are provided in Table S4.

Post-discharge mortality

Of the patients surviving the index event, results for post-discharge mortality were available in 30,597 patients from 41 studies.[17, 32, 33, 36, 37, 39-44, 47-58, 60-75] Baseline characteristics of the pooled data subset are displayed in the Online Supplement (Table S5). Median follow-up time after hospital discharge in these studies was 365 days. In total, 4,662 (15.2%, 95% CI 14.8-15.6) patients died during follow-up. Compared to patients surviving follow-up, non-survivors were less often male, were older, had a lower FEV_1, have had more ECOPD and hospitalizations in the year prior to the index event, spent more days in-hospital during the index event, experienced more dyspnea during the index event, and were more likely to receive (N)IMV, or to be admitted to the ICU during the index event. More than 70% of the post-discharge deaths occurred in the first year of follow-up (71.4% [3,330/4,662]). Percentages of non-survivors per time interval during follow-up after hospital discharge from the index event, for participants with a known time of death, are depicted in Figure S3.

Pooled and stratified 30-day, 90-day and 365-day post-discharge mortality rates per country are shown in Figure 5. The pooled 30-day mortality rate was 2.0% (95% CI 1.9-2.2), the pooled 90-day mortality rate was 6.4% (95% CI 6.1-6.7), and the pooled 365-day mortality rate was

12.2% (95% CI 11.8-12.6). The lowest overall stratified post-discharge mortality rates were observed in Norway (1.0%, n=99), whereas the highest overall stratified post-discharge mortality rates were observed in Iceland (43.2%, n=81). Post-discharge mortality rates and median follow-up time stratified by study are provided in the Online Supplement (Figure S4).

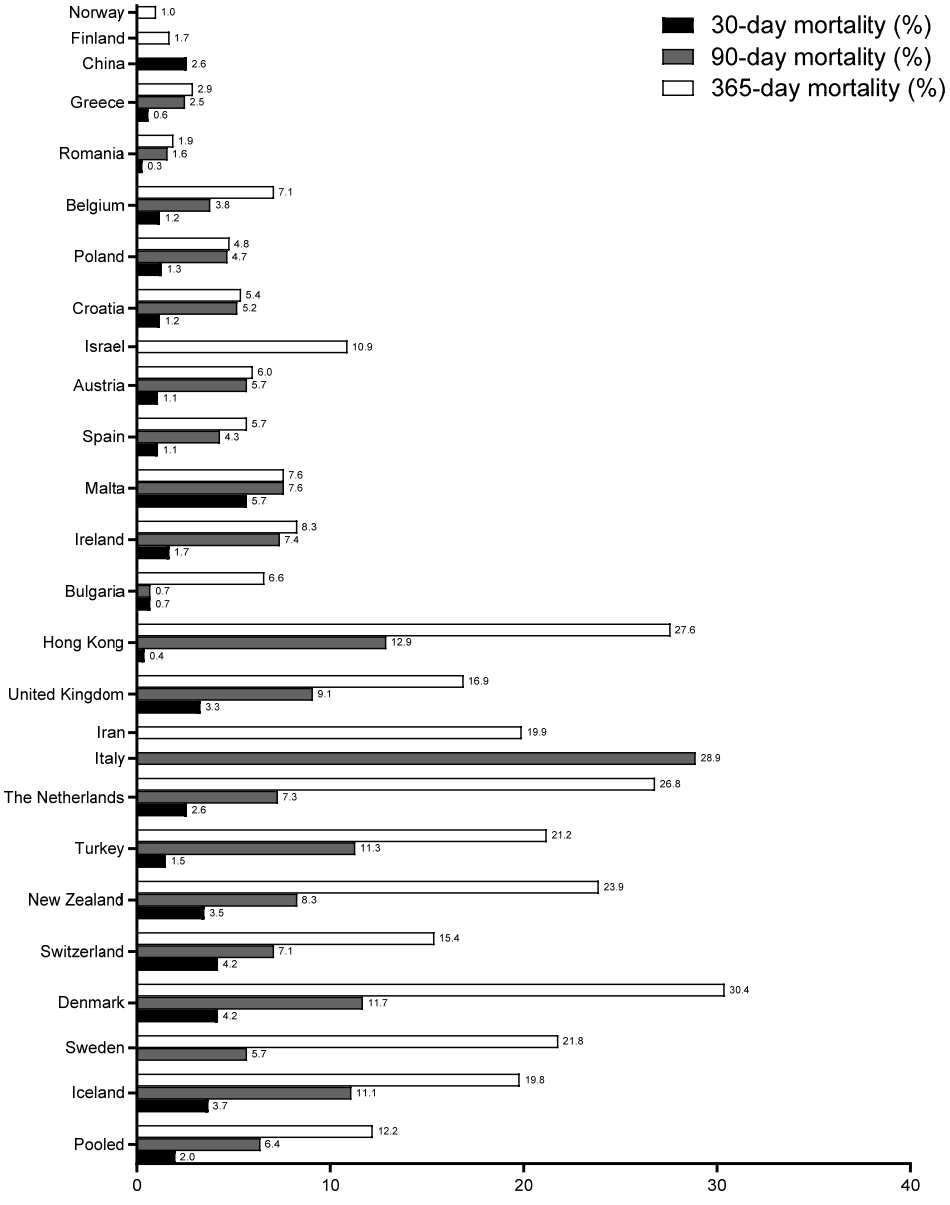

Fig 5. Pooled and stratified 30-day, 90-day and 365-day post-discharge mortality rates per country. Relative percentages are displayed. Norway n=99 (0.3%), Finland n=60 (0.2%), China n=189 (0.6%), Greece n=1,088 (3.6%), Romania n=683 (2.2%): 30- and 90-days n=626, 365-days n=632, Belgium n=773 (2.5%): 30-days n=767, 90-days n=754, 365-days n=507, Poland n=708 (2.3%), Croatia n=405 (1.3%), Israel n=603 (2.0%): 365-days n=64, Austria n=788 (2.6%), Spain n=8,934 (29.2%): 30-days n=8,512, 90-days n=8,560, 365-days n=8,180, Malta n=105 (0.3%), Ireland n=230 (0.8%), , Bulgaria n=151 (0.5%), Hong Kong n=819 (2.7%): 30-days n=569, 90-days n=201, 365-days n=333, United Kingdom n=8,731 (28.5%): 30-days n=6,466, 90-days n=6,456, 365-days n=8,248, Iran n=488 (1.6%), Italy n= 38 (0.1%), The Netherlands n=1,357 (4.4%): 30-days n=1,313, 90-days n=1,336, 365-days n=724, Turkey n=1,206 (3.9%): 30-days n=1,206, 90-days n=1,205, 365-days n=1,196, New Zealand n=1,086 (3.5%): 30-days n=1,019, 90-days n=780, 365-days n=639, Switzerland n=1,290 (4.2%): 30-days n=1,288, 90-days n=1,287, 365-days n=1,271, Denmark n=471 (1.5%), Sweden n=87 (0.3%), Iceland n=81 (0.3%).

The exact time till death after hospital discharge was available in 27 out of the 41 studies included in the post-discharge mortality dataset (n=25,909).[32, 33, 37, 39-42, 47, 49, 50, 52, 55, 56, 58, 61-65, 67, 68, 70, 72-75] Median survival time after discharge from the index event was 5.1 years (95% CI 4.8-5.3), Figure S5. Survival probability was significantly reduced in patients receiving (N)IMV during index hospitalization: median survival time after discharge from the index event was 4.9 years (95% CI 4.5-5.2) in patients without use of NIMV during the index event versus 3.1 years (95% CI 2.8-3.4) in patients on NIMV during the index event (Log Rank $X^2(1)=194.08$, $p<0.001$), Figure S6A. Median survival time after discharge from the index event was 3.8 years (95% CI 3.4-4.1) in patients without use of IMV during the index event versus 2.9 years (95% CI 2.5-3.3) in patients on IMV during the index event (Log Rank $X^2(1)=59.23$, $p<0.001$), Figure S6B.

Age, FEV_1, ethnicity, hospitalization history, mMRC score, use of (N)IMV and ICU stay during the index event were significantly associated with post-discharge mortality in the subcohort with an exact time till event (n=25,909), both in the univariate- and age- and sex adjusted model (Figure 6 and Table S6). The odds of post-discharge mortality was higher with older age, European ethnicity, higher number of previous hospitalizations, higher mMRC scores, use of (N)IMV and ICU admission during the index event, and lower FEV_1.

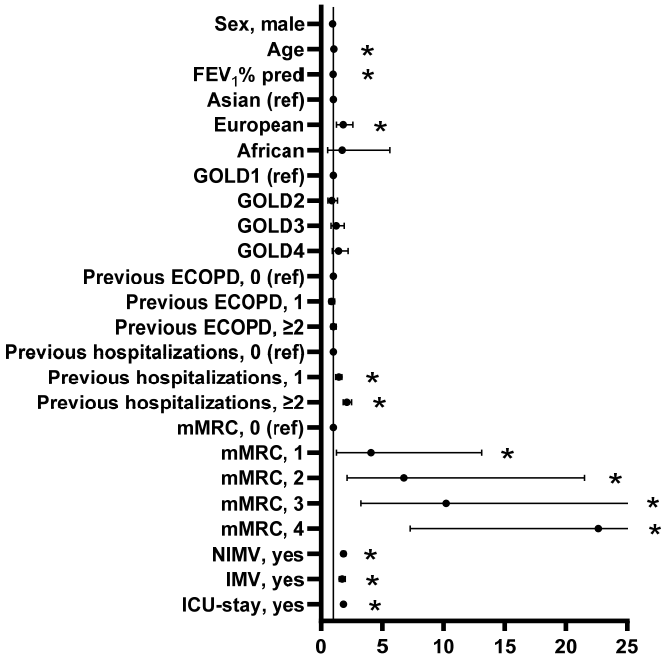

Fig 6. Forest plot displaying Cox proportional hazard ratios for post-discharge mortality in the pooled data subset.

* $p<0.05$. Details are provided in Table S6.

Hospital readmission

Results for hospital readmission were available in 46,297 patients from 30 studies.[17, 32, 35, 36, 39-44, 49, 51, 52, 54-56, 58, 60, 61, 66-75] Baseline characteristics of the pooled data subset are displayed in the Online Supplement (Table S7). Median follow-up time after hospital discharge in these studies was 90 days. In total, 16,646 (36.0%, 95% CI 35.5-36.4) patients were readmitted to the hospital for a subsequent ECOPD after discharge from the index event. Compared to the not readmitted patients, readmitted patients were older, had less severe lung function impairment, had a higher symptom burden, experienced more ECOPD and hospitalizations prior to the index event, and more often needed non-invasive ventilator support or ICU admission during the index event. Virtually all readmissions occurred in the first year of follow-up (97.9% [16,297/16,646]). Percentages of readmitted patients per time interval during follow-up after hospital discharge from the index event, for participants with a known time of readmission, are depicted in Figure S7.

Pooled and stratified 30-day, 90-day and 365-day readmission rates per country are shown in Figure 7. The pooled 30-day mortality rate was 11.8% (95% CI 11.4-12.2), the pooled 90-day mortality rate was 26.5% (95% CI 26.1-26.9), and the pooled 365-day mortality rate was 38.2% (95% CI 37.6-38.8). The lowest overall stratified readmission rates were observed in China (10.1%, n=189), whereas the highest overall stratified readmission rates were observed in Iceland (67.9%, n=81). Hospital readmission rates and median follow-up time stratified by study are provided in the Online Supplement (Figure S8).

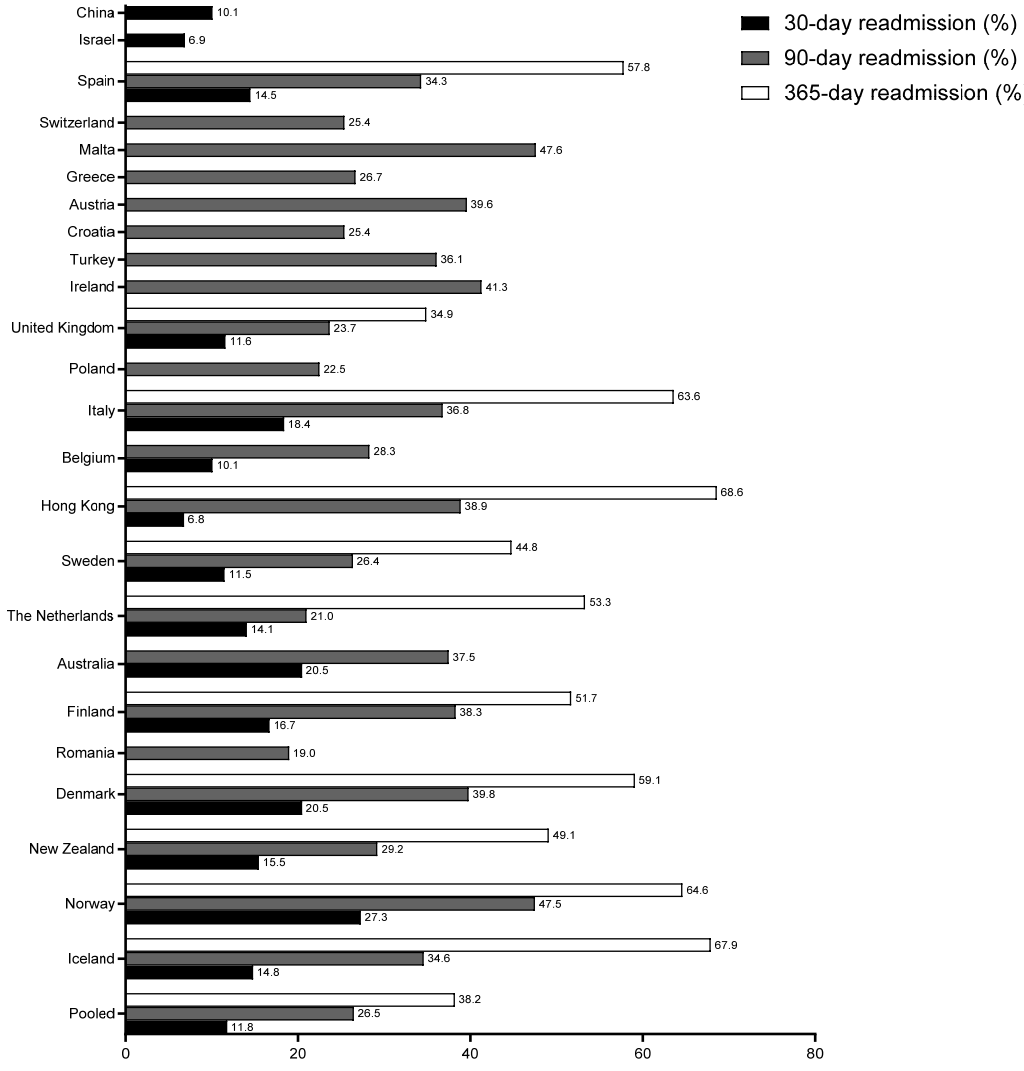

Fig 7. Pooled and stratified 30-day, 90-day and 365-day post-discharge hospital readmission rates per country. Relative percentages are displayed. China n=189 (0.4%), Israel n=539 (1.2%): 30-days n=538, Spain n=8,770 (18.9%): 30-days n=1,279, 90-days n=6,169, 365-days n=902, Switzerland n=279 (0.6%), Malta n=105 (0.2%), Greece n=1,088 (2.4%), Austria n=788 (1.7%), Croatia n=405 (0.9%), Turkey n=592 (1.3%), Ireland n=230 (0.5%), United Kingdom n=27,839 (60.1%): 30-days n=22,512, 90-days n=27,327, 365-days n=22,508, Poland n=708 (1.5%), Italy n=38 (0.1%): 30- and 90-days n=38, 365-days n=22, Belgium n=773 (1.7%): 30-days n=267, 90-days n=756, Hong Kong n=819 (1.8%): 30-days n=819, 90-days n=506, 365-days n=503, Sweden n=87 (0.2%), The Netherlands n=1,127 (2.4%): 30-days n=754, 90-days n=1,088, 365-days n=644, Australia n=88 (0.2%), Finland n=60 (0.1%), Romania n=683 (1.5%): 90-days n=626, Denmark n=88 (0.2%), New Zealand n=782 (1.7%), Norway n=99 (0.2%), Iceland n=81 (0.2%).

The exact time till hospital readmission for a subsequent ECOPD was available in 23 out of the 30 studies included in the hospital readmission data subset (n=27,401).[17, 32, 35, 41-44, 49, 52, 54, 55, 58, 60, 66-74] Median time to hospital readmission after the index event was 2.0 years (95% CI 1.8-2.2), Figure S9. Median time to hospital readmission was significantly reduced in patients receiving NIMV during index hospitalization: median time to hospital readmission was 1.1 years (95% CI 1.0-1.3) in patients without use of NIMV during the index event versus 0.6 years (95% CI 0.5-0.8) in patients on NIMV during the index event (Log Rank $X^2(1)=29.32$, $p<0.001$), Figure S10A. Median to hospital readmission was 1.0 years (95% CI 0.8-1.1) in patients without use of IMV during the index event versus 2.0 years (95% CI 1.5-2.8) in patients on IMV during the index event (Log Rank $X^2(1)=0.50$, $p=0.478$), Figure S10B. It should however be noted that the number of patients with IMV data in the readmission data subset was rather low.

Sex, FEV_1, GOLD grade, ECOPD and hospitalization history, mMRC score, use of NIMV, and ICU admission during the index event were significantly associated with hospital readmission in the subset of patients with an exact time till readmission (n=27,401), both in the univariate- and age- and sex adjusted model (Figure 8 and Table S8). The odds of hospital readmission was higher for male patients, higher GOLD grades, higher number of previous ECOPD and hospitalizations, higher mMRC scores, use of NIMV, and ICU admission during the index event, and lower FEV_1. It should be noted that multicollinearity does not play a role for FEV_1 and GOLD grade as these variables were independently included in the respective models.

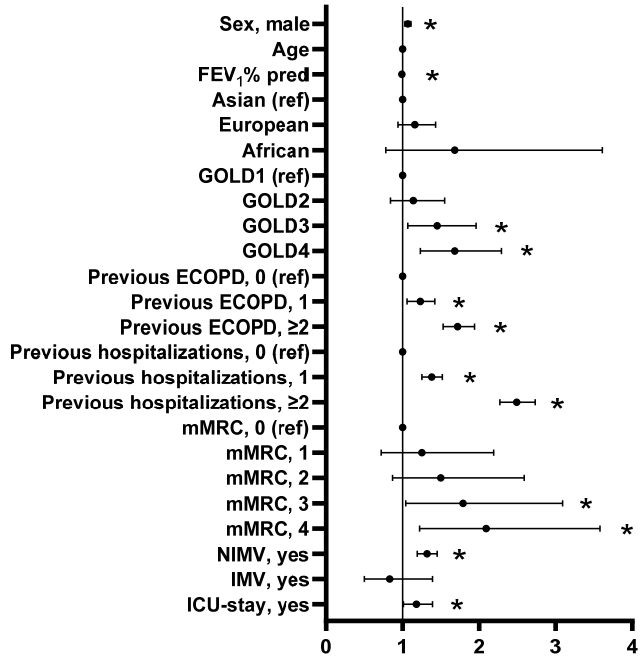

Fig 8. Forest plot displaying Cox proportional hazard ratios for hospital readmission in the pooled data subset. * p<0.05. Details are provided in Table S8.

Discussion

The current IPDMA summarizes in-hospital mortality, post-discharge mortality and hospital readmission rates following ECOPD-related hospitalization in over 65,000 patients with COPD from across the globe. Pooled in-hospital mortality rates of 6.2%, 30-day, 90-day and 365-day post-discharge mortality rates of 2.0%, 6.4% and 12.2%, and 30-day, 90-day and 365-day hospital readmission rates of 11.8%, 26.5% and 38.2%, respectively, were observed. Most deaths (50.2%) occurred within the first week of hospitalization. Furthermore, over 70% of the post-discharge deaths, and almost every readmission (97.9%) occurred in the first year following hospital discharge from the index event, laying bare the target time window. Predictive determinants of mortality and hospital readmission were identified. Some of which can be prevented, such as previous ECOPD-related hospitalizations, and some of which cannot be prevented, including markers of disease severity such as use of (N)IMV. To our knowledge this is the first IPDMA providing a worldwide representation of mortality and readmission rates after ECOPD-related hospitalization. The current findings highlight the poor outcomes

and high heterogeneity of ECOPD-related hospitalization, and underline the need to develop effective ECOPD prevention strategies.

Global heterogeneity

Globally, COPD remains the most prevalent chronic respiratory disease accounting for 55.1% and 54.8% of chronic respiratory disease prevalence in males and females respectively.[76] Between 1990 and 2017 the prevalence of COPD increased by 5.9%, and is expected to continue to increase, especially in developing countries.[77] Over time, the epidemiology of COPD has shifted from a disease mainly affecting smoking white males[78], to a disease affecting both males and females across the globe even in the absence of a smoking history.[77, 79, 80] Indeed, there is an increasing understanding that other risk factors besides tobacco exposure, e.g. genetics and early life-events, may drive the development of COPD. This knowledge has recently led to the proposal of a new definition and classification of COPD.[81] The current IPDMA including patients with COPD from 30 different countries across the globe confirms the high heterogeneity of COPD-related outcomes and provides precise estimates of mortality and readmission rates following ECOPD-related hospitalization.

In-hospital mortality rates ranging between 1.0% in China to 11.8% in Turkey, post-discharge mortality rates ranging between 1.0% in Norway to 43.2% in Iceland, and hospital readmission rates ranging between 10.1% in China to 67.9% in Iceland were observed. This heterogeneity might be the result of differences in characteristics, i.e. disease severity, within and across study populations such as ICU admission. Indeed, the highest in-hospital mortality[37] and hospital readmission rates[51] in the current study were observed in ICU-admitted patients. Other potential drivers of this heterogeneity may be related to differences in health care access and treatment options (both regional differences and differences over time [e.g. introduction of LAMA therapy since the early 2000s, and LABA/LAMA and triple therapy treatment combinations since 2013])[81], regional differences in guidelines related to the management of ECOPD-related hospitalization and/or post-discharge follow-up/monitoring of patients[82-84] and the subsequent clinical utilization/implementation of such guidelines, or patient specific traits such as ethnicity[85, 86] or social-economic status.[87]

The vast majority of patients included in this IPDMA originated from Europe (>93%). Hence, the current study highlights the paucity of outcome data from non-European countries, especially from the African and Asian continents, and low- and middle-income countries with low socio-economic status where there might be a different (i.e. non-smoking) epidemiology of COPD.[79, 80] This lack of outcome data (on a global level) furthermore is of particular importance given the high, or even higher, prevalence and impact (i.e. morbidity and mortality) of COPD in non-European countries.[76] Indeed, challenges with delivering adequate prevention, diagnosis and management of COPD are particularly observed in low- and middle-income countries[88, 89], a potential explanation for their current underrepresentation. Whilst no differences were observed in in-hospital mortality rates between European and non-European countries (6.2% vs. 6.4%, p=0.738), significant differences were found for post-discharge mortality and hospital readmission (14.1% vs. 22.0%, p<0.001, and 35.7% vs. 39.1%, p<0.001, respectively).

Globally, several indications for hospitalization of ECOPD exist.[6] These include presentation of severe symptoms, acute respiratory failure, onset of new physical signs, failure of initial pharmacological therapy, presence of serious comorbidities and/or insufficient home support. Since the cause, severity, impact, treatment and time course of ECOPD varies from patient to patient, healthcare facility- and system, and from country to country, no global standards can be applied to hospital discharge. Whilst this heterogeneity should be acknowledged, the current findings underpin the need for global standardized and guided post-discharge follow-up/monitoring of patients after ECOPD-related hospitalization, especially in the first year post-discharge. Whilst the first attempts at the standardization of the management and follow-up of ECOPD-related hospitalizations have been made[90], this should continue to be the focus of future implementation research.

Predictive determinants of (in)hospital mortality

Older age, use of (N)IMV and ICU admission were significantly associated with a higher odds of (in-hospital) mortality, whereas male sex was significantly associated with a lower odds of in-hospital mortality, but not post-discharge mortality. Older age, use of (N)IMV and ICU admission are known predictors of mortality during and after severe ECOPD.[10, 15, 22, 51, 91-93] Female sex however is not often reported as a risk factor of in-hospital mortality. Indeed, a

study conducted in the US in 1996, including over 71,000 patients admitted to the hospital for ECOPD identified male sex as an independent risk factor for in-hospital mortality. More recent studies, although predominantly including male patients, have also shown an increased risk of in-hospital mortality in males. The current study showed, in contrast, that male sex is associated with a lower odds of in-hospital mortality. A potential explanation for this could be the better reflection of the changing COPD epidemiology, i.e. increased prevalence and mortality amongst females[77, 79], in this IPDMA. Indeed, close to 40% of patients included in this study was female. Furthermore, sex-specific differences in COPD phenotypes exist. Indeed, female sex is significantly associated with the early-onset COPD phenotype[94] and cardiovascular comorbidities such as chronic heart failure[95], which are associated with a higher mortality risk.[96, 97] Another explanation could be the sex-related differences in care-seeking behavior. As such, although the risk of ECOPD may be greater in females[98], female patients are more likely to delay presentation to the hospital during an ECOPD.[99] Unfortunately, sex-related differences in time between onset of disease, or more acutely the deterioration of symptoms and presentation to the hospital for an ECOPD could not be assessed in the current study. Future studies assessing these factors, as well as their interplay in relation to mortality, are indicated.

Sex was not associated with post-discharge mortality. In this view, several differences between predictors of in-hospital mortality and post-discharge mortality were observed. Indeed, FEV_1 and a history of severe ECOPD were significantly associated with a higher odds of post-discharge mortality, but not in-hospital mortality. Whilst no significant differences in moderate ECOPD history were observed between the in-hospital survivors and non-survivors, the post-discharge non-survivors less often had a history of moderate ECOPD compared to the post-discharge survivors. It should however be noted that there were more missing data on ECOPD history in the in-hospital mortality dataset compared to the post-discharge mortality dataset. Nonetheless, previous moderate ECOPD did not predict in-hospital, nor post-discharge mortality. As such, in line with previous studies[100-102], these findings suggest that particularly a history of severe ECOPD, defined by hospital admission, presents an independent risk factor of mortality. Noteworthy, use of (N)IMV during the index event, a marker of disease severity, served as a predictor of mortality both during and after

hospitalization: survival probability was reduced by two years in patients receiving NIMV, and by one year in patients receiving IMV.

Predictive determinants of hospital readmission

In contrast to the lower odds of in-hospital mortality, male sex was associated with a higher odds of hospital readmission. The absence of a statistical difference in the number of males between the readmitted and non-readmitted patients, but that male sex increased the odds of hospital readmissions initially seems contradictory. However, it can be appreciated that still more than half of the readmitted patients was male, and thus responsible for the majority of readmissions. Likewise, the observation that the readmitted patients were marginally older compared to the not-readmitted patients, but that age does not significantly affect the odds of hospital readmission sparks discussion. Previous research has shown that older patients have less knowledge of their disease, undertake less self-care and are less likely to recognize an ECOPD than younger patients with COPD.[103] Suboptimal self-management and healthcare seeking behavior, important pillars to improve the post-discharge prognosis of patients with COPD, might thus be a potential explanation for the marginally older age of the readmitted group. Whilst age may not serve as a predictor of hospital readmission, but rather of mortality, predictors of hospital readmission besides male sex included lower FEV_1, a history of (severe) ECOPD, and use of NIMV during the index event. With respect to the latter, use of NIMV during the index event reduced median time to hospital readmission by six months.

Strengths and limitations

Several strengths and limitations should be noted. The current study is the first IPDMA providing a worldwide representation of in-hospital mortality, post-discharge mortality and hospital readmission rates following ECOPD-related hospitalization in over 65,000 patients with COPD from 47 individual studies. IPDMAs are recognized as the gold standard approach for evidence synthesis and therefore presents a major methodological strength over using aggregate data from publications.[28] The observation periods of the studies included in this IPDMA ranged from January 2000 to February 2018. The current study therefore provided estimates of the outcomes and determinants of severe ECOPD over an extensive time period. Furthermore, clear and easily obtainable independent predictors of mortality and hospital readmission were identified, some of which can be prevented, i.e. a history of frequent

previous ECOPD-related hospitalizations, and some of which cannot be prevented, including markers of disease severity such as use of (N)IMV and ICU admission. These outcomes can be used in clinical decision-making, with the overall aim of improving the prognosis of patients with COPD.

A substantial limitation of the current study is the large number of missing data on certain clinical outcomes, demonstrating the challenges associated with study heterogeneity and the need to collect more standardized data around ECOPD. Of interest, data such as FEV_1, length of hospital stay and mMRC scores were noticeably less available in the in-hospital non-survivors compared to the in-hospital survivors. Although the number of non-survivors was smaller, it could be questioned whether these observations were coincidental. Indeed, in order for FEV_1 data to be included in this IPDMA, lung function tests had to be conducted in the year prior to the index event. As such, missing spirometry data might be an indication of poor disease management/control, or of very advanced disease and subsequent inability to perform lung function testing thereby increasing the risk of in-hospital mortality. In addition, data on maintenance and ECOPD treatment was missing. Confounding factors such as treatment failure, adherence or compliance, and/or suboptimal (baseline) treatment could not be explored. Nevertheless, the primary aim of the current study was not to describe patient/ECOPD characteristics, but rather to provide more precise estimates on the prognostic rates during and after ECOPD-related hospitalization. Furthermore, the studies included in this IPDMA were heterogeneous, at least to some extent, in terms of eligibility criteria (e.g. requiring ventilation or ICU admission), disease severity, data availability, follow-up time and sample size which should be taken into consideration. The one-stage meta-analysis approach is, however, the most optimal statistical approach to handle between-study heterogeneity.[30] Finally, the risk of selection bias inevitably exists with systematic reviews and meta-analyses. Selection bias was however minimized by searching multiple databases, and by using broad search strategy terms. As such, the studies included were widely comparable with respect to admission criteria and baseline characteristics (Table S1).

Conclusions

In conclusion, the current IPDMA provides precise estimates of the outcomes and determinants of ECOPD-related hospitalization in over 65,000 patients with COPD from across the world. With an overall in-hospital mortality rate of 6.2%, one-year post-discharge mortality rate of 12.2% and one-year hospital readmission rate of 38.2%, the impact of ECOPD-related hospitalization remains tremendous around the globe. Whilst strengthened and improved ECOPD prevention strategies are urgently needed, healthcare providers must be aware of these poor prognostic rates, and should cautiously monitor and follow-up patients after ECOPD-related hospitalization. More (funding of) research focusing on the standardization of guidelines for post-discharge follow-up/monitoring of patients after ECOPD-related hospitalization is needed. Moreover, policy makers should prioritize the subsequent guidance of these guidelines, and should reimburse evidence-based therapies that decrease (recurrent) ECOPD to improve these poor prognostic rates.

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Online Supplement

Methods

Search strategy

Online databases PubMed, Embase (OVID), and Web Of Science were searched from database inception until March 31, 2021 for studies reporting mortality during and/or after hospitalization for ECOPD, and/or subsequent ECOPD hospital readmission. Titles, abstracts and full-texts of the search results were evaluated by three independent reviewers (MC, SK, KWS). Agreements upon inclusion were made in consensus with a fourth independent person (MAS). The search strategy included the term COPD and its variants Chronic Obstructive Pulmonary Disease, Chronic Obstructive Lung Disease, Emphysema, Pulmonary emphysema, combined with terms related to disease outcomes: mortality, death, survival, prognostic factors, clinical course, hospital outcome, and restrictions in time: hospitalization, hospital, hospital admission, in-hospital, post hospitalization, exacerbation, clinical deterioration, disease deterioration, acute respiratory failure. Details of the search strategies are listed below.

PubMed

((((((((((((((((((COPD) OR (Chronic Obstructive Pulmonary Disease)) OR (Chronic Obstructive Lung Disease)) OR (Emphysema)) OR (Pulmonary emphysema)) AND (mortality)) OR (death)) OR (survival)) OR (prognostic factors)) OR (clinical course)) OR (hospital outcome)) AND (hospitalization)) OR (hospital)) OR (hospital admission)) OR (in-hospital)) OR (post hospitalization)) OR (exacerbation)) OR (clinical deterioration)) OR (disease deterioration)) OR (acute respiratory failure)

OVID

(AllFields:COPD) OR (AllFields:Chronic Obstructive Pulmonary Disease) OR (AllFields:Chronic Obstructive Lung Disease) OR (AllFields:Emphysema) OR (AllFields:Pulmonary emphysema) AND (AllFields:mortality) OR (AllFields:death) OR (AllFields:survival) OR (AllFields:prognostic factors) OR (AllFields:clinical course) OR (AllFields:hospital outcome) AND (AllFields:hospitalization) OR (AllFields:hospital) OR (AllFields:hospital admission) OR (AllFields:in-hospital) OR (AllFields:post hospitalization) OR (AllFields:exacerbation) OR

(AllFields:clinical deterioration) OR (AllFields:disease deterioration) OR (AllFields:acute respiratory failure)

Web Of Science

TS=((COPD OR Chronic Obstructive Pulmonary Disease OR Chronic Obstructive Lung Disease OR Emphysema OR Pulmonary emphysema) AND (mortality OR death OR survival OR prognostic factors OR clinical course OR hospital outcome) AND (hospitalization OR hospital OR hospital admission OR in-hospital OR post hospitalization OR exacerbation OR clinical deterioration OR disease deterioration OR acute respiratory failure))

Abbreviations: TS; topic.

Results

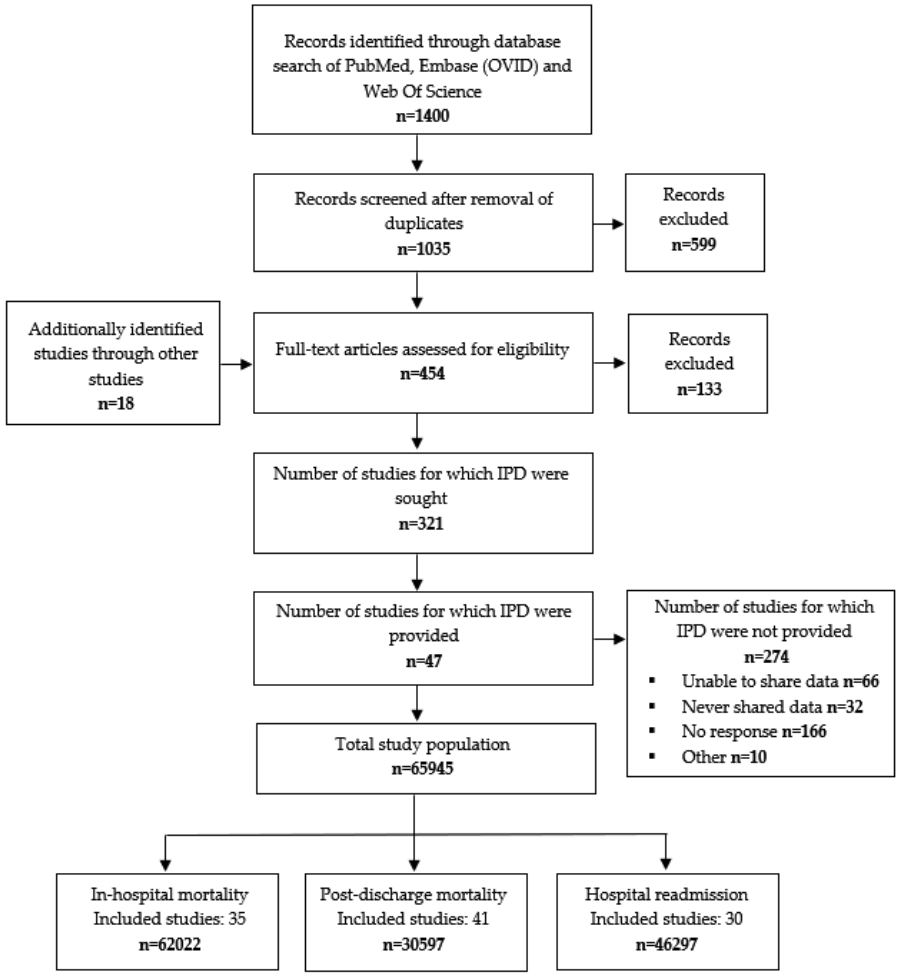


Fig S1. Study selection and individual patient data (IPD) extraction flowchart.

Table S1. Characteristics of the 47 participating studies.

First author (publication year)	Aim	Inclusion/Exclusion criteria	Study design	Follow-up period	Country Study Center	Sample size	Age	Shared sample size
Matkovic et al (2012)[1]	To investigate the evolution of hospitalized COPD patients and to identify predictors of adverse outcome in routine clinical practice.	*Inclusion:* ▪ Patients hospitalized for COPD exacerbation in tertiary acute-care hospital. ▪ Post-bronchodilator $FEV_1/FVC < 0.7$ in clinical records (performed in stable phase prior to admission). *Exclusion:* ▪ Not reported.	Prospective	May 2009 to December 2010	Spain	155	70.0 ± 9.5	155
Guerrero et al (2016)[2]	To estimate, in both short and long-term follow-up periods, the risk of death due to all causes in patients presenting an acute exacerbation within 30 days of discharge and requiring re-hospitalization.	*Inclusion:* ▪ All AECOPD patients admitted to the hospital's Respiratory Department. ▪ Meet criteria for COPD according to the GOLD guidelines. *Exclusion:* ▪ Documented history of concomitant chronic respiratory condition (asthma and bronchiectasis). ▪ Patients with a suspected underlying malignancy. ▪ Patients in who community-acquired pneumonia (CAP) and acute heart failure were identified clinically and by means of chest x-ray.	Prospective	May 2009 to September 2014	Spain	378	71.4 ± 10	449
Stolz et al (2008)[3]	To investigate the potential of plasma BNP levels to predict the need for ICU	*Inclusion:* ▪ The diagnosis of COPD was based on clinical history, physical examination, and spirometric criteria according to Global	Prospective, randomized, open	November 2003 to	Switzerland	208	70.3 ± 9.9	481

	treatment as well as short-term and long-term mortality rates in patients with AECOPD.	Initiation for Chronic Obstructive Lung Disease (GOLD) Guidelines. *Exclusion:* ▪ Patients with cystic fibrosis, active pulmonary tuberculosis, or infiltrates on chest radiographs on presentation. ▪ Severely immunocompromised patients.	intervention trial	March 2005				
Grolimund et al (2015)[4]	To determine the association of exacerbation type, discharge levels of inflammatory biomarkers including procalcitonin, C-reactive protein, white blood cell count and plasma proadrenomedullin, alone or combined with demographic/clinical characteristics, with long-term all-cause mortality in the COPD setting.	*Inclusion:* ▪ Patients with COPD (presence of at least one of the following three criteria: i) spirometric data recorded during a 2-year period pre-/post-index hospitalization, indicating FEV1/FVC <70%; ii) Global Initiative for Chronic Obstructive Lung Disease staging already charted at presentation, without spirometric values; iii) COPD reported, without spirometric values or staging, in charts/by patients at presentation. ▪ Final inpatient diagnosis of pneumonic or non-pneumonic COPD exacerbation. ▪ Surviving hospitalization, and having available discharge ProADM measurements from, the ProHOSP index hospitalization. *Exclusion:* ▪ Language restriction/dementia precluding informed consent ▪ Intravenous drug abuse ▪ Medical comorbidities expected to be rapidly terminal or hospital-acquired pneumonia (chest radiographic infiltrate	Prospective (PoHOSP trial)	October 2006 to March 2013	Switzerland	503 Pneumonic (n=252) Non-pneumonic (n=217)	74 (64-81)	530

		starting ≥ 48 h postindex admission or during hospitalization ≤ 2 weeks pre-ProHOSP enrolment). ▪ Severe immunosuppression or chronic antibiotic therapy at presentation (Patients could be on corticosteroids or could have received short-term antibiotic pretreatment).						
Ringbaek et al (2015)[5]	The aims of this study were to determine whether the use of pre-hospital oxygen in AECOPD was in accordance with the international guidelines (appropriate oxygen therapy), and whether 'inappropriate oxygen therapy' administrated by the ambulance crew in an urban area with expected short transit time was associated with poor outcome.	*Inclusion:* ▪ All patients transported by ambulance and admitted to Hvidovre Hospital with an exacerbation in COPD. ▪ Patients were identified by a primary diagnosis of COPD exacerbation (ICD code J440 or J441) at discharge (including those who died at hospital). *Exclusion:* Not reported.	Retrospective audit	January 2012 to August 2012	Denmark	405	71.6 ± 11.3	405
Fabbian et al (2016)[6]	The aim of this study, based on discharge hospital records (DHR), was to evaluate the relationship between the presence of renal dysfunction, both chronic kidney disease (CKD) and acute kidney	*Inclusion:* ▪ All hospital admission for COPD exacerbation (diagnosis of COPD exacerbation (ICD-9-CM 491.21)). *Exclusion:* ▪ Subjects with different COPD-related diagnoses such as 491.xx (chronic bronchitis), 492.xx (emphysema), and	Retrospective /database	January 2000 to December 2013	Italy	7,073	76.7 ± 9.8	7,073

	injury (AKI), and in-hospital mortality (IHM) in patients admitted to the Internal Medicine wards of our hospital because of severe COPD exacerbation.	496.xx (chronic airway obstruction, not elsewhere classified) . ▪ Renal dysfunction ICD-9-CM codes used were 585.xx for CKD and 584.xx for AKI. ▪ Subjects with history of renal replacement therapy. ▪ Hypertension was identified by ICD-9-CM codes 401–405.						
Mekov et al (2016)[7]	The aim of this study is to examine the one-year mortality in COPD patients after severe exacerbation and the correlation between mortality and patients' characteristics and comorbidities.	*Inclusion:* ▪ Patients hospitalized for sever exacerbation of COPD. ▪ COPD diagnosis was established according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. ▪ All patients with post bronchodilator obstruction (FEV1/FVC < 0.70). *Exclusion:* ▪ The patients who did not comply with the study procedures.	Prospective	January 2013 to January 2015	Bulgaria	152	65 ± 10	151
Harries et al (2015)[8]	This study aimed to describe LOS of all COPD hospital admissions of patients registered with general practices in London over a 4-year period and to determine the variation in LOS of COPD admissions between hospitals.	*Inclusion:* ▪ Patients whose first COPD admission during the study period had been preceded by a period of at least 12 months without a COPD admission. ▪ Were aged ≥45 years at time of that current admission. ▪ Hospital trusts were identified by their provider codes and were included in the analysis if they had a record of ≥100 COPD patient admissions during the study period. *Exclusion:*	Retrospective	April 2006 to March 2010	United Kingdom	51,305 COPD admissions from 26,007 patients	72.8 ± 11.1	25,729 admitted patients with COPD exacerbations

		▪ Admissions to hospitals specializing in operative procedures for COPD including bronchial stenting, bullectomy, lung volume reduction, and transplantation. ▪ Younger patients.						
Wang et al (2016)[9]	The aim was to study whether AECOPD patients with a PCT level of <0.1 ng/ml would benefit from antibiotic treatment.	*Inclusion:* ▪ All patients with AECOPD admitted to the department of respiratory and critical care medicine. ▪ COPD according to the GOLD 2014 criteria was required. ▪ Aged ≥40 years. ▪ Patients had sound understanding and language abilities. ▪ PCT level <0.1 ng/ml. *Exclusion:* ▪ Fever (>38.0 degrees Celsius). ▪ Tracheal intubation within 24h after hospital admission. ▪ PCT level of >0.1 ng.ml on admission. ▪ Pneumonia. ▪ Chronic renal failure. ▪ History of malignant disease. ▪ Immunosuppressive therapy. ▪ Refusal to participate.	Single-center prospective RCT	June 2014 to September 2015	China	457 patients with AECOPD were screened (191 cases included) Antibiotics n=95 Control n=96	Antibiotic 73.4 ± 10.1 Control 72.5 ± 9.2	191
Lun et al (2016)[10]	This study aimed to: 1. Compare baseline factors among patients surviving AE-COPD with normocapnia (normal carbon dioxide), compensated respiratory acidosis	*Inclusion:* ▪ Age greater or equal to 40 years old. ▪ With a known diagnosis of COPD with post-bronchodilator FEV1/FVC < 70%. ▪ Admitted for acute exacerbation defined as background COPD presented with at least two major symptoms (increased dyspnea, increased sputum purulence or	Prospective observational study	August 2011 to August 2012	China	825 admitted for AECOPD were screened	76.7 ± 7.6	250

	(PaCO2 > 6 kPa and pH ≥ 7.35) and decompensated respiratory acidosis (PaCO2 > 6 kPa and pH < 7.35) on admission. 2. Perform a 1-year cohort study on these patients, comparing the occurrences of readmission, life-threatening events (decompensated respiratory acidosis requiring NIV or intubation) and death among patients in these three groups. 3. Explore the predictive factors for life-threatening events in this cohort.	increased sputum volume), or one major and one minor symptoms (nasal discharge/ congestion, wheezes, sore throat or cough) for at least two consecutive days. ▪ Agreed to participate in the study. *Exclusion:* ▪ Presence of coexisting pulmonary diseases including asthma, bronchiectasis, active lung cancer, moderate or severe obstructive sleep apnea, or other chronic lung diseases apart from COPD. ▪ History of lung resection. ▪ Lack of previous spirometric data to confirm the diagnosis of COPD. ▪ Active malignancy or other organ failure, for example, acute myocardial infarction, severe heart failure, severe renal failure, advanced dementia, that may influence readmission or mortality during the study period. ▪ Refused to participate or mentally incapacitated to answer questionnaires. ▪ Death during the index admission.				*Inclusion:* 245 met inclusion		
Ergan et al (2016)[11]	The aim was to identify whether anemia is related with higher in-hospital deaths in severe COPD exacerbations. Secondary end points were to evaluate the impact of anemia on	*Inclusion:* ▪ All consecutive COPD exacerbation patients who developed acute respiratory failure. ▪ Admitted to the ICU of a tertiary reference hospital. ▪ Diagnosis of COPD was confirmed, according to the Global initiative for chronic Obstructive Lung Disease (GOLD),	Prospective	April 2012 to September 2015	Turkey	Screened 124 Included 106	71.0 (62.0-76.0)	106

	noninvasive ventilation (NIV) failure and long-term survival.	from medical records, and if available pulmonary function tests (PFTs) within the previous year. In patients for who PFTs were unavailable, COPD diagnosis was confirmed with GOLD clinical criteria (age >40 years, >10 pack-year smoking or biomass history). *Exclusion:* ▪ Suspected alternative/additional cause for respiratory failure such as pneumonia, pulmonary embolism, cardiogenic pulmonary edema, severe sepsis, acute respiratory distress syndrome. ▪ Presence of active bleeding. ▪ Presence of a disease/treatment possibly associated with bone marrow suppression (renal failure with glomerular filtration rate <30 mL/min/1.73 m^2, malignancy, hematologic disorders), and recent operation or transfusion history.						
Ergan et al (2016)[12]	To determine whether the level of serum PCT at admission in severe AECOPD serves as a prognostic biomarker for hospital mortality. The secondary aim was to determine the role of PCT in identifying bacterial exacerbation.	*Inclusion:* ▪ All patients had acute respiratory failure and were supported by either invasive ventilation or NIV. ▪ Admitted to the ICU of a tertiary university hospital. ▪ All patients with a history of COPD diagnosed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (age >40 years, >10 pack-years of smoking, or biomass history). *Exclusion:*	Retrospective	May 2007 to July 2009	Turkey	63	71 (62.0 - 78.0)	63

		▪ Clinical and radiological suspicion for an alternative cause of respiratory failure, such as pulmonary embolism, pneumonia, severe sepsis, congestive heart failure, or acute respiratory distress syndrome. ▪ Staying in the ICU for <24 h, and no PCT level available within 24h of admission.						
Quintana et al (2014)[13]	To develop a clinical prediction rule for short-term death following AECOPD. Short-term as any time during the hospital admission or within 1 week after discharge from the ED to home.	*Inclusion:* ▪ Presented to the ED with symptoms consistent with AECOPD. ▪ COPD was confirmed if the patient had a FEV1/FVC <0.7. ▪ Exacerbation was defined as an event in the natural course of the disease characterized by a change in the patients baseline dyspnea, cough, and/or sputum that was beyond normal day to day variations and may have warranted a change in regular medication in a patient with underlying COPD. ▪ Cases of COPD newly diagnosed in the ED had to be confirmed by spirometry within 60 days after the index episode at a time when the patient was stable. *Exclusion:* ▪ If they had AECOPD complicated by a comorbidity such as pneumonia, pneumothorax, pulmonary embolism, lung cancer, or left cardiac insufficiency. ▪ A diagnosis of asthma, extensive bronchiectasis, sequelae of tuberculosis, pleural thickening, or restrictive disease.	Multi-center prospective cohort study	June 2008 to September 2010	Spain	2,487	Derivation 72.3 ± 9.8 Validation 73.2 ± 9.5	2,486

		▪ Patients who not wish to participate.						
López-Campos et al (2013)[14]	To evaluate clinical practice as well as clinical and organizational factors related to outcomes for COPD admissions across Europe.	*Inclusion:* ▪ Patients who were admitted to hospital for >12 h with a senior clinician-made diagnosis of COPD exacerbation or any other synonym, confirmed at discharge as judged by the investigator/audit lead. ▪ Patients who were admitted to hospital for >12 h with a respiratory cause of admission as indicated by the discharge report and a history compatible with COPD. ▪ Critically, patients admitted with a senior clinician-made diagnosis of COPD exacerbation and treated as such were included within the audit, regardless of the findings on the chest radiograph. *Exclusion:* ▪ A patient admitted as a clinical case of COPD exacerbation that is later judged to have another primary diagnostic reason for admission, e.g. the subsequent diagnosis is changed from COPD to heart failure. ▪ Any other primary cause of deterioration and hospital admission, such as: o Pneumonia o Pulmonary embolism o Pulmonary oedema o Pneumothorax o Thoracic trauma o Pleural effusion o Asthma	Prospective, observational, non-interventional cohort trial	October to December 2010 or from January until February 2011 according to the seasonal peak of COPD exacerbations of the participating countries	European COPD audit	16,016	70.8 ± 10.8	16,014

		○ Pulmonary fibrosis ○ Sleep apnea with no treatment ○ Kyphoscoliosis ○ Obesity-hypoventilation syndrome ○ Neuromuscular pathology ○ Tracheal or upper airway stenosis ○ Severe bronchiectasis ○ Severe tuberculosis sequelae ○ Bronchogenic carcinoma or any other thoracic neoplasm ▪ Extrapulmonary diseases as the primary diagnosis for admission that may produce similar symptoms, such as: ○ Extensive cancer ○ Hepatic insufficiency ○ Renal insufficiency ○ Cardiac failure Any other condition as judged by the investigator.						
Ellis et al (2017)*	The COPD Admission Study (COAST) aims to validate the CANT (Composite score of CUBR-65 score, Acidaemia, NT-proBNP and Troponin) prognostic score developed from a previous cohort study conducted at Waikato Hospital and to identify additional factors that contribute to hospital admission for acute	*Inclusion:* ▪ Primary COPD exacerbation diagnosis on hospital admission. *Exclusion:* ▪ COPD exacerbation is not the primary cause of hospital admission. ▪ Evidence of pneumonia on chest x-ray at index admission. ▪ Likely to be lost to follow-up during the study period (e.g. living out of area). ▪ Patients who decline to participate. ▪ Patients who are unable to complete informed consent.	Prospective (COAST)	June 2015 to June 2016	New Zealand	305	69.2 ± 9.8	311

	exacerbation of COPD, particularly in patients who are deemed to have a favorable prognosis on admission.							
Shafuddin et al (2018)[15]	To measure NT-proBNP and troponin levels during exacerbations of COPD and link these to COPD exacerbation severity and its treatment.	*Inclusion:* ▪ Patients had spirometrically-confirmed COPD. ▪ ≥10 pack-year smoking history. ▪ Symptoms of worsening dyspnoea, cough, or sputum purulence, respiratory failure (arterial partial pressure of oxygen (PaO2) < 60 mmHg or arterial partial pressure of carbon di-oxide (PaCO2) > 45 mmHg), or a change in mental status due to an exacerbation of COPD. *Exclusion:* ▪ Patients whose primary reason for admission was another respiratory or non-respiratory disorder. ▪ Acute myocardial infarction. ▪ Heart failure. ▪ End-stage renal disease. ▪ Terminal malignancy. Unable to give informed consent.	Prospective (BREATHE)	August 2012 to July 2013	New Zealand	176	69.5 ± 10.4	176
Chang et al (2011)[16]	To prospectively assess the ability of CURB65 score to predict mortality in acute COPD exacerbation	*Inclusion:* ▪ COPD exacerbation requiring hospitalization. Exacerbations were diagnosed by the admitting physicians and were defined as: dyspnoea, cough or sputum purulence severe enough to	Prospective (COPDEC)	July 2006 to July 2007	New Zealand	252	71.7 (41-95)	247

	requiring hospitalization.	warrant hospitalization; respiratory failure (pO2< 60 mm Hg or pCO2 > 45 mm Hg) or change in mental status due to COPD. ▪ Whenever possible, COPD was confirmed by spirometry, which was performed when the patients were stable. *Exclusion:* ▪ History of other respiratory illnesses such as acute asthma, bronchiectasis or interstitial lung disease. ▪ Consolidation on chest radiograph (i.e. pneumonia) as reported by either the respiratory physician or radiologist. ▪ Hospitalization for reasons other than COPD exacerbation.						
Ellis et al (2018)**	To collect clinical notes from patients with COPD admitted to four New Zealand hospitals (Middlemore, Waikato, Wellington and Christchurch) with a primary diagnosis of exacerbation of COPD to study mortality due to any cause and/or readmissions within a 2 year follow-up period.	*Inclusion:* ▪ Patients with COPD admitted to the hospital due to exacerbation of the disease. *Exclusion:* ▪ Patients admitted primarily for cardiac diagnoses. However, cardiac events were recorded if they occurred during the index admission, but were not the primary reason for admission, or if they occurred after discharge and required readmission to hospital. Cardiac events in this study were categorised as; acute coronary syndrome (angina, myocardial infarction), heart failure or other cardiac events.	Retrospective (COPDAudit)	2011 to 2012	New Zealand	392	70.5 ± 11.0	392

		▪ Patients living outside the admitting area (District Health Board area).						
Gudmundsson et al (2006)[17]	To analyze mortality in COPD patients after hospitalization and associated risk factors, with special emphasis on health status, medications and co-morbidity.	*Inclusion:* ▪ Consecutive patients from each of the participating hospitals, provided that they had been admitted with acute exacerbations of COPD. ▪ All patients fulfilled the criteria for COPD according to stage 1 or higher of the GOLD. All records were reviewed by the investigators to confirm the diagnosis and GOLD criteria were used to diagnose COPD. ▪ Patients needed to be admitted for more than 24 hours. *Exclusion:* Patient thought to have asthma.	Prospective	January 2000 to December 2001	Nordic countries (Norway, Sweden, Denmark, Finland, Iceland)	416	Alive 68.2 ± 10.9 Death 72.1 ± 8.7	415
Almagro et al (2012)[18]	To determine whether the isolation of PA in sputum culture during hospitalization for COPD exacerbation was associated with a poorer prognosis after discharge independently of other well-known mortality predictors.	*Inclusion:* ▪ Hospitalization in a medical ward for acute exacerbation of COPD and baseline forced spirometry showing FEV1 <70% of the reference value and β2-agonist reversibility of predicted FEV1 of <15% and/or 200 ml with FEV1/FVC <70%. *Exclusion:* ▪ History of asthma or bronchiectasis as a predominant illness, pneumonia or pulmonary edema at admission, hospitalization for causes other than acute exacerbation of COPD. ▪ Patient refusal to participate in the study. Patients who died during initial admission.	Prospective	June 2003 to September 2004	Spain	181	72 ± 9.8	181

Epstein et al (2018)[19]	To evaluate the usefulness of RDW in predicting early adverse outcomes in patients hospitalized due to AECOPD.	*Inclusion:* ▪ Patients 18 years or older with a primary discharge diagnosis of AECOPD as mentioned in the discharge report. *Exclusion*: ▪ Patients who died during an index hospitalization, patients who were discharged against medical advice, and patients transferred from or to another acute care facility.	Population-based retrospective cohort study	January 2011 to December 2013	Israel	539	69.2 ± 11.8	539
Miravitlles et al (2015)[20]	To evaluate the predictive value of different health-related quality of life and severity questionnaires in patients with COPD and with a high risk of experiencing exacerbations.	*Inclusion*: ▪ Patients aged 40 years or above with COPD demonstrated by spirometry performed in stable state not more than 12 months before recruitment, with a post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.7. ▪ Smoker or former smoker of at least 10 pack-years. ▪ Experienced an exacerbation defined as an increase in respiratory symptoms that requires treatment with systemic corticosteroids, antibiotics or both, and/or hospitalization. *Exclusion*: ▪ Patients with another chronic respiratory disease. ▪ Patients with a COPD exacerbation due to other causes such as pneumonia, pneumothorax, and decompensated congestive heart failure.	Observational, multicenter, prospective study	October 2010 to June 2011	Spain	497	68.7 ± 9.2	342 (only hospital admitted AECOPD)

		▪ Patients requiring invasive or non-invasive mechanical ventilation. ▪ Patients who, in the opinion of the investigator, did not retain sufficient cognitive capacity, presenting sensory or psychiatric disability or language barriers that prevent or hinder a normal conduction of the study. ▪ Patients participating in another study or clinical trial.						
Lacoma et al (2011)[21]	To determine the levels of inflammatory markers in COPD patients in a clinically stable period, during an exacerbation and during pneumonia. To establish if the biomarker levels, together with the presence of clinical symptoms, can help to identify the etiological origin of the exacerbations. And finally, to examine whether biomarkers can be used to predict short- and long-term prognosis after an exacerbation episode.	*Inclusion*: ▪ Diagnosis of COPD based on clinical history, physical examination and spirometric criteria according to the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) guidelines. *Exclusion*: ▪ Patients with history of asthma, cystic fibrosis or active pulmonary tuberculosis, and patients with no adequate clinical samples available (serum samples).	Retrospective study	September 2001 to September 2005	Spain	217 (undergoing a hospitalized exacerbation)	71.4 ± 9.9	217
Osadnik et al (2013)[22]	To determine whether the addition of PEP therapy to usual	*Inclusion:* ▪ Patients hospitalised due to an AECOPD (those with evidence of	Multicenter randomised	August 2010 to	Australia	Control n=45	Control 67.8 ± 11.6	90

	medical care improved symptoms, QOL and incidence of future exacerbations in patients hospitalised with an AECOPD. The secondary aim was to identify whether any baseline characteristics were associated with improved symptoms at discharge.	sputum expectoration or a history of chronic sputum production ('regularly expectorated sputum on most days') who provided informed consent were recruited from respiratory units within 48 h of admission). *Exclusion:* ▪ Patients with a respiratory condition deemed more significant than COPD (eg, clinical history of primary bronchiectasis, asthma or lung cancer requiring active therapy) even if coexistent with COPD. ▪ Patients who established airway clearance routines, breathing via an artificial airway or PEP therapy (undrained pneumothorax; significant haemoptysis; recent facial, oral, oesophageal or skull surgery/trauma; surgical or nonsurgical lung volume reduction procedures, lung transplantation or pneumonectomy within the last 6 months).	controlled trial (RCT)	January 2013		PEP n=45	PEP 69.5 ± 9.8	
Alía et al (2011)[23]	To evaluate the efficacy and safety of systemic corticosteroid therapy in patients with an acute exacerbation of COPD who were receiving ventilatory support.	*Inclusion:* ▪ All patients 18 years or older with known COPD and who were hospitalized because of an exacerbation that required ventilator support in participating ICUs. *Exclusion:* ▪ Patients were excluded if they had a history of (1) asthma or atopy; (2) use	Mutlicenter double-blind placebo-controlled trial	July 2005 to July 2009	Spain, Mexico, Colombia and United States	Placebo n=40 corticosteroid n=43	Placebo 67.6 ± 10.7 Corticosteroid 69.1 ± 9.7	64 (Cardiac failure, sepsis and post-operative induced AECOPD

		of systemic corticosteroids within the preceding month; (3) use of systemic corticosteroids for the treatment of COPD exacerbation for more than 24 hours at the time of randomization; (4) clinical or radiologic evidence of pneumonia; (5) uncontrolled left ventricular failure requiring the use of inotropes or vasoactive drugs, (6) uncontrolled arterial hypertension; (7) uncontrolled diabetes mellitus; (8) a neuromuscular disease; or (9) allergy and or adverse reaction to corticosteroid therapy.						were excluded)
Spannella et al (2019)[24]	To evaluate components of a comprehensive geriatric assessment and clinical and laboratory parameters to find the most relevant predictors of in-hospital mortality and identify the need for post-acute care in patients aged 80 years and older hospitalized for AE-COPD.	*Inclusion:* ▪ Patients aged ≥80 years with a history of COPD, with at least 1 documented spirometry showing airflow obstruction [forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) < lower limit of normal, an admission diagnosis of AECOPD confirmed by a pulmonologist after clinical and radiologic evaluations in the emergency department. Patients with concomitant pneumonia were included because of the highly prevalent coexistence of AE-COPD and pneumonia in older adults. *Exclusion:* ▪ Patients with a life expectancy of less than 1 year due to conditions such as end-stage renal disease,	Prospective observational study	January 2017 to December 2017	Italy	121	87.0 ± 4.9	121

		decompensated cirrhosis, or advanced cancer.						
Takir et al (2014)[25]	To evaluate the reasons for ICU admission and long-term outcome after ICU discharge for patients with COPD.	*Inclusion:* ▪ All consecutive patients with previously diagnosed COPD, who were admitted to the ICU due to ARF. COPD diagnosis was established by a physician who evaluated airflow obstruction on spirometry, i.e. forced expiratory volume in 1 second (FEV1) of 70% predicted or less, and an FEV1 and forced vital capacity ratio of 70% or less. *Exclusion:* ▪ Only those patients who were admitted to the ICU for the first time with ARF were evaluated in case of recurrent admissions to the ICU during the study period.	Retrospective, observational, cohort study	November 2007 to April 2012	Turkey	962	70.0 ± 10.0	640 (ARF due to AECOPD only)
Aliyali et al (2015)[26]	To assess the effect of comorbid IHD on the duration of hospitalization, risk of ICU admission and death as indicators of the outcome of hospital care among patients admitted for AECOPD.	*Inclusion:* ▪ Patients aged ≥50 years with smoking history of more than 10 packs/year who were admitted for AECOPD. *Exclusion:* ▪ Patients with pneumonia, bronchiectasis, pulmonary thromboembolism, obstructive sleep apnea/hypopnea syndrome and intrathoracic malignancies were excluded from the study.	Historical cohort study	September 2008 to March 2014	Iran	AECOPD without IHD n=361 AECOPD with IHD n=146	AECOPD without IHD 68.6 ± 11.5 AECOPD with IHD 66.9 ± 11.3	507

Utens et al (2012)[27]	To determine the effectiveness of early assisted discharge for chronic obstructive pulmonary disease (COPD) exacerbations, with home care provided by generic community nurses, compared with usual hospital care.	*Inclusion:* ▪ Patients diagnosed with COPD (defined as at least GOLD stage I and 10 pack years of smoking), aged ≥40 years and hospitalized for COPD exacerbation. Competence to give informed consent. *Exclusion:* ▪ Major uncontrolled comorbidity, including pneumonia that is prominent, heart failure that is prominent or acute changes on ECG and (suspected) underlying malignancy. ▪ Mental disability, including dementia, impaired level of consciousness and acute confusion. ▪ Living outside care region of the home care organization. ▪ Inability to understand the programme. ▪ Indication for admission to intensive care unit or for non-invasive ventilation. ▪ Active alcohol and/or drug abuse. ▪ Insufficient availability of informal care at home.	Randomized controlled trial	November 2007 to March 2011	The Netherlands	Usual care n=69 Early assisted discharge n=70	Usual care 67.8 ± 11.3 Early assisted discharge 68.3 ± 10.3	138 (Length of hospital stay excluded due to standardization)
Smulders et al (2020)[28]	To investigate the clinical exacerbation risk, as well as the time to readmission and the mortality risk, in patients with COPD hospitalized for an acute exacerbation	*Inclusion:* ▪ Patients with COPD admitted to the hospital with a clinical diagnosis of COPD exacerbation. *Exclusion:* ▪ No BMI available, predominant asthma symptoms (identified by thorough	Retrospective, observational study	January 2010 to May 2012	The Netherlands	604	68.0 ± 11.0	604

	who were stratified into BMI groups.	chart review for each individual), no COPD based on pulmonary function testing and pregnancy.						
Ko et al (2017)[29]	To assess whether a comprehensive care programme decreases hospital readmissions and length of hospital stay (LOS) for patients with COPD.	*Inclusion:* ▪ Patients who had been admitted to the hospital with AECOPD. *Exclusion:* ▪ age <40 years. ▪ Asthma. ▪ Chronic lung diseases other than COPD. ▪ Very severe medical illness that would affect the patient's ability to participate in this study (e.g. terminal malignancy). ▪ Unable to give informed consent.	Randomized control trial	June 2010 to June 2012	Hong Kong	Intervention n=90 Usual care n=90	Intervention 74.9 ± 7.9 Usual care 74.6 ± 8.6	180
Ko et al (2019)[30]	To evaluate the prevalence of different viruses (including the typing of HRV) in relation to acute exacerbations of asthma and COPD. The secondary aim was to assess if certain pathogens had associations with clinical outcomes including duration of hospitalization, 30 and 60-day readmissions and mortality.	*Inclusion:* ▪ Subjects with asthma exacerbation or AECOPD admitted to the Prince of Wales Hospital. AECOPD was defined when a patient with age ≥ 40 years and background COPD (lung function parameters of FEV1/FVC ratio < 70%) presented with at least two of the following major symptoms (increased dyspnoea, increased sputum purulence, increased sputum volume) or one major and one minor symptom (nasal discharge/ congestion, wheeze, sore throat, cough) for at least two consecutive days. All recruited COPD subjects should have an FEV1/ FVC ratio of < 70%.	Observational	August 2016 to July 2017	Hong Kong	AECOPD n=402	77.4 ± 8.6	401

		Exclusion: ▪ Patients with a history of lung resection or other significant pulmonary diseases such as pulmonary fibrosis, active infection such as pulmonary tuberculosis and having short life expectancies including subjects with terminal malignancy or intractable heart failure were excluded from this study.						
Trethewey et al (2019)[31]	To study the relationship between time from hospital presentation to diagnosis of AHRF and in-hospital mortality[32] as well as to study temporal trends in in-hospital mortality in COPD patients undergoing a first episode of ward-based NIV for AHRF.[31]	*Inclusion:* ▪ Patients with COPD undergoing a first episode of ward-based NIV for AHRF. Clinical diagnoses of COPD were confirmed with spirometry (FEV1/FVC ratio < 0.7). In patients without spirometry, discharge letters, respiratory clinic letters, chest x-rays and computed tomography (CT) findings were reviewed to verify clinical diagnoses. *Exclusion:* Not reported.	Single center, retrospective, observational cohort study	July 2004 to November 2017	United Kingdom	547	70.6 (63.78 – 78.13)	546
Steriade et al (2019)[33]	To evaluate known risk factors and to identify new such predictive indicators that influence NIV outcomes in our study population in a newly established RICU.	*Inclusion:* ▪ Patients with severe COPD exacerbation and respiratory acidosis that were non-invasively ventilated with BPAP with volume assured pressure support (VAPS) mode. *Exclusion:* ▪ Refusal of NIV, deep hypercapnic coma; facial deformity; upper	Observational prospective cohort study	2016 to 2017	Romania	89	67.6 ± 10.1	89

		gastrointestinal bleeding; tracheal stenosis; acute ischemic heart disease; psychomotor agitation requiring sedation or need for urgent intubation due to cardiac or respiratory arrest.						
Murphy et al (2017)[34]	To investigate the effect of home NIV plus oxygen on time to readmission or death in patients with persistent hypercapnia after an acute COPD exacerbation.	*Inclusion:* ▪ Patients admitted with acute decompensated hypercapnic exacerbations of COPD requiring acute noninvasive ventilation. *Exclusion:* ▪ Patients were excluded if they (1) were not assessed within 4 weeks of resolution of the index COPD exacerbation, (2) required intubation and invasive mechanical ventilation during the index exacerbation, (3) were currently using noninvasive home mechanical ventilation, (4) exhibited cognitive impairment or unstable psychiatric morbidity, (5) were undergoing renal replacement therapy, (6) had active unstable coronary artery syndrome, (7) were younger than 18 years, and (8) were homeless.	Multicenter randomized clinical trial	February 2010 to April 2015	United Kingdom	116	66.7 ± 9.6	112
Vermeersch et al (2019)[35]	To investigate the effectiveness of azithromycin in the acute treatment of COPD exacerbations requiring hospitalization.	*Inclusion:* ▪ Eligible patients were 18 years or older, had an established diagnosis of COPD (based on clinical history and a pulmonary function test), had a history of one or more exacerbations treated with systemic corticosteroids and/or antibiotics in the previous year, were	Investigator-initiated, multicenter, randomized, double-blind, placebo controlled trial	August 2014 to April 2017	Belgium	Treatment 147 Placebo 154	Treatment 66 ± 9 Placebo 67 ± 10	301

		current smokers or had a smoking history of >10 pack-years, had a normal QT interval corrected according to Bazett's formula, and were hospitalized for an AECOPD that was deemed infectious by the local investigator within the 48-hour screening period from hospital admission. *Exclusion:* ▪ Contraindications to azithromycin, respiratory insufficiency requiring mechanical or noninvasive ventilation at the time of randomization, chronic systemic corticosteroid use (.4 mg methylprednisolone/d for >2 mo), and the use of macrolide antibiotics during >2 weeks preceding inclusion. Presentation of lobar pneumonia was an exclusion criterion. None of the patients were taking phosphodiesterase-4 inhibitors (which are not commercialized in Belgium).						
Zilberman-Itskovich et al (2019)[36]	To evaluate the extent of prolonged-QTc syndrome in COPD patients upon admission to an internal medicine department with acute exacerbation, its relationship to hypomagnesemia, hypokalemia, and	*Inclusion:* ▪ Patients were eligible to participate in the study if they were ≥18 years old, capable of signing informed consent, and had been diagnosed with COPD according to the standard criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines: symptoms of chronic (minimum 3 months) dyspnea, cough, or sputum in combination with	Prospective, observational, cohort clinical trial	September 2016 to December 2017	Israel	67	70 ± 11	67

	hypocalcemia, and the effect of COPD treatment on mortality during hospital stay.	spirometry test demonstrating irreversible obstructive disease. *Exclusion:* ▪ Exclusion criteria were pulmonary congestion, severe pleural effusion, pneumothorax, diagnosis of restrictive disease according to a pulmonologist, or spirometry demonstrating FEV1/FVC>0.7, dementia, unconscious at admission, and pregnancy.						
Steer and Echevarria et al (DECAF derivation [37] and DECAF validation[38] cohorts)	To study if in-hospital mortality in patients hospitalized with acute exacerbations of COPD can be predicted using the DECAF Score.	*Inclusion:* ▪ Primary diagnosis of AECOPD supported by spirometric evidence of airflow obstruction (forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.70) when clinically stable; age ≥35 years; smoking history of ≥10 cigarette pack years; and admission from the primary residence. *Exclusion:* ▪ Previous inclusion in the study; domiciliary ventilation; comorbidity expected to limit survival to <12 months (principally metastatic malignancy); or a primary reason for admission other than AECOPD.	Observational prospective cohort study	Derivation December 2008 to June 2010 Validation January 2012 to May 2014	United Kingdom	Derivation 920 Validation 1,725	Derivation 73.1 ± 10.0 Validation 73.1 ± 10.3	2,477

Hartley et al (2021)[39]	To predict in-hospital mortality in exacerbations of COPD requiring assisted ventilation using the NIV Outcomes (NIVO) Score.	*Inclusion:* ▪ AECOPD as primary diagnosis, preadmission spirometry evidence of airflow obstruction (forced expiratory volume in one second (FEV1)/ vital capacity (VC). *Exclusion:* ▪ Previous inclusion in study or illness other than COPD likely to limit life to less than one year (principally metastatic cancer).	Observational prospective cohort study	Derivation November 2008 to May 2013 Validation October 2016 to February 2018	United Kingdom	Derivation 489 Validation 733	Derivation 72.8 ± 10.0 Validation 70.5 ± 9.3	733
Abadias Medrano (2018)[40]	To describe the characteristics of patients visiting the hospital emergency department due to COPD exacerbation and to evaluate their management.	*Inclusion:* ▪ Confirmed diagnosis of COPD, *Exclusion:* ▪ Presence of any identifiable causes of worsening of symptoms (pneumonia, pneumothorax, decompensated or unrecognized arrhythmia, ischemic heart disease, pulmonary thromboembolism and left heart failure), need for invasive mechanical ventilation, or monitoring and control by home care programs or palliative care units.	Descriptive cross-sectional study	January to May 2016	Spain	219	75.9 ± 11.1	217
Sprooten et al (2019)[41]	To (i) assess the short-term (in-hospital and 90-day) mortality rate of AECOPD; (ii) identify clinically available predictors for 90-day mortality risk in patients admitted for	*Inclusion:* ▪ Severe AECOPD according to the global initiative for chronic obstructive lung disease (GOLD) definition and (ii) confirmation of obstructive lung function by a ratio of post-bronchodilator forced expiratory volume in 1 s to forced vital capacity	Retrospective observational cohort study	June 2011 to December 2014	The Netherlands	364	70.5 ± 10.2	364

	severe AECOPD; and (iii) to construct an easy, feasible and comprehensive predictive algorithm for 90-day mortality in this patient population.	(FEV1/FVC) < 70% in the medical record of the patient. *Exclusion:* ▪ Age < 40 years, a previous diagnosis with asthma, active pulmonary malignancy, follow-up in another hospital and primary reason for hospitalization other than AECOPD.						
Sprooten et al (2020)[42]	To investigate predictors for short- and long-term mortality in COPD patients requiring NIV for the treatment of acute respiratory failure related to AECOPD for the first time in the course of their disease.	*Inclusion:* ▪ (1) AECOPD, defined as sudden increase in one or more of the following; dyspnea, cough or sputum production and treatment with systemic glucocorticoids and/or antibiotics, (2) confirmation of obstructive lung function by a ratio of post-bronchodilator forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) <70% in the medical records of the patient and (3) requiring NIV for the first time assessed by a chest physician according to international guidelines: pH <7.35, $PaCO_2$ >6.5kPa, respiratory rate (RR) >23/min). *Exclusion:* Not specified.	Retrospective observational cohort study	January 2009 to December 2011	The Netherlands	78	In-hospital survivors 69.9 ± 10.8 in-hospital deaths 77.5 ± 7.3	78
Russell et al (2019)[43]	The primary objective of the study was to use routinely collected data at presentation to the ED to see if any were predictive of outcome.	*Inclusion:* ▪ Patients admitted for an AECOPD defined according to the Anthonisen criteria and health-care utilization, and the primary ICD-10 diagnostic code J44.1.	Retrospective case note review	February 2014 to July 2015	United Kingdom	537	71 (30-101)	537

		Exclusion: ▪ Patients with any diagnosis other than AECOPD.						
Faverio et al (2019)[44]	To present and test the feasibility of the NIV weaning strategy used in patients with AHRF due to AECOPD admitted in the intermediate respiratory care unit.	*Inclusion:* ▪ In our study population, AECOPD was the primary admission diagnosis according to the physician in charge. Patients who also had pneumonia or congestive heart failure as secondary diagnoses were not excluded from the study. *Exclusion:* Not specified.	Retrospective cohort study	January 2015 to April 2017	Italy	51	79 (55-85)	40 (only index AECOPD hospitalization)
Cross et al (2012)[45]	To assess the effectiveness of manual chest physiotherapy on disease-specific quality of life in patients with COPD hospitalized with acute exacerbation.	*Inclusion:* ▪ Patients with a diagnosis of COPD, as defined by the British Thoracic Society, who were admitted to the hospital with an exacerbation of COPD. *Exclusion:* ▪ Patients with any contraindication to the use of MCP techniques or with no evidence of excess sputum production on auscultation. Contraindications included osteoporosis, haemoptysis, bronchial hyper-reactivity, respiratory system malignancy, raised intracranial pressure, uncontrolled hypertension (diastolic> 110), pulmonary embolism, coagulopathy (platelets <50 and/or INR ≥3), bronchopleural fistula, subcutaneous emphysema and left ventricular failure as primary diagnosis.	Multicentre, randomised controlled trial	November 2005 to April 2008	United Kingdom	527	MCP arm 69.1 ± 9.9 No MCP arm 69.6 ± 9.5	516

Prins et al (2019)[46]	To determine if CRP-guided antibiotic therapy leads to a reduction in antibiotic therapy, without increasing the rate of treatment failure or adverse events within 30 days. within 24 h of admission compared to patient reported sputum purulence, in patients with acute exacerbations of COPD admitted to hospital.	*Inclusion:* ▪ Age 40 years and older. Written informed consent obtained. AECOPD according to the GOLD guideline. Former of current smoker with a minimum smoking history of 10 pack years. Patients have to be capable of ingesting oral medication. Patients have to be mentally capable of participating in the study (able to complete questionnaires and perform lung function tests). Life expectancy ≥ 30 days. *Exclusion:* ▪ Pregnant or lactating women, or women of childbearing age not using an acceptable method of contraception. Pre-treatment with corticosteroids (cumulative dose >210 mg) for the present exacerbation. Strong clinical suspicion of pneumonia. Progression or new radiographic abnormalities on the chest X-ray. Cystic fibrosis. Tuberculosis. Immunodeficiency disorders such as AIDS, humoral immune defect, ciliary dysfunction etc., and the use of immunosuppressive drugs (>30 mg prednisolone/day maintenance dose or equivalent for more than 4 weeks). Recent or unresolved lung malignancy. Other disease likely to require antibiotic therapy, such as recurrent	Investigator-initiated, multicentre, randomised, controlled open intervention clinical trial	July 2011 to February 2015	The Netherlands	220	GOLD group 70.8 ± 11.8 CRP group 68.4 ± 12.0	220

		sinusitis or urinary tract infection. Significant gastrointestinal or other conditions that may affect study drug absorption. Instable congestive heart failure or recent stroke. Newly diagnosed pulmonary embolism.						

** This data was presented as a Master Thesis by Ellis H at the Master Medical Science at the University of Otago in 2017. Master Thesis entitled: Hospital Admissions for Acute Exacerbations of Chronic Obstructive Pulmonary Disease; Contributing Factors, Risk Prediction and Prognosis.*

***This data was presented at TSANZ ASM and was published as such: Ellis H, Chang CL, Shafuddin E, Beasley R, Beckert L, Wong C, Hancox R. Cardiac events and mortality following acute exacerbations of COPD: an Audit of four New Zealand Hospitals. Respirology 2018; 23(S1) 104-215. TO105*

Table S2. Sample sizes of the three data subsets: in-hospital mortality, post-discharge mortality and hospital readmission.

First author (publication year)	In-hospital mortality	Post-discharge mortality	Hospital readmission
Matkovic et al (2012)[1]	155	154	154
Guerrero et al (2016)[2]	449	362	403
Stolz et al (2008)[3]	-	481	-
Grolimund et al (2015)[4]	-	530	-
Ringbaek et al (2015)[5]	405	383	-
Fabbian et al (2016)[6]	7,073	-	-
Mekov et al (2016)[7]	-	151	-
Harries et al (2015)[8]	25,729	-	19,551
Wang et al (2016)[9]	191	189	189
Lun et al (2016)[10]	-	250	250
Ergan et al (2016)[11]	106	67	-
Ergan et al (2016)[12]	63	-	-
Quintana et al (2014)[13]	2,486	2,430	2,430
López-Campos et al (2013)[14]	16,014	15,224	15,224
Ellis et al (2017) (COAST)*	311	305	-
Shafuddin et al (2018) (BREATHE)[15]	176	169	169
Chang et al (2011) (COPDEC)[16]	247	234	235
Ellis et al (2018) (COPDAudit)**	392	378	378
Gudmundsson et al (2006)[17]	-	415	415
Almagro et al (2012)[18]	-	181	181
Epstein et al (2018)[19]	-	539	539
Miravitlles et al (2015)[20]	-	342	342
Lacoma et al (2011)[21]	217	215	215
Osadnik et al (2013)[22]	90	87	88
Alía et al (2011)[23]	64	-	-
Spannella et al (2019)[24]	121	-	-
Takir et al (2014)[25]	640	547	-
Aliyali et al (2015)[26]	507	488	-
Utens et al (2012)[27]	-	138	138
Smulders et al (2020)[28]	-	604	588
Ko et al (2017)[29]	-	180	180
Ko et al (2019)[30]	401	389	389
Trethewey et al (2019)[31]	546	442	-
Steriade et al (2019)[33]	89	57	57
Murphy et al (2017)[34]	-	112	111
Vermeersch et al (2019)[35]	301	274	274
Zilberman-Itskovich et al (2019)[36]	67	64	-

Steer and Echevarria et al (DECAF derivation [37] and DECAF validation[38] cohorts)	2,477	2,264	2,264
Hartley et al (2021)[39]	733	586	586
Abadias Medrano (2018)[40]	217	205	-
Sprooten et al (2019)[41]	364	334	334
Sprooten et al (2020)[42]	78	67	67
Russell et al (2019)[43]	537	-	-
Faverio et al (2019)[44]	40	38	38
Cross et al (2012)[45]	516	508	508
Prins et al (2019)[46]	220	214	-
Total	62,022	30,597	46,297

NB: the post-discharge mortality and hospital readmission data subsets represent all patients surviving the index event (i.e. in-hospital mortality), and having post-discharge mortality and/or readmission data. ** This data was presented as a Master Thesis by Ellis H at the Master Medical Science at the University of Otago in 2017. Master Thesis entitled: Hospital Admissions for Acute Exacerbations of Chronic Obstructive Pulmonary Disease; Contributing Factors, Risk Prediction and Prognosis. **This data was presented at TSANZ ASM and published as: Ellis H, Chang CL, Shafuddin E, Beasley R, Beckert L, Wong C, Hancox R. Cardiac events and mortality following acute exacerbations of COPD: an Audit of four New Zealand Hospitals. Respirology 2018; 23(S1) 104-215. TO105*

Table S3. Baseline characteristics in-hospital mortality data subset.

	Total cohort (n=62022)	**Survivors (n=58154)**	**Non-survivors (n=3868)**	***p*-value**
Sex, male	36530 (58.9)	34343 (59.1)	2187 (56.5)	0.002
Age, years	74.0 (65.0-80.0)	73.0 (65.0-80.0)	79.0 (73.0-85.0)	<0.001
FEV_1, % pred	42.0 (31.9-56.0)	42.0 (32.0-56.0)	37.0 (29.0-47.0)	<0.001
%N	7.3	7.5	4.3	
Ethnicity				0.139
European	1646 (99.1)	1369 (99.1)	277 (99.3)	
African	10 (0.6)	10 (0.7)	-	
Asian	5 (0.3)	3 (0.2)	2 (0.7)	
%N	2.7	2.4	7.2	
GOLD classification				0.006
I	180 (4.0)	178 (4.1)	2 (1.2)	
II	1379 (30.6)	1343 (31.0)	36 (21.6)	
III	2018 (44.8)	1934 (44.6)	84 (50.3)	
IV	929 (20.6)	884 (20.4)	45 (26.9)	
%N	7.3	7.5	4.3	
Number of exacerbations ≤12 months before index admission				0.253
0	811 (25.1)	768 (25.1)	43 (26.2)	
1	633 (19.6)	609 (19.9)	24 (14.6)	
≥2	1782 (55.2)	1685 (55.0)	97 (59.1)	
%N	5.2	5.3	4.2	
Number of hospitalizations ≤12 months before index admission				<0.001
0	4143 (57.1)	3903 (57.6)	240 (49.4)	

1	1649 (22.7)	1534 (22.7)	115 (23.7)	
≥2	1466 (20.2)	1335 (19.7)	131 (27.0)	
%N	11.8	11.6	12.6	
In-hospital time, days	7.0 (4.0-11.0)	7.0 (4.0-11.0)	7.0 (3.0-16.0)	<0.001
%N	52.5	53.6	35.3	
mMRC-score during index event				<0.001
0	234 (5.7)	234 (5.8)	-	
1	818 (20.0)	817 (20.4)	1 (1.3)	
2	771 (18.9)	764 (19.0)	7 (9.3)	
3	1155 (28.3)	1140 (28.4)	15 (20.0)	
4	1110 (27.2)	1058 (26.4)	52 (69.3)	
%N	6.6	6.9	1.9	
Non-invasive mechanical ventilation	4058 (17.7)	3475 (16.1)	583 (42.8)	<0.001
%N	37.0	37.2	35.2	
Invasive mechanical ventilation	882 (4.2)	708 (3.6)	174 (13.5)	<0.001
%N	33.8	33.9	33.3	
ICU stay	1469 (16.6)	1207 (14.8)	262 (40.4)	<0.001
%N	14.2	14.1	16.8	

Variables are presented as n (%), mean ± SD, and median (IQR) as appropriate. %N indicates the percentage of cases for which the variable of interest was available. Abbreviations: FEV_1 = Forced Expiratory Volume in 1 second, GOLD = Global Initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council, ICU = Intensive Care Unit. P-values denote statistical difference between the in-hospital survivors and non-survivors.

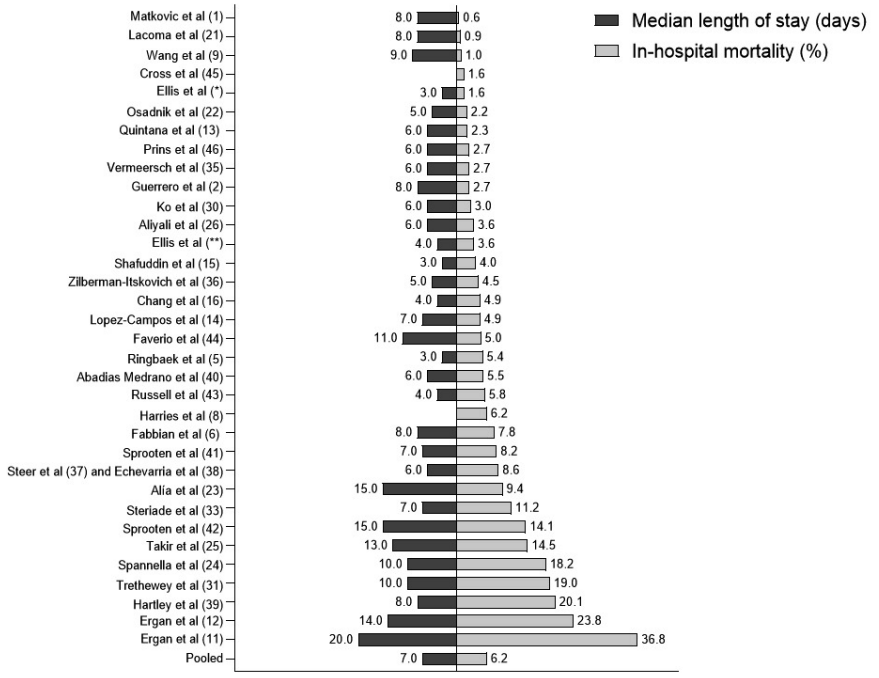


Fig S2. Stratified (per study) and pooled median length of hospital stay (left) and in-hospital mortality rates (right) during the index event. Relative percentages are displayed. *NB: length of hospital stay was missing for Cross et al (45) and Harries et al (8). (*) This data was presented as a Master Thesis by Ellis H at the Master Medical Science at the University of Otago in 2017. Master Thesis entitled: Hospital Admissions for Acute Exacerbations of Chronic Obstructive Pulmonary Disease; Contributing Factors, Risk Prediction and Prognosis. (**) This data was presented at TSANZ ASM and published as: Ellis H, Chang CL, Shafuddin E, Beasley R, Beckert L, Wong C, Hancox R. Cardiac events and mortality following acute exacerbations of COPD: an Audit of four New Zealand Hospitals. Respirology 2018; 23(S1) 104-215. TO105.*

Table S4. Cox proportional hazard regression of in-hospital mortality.

		Univariate			Age- and sex adjusted	
Covariates	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Sex, male	0.82	0.73-0.91	<0.001			
%N	52.5					
Age, years	1.06	1.05-1.06	<0.001			
%N	52.5					
FEV_1, % pred	1.00	0.99-1.01	0.334			
%N	5.9					
Ethnicity						
European	0.17	0.04-0.69	0.013	0.18	0.04-0.73	0.016
African	<0.001	<0.001-	0.934	<0.001	<0.001-	0.935
Asian	Reference	<0.001			<0.001	
%N	2.6					
GOLD classification						
I	Reference					
II	1.54	0.37-6.41	0.554			
III	1.86	0.46-7.58	0.388			
IV	1.74	0.42-7.23	0.443			
%N	5.9					
Number of exacerbations ≤12 months before index admission						
0	Reference					
1	0.87	0.53-1.44	0.594			
≥2	1.25	0.87-1.79	0.225			
%N	5.1					
Number of hospitalizations ≤12 months before index admission						
0	Reference					
1	1.02	0.81-1.30	0.843			
≥2	1.20	0.96-1.49	0.111			
%N	10.0					
NIMV, yes	3.64	3.09-4.29	<0.001	4.09	3.47-4.83	<0.001
%N	35.7					
IMV, yes	2.23	1.78-2.80	<0.001	2.65	2.12-3.33	<0.001
%N	32.4					
ICU-stay, yes	1.52	1.29-1.80	<0.001	1.75	1.48-2.07	<0.001
%N	12.5					

%N indicates the percentage of cases for which the variable of interest was available. Abbreviations: CI = Confidence Interval, HR = Hazard Rate, ICU = Intensive Care Unit, IMV= invasive mechanical ventilation, NIMV = non-invasive mechanical ventilation. Estimates for the modified Medical Research Council (mMRC) could not be created due to sample size constraints.

Table S5. Baseline characteristics post-discharge mortality data subset.

	Total cohort (n=30597)	Survivors (n=25935)	Non-survivors (n=4662)	*p*-value
Sex, male	20222 (66.1)	17327 (66.8)	2895 (62.1)	<0.001
Age, years	72.0 (63.0-79.0)	71.0 (63.0-78.0)	75.0 (67.0-81.0)	<0.001
FEV_1, % pred	41.0 (31.0-55.0)	42.0 (32.0-56.0)	38.0 (28.0-50.0)	<0.001
%N	18.2	17.8	20.4	
Post-discharge follow-up time, days	365.0 (365.0-365.0)	365.0 (365.0-365.0)	231.0 (59.0-457.0)	<0.001
Ethnicity				0.444
European	1920 (90.9)	1495 (90.6)	425 (92.0)	
African	10 (0.5)	7 (0.4)	3 (0.6)	
Asian	183 (8.7)	149 (9.0)	34 (7.4)	
%N	6.9	6.4	9.9	
GOLD classification				<0.001
I	205 (3.7)	175 (3.8)	30 (3.2)	
II	1650 (29.6)	1436 (31.1)	214 (22.5)	
III	2499 (44.9)	2061 (44.7)	438 (46.0)	
IV	1211 (21.8)	941 (20.4)	270 (28.4)	
%N	18.2	17.8	20.4	
Number of exacerbations ≤12 months before index admission				0.005
0	1094 (26.2)	836 (25.3)	258 (29.3)	
1	928 (22.2)	764 (23.2)	164 (18.6)	
≥2	2158 (51.6)	1700 (51.5)	458 (52.0)	
%N	13.7	12.7	18.9	
Number of hospitalizations ≤12 months before index admission				<0.001
0	4231 (52.8)	3607 (54.8)	624 (43.9)	
1	1953 (24.4)	1602 (24.3)	351 (24.7)	
≥2	1825 (22.8)	1377 (20.9)	448 (31.5)	
%N	26.2	25.4	30.5	
In-hospital time during index event, days	7.0 (4.0-10.0)	6.0 (4.0-6.0)	8.0 (5.0-14.0)	<0.001
%N	91.0	91.4	89.3	
mMRC-score during index event				<0.001
0	242 (5.3)	239 (5.8)	3 (0.6)	
1	910 (19.8)	862 (21.0)	48 (9.9)	
2	920 (20.1)	847 (20.6)	73 (15.1)	
3	1266 (27.6)	1129 (27.5)	137 (28.3)	
4	1250 (27.2)	1027 (25.0)	223 (46.1)	
%N	15.0	15.8	10.4	
Non-invasive mechanical ventilation during index event	3641 (16.1)	2666 (13.7)	975 (31.2)	<0.001
%N	73.9	75.1	67.1	
Invasive mechanical ventilation during index event	663 (3.3)	417 (2.4)	246 (10.1)	<0.001
%N	65.7	68.1	52.1	

ICU stay during index event	1209 (13.3)	631 (9.3)	578 (24.6)	<0.001
%N	29.8	26.1	50.4	

Variables are presented as n (%), mean ± SD, and median (IQR) as appropriate. %N indicates the percentage of cases for which the variable of interest was available. Abbreviations: FEV_1 = Forced Expiratory Volume in 1 second, GOLD = Global Initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council, ICU = Intensive Care Unit. P-values denote statistical difference between the survivors and non-survivor during post-discharge follow-up.

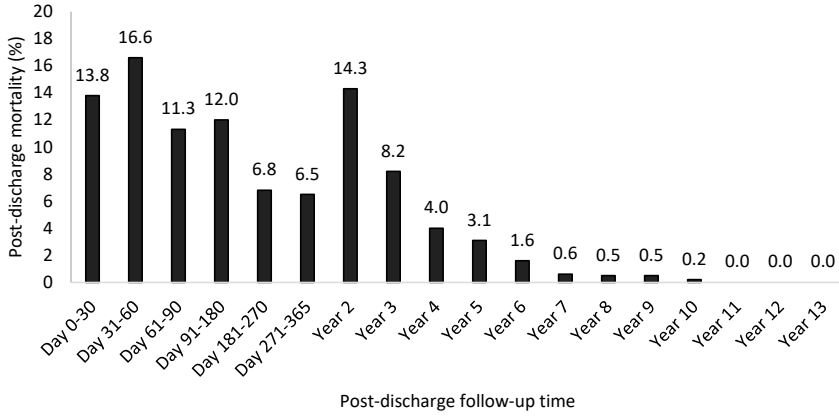


Fig S3. Percentage of non-survivors, with a known time of death (n=3,866/25,909), per time interval during follow-up after hospital discharge from the index event.

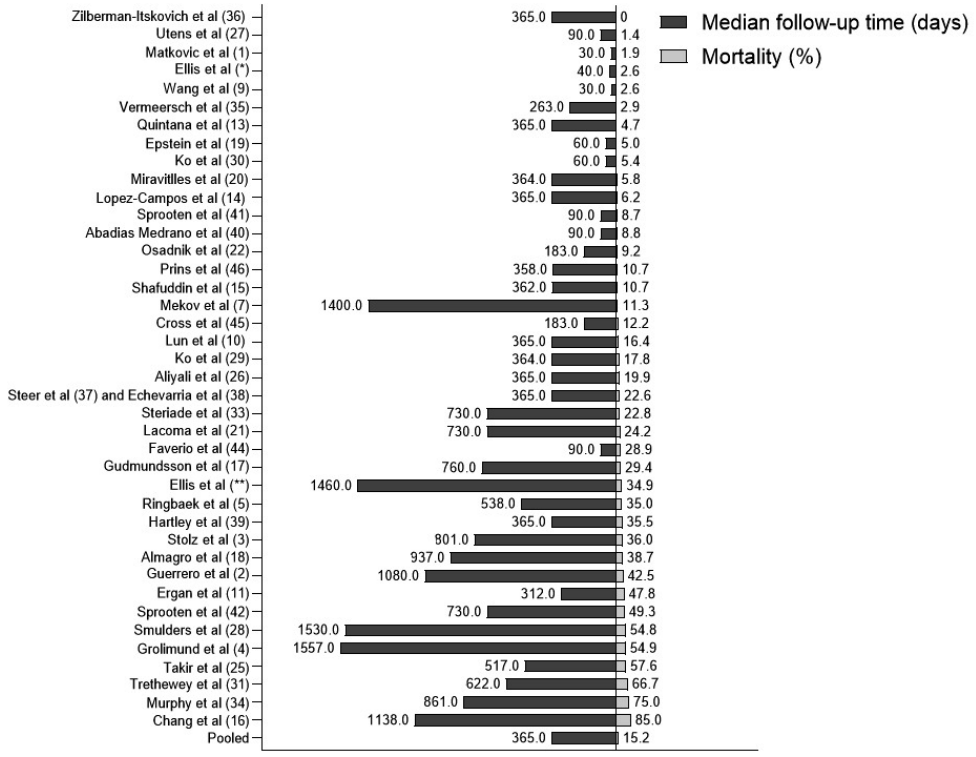
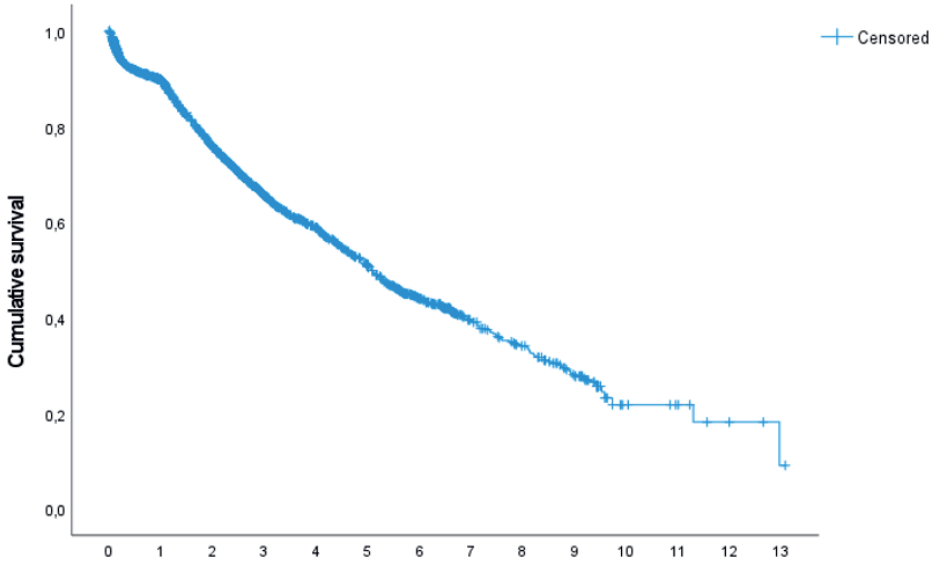


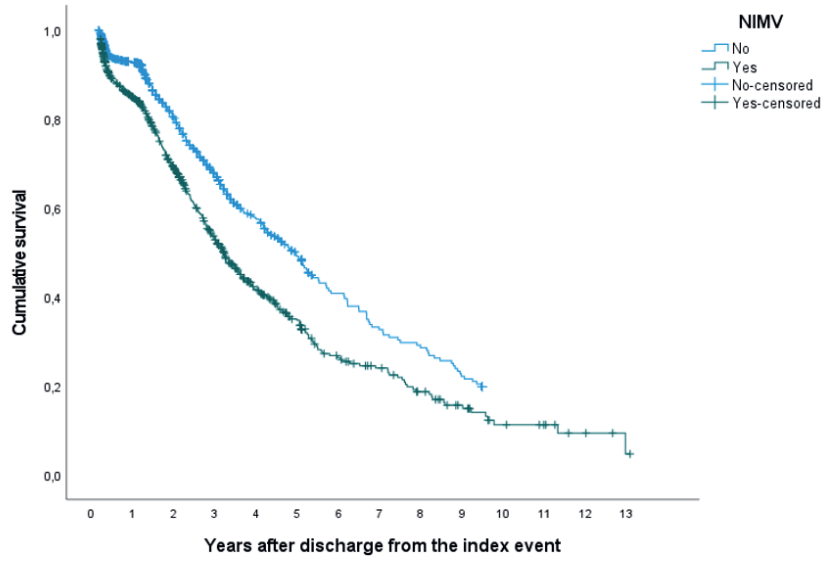
Fig S4. Stratified (per study) and pooled median follow-up time (left) and mortality rates (right) after hospital discharge from the index event. Relative percentages are displayed. *(*) This data was presented as a Master Thesis by Ellis H at the Master Medical Science at the University of Otago in 2017. Master Thesis entitled: Hospital Admissions for Acute Exacerbations of Chronic Obstructive Pulmonary Disease; Contributing Factors, Risk Prediction and Prognosis. (**) This data was presented at TSANZ ASM and published as: Ellis H, Chang CL, Shafuddin E, Beasley R, Beckert L, Wong C, Hancox R. Cardiac events and mortality following acute exacerbations of COPD: an Audit of four New Zealand Hospitals. Respirology 2018; 23(S1) 104-215. TO105.*



N at risk	25909	20935	2810	1639	1174	750	301	149	116	80	11	8	3	1
Censored	2391	17567	855	310	303	389	128	14	17	60	3	4	1	1
N events	2583	558	316	155	121	60	24	19	19	9	0	1	1	0
Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13

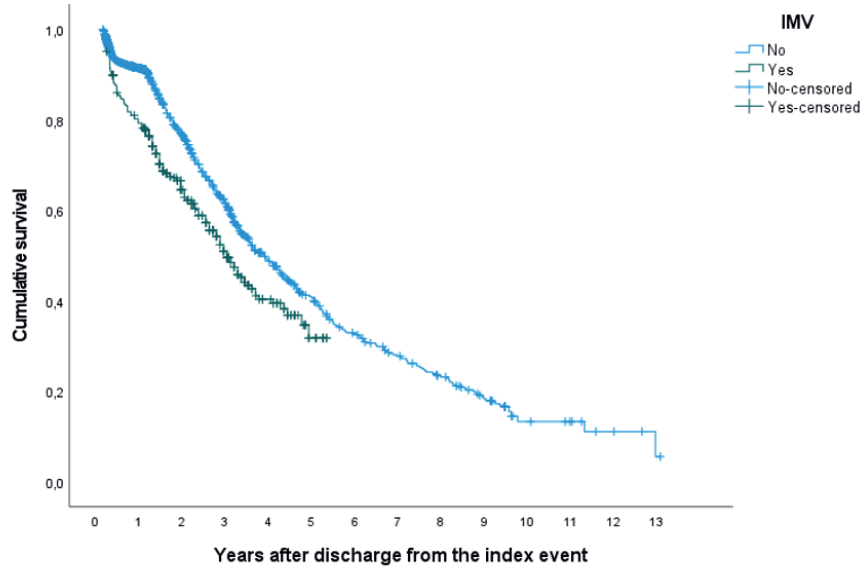
Fig S5. Kaplan-Meier survival curve after hospital discharge from the index event.

A.



N at risk														
No	15961	13362	877	507	403	314	70	55	49	38	0	0	0	0
Yes	3038	2333	453	255	172	117	56	46	33	20	11	8	3	1
Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13

B.



N at risk														
No	18517	15109	744	324	227	164	127	102	83	59	11	8	3	1
Yes	653	495	184	94	46	9	0	0	0	0	0	0	0	0
Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13

Fig S6. Kaplan-Meier survival curve after hospital discharge from the index event stratified by (N)IMV use during the index event. (A) Survival probability stratified by NIMV use during the index event. (B) Survival probability stratified by IMV use during the index event.

Table S6. Cox proportional hazard regression of post-discharge mortality.

	Univariate			Age- and sex adjusted		
Covariates	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Sex, male	0.94	0.88-1.00	0.060			
Age, years	1.04	1.03-1.04	<0.001			
FEV_1, % pred	0.99	0.98-0.99	<0.001	0.98	0.98-0.99	<0.001
%N	15.2					
Ethnicity						
European	1.82	1.27-2.59	<0.001	1.90	1.31-2.74	0.001
African	1.73	0.53-5.63	0.363	1.65	0.50-5.37	0.409
Asian	Reference					
%N	5.5					
GOLD classification						
I	Reference					
II	0.87	0.56-1.35	0.536			
III	1.24	0.81-1.89	0.319			
IV	1.43	0.93-2.21	0.104			
%N	15.2					
Number of exacerbations ≤12 months before index admission						
0	Reference					
1	0.86	0.67-1.11	0.256			
≥2	1.00	0.81-1.24	0.967			
%N	7.2					
Number of hospitalizations ≤12 months before index admission						
0	Reference					
1	1.44	1.20-1.71	<0.001	1.42	1.19-1.69	<0.001
≥2	2.11	1.80-2.48	<0.001	2.09	1.78-2.45	<0.001
%N	18.8					
mMRC-score during index event						
0	Reference					
1	4.07	1.26-13.12	0.019	3.76	1.16-12.12	0.027
2	6.77	2.13-21.51	0.001	6.25	1.97-19.85	0.002
3	10.21	3.25-32.09	<0.001	9.07	2.88-28.51	<0.001
4	22.64	7.27-70.93	<0.001	21.56	6.87-67.64	<0.001
%N	15.8					
NIMV, yes	1.84	1.69-2.01	<0.001	2.02	1.85-2.21	<0.001
%N	73.3					
IMV, yes	1.72	1.50-1.98	<0.001	1.85	1.61-2.13	<0.001
%N	74.0					
ICU-stay, yes	1.84	1.66-2.03	<0.001	2.02	1.83-2.23	<0.001
%N	29.8					

%N indicates the percentage of cases for which the variable of interest was available. Abbreviations: CI = Confidence Interval, GOLD = Global Initiative for Chronic Obstructive Lung Disease, HR = Hazard Rate, ICU = Intensive Care Unit, IMV= invasive mechanical ventilation, mMRC = modified Medical Research Council, NIMV = non-invasive mechanical ventilation. N complete cases = 25,909.

Table S7. Baseline characteristics hospital readmission data subset.

	Total cohort (n=46297)	Not readmitted (n=29651)	Readmitted (n=16646)	*p*-value
Sex, male	28067 (60.6)	17991 (60.7)	10076 (60.5)	0.760
Age, years	72.2 (64.0-79.0)	72.0 (64.0-79.0)	73.0 (65.0-80.0)	<0.001
FEV_1, % pred	41.0 (31.0-55.0)	43.0 (32.0-57.4)	40.0 (30.0-52.0)	<0.001
%N	10.6	9.6	12.3	
Post-discharge follow-up time, days	90.0 (90.0-365.0)	365.0 (90.0-365.0)	90.0 (47.0-117.0)	<0.001
Ethnicity				<0.001
European	1789 (90.3)	1194 (94.0)	595 (83.6)	
African	10 (0.5)	3 (0.2)	7 (1.0)	
Asian	183 (9.2)	73 (5.7)	110 (15.4)	
%N	4.3	4.3	4.3	
GOLD classification				<0.001
I	174 (3.6)	117 (4.1)	57 (2.8)	
II	1452 (29.7)	911 (32.1)	541 (26.4)	
III	2215 (45.3)	1266 (44.6)	949 (46.2)	
IV	1051 (21.5)	545 (19.2)	506 (24.6)	
%N	10.6	9.6	12.3	
Number of exacerbations ≤12 months before index admission				<0.001
0	1044 (28.5)	633 (33.9)	411 (22.9)	
1	796 (21.7)	422 (22.6)	374 (20.8)	
≥2	1826 (49.8)	813 (43.5)	1013 (56.3)	
%N	7.9	6.3	10.8	
Number of hospitalizations ≤12 months before index admission				<0.001
0	4136 (53.8)	2989 (67.0)	1147 (35.5)	
1	1844 (24.0)	920 (20.6)	924 (28.6)	
≥2	1714 (22.3)	550 (12.3)	1164 (36.0)	
%N	16.6	15.0	19.4	
In-hospital time during index event, days	7.0 (4.0-10.0)	7.0 (4.0-10.0)	7.0 (4.0-10.0)	0.001
%N	53.1	50.5	57.8	
mMRC-score during index event				<0.001
0	229 (5.5)	178 (7.1)	51 (3.0)	
1	873 (20.9)	624 (25.0)	294 (14.8)	
2	862 (20.6)	531 (21.3)	331 (19.7)	
3	1176 (28.2)	718 (28.8)	458 (27.2)	
4	1037 (24.8)	444 (17.8)	593 (35.3)	
%N	9.0	8.4	10.1	
Non-invasive mechanical ventilation during index event	2962 (14.5)	1782 (14.1)	1180 (15.2)	0.043
%N	44.0	42.5	46.7	
Invasive mechanical ventilation during index event	261 (1.4)	168 (1.4)	93 (1.4)	0.845
%N	39.5	39.4	39.8	

ICU stay during index event	356 (5.8)	174 (4.6)	182 (7.8)	<0.001
%N	13.2	12.9	13.9	

Variables are presented as n (%), mean ± SD, and median (IQR) as appropriate. %N indicates the percentage of cases for which the variable of interest was available. Abbreviations: FEV_1 = Forced Expiratory Volume in 1 second, GOLD = Global Initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council, ICU = Intensive Care Unit. P-values denote statistical difference between the readmitted and not readmitted patients during post-discharge follow-up.

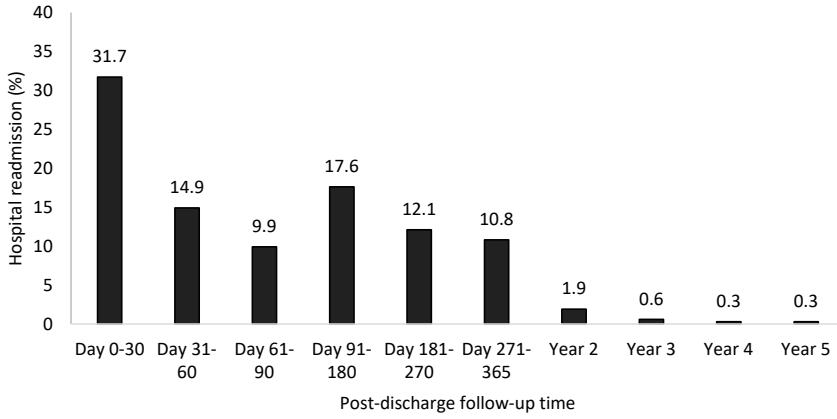


Fig S7. Percentage of readmitted patients, with a known time of readmission (n=10,232/27,401), per time interval during follow-up after hospital discharge from the index event.

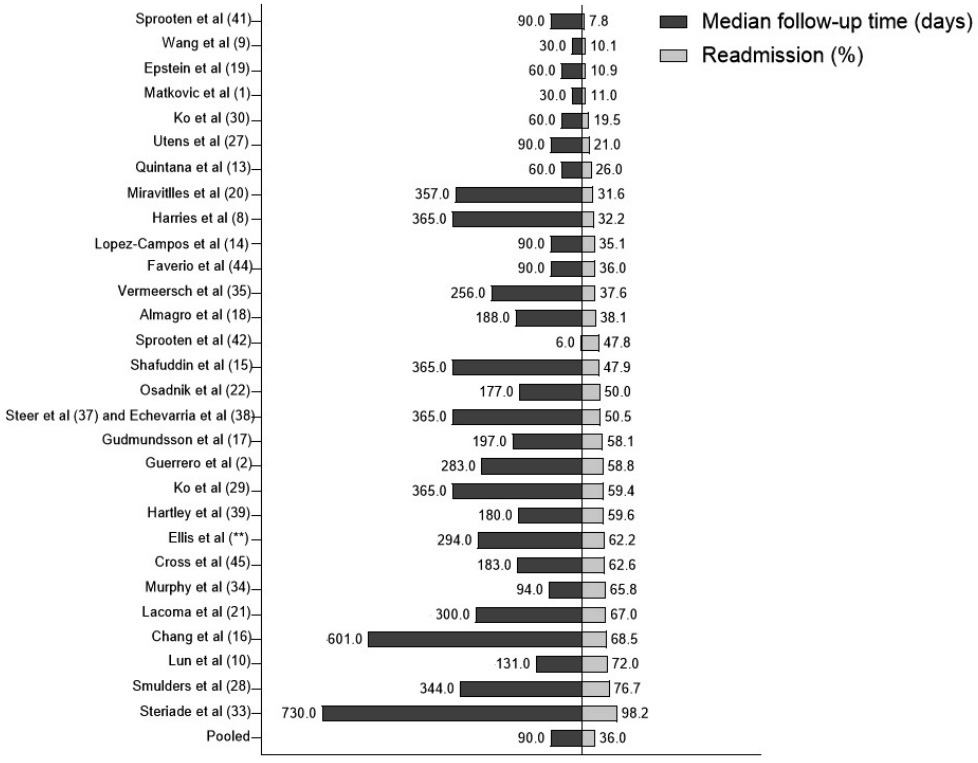
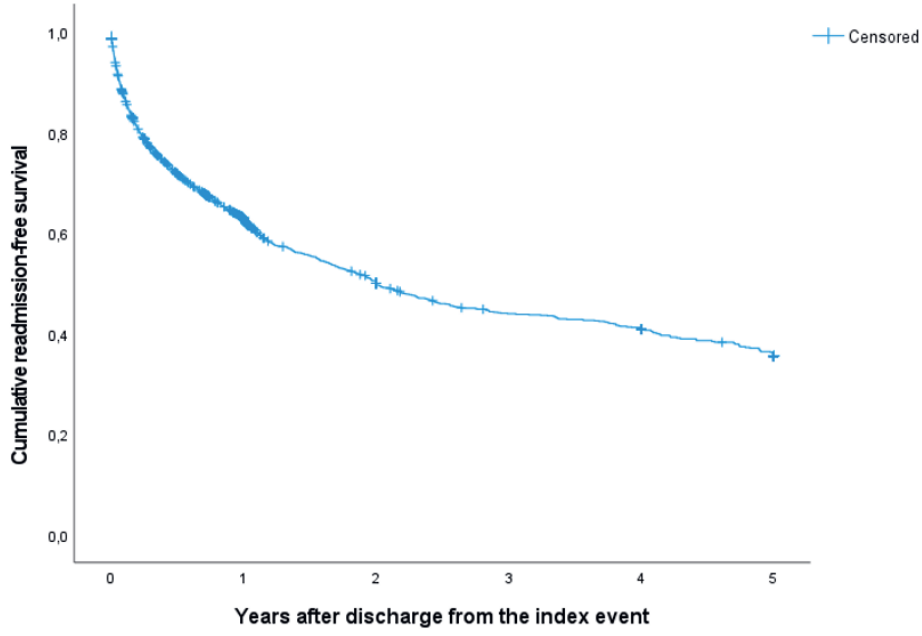


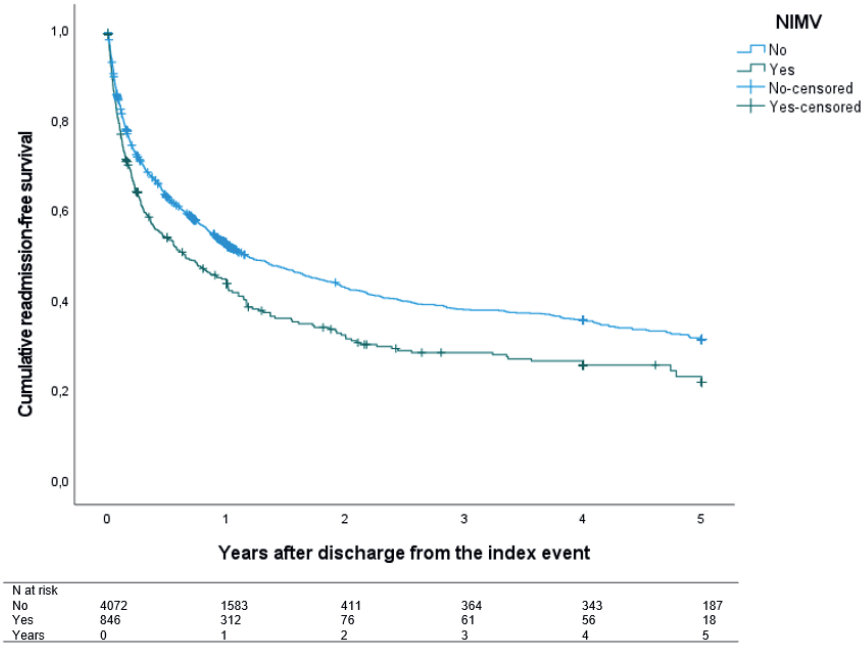
Fig S8. Stratified (per study) and pooled median follow-up time (left) and hospital readmission rates (right) after hospital discharge from the index event. Relative percentages are displayed. *(**) This data was presented at TSANZ ASM and published as: Ellis H, Chang CL, Shafuddin E, Beasley R, Beckert L, Wong C, Hancox R. Cardiac events and mortality following acute exacerbations of COPD: an Audit of four New Zealand Hospitals. Respirology 2018; 23(S1) 104-215. TO105.*



N at risk	27401	16126	738	437	409	212
Censored	1412	15146	236	0	167	208
N events	9863	242	65	28	30	4
Years	0	1	2	3	4	5

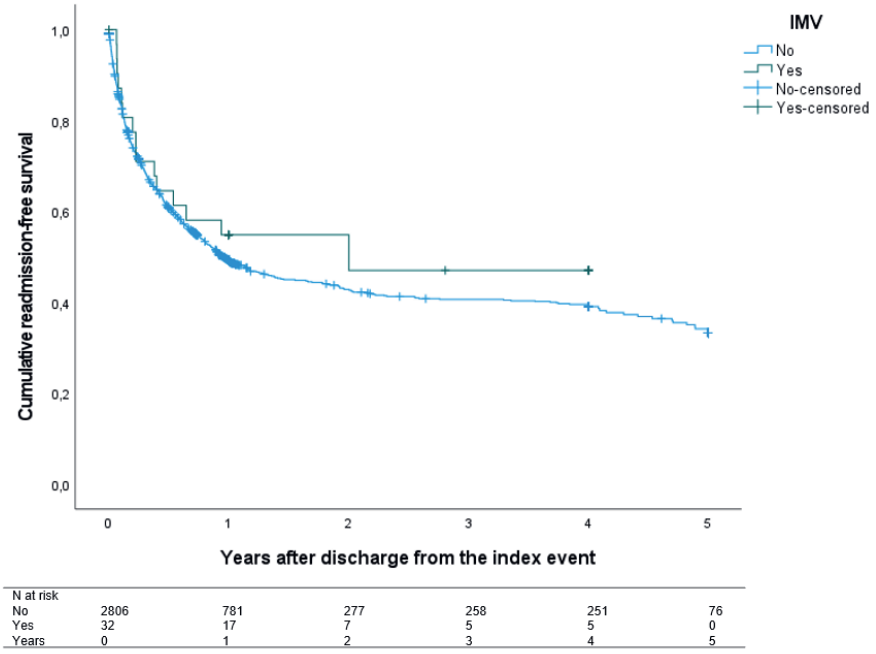
Fig S9. Kaplan-Meier median time to readmission after hospital discharge from the index event.

A.



N at risk						
No	4072	1583	411	364	343	187
Yes	846	312	76	61	56	18
Years	0	1	2	3	4	5

B.



N at risk						
No	2806	781	277	258	251	76
Yes	32	17	7	5	5	0
Years	0	1	2	3	4	5

Fig S10. Kaplan-Meier median time to readmission after hospital discharge from the index event stratified by (N)IMV use during the index event. (A) Median time to readmission stratified by NIMV use during the index event. (B) Median time to readmission stratified by IMV use during the index event.

Table S8. Cox proportional hazard regression of hospital readmission.

	Univariate			Age- and sex adjusted		
Covariates	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Sex, male	1.07	1.03-1.11	0.001			
Age, years	1.00	0.99-1.00	0.502			
FEV_1, % pred	0.99	0.99-0.99	<0.001	0.99	0.99-0.99	<0.001
%N	9.5					
Ethnicity						
European	1.16	0.94-1.43	0.171			
African	1.68	0.78-3.61	0.183			
Asian	Reference					
%N	5.8					
GOLD classification						
I	Reference					
II	1.14	0.84-1.55	0.441	1.14	0.83-1.55	0.423
III	1.45	1.07-1.96	0.017	1.47	1.09-1.99	0.012
IV	1.68	1.23-2.29	0.001	1.78	1.31-2.43	<0.001
%N	9.5					
Number of exacerbations ≤12 months before index admission						
0	Reference					
1	1.23	1.06-1.42	0.006	1.22	1.06-1.41	0.007
≥2	1.72	1.53-1.94	<0.001	1.76	1.56-1.98	<0.001
%N	12.6					
Number of hospitalizations ≤12 months before index admission						
0	Reference					
1	1.38	1.25-1.52	<0.001	1.38	1.25-1.52	<0.001
≥2	2.49	2.27-2.73	<0.001	2.50	2.28-2.73	<0.001
%N	17.9					
mMRC-score during index event						
0	Reference					
1	1.25	0.72-2.19	0.428	1.19	0.68-2.08	0.543
2	1.50	0.87-2.59	0.146	1.43	0.82-2.47	0.205
3	1.79	1.04-3.09	0.035	1.76	1.02-3.03	0.043
4	2.09	1.22-3.58	0.008	2.05	1.20-3.53	0.009
%N	4.9					
NIMV, yes	1.32	1.19-1.45	<0.001	1.32	1.19-1.46	<0.001
%N	17.9					
IMV, yes	0.83	0.50-1.39	0.482			
%N	10.4					
ICU-stay, yes	1.18	1.01-1.39	0.042	1.17	0.99-1.37	0.060
%N	10.8					

%N indicates the percentage of cases for which the variable of interest was available. Abbreviations: CI = Confidence Interval, GOLD = Global Initiative for Chronic Obstructive Lung Disease, HR = Hazard Rate, ICU = Intensive Care Unit, mMRC = modified Medical Research Council, NIMV = non-invasive mechanical ventilation. N complete cases = 27,401.

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CHAPTER 3

3

All-cause admissions following a first ever exacerbation-related hospitalization in COPD

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Abstract

Background: Hospital admissions are important contributors to the overall burden of chronic obstructive pulmonary disease (COPD). Understanding the patterns and causes of hospital admissions will help to identify targets for preventive interventions. This study aimed to determine the five-year all-cause hospital admission trajectories of patients with COPD following their first-ever exacerbation-related hospitalization.

Methods: Patients with COPD were identified from the Danish national registries. Patients experiencing their first-ever exacerbation-related hospitalization, defined as the index event, between 2000 and 2014 were included. All-cause hospital admissions were examined during a subsequent five-year follow-up period, and categorized using the International Classification of Diseases, 10th revision (ICD-10).

Results: In total, 82964 patients with COPD were included. The average age was 72 (SD 10) years and 48% was male. Comorbidities were present in 58%, and 65% of the patients collected inhalation medication ≤6 months prior to the index event. In total, 337066 all-cause hospital admissions were identified, resulting in a five-year admission rate of 82%. Most admissions were due to non-respiratory causes (59%), amongst which cardiac events were most common (19%).

Conclusions: Hospital admissions following a first exacerbation-related hospitalization are common, non-respiratory events constitute the majority of admissions. Besides the respiratory causes, treatment targeting the non-respiratory causes of hospital admission should be considered to effectively decrease the burden of hospitalization in COPD.

Background

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) play a central role in the clinical course and disease-burden of the condition. Each event induces a decline in lung function, physical activity, mental health and overall quality of life which enhance the risk of further and substantially earlier AECOPD, as well as death.[1, 2] Moreover, the degree of the disease severity contributes to the risk of AECOPD hospital admission. Indeed, the hospitalization rate increases from 11% to 54% in patients with incrementing airflow limitation from moderate to very severe COPD, respectively.[3] The prognosis of hospitalized AECOPD is poor. In-hospital mortality rates of up to 10%[4], and two-year post-discharge mortality rates of 36% have been reported.[5] Furthermore, patients hospitalized due to AECOPD are significantly predisposed to hospital readmission. Approximately one-third of patients is readmitted within 90 days.[6] As such, exacerbation-related hospitalizations contribute to the majority of COPD-related healthcare costs.[7]

Patients with COPD often suffer from multiple comorbidities.[8] A recent systematic review and meta-analysis concluded that comorbidities were the most-commonly reported significant risk factor associated with 30- and 90-day all-cause hospital readmission following exacerbation-related hospitalization.[9] Other major risk factors include prior exacerbations and hospitalizations, as well as prolonged length of hospital stay.[9] Whilst comorbidities may play a role in the susceptibility to readmission following exacerbation-related hospitalization, AECOPD itself may also affect comorbidities. Exacerbation-related systemic manifestations, such as systemic inflammation, physical inactivity as well as pharmacological therapy with high-dose β_2 agonists may result in the onset and/or aggravation of metabolic and cardiovascular comorbidities, both during and after AECOPD.[1, 10-12] Hence, whilst hospital readmissions for AECOPD are common, the causes of hospital admission following exacerbation-related hospitalization may well extend beyond the lungs.[13]

To the best of our knowledge, the trajectories from first-ever exacerbation-related hospitalization to subsequent all-cause hospital admissions have not been studied to date. Therefore, the primary aim of this study is to explore the all-cause hospital admissions of patients with COPD in the first five years after their first exacerbation-related hospitalization.

Secondary aims are to study the differences between the short- and long-term, and frequently and less-frequently admitted patients.

Methods

Study design and ethical approval

This Danish nationwide observational population-based study used a retrospective follow-up design. Retrospective registry research does not require ethical approval by Danish law. Access to the data was granted by the Capital Region of Denmark (approval number P-2019-191). This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study setting

All 5.33 million (anno 2000) Danish citizens have a unique civil personal registration number (CPR) which is used as an identifier in the Danish registries. All citizens have access to free health care which is financed through the Danish taxpaying system. Medical doctors do not have financial incentives to admit patients within this system. The CPR number was used to identify individuals across multiple different Danish registries.[14]

Data sources

Information on hospital admissions and preexisting comorbidities was gathered from the Danish National Patient Registry (DNPR) using the ICD-10 discharge diagnosis.[14] The Danish National Prescription Registry was used to gather information on medication use collected in the 6 months prior to the index admission. The Danish Cause of Death Registry was used to gather the date of death. Finally, information on age, sex and educational level was gathered from The Statistics of Denmark Registry.

Study population

Patients with COPD admitted to any Danish hospital for their first-ever (i.e. lifetime) exacerbation-related hospitalization, also referred to as the index event, between January 1, 2000, and January 29, 2014, were included in the current study. Therefore, all first-time acute

hospital episodes with a primary discharge diagnosis of COPD (J44), or a primary discharge diagnosis of acute respiratory failure (J96) or pneumonia (J13-J18) in combination with a secondary diagnosis of COPD were retrieved. These diagnostic criteria were previously validated with a predictive value ≥90%.[15] Only admissions to a department with 24-hour surveillance (hereby excluding emergency room contacts not leading to admission) were recorded to enhance the comparability of the current cohort. As such, emergency room visits have been without prior visitation in Denmark for a greater part of the inclusion period. Therefore, visits without subsequent admission would include a number of moderate AECOPD. Furthermore, patients aged below 40 or above 90 years, and patients with chronic asthmatic bronchitis (J44.8B) or a (previous) diagnosis of asthma (J45) were excluded.

Outcomes and definitions

The primary outcome was all-cause hospital admission during a subsequent five-year follow-up period after the first exacerbation-related hospitalization. Mortality was explored during the same period. Admission causes were characterized according to their ICD-10 code: an overview is provided in online supplementary table 1. Specific diagnoses were characterized using the first subsequent digit. As such, respiratory related admissions were characterized using the ICD-10 code J, whereas specific diagnoses such as acute infections of the upper respiratory tract would be denoted by J0-J06. The diagnostic codes H, L, O-Q and Z were combined in the 'other' cluster due to their low incidence. Short- and long-term outcomes were characterized by 30-day and five-year time-windows, respectively. Furthermore, frequently admitted patients were characterized by four or more admissions whereas less-frequently admitted patients were characterized by three or less admissions during follow-up.

Data collection

The following data was recorded from the index event: date of admission and discharge, discharge diagnosis and time until discharge. Time till first readmission was calculated based on the time between discharge from the index event and the admission date of the first admission. Likewise, time till death was calculated based on the time between discharge from the index event and the date of death.

Basic characteristics included age, sex, educational level according to the International Standard of Education (ISCED)[16]: lower secondary education (0-2), upper secondary education (3), tertiary education or Bachelor's degree (5-6) and Master's or Doctoral degree (7-8). Please note that ISCED level 4 is not a part of the Danish education system. In addition, cohabitation status (i.e. living alone or together) and comorbidities ≤5 years prior to the index admission (using the Charlson Comorbidity Index [CCI][17]) were collected. Of note, the comorbidities anxiety, depression, and diabetes were defined using both the DNPR (for the corresponding ICD-10 codes) and the Danish National Prescription Registry for the corresponding medications (using the anatomic therapeutic chemic codes N05B, NO6A and A10, respectively). Furthermore, use of inhalation medication ≤6 months prior to the index admission was recorded as the following exclusive categories: short acting β2 agonist (SABA); long-acting muscarinic agonist (LAMA); long acting β2 agonist (LABA); inhaled corticosteroid (ICS); LAMA/LABA; ICS/LAMA; ICS/LABA; triple therapy (LAMA/LABA/ICS), and no treatment.

Statistical analysis

Continuous variables were presented using mean and standard deviation (SD) when normally distributed, otherwise using median and interquartile ranges (IQR). Categorical data was presented using absolute counts and relative percentages. Admission and mortality rates were displayed using two distinct methods. First, cumulative incidence plots of first-time all-cause hospital admission and mortality were created for the five-year follow-up period. The Aalen-Johanson estimator was used to account for competing risk of death in the all-cause admissions curve. Secondly, admission and mortality trajectories after the index event were displayed irrespective of time using Sankey diagrams. Furthermore, mean cumulative counts were displayed using the mean cumulative function.[18] The 95% confidence interval (CI) was constructed assuming Poisson distribution. The median admission rate per patient was simultaneously calculated as ([total admissions/days till death or end of follow-up period])/[365.25*5]). Corresponding IQR were created. Data management and analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R (version 4.0.3).

Results

A total of 96335 patients with COPD experienced their first-ever exacerbation-related hospitalization during 2000-2014 in Denmark. After excluding patients aged below 40 or above 90 years, patients with chronic asthmatic bronchitis (J44.8B) or a (previous) diagnosis of asthma (J45), a total of 82964 patients were included (Figure 1). An overview of the characteristics of these patients at the index event is provided in table 1. Briefly, the average age of the population was 72 ± 10 years, and there was no sex predominance. The majority collected any inhalation medication in the six months prior to the index event (65.2%) and had at least one preexisting comorbidity (57.5%). Chronic heart failure, (complicated) diabetes and cerebrovascular disease were most prevalent.

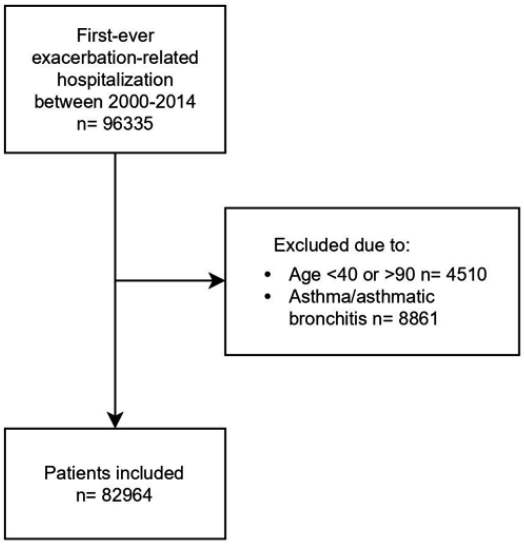

Fig 1. Flowchart of the study population

Table 1. Baseline characteristics of patients with COPD at their first exacerbation-related hospitalization

		Total (n= 82964)
Age	Years	72.2 ± 10.2
Sex	Male	39716 (47.9)
	Female	43248 (52.1)
Education[1]	Lower secondary education	45900 (61.0)
	Upper secondary education	22985 (30.6)
	Tertiary education or Bachelor degree	5246 (7.0)
	Master's or Doctoral degree	1083 (1.4)
Cohabitation status[2]	Living alone	39765 (53.8)
	Living together	34178 (46.2)
Inhalation medication	SABA	7160 (8.6)
	LAMA	4490 (5.4)
	LABA	2704 (3.3)
	ICS	8105 (9.8)
	LAMA and LABA	1120 (1.3)
	LAMA and ICS, or LABA and ICS	17031 (20.5)
	Triple therapy	13510 (16.3)
	Inhalation medication, total	54120 (65.2)
	No treatment	28844 (34.8)
Comorbidities	Chronic heart failure	13692 (16.5)
	(Complicated) Diabetes	10137 (12.2)
	Cerebrovascular disease	9059 (10.9)
	Peripheral vascular disease	8293 (10.0)
	Cancer	7886 (9.5)
	Myocardial infarction	6551 (7.9)
	Depression	4334 (5.2)
	Peptic ulcer disease	4264 (5.1)
	Rheumatic diseases	3459 (4.2)
	Chronic renal disease	2822 (3.4)
	Dementia	2342 (2.8)
	Anxiety	2310 (2.8)
	(Severe) Hepatic disease	1523 (1.8)
	Metastatic cancer	1102 (1.3)
	Hemiplegia	277 (0.3)
	AIDS	82 (0.1)
Comorbidities, total	0	35256 (42.5)
	1	20499 (24.7)
	2	12901 (15.6)
	≥3	14308 (17.2)
Characteristics index event		
Time until discharge	Days	4 [2, 8]

Total (%), mean ± SD and median [IQR] are presented. [1]n total=75214. [2]n total=73943. Abbreviations: ICS; inhaled corticosteroid, LABA; long-acting β2 agonist, LAMA; long-acting muscarinic antagonist, SABA; short-acting β2 agonist.

In total, 56.0% (95% CI 55.6-56.3) of patients had been admitted during the first 12 months after hospital discharge from the index event (Figure 2A). After five years of follow-up, 81.8% (95% CI 81.6-82.1) of patients had been admitted. Moreover, 5.5% (4554/82964) died during the index event. An additional 4029 patients died during the first 30 days post-discharge, resulting in a 30-day mortality rate of 10.4%. After five years of follow-up, 58.2% of patients had died (Figure 2B).

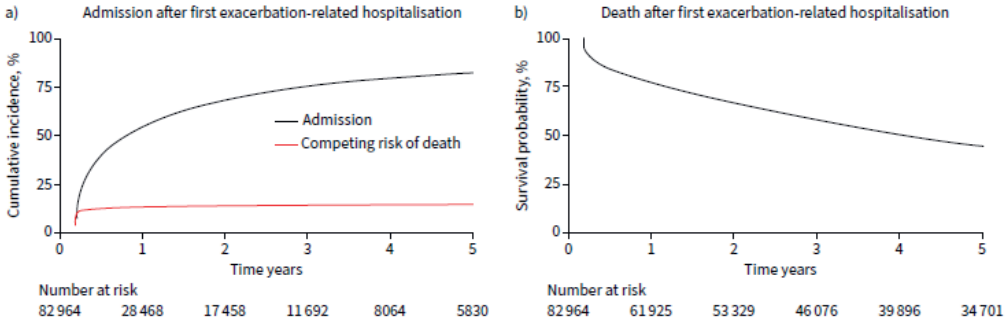

Fig 2. A: Five-year cumulative incidence of experiencing a first all-cause hospital admission after hospital discharge from the index event. B: Five-year survival probability.

The cumulative average of the total number of hospital admissions during the first 30 days post-discharge was 0.27 (95% CI 0.27-0.28) per patient (Figure 3). A linear increase in the mean cumulative count was observed over time. After five years of follow-up, the mean cumulative number of hospital admission was 6.4 (95% CI 6.4-6.4), which corresponds to the median admission rate of 6 (IQR 2-14) per patient.

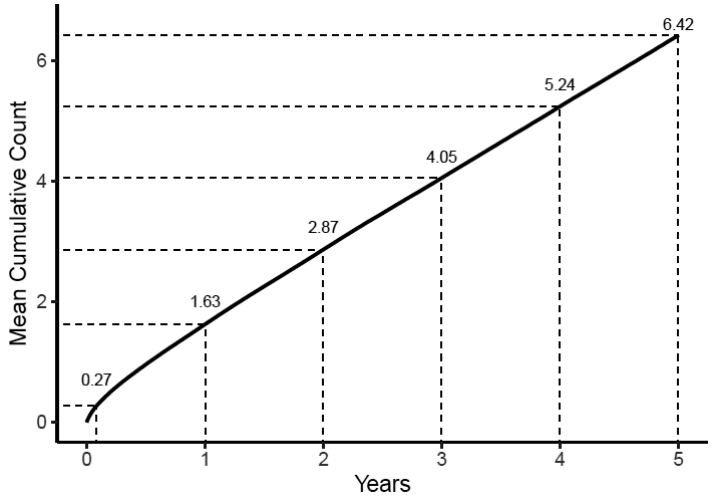

Fig 3. Mean cumulative count of subsequent hospital admissions during the five-year follow-up.

Irrespective of time, 81.8% of patients (67882/82964) had experienced at least one subsequent hospital admission, 7.0% of patients (5821/82964) had not been admitted and 11.2% of patients (9261/82964) had died (Figure 4). Looking at the proportion of patients that had been admitted, non-respiratory admissions accounted for 57.2% (38852/67882) of the first hospital admission. Of these non-respiratory causes, cardiac-related events were most common (21.0% [8174/38852]). Respiratory causes accounted for 42.8% (29030/67882) of the first admission. Similar patterns were observed during subsequent admissions: non-respiratory causes remained the main cause of a second and third hospital admission.

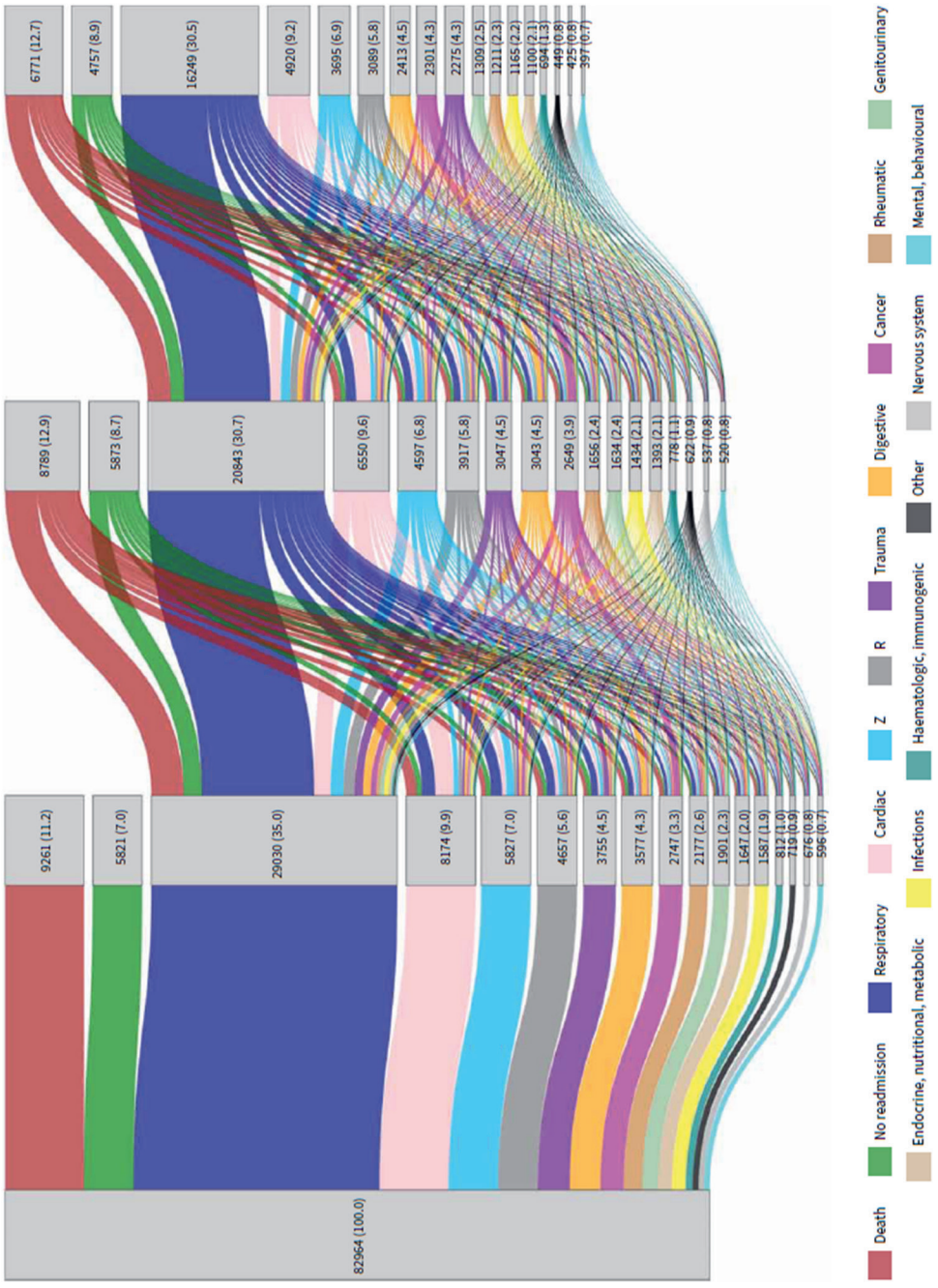

Fig 4. Sankey diagram displaying the diagnoses of the first three hospital admissions after the index event. Total number of patients (%) are presented.

A similar distribution of the main diagnostic clusters was observed during the first 30 days post-discharge compared to five years post-discharge after the index event (Table 2). Cardiac events remained the main non-respiratory cause of hospital admission over time (18.5% [36586/337066-139272]). The specific diagnoses of the two most common diagnostic clusters are shown in Figure 5.

Table 2. Short-term (30-days post-discharge) versus long-term (five-years post-discharge) diagnoses of subsequent hospital admissions

	30-day	**5-year**
Total number of admissions	20894	337066
Respiratory	10194 (48.8)	139272 (41.3)
Cardiac	2419 (11.6)	36586 (10.9)
Other	1900 (9.1)	33149 (9.8)
Symptoms and signs not elsewhere classified	1406 (6.7)	25551 (7.6)
Cancer	963 (4.6)	16751 (5.0)
Digestive	854 (4.1)	18621 (5.5)
Trauma	648 (3.1)	16915 (5.0)
Infections	548 (2.6)	9180 (2.7)
Endocrine, nutritional, metabolic	544 (2.6)	8834 (2.6)
Genitourinary	530 (2.5)	10655 (3.2)
Musculoskeletal, connective tissue	262 (1.3)	8917 (2.6)
Mental, behavioral	209 (1.3)	3678 (1.1)
Hematologic, immunogenic	245 (1.2)	5674 (1.7)
Nervous system	172 (0.8)	3283 (1.0)

Total (%) are presented.

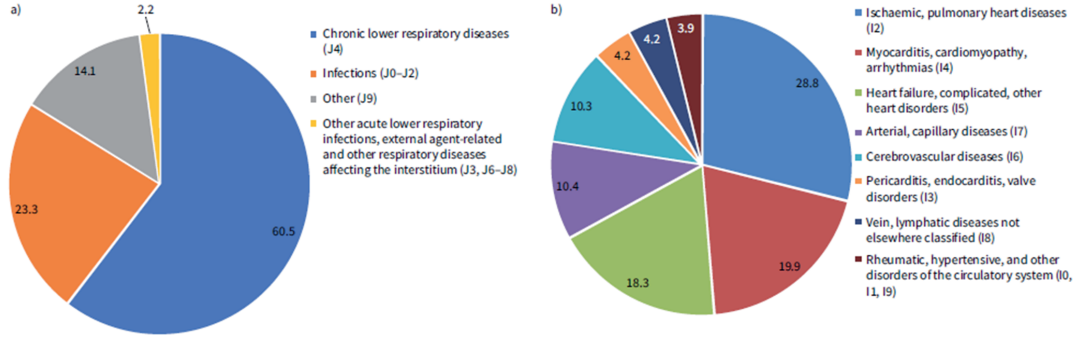

Fig 5. Specific diagnoses of the two most common causes of hospital admission at the end of the five-year follow-up. Relative percentages of the total number of admissions are presented. A: Specific diagnoses of the 139272 respiratory-related admissions. B: Specific diagnoses of the 36586 cardiac-related admissions.

At the end of follow-up, 80.9% of all admissions occurred in a group of frequently admitted patients experiencing four or more hospital admissions. Differences in baseline characteristics were observed between the frequently and less-frequently admitted patients (Table 3). As such, the number of patients without preexisting comorbidities surviving follow-up was higher in the less-frequently admitted patients compared to the frequently admitted patients. Moreover, the average age was highest in the less-frequently admitted patients not surviving follow-up. In this view, regardless of the number of admissions, the patients not surviving follow-up were older, had more comorbidities and a longer hospital stay during the index event compared to the surviving patients.

Table 3. Baseline characteristics of the frequently (≥4 admissions) and less-frequently (≤3 admissions) admitted patients during the five-year follow-up period

		≤3 admissions		≥4 admissions		
		Alive (n=20200)	**Death (n=29937)**	**Alive (n=14466)**	**Death (n=18361)**	**Total (n=82964)**
Age	Years	67.5 ± 10.5	76.3 ± 8.7	68.7 ± 10.1	73.5 ± 9.1	72.2 ± 10.2
Sex	Male	8484 (42.0)	15173 (50.7)	6459 (44.6)	9600 (52.3)	39716 (47.9)
	Female	11716 (58.0)	14764 (49.3)	8007 (55.4)	8761 (47.7)	43248 (52.1)
Education[1]	Lower secondary education	11053 (58.0)	16520 (63.6)	8097 (59.6)	10230 (61.7)	45900 (61.0)
	Upper secondary education	6182 (32.4)	7376 (28.4)	4365 (32.1)	5062 (30.5)	22985 (30.6)
	Tertiary education or Bachelor degree	1540 (8.1)	1668 (6.4)	970 (7.1)	1068 (6.4)	5246 (7.0)
	Master's or Doctoral degree	295 (1.5)	397 (1.5)	162 (1.2)	229 (1.4)	1083 (1.4)
	n[1]	19070	25961	13594	16589	75214
Cohabitation status[2]	Living alone	9473 (47.0)	13305 (62.1)	7204 (49.8)	9783 (54.6)	39765 (53.8)
	Living together	10677 (53.0)	8111 (37.9)	7253 (50.2)	8137 (45.4)	34178 (46.2)
	n[2]	20150	21416	14457	17920	73943
Inhalation medication	SABA	2033 (10.1)	2363 (7.9)	1264 (8.7)	1500 (8.2)	7160 (8.6)
	LAMA	987 (4.9)	1746 (5.8)	722 (5.0)	1035 (5.6)	4490 (5.4)
	LABA	705 (3.5)	909 (3.0)	495 (3.4)	595 (3.2)	2704 (3.3)
	ICS	2306 (11.4)	2562 (8.6)	1511 (10.4)	1726 (9.4)	8105 (9.8)
	LAMA and LABA	231 (1.1)	382 (1.3)	216 (1.5)	291 (1.6)	1120 (1.3)
	LAMA and ICS, or LABA and ICS	4112 (20.4)	5705 (19.0)	3306 (22.8)	3908 (21.3)	17031 (20.5)
	Triple therapy	2582 (12.8)	4764 (15.9)	2510 (17.4)	3654 (19.9)	13510 (16.3)
	Inhalation medication, total	12956 (64.1)	18431 (61.6)	10024 (69.3)	12709 (69.2)	54120 (65.2)
	No treatment	7244 (35.9)	11506 (38.4)	4442 (30.7)	5652 (30.8)	28844 (34.8)
Comorbidities, total	0	12843 (63.6)	9597 (32.1)	6683 (46.2)	6133 (33.4)	35256 (42.5)
	1	4400 (21.8)	7594 (25.4)	3855 (26.6)	4650 (25.3)	20499 (24.7)
	2	1825 (9.0)	5675 (19.0)	2064 (14.3)	3337 (18.2)	12901 (15.6)
	≥3	1132 (5.6)	7071 (23.5)	1864 (12.9)	4241 (23.1)	14308 (17.2)

Characteristics index event						
Time until discharge	Days	3 [1, 7]	6 [2, 10]	4 [1, 7]	5 [2, 8]	4 [2, 8]
Time until death	Days		177 [20, 656]		969 [566, 1,379]	

Total (%), mean ± SD and median [IQR] are presented. [1,2] n is stated otherwise. Abbreviations: ICS; inhaled corticosteroid, LABA; long-acting β2 agonist, LAMA; long-acting muscarinic antagonist, SABA; short-acting β2 agonist.

Discussion

This study showed the five-year all-cause hospital admission trajectories of more than 80000 patients with COPD following their first-ever exacerbation-related hospitalization. The vast majority of patients had been admitted to the hospital for any cause five years after their first exacerbation-related hospitalization. Whilst the causes of hospital admission varied widely, more than half of the admissions were non-respiratory. Furthermore, more than half of the patients had died during follow-up. To the best of our knowledge, this is the first study to demonstrate the all-cause hospital admission trajectories of patients with COPD following their first-ever exacerbation-related hospitalization.

For many years it has been well established that after an exacerbation-related hospitalization patients with COPD will be admitted for a subsequent AECOPD.[2, 4, 6] As such, the main goals in treating AECOPD are to minimize the negative impact of the current event and to prevent subsequent events.[19] In this study we showed that, not surprisingly, respiratory admissions were most frequent. However, non-respiratory admissions accounted for the majority of subsequent admissions, both on the short- and long-term. Indeed, we demonstrated the patterns of incidence over time. Hence, it could be observed that admissions related to cancer, the digestive- and genitourinary tract became more incident over time. These findings hold important implications for clinical practice, challenging the current global post-AECOPD management goals.

The most common non-respiratory cause of hospital admission included cardiac events: ischaemic- and pulmonary heart diseases followed by myocarditis, cardiomyopathy and arrhythmias were most common. Indeed, cardiac diseases remain the leading cause of death worldwide.[20] With an estimated prevalence ranging from 30% to 60%, COPD and cardiac diseases frequently co-occur.[21, 22] This relationship is likely owned by shared risk factors such as smoking, low physical activity as well as persistent low-grade pulmonary and systemic inflammation.[21] Additionally, cardiac related conditions are important differential diagnoses of AECOPD, underlining the challenges associated with the current AECOPD definition.[19] Indeed, the question may arise to what extent the index AECOPD may have been affected by preexisting, or concurrent cardiovascular diseases, and whether such cardiovascular diseases

were misclassified as AECOPD during the index admission. The current real-world data reflects the diagnostic difficulties clinicians are faced with. Nevertheless, it is unlikely that such single misclassifications have had an impact on the outcomes of the current study given its substantial cohort size. More so, we believe that these results are a true reflection of the impact of cardiac comorbidities on the need for hospitalization in patients with COPD.

Research has pointed out that comorbidities, previous AECOPD and hospitalizations as well as an increased length of hospital stay are major risk factors for all-cause hospital readmission following exacerbation-related hospitalization.[9] In line with previous studies[23], more than half of the patients in the current study had one or more preexisting comorbidity. One might question whether these comorbidities rather than the AECOPD per se were the major driver of the observed subsequent hospital admission(s). Yet, previous research in patients with COPD showed that AECOPD confer an increased risk of subsequent cardiovascular events, regardless of preexisting cardiac comorbidities.[24] The current findings may therefore substantiate the previously identified increased risk of cardiovascular events following AECOPD.

Other non-respiratory causes of hospital admission included e.g. cancer, digestive- and genitourinary disorders. Close to one-third of the cancer-related admissions were driven by malignancies of the respiratory and intrathoracic organs. Indeed, patients with COPD are at high risk of lung cancer, irrespective of smoking status.[25] However, digestive- and genitourinary related admissions are unreported in the current literature. Future studies are indicated to explore the mechanisms linking these types of admissions to AECOPD.

Respiratory-related admissions contributed to less than half of the observed admissions. The majority could be attributed to chronic lower respiratory diseases followed by acute respiratory infections. It is well recognized that a history of AECOPD predisposes patients to subsequent AECOPD[3], and that respiratory infections trigger these events.[26] Indeed, the majority of the observed respiratory admissions was exacerbation-related.

Besides their cause, it is essential to understand the timing and rates of hospital admissions whilst striving to reduce their occurrence. The current study showed that most patients

experienced their first hospital admission within the first year after hospital discharge from the index event. A linear increase in the cumulative average of the total number of admissions was observed over time. By the end of follow-up, the average number of admissions was six per patient. These findings underline the need for close monitoring, especially in the first year after AECOPD hospital discharge.

We noted an in-hospital mortality rate of 5.5% during the index event. This is in line with previously reported in-hospital mortality rates of first-ever hospitalized AECOPD.[27, 28] Importantly, although mortality rates are heterogeneous across studies, similar in-hospital mortality rates were reported among patients with a (severe) AECOPD history.[4] Moreover, the observed long-term mortality rates are in accordance with previous reports[29, 30], underlining the external validity of our findings. Thus, the prognosis of patients with COPD at their first exacerbation-related hospitalization may be as poor as during subsequent events, both during and after hospitalization.

A substantial part of the population had died after less than four subsequent admissions. We noted that, consistent with the general population[31], the worst prognosis (i.e. death) was not necessarily related to the number of admissions but rather to an older age, a higher number of comorbidities and a longer duration of hospital stay during the index event. These findings highlight the need to incorporate these well recognized risk factors of mortality after exacerbation-related hospitalization in discharge planning.[32] Moreover, over 30% of patients did not use inhalation medication prior to the index event. This group includes patients without a prior diagnosis of COPD, and non-adherent patients, indicating a need for earlier diagnosis and improved adherence. It may also represent a group of patients with mild disease, who have not received treatment for COPD. The likelihood of another respiratory admission may therefore be less likely, which could have contributed to the observed high number of non-respiratory admissions. However, our findings do underline that morbidity in COPD may not only be contributed to the disease itself.

Several strengths and limitations should be noted. A major strength of the current study was its unique national hospital dataset covering all first-time exacerbation-related hospitalizations in Denmark between 2000 and 2014. The substantial sample size and follow-

up period allowed us to study the nationwide all-cause hospital admission trajectories following this index event. At the same time, the dataset presented important limitations. First, the dataset was administrative in nature and did not include information on certain clinical data (e.g. spirometry). The current definition used to characterize a (first) exacerbation-related hospitalization has been widely used in Danish registry research and was previously validated (i.e. >90% positive predictive value).[15] Yet, some inaccuracy is introduced which should be taken into consideration when interpreting the results. Furthermore, this study did not differentiate between less severe and very severe hospital admissions. To limit this bias, only admissions to a department with 24-hour surveillance were counted. Moreover, given that approximately 10% of patients had died after each hospital admission may indicate that these events were likely less severe. In this view, and whilst a control population was currently missing, the prognosis of more severe procedures is worse for patients with COPD than for patients without COPD.[33]

Conclusions

Taken together, we showed that all-cause hospital admissions following a first exacerbation-related hospitalization are common and predominantly caused by non-respiratory events. Hence, besides the respiratory causes, treatment targeting the non-respiratory causes of hospital admission should be considered to effectively decrease the burden of hospitalization in COPD. Awareness amongst clinicians should be raised to proactively and comprehensively screen patients before hospital discharge, and to monitor patients accordingly post-discharge. The current findings show that particularly cardiac comorbidities should be monitored. This knowledge should be included in the patient's written action plans.

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Online Supplement

Methods

Table S1. Diagnoses and corresponding ICD-10 codes used to characterize the causes of hospital admission following the index event

	ICD-10 code
Infections and parasitic diseases	A00-B99
Neoplasms	C00-D48
Hematologic, immunogenic diseases	D50-D89
Endocrine, nutritional, metabolic diseases	E00-E90
Mental and behavioral disorders	F00-F99
Diseases of the nervous system	G00-G99
Diseases of the eye and adnexa	H00-H59
Diseases of the ear and mastoid	H60-H95
Diseases of the circulatory system	I00-I99
Diseases of the respiratory system	J00-J99
Diseases of the digestive system	K00-K93
Diseases of the skin and subcutaneous tissue	L00-L99
Diseases of the musculoskeletal system and connective tissue	M00-M99
Diseases of the genitourinary system	N00-N99
Pregnancy, childbirth and the puerperium	O00-O99
Conditions originating in the perinatal period	P00-P96
Congenital malformations, deformations, and chromosomal abnormalities	Q00-Q99
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	R00-R99
Trauma and accidents	S00-T98, X00-X99
Factors influencing health status and contact with health services	Z00-Z99

CHAPTER 4

4

CHAPTER 5

5

Alterations in plasma hyaluronic acid in patients with clinically stable COPD versus (non)smoking controls

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Abstract

Hyaluronic acid (HA) is a key component of the extracellular matrix. HA and its metabolism are suggested to be altered in the lungs of patients with chronic obstructive pulmonary disease (COPD). The present study explored systemic HA, and its metabolic regulators, in patients with clinically stable COPD and smoking and non-smoking controls. Furthermore, associations of HA with acute exacerbations (AECOPD), airway-related hospitalizations, systemic inflammation and cardiovascular risk were studied. In total, 192 patients with moderate to very severe COPD (aged 62.3 y (± SD 7.0)), 84 smoking controls (aged 61.8 y (± 5.7)), and 107 non-smoking controls (aged 60.1 y (± 7.0)) were included. Plasma HA was reduced in patients with COPD compared to non-smoking controls (p=0.033), but was comparable after adjusting for age and sex. Expression of HAS-3 did not differ between groups, but was substantially less detectable in more patients with COPD than (non)smoking controls (p<0.001). Expression of HYAL-2 was enhanced in patients with COPD versus smoking (p=0.019) and non-smoking (p<0.001) controls, also in the age- and sex- adjusted model (p<0.001). Plasma HA was not associated with AECOPD, airway-related hospitalizations in the previous year, or systemic inflammation in COPD. Arterial pulse wave velocity explained some of the variance (<10%) in plasma HA (p=0.006). Overall, these results indicate that expression of HYAL-2, but not plasma HA nor HAS-3, is enhanced in patients with COPD compared to (non)smoking controls. Furthermore, HA was not associated with clinical outcomes, yet, cardiovascular risk might play a role in its systemic regulation in stable COPD.

Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous chronic lung disease that is characterized by persistent airflow limitation and respiratory symptoms.[1-3] At present, there is a growing understanding of the essential role of extracellular matrix (ECM) integrity in the pathophysiology of COPD.[4-10] Attracting a particular interest is the ECM's most abundant non-sulphated glycosaminoglycan (GAG) hyaluronic acid (HA), or also referred to as hyaluronan. Depending on its molecular size, HA may exert different biological functions.[5, 6, 11] As such, high-molecular weight (HMW) HA (>500 kDa) has anti-inflammatory and immunosuppressive properties and contributes to tissue hydration and stability, whereas low-molecular weight (LMW) HA (<250 kDa) is positively associated with inflammation and tissue injury.[6, 12-14]

The role of HA in COPD is still largely unknown. Several studies have reported increased HA, in particular LMW, in the lungs of patients with COPD[12, 15], whereas others showed decreased levels in isolated airway smooth muscle cells (ASMCs).[16] Moreover, alterations in the expression and activity of the enzymatic regulators of HA metabolism, HA synthases (HAS) and hyaluronidases (HYAL), have been reported in the lungs[15] and ASMCs of patients with COPD[16], as well as in cigarette smoke-exposed mice[17] and primary human lung-derived models.[18] The intracellular synthesis of HA is conducted by HAS, whereas HYAL metabolically degrade HA[6], each isoform at a distinct catalytic rate, yielding HA of distinct molecular masses.[19, 20] The formation of smaller fragments of HA is now suggested to contribute to the continuation of inflammation.[6, 19, 21-23]

Indeed, positive associations of pulmonary HA with local inflammation and decreased lung function have been reported in COPD.[12, 13, 15] Furthermore, HA seems to be associated with acute exacerbations of COPD (AECOPD). These episodic acute events, that are characterized by increased respiratory symptoms, play a pivotal role in the natural course of COPD and worsen quality of life and physical activity.[1] Also, they are associated with increased risk of hospitalization, disease progression and mortality, and significantly contribute to healthcare costs.[3, 24, 25] During these events, increased HYAL activity and subsequent degradation of HA were observed in the lungs of patients with COPD, and therefore suggested as potential targets to control airway inflammation and remodeling.[12] These findings were recently also

shown, for the first time, in serum of exacerbating patients with COPD.[11] Hence, the potential of HA to serve as a biomarker of COPD disease severity and/or progression, was suggested. However, the role and clinical usefulness of HA as biomarker remains unknown while case-control studies remain lacking.

Furthermore, although COPD, particularly during AECOPD, is characterized by transiently increased airway- and systemic inflammation[1, 24], which may result in decreased integrity of the ECM[6, 26-29], systemic HA was shown not to be associated with emphysema[11, 12] and may therefore not originate from degradation of the parenchymal ECM. Instead, a cardiovascular origin seems plausible since cardiovascular pathologies are highly associated with dysfunction and degradation of the HA-rich endothelial glycocalyx.[30, 31] Indeed, individuals at increased cardiovascular risk exhibit increased serum HA.[32] Though, degradation of the endothelial glycocalyx can also be inflammatory-mediated.[30, 31, 33] Moreover, circulating immune cells may be a direct source of HA due to their CD44 dependent pericellular HA-rich coat.[6, 21, 34-37] Finally, immune cells may also exhibit HYAL activity[38, 39], which might further enhance systemic levels of HA by increased HA fragmentation.[6, 20] Taken together, a cardiovascular and/or systemic inflammatory origin of systemic HA is presumable, yet it is unexplored.

The present study was designed to assess 1) whether, and to what extent, systemic HA and HA metabolism differ between patients with COPD and (non)smoking controls, and 2) to study the associations of HA with AECOPD frequency, airway-related hospitalizations, systemic inflammation and cardiovascular risk in COPD. We hypothesize that systemic HA is increased, and related to the number of past AECOPD and airway-related hospitalizations, in patients with COPD. Moreover, a shared cardiovascular and systemic inflammatory origin is expected.

Methods

Study population

The present study is a *post-hoc* cross-sectional analysis of baseline data of the "Individualized COPD Evaluation in relation to Ageing" (ICE-Age) study; a single-center, longitudinal, observational study conducted between December 2010 and August 2016 at Ciro, a tertiary care center for patients with chronic respiratory diseases in Horn, the Netherlands. The ICE-

Age study was approved by the local ethics and review board of the Maastricht University Medical Centre (Maastricht, The Netherlands; MEC 10-3-033) and is ISRCTN registered (ISRCTN86049077). The ICE-Age study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Detailed information about the aims, inclusion and exclusion criteria of the ICE-Age study has previously been described elsewhere.[40, 41]

Clinical characteristics

Demographics and clinical characteristics were collected[40, 41], please visit the online supplement for an overview. Of note, clinical stability, defined by the absence of respiratory tract infection or exacerbation for <4 weeks before study entry, had to be met for patients with COPD to be included in the ICE-Age study. The number of AECOPD in the previous 12 months was documented at study entry and relied on self-report.[40] An exacerbation was defined by the acute need of oral glucocorticosteroids or antibiotics and/or hospitalization, due to acute respiratory worsening. Based on the Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document[1] the following subgroups were identified; infrequent exacerbators (i.e. patients experiencing <2 AECOPD in the past year) and frequent exacerbators (i.e. patients experiencing ≥2 AECOPD in the past year). Furthermore, the number of self-reported hospital admissions for airway disease in the last 12 months was recorded. Patients with a moderate disease history (i.e. no hospital admissions in the past year) and patients with a severe disease history (i.e. ≥1 hospital admission in the past year) were identified. The control group was divided into smoking (i.e. ≥10 pack years) and non-smoking (i.e. <10 pack years) controls. Arterial pulse wave velocity (APWV)[40] was included to study cardiovascular risk. The validated threshold value of 10 m/s was used to discriminate between normal and pathological patterns.[42] Moreover, a panel of systemic inflammatory markers, including total leukocyte counts, fibrinogen, interleukin (IL) 6 and 8, tumor necrosis factor (TNF) alpha and high-sensitivity C-reactive protein (CRP)[41] were included to study the association with systemic inflammation.

Plasma HA measurements

Fasted venous blood samples were collected in ethylene diamine tetra acetic acid (EDTA) containing tubes and stored at -80°C until further analysis, as previously described.[41] Plasma samples obtained at baseline, available for secondary research were used in the present study;

only blood samples of subjects who provided written approval for use of body material for secondary research purposes were used. Natural plasma HA was measured using a solid phase HA binding protein-based sandwich enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's protocol (Hyaluronan DuoSet ELISA, R&D Systems, Minneapolis, MN, USA). Samples were measured in duplicate, and phosphate buffered saline samples were included and confirmed as negative controls. Results were analyzed in Excel (Microsoft Excel 2007, Redmond, WA, USA). The average intra-assay coefficient of variation was 12.6%. A power calculation is provided in the online supplement.

mRNA expression of HAS and HYAL

cDNA from peripheral blood mononuclear cells (PBMC) was available from a subset of subjects to measure gene expression of the enzymatic regulators of HA; HAS and HYAL. Specifically, expression levels of HAS-3 and HYAL-2 were assessed, whereas HAS-1, HAS-2 and HYAL-1 were excluded due to their lack of expression in PBMC.[43] Since HAS-3 is the most active HAS isoform[19], and due to its expression in T-cells[43], the most prominent cell type in PBMC, HAS-3 was included in the present study. Moreover, HYAL-2 is widely expressed in PBMC, including monocytes, T-cells and natural killer cells, and was therefore included as well.[43] In total, samples of 143 patients with COPD, 21 smoking controls and 20 non-smoking controls were available for the present analyses. Please see the online supplement for the quantitative polymerase chain reaction (qPCR) procedure, the primer sequences of HAS-3, HYAL-2, and the housekeeping genes ribosomal protein P0, ribosomal protein L13A and beta-globin. Of note, expression of HAS-3 was below the threshold in a substantial number of samples, please see results. However, the low expression of HAS-3 was not related to the quality of these samples since the housekeeping genes were expressed. Expression levels of HAS-3 were therefore extrapolated in these samples. Please see the online supplement for a detailed description. For visual presentation, expression levels of HAS-3 were multiplied by a factor of 1.000.000, and expression levels of HYAL-2 were multiplied by a factor of 1.000. Measurements of plasma HA as well as HAS and HYAL expression were performed in a random order and single-blinded.

Statistical analyses

Statistical analyses and visualization were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.3.5. (GraphPad Software, La Jolla, CA, USA).

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were tested for normality using the Shapiro–Wilk test and visual inspection of histograms, and were expressed accordingly as mean and standard deviation (SD), or as median and interquartile range (IQR). The Pearson Chi-Square test was used to assess differences in dichotomous variables between groups. Differences in continuous variables were analyzed using the one-way analysis of variance (ANOVA) test, Mann-Whitney U test and Kruskal-Wallis H-test, as appropriate. *Post hoc* pairwise comparisons were performed and corrected for multiple comparisons with a Bonferroni correction, adjusted *p*-values were selected. The analysis of covariance (ANCOVA) was performed to adjust for the covariates age and sex. Correlations were assessed using the nonparametric Spearman's rho correlation test. The magnitude of correlations was interpreted using Cohen's effect sizes; correlation coefficients of <0.10 represent a poor correlation, correlation coefficients of 0.30 represent a moderate correlation and correlation coefficients of >0.50 represent a strong correlation.[44]

Furthermore, multiple regressions were performed to study the association between HA and APWV, as well as markers of systemic inflammation. The dependent variable HA, and independent variables APWV, total leukocytes, fibrinogen, IL-6, IL-8, TNF-alpha and CRP were added to the regression models. Moreover, age, sex and COPD-specific medications including long-acting β2-agonists (LABA), inhaled corticosteroids (ICS) and a combination thereof were included as covariates. The latter for their known effects on HA metabolism.[45] Univariate models were performed in model 1. Significant variables were considered for inclusion in the covariate adjusted model 2. *A priori*, *p*-values ≤0.05 were considered statistically significant.

Results

Baseline clinical characteristics

In total, 192 patients with moderate to severe COPD, 84 smoking and 107 non-smoking controls were analyzed. The majority of patients with COPD and smoking controls was male, whereas non-smoking controls were mainly female and 2 years younger than patients with COPD (table 1). The vast majority of patients was classified as GOLD II, and used long-acting muscarinic antagonists (LAMA), LABA and/or ICS. Most patients were highly symptomatic as expressed by a medical research council (MRC) dyspnea score of three or higher. Furthermore,

almost half of the patients experienced two or more AECOPD in the previous year, while close to one third experienced at least one airway-related hospital admission in the last year. Smoking and non-smoking controls had significantly less pack years than patients with COPD. Finally, groups were similar in body mass index (BMI) and were mainly overweight. Please see the online supplement for baseline cardiovascular- and inflammatory measures (Table S2). Briefly, APWV, total leukocyte counts, fibrinogen, IL-8 and CRP were significantly higher in patients with COPD compared to smoking and non-smoking controls. Furthermore, TNF-alpha was significantly higher in smoking controls compared to patients with COPD.

Table 1. Baseline clinical characteristics of the 192 patients with chronic obstructive pulmonary disease (COPD), 84 smoking controls (SC) and 107 non-smoking controls (NSC).

	COPD n=192	SC n=84	NSC n=107	*p*-value
General characteristics				
Male, n (%)	111 (57.8)	49 (58.3)	38 (35.5)	<0.001[bc]
Age, years	62.3 ± 7.0	61.8 ± 5.7	60.1 ± 7.0	0.021[b]
Lung function				
FEV_1, % pred.	50.1 ± 15.5	116.9 ± 13.8	121.3 ± 15.3	<0.001[ab]
FVC, % pred.	98.0 ± 20.6	121.5 ± 15.4	125.8 ± 15.4	<0.001[ab]
FEV_1/FVC, %	41.4 ± 11.4	77.8 ± 4.2	79.4 ± 4.7	<0.001[ab]
TLCO, % pred.	55.1 ± 18.5[1] n=184	91.4 ± 12.7[1] n=83	95.1 ± 13.8	<0.001[ab]
RV, % pred.	158.1 ± 44.8[1] n=187	94.9 ± 16.5	94.8 ± 19.0	<0.001[ab]
Current smoker, n (%)	27 (14.1)	21 (25)	4 (3.7)	<0.001[abc]
Pack years	43.0 (30.8-59.0)[1] n=191	20.7 (14.1-31.9)	0.0 (0.0-3.5)[1] n=102	<0.001[abc]
Body composition				
BMI, kg/m^2	27.0 (22.9-30.4)	27.2 (25.4-29.0)	26.0 (24.0-28.4)	0.497
Laboratory				
eGFR, ml/min	76.8 (63.4-93.3)[1] n=191	86.7 (76.7-99.4)	82.9 (68.6-98.8)	<0.001[a]
ALT ♂, U/l	23.0 (17.0-31.0)[1] n=101	25.0 (18.8-31.3)[1] n=42	23.0 (19.0-30.8)[1] n=36	0.633

ALT ♀, U/l	17.0 (14.0-21.0)[1]	19.0 (15.0-24.0)[1]	17.0 (14.0-21.0)[1]	0.443
	n=76	n=35	n=67	
COPD specific characteristics				
GOLD, n (%)				
II	101 (52.6)			
III	75 (39.1)			
IV	16 (8.3)			
Total number of AECOPD in past year, n (%)*				
0	41 (22.7)			
1	54 (29.8)			
2	30 (16.6)			
≥3	56 (30.9)			
Total number of airway-related hospitalizations in past year, n (%)				
0	131 (68.9)			
1	57 (30.0)			
2	0 (0.0)			
≥3	2 (1.1)			
MRC grade, n (%)[1]				
≤2	42 (29.8)			
≥3	99 (70.2)			
	n=141			
Medication, n (%)[1]				
LAMA	153 (81.4)			
LABA	176 (93.6)			
ICS	162 (86.2)			
	n=188			

Variables are presented as n (% n), mean ±SD and median (IQR) with overall *p*-values. Abbreviations: AECOPD; acute exacerbation of COPD, ALT; alanine aminotransferase, BMI; body mass index, eGRF; estimated glomerular filtration rate, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, GOLD; global initiative for chronic obstructive lung disease, ICS; inhaled corticosteroid, LABA; long-acting β2 agonist, LAMA; long-acting muscarinic antagonist, MRC; medical research council, RV; residual volume, TLCO; transfer factor for carbon

monoxide, % pred; % of predicted. * Mild to severe AECOPD. [1] n is stated otherwise. Significant *post hoc* pairwise comparison between [a] COPD-SC [b] COPD-NSC [c] NSC-SC. *Post hoc* comparisons are corrected for multiple testing.

Plasma HA and its enzymatic regulators

Plasma HA was lower in patients with COPD compared to non-smoking controls, but did not differ compared to smoking controls, neither between both control groups (Figure 1A). However, after correcting for baseline differences in age and sex, plasma HA was comparable between patients with COPD and non-smoking controls (p=0.185). Expression of HAS-3 did not differ between the groups (Figure 1B), yet a below limit detection was observed in significantly more samples of patients with COPD (n=80, 56.0%) than smoking controls (n=7, 33.3%) and non-smoking controls (n=2, 10.0%), p<0.001. Excluding these samples, i.e. a below limit detection of HAS-3 expression, revealed enhanced expression in patients with COPD compared to smoking controls (Figure S1, online supplement), yet, no longer when adjusting for age- and sex (p=0.231). Expression of HYAL-2 was significantly higher in patients with COPD compared to both smoking and non-smoking controls, but did not differ between the control groups (Figure 1C). These findings did not change when adjusted for age and sex (p<0.001).

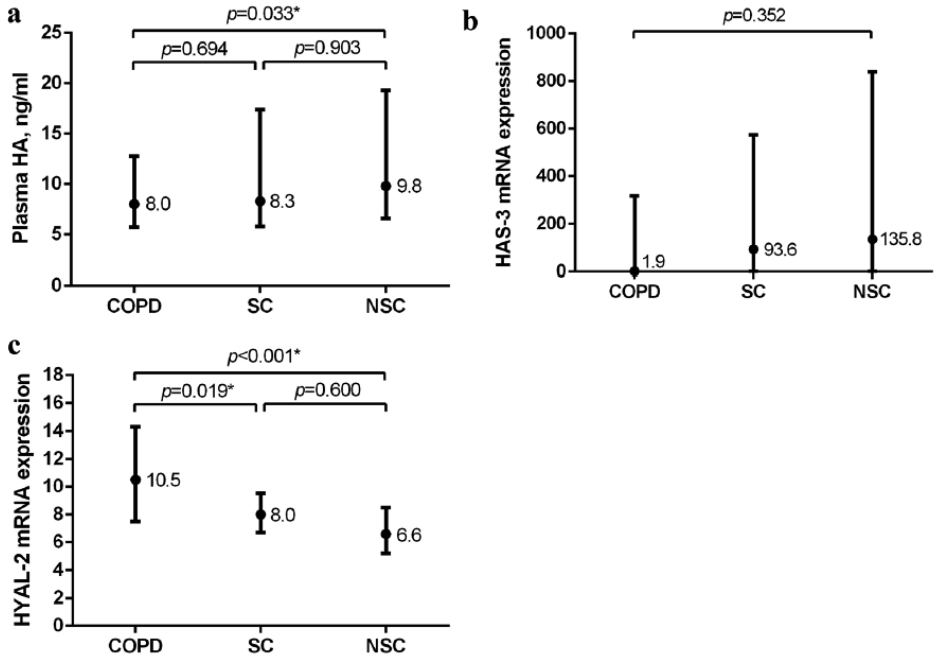

Fig 1. A) Plasma hyaluronic acid (HA) in patients with COPD (n=192), smoking controls (SC, n=84) and non-smoking controls (NSC, n=107). B) mRNA expression of HAS-3 and; C) HYAL-2 in patients with COPD (n=143), SC (n=21) and NSC (n=20). Median and interquartile ranges are presented. *Significant *post-hoc* pairwise comparison. Figures created using GraphPad Prism 8.3.5, https://www.graphpad.com/scientific-software/prism/

Subdividing the COPD group based on plasma HA levels below and above the median of 8.0 ng/ml did not reveal any differences in HAS-3 (p=0.497) or HYAL-2 (p=0.219) expression. Yet, HA was significantly correlated with HAS-3 and HYAL-2 in patients with COPD (respectively negative and positive correlations, Table S3, online supplement). Furthermore, a complete-case analysis on plasma HA, HAS-3 and HYAL-2 revealed a slightly reduced median of plasma HA in the patient group (7.18 ng/ml, n=143), whereas higher medians were found in smoking (9.02 ng/ml, n=21) and non-smoking (10.4 ng/ml, n=20) controls (p=0.040). The previously observed group differences in HAS-3 (p=0.352) and HYAL-2 expression (p<0.001) did not change in this complete-case analysis.

Association of HA with previous AECOPD and airway-related hospitalizations

No significant differences were observed in plasma HA between frequent and infrequent exacerbating patients with COPD (Figure 2A) or between patients with a moderate and severe disease history in the last year (Figure 2B). In line with these findings, no significant correlations were observed between HA and the number of AECOPD [(r=0.006, p=0.935) n=181] or airway-related hospital admissions [(r=0.142, p=0.051) n=190]. With respect to HAS-3 and HYAL-2, no significant differences were observed between frequent and infrequent exacerbating patients (Figure 2C and 2E) or between patients with a moderate and severe disease history in the last year (Figure 2D and 2F). Similarly, no significant correlations were observed between HAS-3 and HYAL-2 and the number of AECOPD [(r= -0.072, p=0.405 and r= -0.070, p=0.421 respectively) n=136] or the number of airway-related hospitalizations [(r= -0.035, p=0.681 and r= -0.008, p=0.921 respectively) n=141].

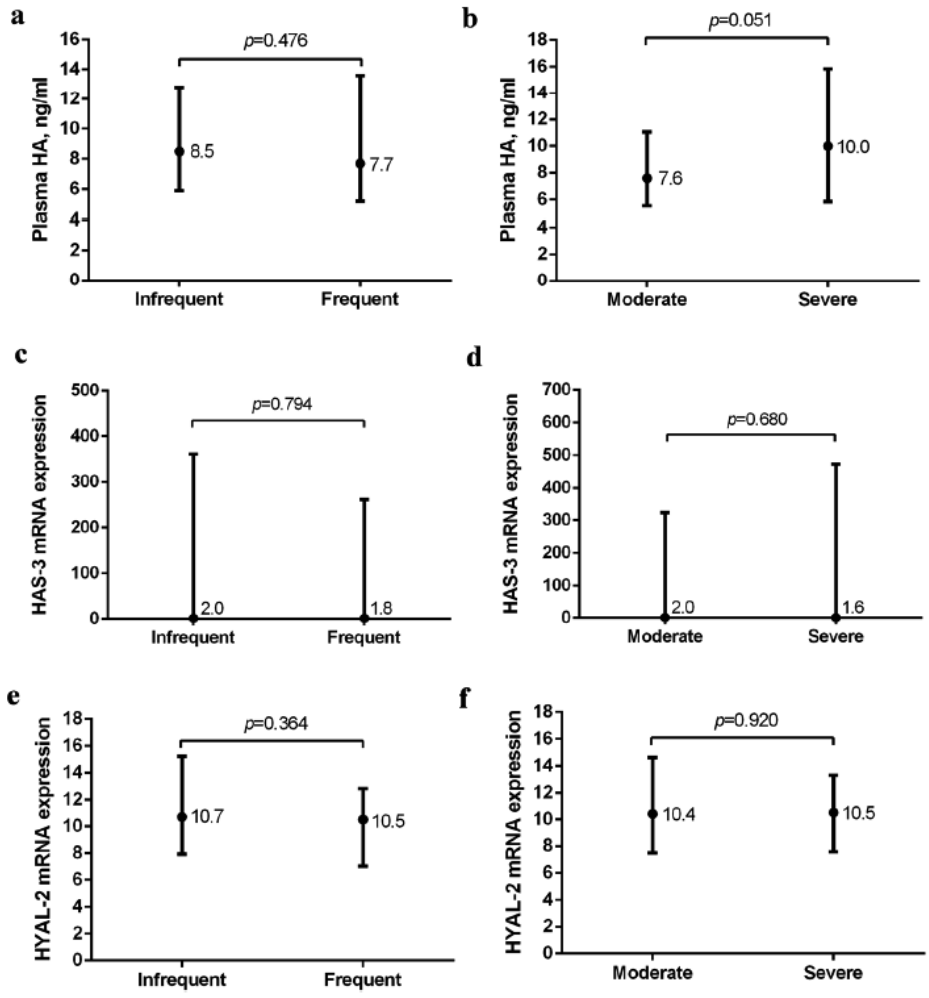

Fig 2. Differences in plasma HA and expression of HAS-3 and HYAL-2 in patients with COPD grouped by AECOPD frequency, and disease severity in the past year*. A) Plasma HA in infrequent (n=95) and frequent exacerbating patients (n=86). B) Plasma HA in patients with a moderate (n=131) and severe disease history (n=59). C) Expression of HAS-3; and E) expression of HYAL-2 in infrequent (n=72) and frequent exacerbating patients (n=64). D) Expression of HAS-3; and F) expression of HYAL-2 in patients with a moderate (n=100) and severe disease history (n=41). *Infrequent AECOPD were defined by <2 AECOPD and frequent AECOPD by ≥2 AECOPD in the past year. A moderate disease history was defined by no airway-related hospitalizations and a severe disease history by ≥1 airway-related hospitalization in the past year. Median concentrations/expression levels and interquartile ranges are presented. Figures created using GraphPad Prism 8.3.5, https://www.graphpad.com/scientific-software/prism/

Association of plasma HA with systemic inflammation and cardiovascular risk

Plasma HA was positively correlated with IL-6, and negatively correlated with IL-8, in patients with COPD (table 2). No significant correlations were observed in the control groups. With respect to cardiovascular risk, a positive correlation with APWV was observed in patients with COPD, but not in smoking and non-smoking controls. Furthermore, except for a positive correlation between HA and age in all groups, no significant correlations with any of the clinical outcomes were observed (Table S3, online supplement).

With respect to our regression models, APWV was significantly associated with plasma HA in patients with COPD, in both the univariate and multivariate model (table 3). Though, the explained variance (R^2) was less than 10% in both models (univariate; 6.8%, multivariate; 8.7%). No significant results were observed in the control groups (data not shown). Of note, subdividing patients with COPD based on APWV scores below and above the cut-off value that discriminates between cardiovascular risk, revealed significantly elevated plasma HA levels in patients at increased cardiovascular risk (9.32 ng/ml, n=78) compared to patients who were not (7.14 ng/ml, n=93), *p*=0.015. Yet, expression of HAS-3 and HYAL-2 did not differ between the latter groups (data not shown).

Table 2. Correlations between plasma HA and cardiovascular and inflammatory markers in patients with COPD, smoking controls (SC) and non-smoking controls (NSC).

	COPD	SC	NSC
APWV, m/s	0.181*	0.095	-0.032
	n=171	n=81	n=104
Leukocytes, 10^9/l	-0.038	0.026	-0.068
	n=173	n=41	n=59
Fibrinogen, g/dl	-0.061	-0.067	0.074
	n=182	n=79	n=100
IL-6, pg/ml	0.207*	-0.037	0.045
	n=187	n=79	n=104
IL-8, pg/ml	-0.162*	-0.040	0.045
	n=187	n=78	n=104
TNF-alpha, pg/ml	-0.144	-0.091	-0.180
	n=164	n=64	n=96

CRP, mg/l	0.062	0.023	-0.019
	n=191	n=82	n=104

Abbreviations: APWV; arterial pulse wave velocity, CRP; c-reactive protein, IL; interleukin, TNF-alpha; tumor necrosis factor alpha. *$p \leq 0.05$

Table 3. Multiple regressions of cardiovascular and inflammatory markers on plasma HA in patients with COPD.

	Model 1			Model 2		
	B	CI	β	B	CI	β
APWV, m/s	3.616*	1.577, 5.655	0.260	3.370*	0.990, 5.750	0.241
Leukocytes, 10^9/l	-0.503	-3.208, 2.202	-0.028			
Fibrinogen, g/dl	-1.133	-7.372, 5.106	-0.027			
IL-6, pg/ml	0.124	-0.329, 0.576	0.040			
IL-8, pg/ml	-0.184	-0.801, 0.434	-0.043			
TNF-alpha, pg/ml	-0.224	-0.712, 0.264	-0.071			
CRP, mg/l	-0.076	-0.356, 0.204	-0.039			

Model 1; univariate model. Model 2; covariate adjusted (i.e. age, sex, LABA, ICS and combined ICS and LABA use). Abbreviations: APWV; arterial pulse wave velocity, B; unstandardized regression coefficient, β; standardized regression coefficient, CI; 95% confidence interval, CRP; c-reactive protein, ICS; inhaled corticosteroids, IL; interleukin, LABA; long-acting β2-agonists, TNF; tumor necrosis factor. *$p \leq 0.05$

Discussion

This study provides novel insights into the alterations of systemic HA and its metabolism in patients with clinically stable COPD. Our results revealed that expression of HYAL-2, but not plasma HA nor HAS-3, was enhanced in patients with COPD compared to (non)smoking controls. Furthermore, while cardiovascular risk was positively associated with plasma HA in COPD, no additional associations with clinical outcomes were found. To the best of our knowledge this is the first study to report plasma levels of HA in patients with COPD and non-

COPD controls, and to show that cardiovascular risk might be involved with its systemic regulation in stable COPD.

In contrast to our hypothesis, plasma HA did not differ between patients with COPD and (non)smoking controls. While these results initially may seem to contradict previous findings, it should be noted that patients with stable COPD, defined by the absence of AECOPD at least 4 weeks prior to inclusion, were included in the present study. Previous studies have reported elevated levels of serum HA at exacerbation of COPD compared to a convalescent disease state.[11] Moreover, to date no controls were included in such studies. Hence, our data cannot be compared. In this respect, to what extent background heterogeneity may have confounded the present results remains unknown. Therefore, case-control studies with longitudinal follow-up are indicated to validate our findings as well as to compare the effects of an exacerbation. Nonetheless, while the present cross-sectional design by no means allows us to study the biomarker potential of HA, we hypothesize that its clinical potential, if any, may be acute rather than predictive/prognostic. Studies are warranted to elaborate further on this. Noteworthy, the observed concentrations of HA in plasma were lower compared to previous findings in serum of patients with COPD.[11] Whether these differences are of physiological relevance, remains unknown.

Serum levels of HA were previously reported to remain significantly elevated during, and up to 4 weeks after an AECOPD.[11] Therefore, elevated levels of plasma HA may have been expected in the current frequent exacerbating group. However, plasma HA, nor HAS-3 and HYAL-2, differed between frequent and infrequent exacerbating patients with COPD, or between patients with a moderate and severe disease history in the past year. These findings may further support opposite acute and chronic effects, in which enhanced levels of systemic HA may be observed during AECOPD[11], in contrast to lower levels in stable disease. Furthermore, serum HA was reported to associate with the severity of AECOPD.[11] Indeed, although lacking statistical significance, we observed a close trend towards higher plasma HA levels in patients with a severe disease history (Figure 2B), as well as a positive association with airway-related hospital admissions. Notwithstanding, plasma HA did not differ between patients with COPD with different GOLD stages (p=0.952).

Systemic HA is cleared by the lymphatic system, liver and kidney.[46] As a result, differential clearance rates may have affected the observed differences in plasma HA. In the present study, hepatic function did not differ between the groups. Furthermore, although patients with COPD had a lower estimated glomerular filtration rate (eGFR) than smoking controls, renal dysfunction was not observed. Nevertheless, to ensure that clearance rate variability was accounted for when comparing plasma HA across the groups, we adjusted for these markers of renal- and hepatic function in addition to age and sex. The latter did not reveal any differences in plasma HA between the groups (p=0.283). Noteworthy, eGFR (p=0.565) nor alanine aminotransferase (ALT) (p=0.263) contributed significantly to the model. It is unknown whether renal- and/or hepatic dysfunction may have affected the previously observed concentrations of HA in serum.[11]

While increased expression of HAS-3 may have been expected in patients with COPD, due to the low-grade systemic inflammation that is associated with the disease[47] and known to increase its expression[21], no differences in HAS-3 expression were observed between patients with COPD and (non)smoking controls in the present study. However, having included stable patients with COPD may explain these findings due to the absence of acute stress and/or inflammation. Indeed, it may require an acute increase in inflammation, as typically observed during AECOPD[24], for increased expression of HAS-3 to be reflected systemically, and thus to yield differences compared to non-COPD controls.

With respect to HYAL-2, increased expression was observed in patients with COPD compared to both smoking and non-smoking controls. These results are in line with previous findings in sputum of stable-[15], as well as in serum and the lungs of exacerbating patients with COPD.[11, 12] Although these results may suggest a clinical potential of HYAL-2, rather than HA and HAS-3, no associations with clinical outcomes of COPD were found (data not shown). Nonetheless, the observed group differences in HYAL-2 expression may provide an indication of the molecular size of HA. Indeed, plasma HA was measured by ELISA (R&D Systems), which detects HA of low (15-40 kDa), medium (75-350 kDa) and high (>950 kDa) MW. However, this assay does not distinguish between these different molecular sizes, and thus biological effects of HA. Therefore, while the net result of HYAL-2 activity is an increase in LMW-HA[6, 19, 20], it is tempting to presume its enhancement in the patient group. In this view, a positive correlation

between plasma HA and HYAL-2 was observed in patients with COPD. Thus, while the overall concentration of plasma HA in the patient group may have been low, it is plausible that the increased expression of HYAL-2 elicited an increased pool of the pro-inflammatory LMW-HA in patients with COPD compared to non-COPD controls.

Previous studies reported that HA was not related to markers of emphysema.[11, 12] Although CT-scan parameters were lacking, HA and TLCO were also not correlated in the present study. Therefore, the association of HA with markers of systemic inflammation and cardiovascular risk was explored. In line with others[48, 49], and as previously published[40], we observed that APWV was increased in patients with COPD compared to controls. Yet, the median value did not exceed the cutoff value of 10 m/s that is indicative of increased cardiovascular risk.[50] Our regression models showed that APWV, but none of the inflammatory markers, explained some of the variance (R^2 <10%) in plasma HA of patients with COPD. Thus, cardiovascular risk, rather than systemic inflammation, may be involved with the regulation of systemic HA in stable COPD. Indeed, increased plasma HA levels were observed in patients with COPD at increased cardiovascular risk. In light of the mentioned reduced eGFR in patients with COPD, the addition of this marker to our regression model was explored next. While eGFR did not contribute significantly to the prediction of plasma HA (p=0.521), the model improved (p=0.035) and APWV remained significantly associated with plasma HA (p=0.007).

Patients with COPD often have (multiple) cardiovascular comorbidities[40] that are characterized by increased endothelial dysfunction and turnover.[51] Increased HA shedding from the glycocalyx may result in aggravated destabilization of the endothelial glycocalyx and subsequent vascular complications such as angiopathy.[52, 53] Bearing in mind the increased expression of HYAL-2, protecting the endothelial glycocalyx from HA shedding, an increasingly recognized goal in the management of sepsis and diabetes mellitus[52, 53], may warrant attention in patients with COPD as well. Nevertheless, cardiovascular risk only explained a minority of the variance in plasma HA. This emphasizes that our knowledge of its origin still is in its infancy. Indeed, although our data support a systemic origin, it does not provide proof, causal relationships or mechanistic insight, nor does it rule out a pulmonary or different organ origin.

Major strengths of the present study were the comprehensive clinical characterization and the large sample size to study plasma HA. Moreover, plasma samples, as well as PBMC, available for secondary analyses were used in this study. This led to optimum use of biological samples, preventing unnecessary waste. Still, several limitations were encountered. First, the sample size of the available PBMC samples to study mRNA expression of HAS-3 and HYAL-2 was substantially smaller in the control groups. In view of this, these analyses were also performed not dividing the control group into smoking and non-smoking controls. The latter revealed similar results, even after adjustment for age, sex and pack years. Furthermore, the number of AECOPD and airway-related hospital admissions in the previous year relied on self-report. In this respect, patients with COPD included in the study were not matched for disease severity and/or specific clinical features. Hence, the degree to which heterogeneity of disease has confounded the present results remains unknown and warrants further research. Finally, since cross-sectional data was presented, causal relations remain unknown. Therefore, longitudinal case-control studies including different sample types are suggested to provide a better understanding of the differences in local and systemic HA, within and across individuals over time. However, careful attention must be paid to the burden as well as costs of such extensive sampling, keeping future clinical implementation in mind.

Conclusions

Taken together, this study showed that expression of HYAL-2, but not plasma HA nor HAS-3, was enhanced in patients with clinically stable COPD compared to (non)smoking controls. Plasma HA was not associated with the frequency of AECOPD and airway-related hospitalizations in the past year, nor systemic inflammation in COPD. Nevertheless, the results suggested that cardiovascular risk might play a role in the regulation of systemic HA in stable COPD. Future studies are warranted to further increase our understanding of systemic HA, as well as its enzymatic regulators, in patients with COPD to support clinical recommendations.

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Online supplement

Methods

Basic clinical characteristics

Basic demographics such as sex, age and medication use were documented at study entry.[1] Post bronchodilator spirometry measurements of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), their ratio, residual volume (RV) and transfer factor for carbon monoxide (TLCO) were assessed using a standardized spirometer (Masterlab, Jaeger, Würzburg, Germany).[2] Disease severity of patients with COPD was defined as moderate to severe based on FEV_1 % of predicted, according to the global initiative for chronic obstructive lung disease (GOLD) strategy document (i.e. GOLD categories II-IV).[3] The medical research council (MRC) questionnaire was assessed to identify patients with a moderate (MRC <3) or severe (MRC ≥3) degree of dyspnea.[1] Smoking status was assessed and habitual and occasional smokers were defined as current smokers.[2] Pack years were calculated as (number of cigarettes smoked per day/20) × number of years smoked.[2] Body mass index (BMI) was assessed [body weight in kg/(height in $m)^2$].[1] In addition, diastolic and systolic peripheral blood pressure measurements were performed.[1] To assess renal function, plasma creatinine was assessed[1] to calculate the estimated glomerular filtration rate (eGFR), using the simplified Modification of Diet in Renal Disease (MDRD) equation.[4] An eGFR of less than 60 ml/min/1.73 m^2 corresponds with stage 3 chronic kidney disease[5] and was used to indicate renal impairment.[1] Furthermore, plasma alanine aminotransferase (ALT) was measured to assess hepatic function. Levels above 33 U/l for males, and levels above 25 U/l for females were used to indicate hepatic injury.[6]

Power calculation

A *post-hoc* power calculation was performed to assess whether the achieved power was sufficient to detect significant differences in plasma HA between patients with COPD and (non)smoking controls. Power calculations were performed using the two-tailed non-parametric Wilcoxon-Mann-Whitney test with an effect size of 0.5, in the software program G*Power 3.1.[7] The power to detect significant differences in HA between the available plasma samples of patients with COPD, smoking and non-smoking controls was >91.5%, which is an adequate power to detect statistical significant differences.[8]

mRNA expression of HAS-3 and HYAL-2

First, according to the manufacturer's protocol RNA was isolated from peripheral blood mononuclear cells (PBMC) from EDTA anticoagulated blood stored in RNA later, using the RiboPure RNA Isolation kit (Ambion, Life Technologies, CA, USA). Next, RNA was reverse transcribed into cDNA using the Transcriptor cDNA Synthesis kit (Roche Applied Sciences, Mannheim, Germany), using the manufacturer's protocol. cDNA was amplified with quantitative polymerase chain reactions (qPCR) using a Power SYBR Green PCR Master Mix (Applied Biosystems, Foster city, CA, USA) on the ABI 7900HT qPCR cycler (Applied Biosystems, Foster city, CA, USA). Primer sequences of HAS-3, HYAL-2 and the housekeepers can be observed below in table 1. Data was exported from LightCycler480 software and converted in LC480 conversion software (Bio-Rad Laboratories, Berkeley, CA, USA). The converted data was subsequently analyzed in LinRegPCR[9] and Excel (Microsoft Excel 2007, Redmond, WA, USA). Ribosomal protein P0 and 13A were the most stable housekeeping genes (M=0.882) and were selected for normalization. Mean N0 values of the genes of interest were divided by mean N0 values of the housekeepers. Nuclease-free water samples were included and confirmed as negative controls. To be able to calculate an expression level in the samples with a below limit detection of HAS-3 expression, the maximum quantitation cycle (i.e. 45 cycles) was used to obtain the expression value of HAS-3 at this threshold cycle. In this manner, a lower detection limit was calculated, applying the formula provided in LinRegPCR.[9]

Table S1. Primer sequences of qPCR measurements

	Forward primer 5'-3'	Reverse primer 3'-5'
HAS-3	CAGACTTCGCTAAGGGCTTGTTT	CTACCTGTACCTGCCTGTTTTTGA
HYAL-2	CGCAGCTGGTGTCATCCTCT	CAGGACACATTGACCACGTAGG
RPLP0	TCTACAACCCTGAAGTGCTTGATATC	GCAGACAGACACTGGCAACATT
RPL13A	CCTGGAGGAGAAGAGGAAAGAGA	TTGAGGACCTCTGTGTATTTGTCAA
Beta globin	AGCTGTGCTCGCGCTACTCT	CGGATGGATGAAACCCAGAC

Abbreviations: HAS; hyaluronic synthase, HYAL; hyaluronidase, RPL; ribosomal protein.

Results

Outliers of plasma HA and its enzymatic regulators

Plasma HA concentrations ranged from 3.1 ng/ml to 351.6 ng/ml in patients with COPD, from 3.7 ng/ml to 300.3 ng/ml in smoking controls and from 3.0 ng/ml to 258.6 in non-smoking controls. Analysis of the outliers revealed that these were not high leverage or highly influential points, and were therefore included in further analyses. Likewise, analysis of the outliers of HAS-3 and HYAL-2 expression revealed that these were not high leverage or highly influential points and were therefore included.

Table S2. Baseline cardiovascular and inflammatory measures in patients with chronic obstructive pulmonary disease (COPD), smoking (SC) and non-smoking controls (NSC).

	COPD	SC	NSC	*p*-value
	n=192	n=84	n=107	
Cardiovascular				
Systolic BP, mmHg	145.5 ± 22.3	143.3 ± 18.9	142.4 ± 21.0	0.434
Diastolic BP, mmHg	83.9 ± 8.7	84.0 ± 9.6	83.3 ± 9.6	0.822
APWV, m/s	9.6 (8.1-11.5)[1]	8.5 (7.6-9.8)[1]	8.1 (7.2-9.3)[1]	<0.001[ab]
	n=171	n=81	n=104	
Inflammatory				
Leukocytes, 10^9/l	7.0 (6.1-8.2)[1]	5.9 (5.2-7.0)[1]	5.2 (4.4-6.1)[1]	<0.001[ab]
	n=173	n=41	n=59	
Fibrinogen, g/dl	3.2 (2.7-3.7)[1]	2.7 (2.4-3.1) [1]	2.6 (2.4-2.9)[1]	<0.001[ab]
	n=182	n=79	n=100	
IL-6, pg/ml	5.8 (3.2-11.7)[1]	5.5 (2.2-15.8)[1]	4.5 (2.0-12.9)[1]	0.137
	n=187	n=79	n=104	
IL-8, pg/ml	7.9 (3.8-12.7)[1]	4.8 (0.4-9.5)[1]	3.7 (0.4-7.9)[1]	<0.001[ab]
	n=187	n=78	n=104	
TNF-alpha, pg/ml	0.5 (0.2-6.5)[1]	3.0 (0.2-18.5)[1]	0.7 (0.2-26.9)[1]	0.013[a]
	n=164	n=64	n=96	
CRP, mg/l	2.9 (0.9-7.2)[1]	1.0 (0.4-2.4)[1]	0.7 (0.3-1.3)[1]	<0.001[ab]
	n=191	n=82	n=104	

Variables are presented as mean ±SD and median (IQR) with overall *p*-values. Abbreviations: APWV; arterial pulse wave velocity, BP; blood pressure, CRP; c-reactive protein, IL; interleukin, TNF-alpha; tumor necrosis factor alpha. [1] n is stated otherwise. *Post hoc* pairwise comparison between [a] COPD-SC [b] COPD-NSC [c] NSC-SC.

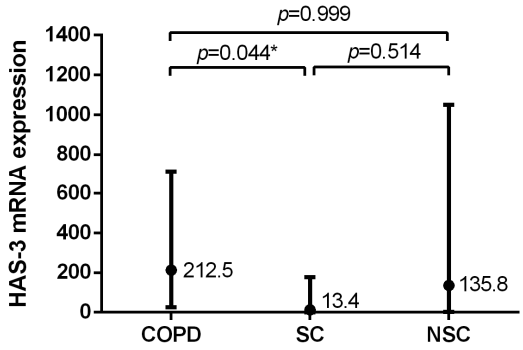

Fig S1. Expression of hyaluronic acid synthase 3 (HAS-3) in patients with COPD (n=63), smoking controls (SC, n=14) and non-smoking controls (NSC, n=18); excluding samples with a below limit detection. Median and interquartile ranges are presented. *Significant *post-hoc* pairwise comparison. Figure created using GraphPad Prism 8.3.5, https://www.graphpad.com/scientific-software/prism/

Table S3. Correlation analyses of plasma HA in patients with chronic obstructive pulmonary disease (COPD), smoking (SC) and non-smoking controls (NSC).

	COPD	SC	NSC	*p*-value
	n=192	n=84	n=107	
Age, years	0.341*	0.350*	0.247*	0.058
Sex, male	0.055	0.103	-0.001	0.150
FEV_1, % pred.	0.079	-0.038	0.058	0.801
FVC, % pred.	0.123	-0.018	0.099	0.334
FEV_1/FVC, % pred.	-0.056	-0.111	-0.223*	0.944
TLCO, % pred.	-0.056[1]	0.009[1]	-0.025	0.070
	n=184	n=83		
RV, % pred.	-0.019[1]	0.046	-0.024	0.928
	n=187			
Pack years	-0.010[1]	0.093	0.060[1]	0.286
	n=191		n=102	
Smoking status, current smoker	-0.058	-0.090	0.037	0.153
BMI, kg/m^2	0.072	0.100	0.086	0.138
HAS-3 expression	-0.198[1*]	-0.040[1]	-0.155[1]	0.103
	n=143	n=21	n=20	
HYAL-2 expression	0.181[1*]	-0.378[1]	-0.056[1]	0.108
	n=143	n=21	n=20	

Correlation coefficients (r) are presented. Abbreviations: BMI; body mass index, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, HAS; hyaluronic acid synthase, HYAL; hyaluronidase, RV; residual volume, TLCO; transfer factor for carbon monoxide, % pred; % predicted. The *p*-value indicates differences in correlations between the groups tested with a multiple regression model. * $p \leq 0.05$. [1] n is stated otherwise.

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CHAPTER 6

Impact of Coronavirus Disease 2019-related infection prevention and control measures on the occurrence of COPD exacerbations during inpatient pulmonary rehabilitation

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Abstract

Rationale: A significant reduction in hospitalizations for acute exacerbations of COPD (AECOPD) has been reported during the COVID-19 pandemic. It remains unclear whether this reduction is the result of healthcare avoidance by patients, or of infection prevention and control (IPC) measures.

Objectives: To explore the impact of COVID-19-related IPC measures on the occurrence of AECOPD in a real-life inpatient pulmonary rehabilitation (PR) setting, thereby ruling out potential effects of healthcare avoidance.

Methods: Patients with COPD admitted for eight weeks of inpatient PR at Ciro (Horn, the Netherlands) between October 2020 and March 2021, the first winter with full COVID-19-related IPC measures, were compared to patients admitted during the same period in previous years (2017-2018, 2018-2019 and 2019-2020). Electronic medical records were retrospectively screened for the occurrence of moderate to severe AECOPD, drop-out and mortality.

Results: A total of 501 patients with COPD (median age 66.6 [IQR 60.3-71.9] years, 43.1% male, FEV_1 35.9 [26.8-50.6] % predicted) were analyzed. During 2020-2021, 22 patients (31.0%) experienced ≥1 AECOPD compared to 43 patients (33.6%) in 2019-2020, 55 patients (36.9%) in 2018-2019 and 83 patients (54.2%) in 2017-2018. This represents a 25.4% reduction in 2020-2021 compared to the average of the previous three periods, p=0.077. No differences in AECOPD severity, drop-out, nor mortality were observed.

Conclusions: COVID-19-related IPC measures did not significantly reduce the AECOPD rate during inpatient PR in a single-center setting. The current findings suggest that avoidance of healthcare may be an important factor in the observed reduction of AECOPD-related hospitalizations during the pandemic, and that the value of the strict COVID-19-related IPC measures for the prevention of AECOPD warrants further research.

Background

During the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) induced COVID-19 pandemic, a worldwide reduction in the number of hospital-admitted acute exacerbations of chronic obstructive pulmonary disease (AECOPD) ranging between 44% to 78% has been observed.[1-8] COVID-19-related infection prevention and control (IPC) measures, including social distancing, wearing face masks and overall enhanced hygiene[9, 10], may explain this reduction in hospitalizations by also affecting the transmission of other respiratory viruses than SARS-CoV-2. Since viral infections are an important cause of AECOPD[11-13], reducing transmission with IPC measures will likely reduce the number of AECOPD. Avoidance of hospital care by patients due to fear of contracting a SARS-CoV-2 infection may also contribute to the reduction of AECOPD-related hospitalizations.[14-16] However, healthcare avoidance would not reduce the number of AECOPD per se, but rather presentation to the hospital. This would reconcile the increased numbers of AECOPD managed in community settings[15] with the decreased hospitalization rates. At present, it is unclear whether IPC measures or healthcare avoidance by patients has been driving the lower AECOPD hospitalization rates. It is important to distinguish between these two different causes as it may hold important implications for the post-pandemic management of (AE)COPD.

The COVID-19 pandemic has placed an immense burden on healthcare systems. Adjusted, remote, postponed, or cancelled care are examples of such challenges introduced by COVID-19. The care provided at Ciro, a pulmonary rehabilitation (PR) center located in Horn, the Netherlands, was equally affected by COVID-19 and measures were taken correspondingly. COVID-19-related IPC measures were introduced during the first COVID-19 wave, in addition to pre-existing IPC measures (e.g. no handshaking policy), and included social distancing, wearing face masks and weekly SARS-CoV-2 polymerase chain reaction (PCR) testing, amongst others. The current study was designed to explore the impact of COVID-19-related IPC measures on the occurrence of AECOPD in patients with COPD admitted for inpatient PR. In addition, drop-out and mortality rates were assessed given their close relationship with AECOPD.[17, 18] Because of the daily nursing, and continuous access to AECOPD-related care at Ciro, the potential effect of healthcare avoidance could be ruled out. It was hypothesized that

the inpatient AECOPD rate would reduce during the COVID-19 pandemic compared to previous years as a result of the implementation of COVID-19-related IPC measures.

Methods

Study setting

This retrospective study was conducted at Ciro, a specialized center for comprehensive PR (Horn, the Netherlands). PR at Ciro consists of a state-of-the art, multidisciplinary, patient-tailored program (Monday to Friday; patients in need of medical or nursing care also receive inpatient care during weekends).[19] Patients are supervised by the medical staff including chest physicians throughout the PR program.

Study design

Patients admitted between October 1st 2020 and March 1st 2021, the first winter season with COVID-19-related IPC measures in place, were compared to patients admitted during the same period in previous years (2017-2018, 2018-2019 and 2019-2020). The inclusion period was carefully selected given the known rise in AECOPD during the autumn and winter months in the northern hemisphere.[20-23] Electronic medical records were retrospectively screened for the occurrence of AECOPD, drop-out and mortality rates during PR. The Medical Ethical Teaching Committee (METC) of the Maastricht University Medical Centre (MUMC+) confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to the current study. Therefore, approval was waived by the committee (METC 2021-2631). This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study population

Patients with a diagnosis of COPD established by a chest physician, and confirmed by spirometry (i.e. post-bronchodilator ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) of less than 0.70[24]), admitted for an eight-week inpatient PR program during the observation periods were eligible for inclusion. Patients may attend PR multiple times over several years; if patients were admitted for multiple PR programs during

the observation period, only the first course was recorded. Furthermore, patients who dropped-out during the first week of PR (≤5 days) were excluded. Due to the real-life retrospective electronic medical records based study design no sample size calculation was performed.

Outcomes

Exacerbations were defined by an increase in respiratory symptoms and the need for additional pharmacological treatment according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document.[24] Exacerbation-like events were evaluated by a chest physician or physician assistant. If indicated, chest X-ray, electrocardiography (ECG) and venous blood were collected as part of routine AECOPD diagnosis to rule out differential diagnoses such as pneumonia, pneumothorax and cardiac abnormalities. AECOPD were scored according to treatment intensity: moderate AECOPD were defined as AECOPD necessitating treatment with systemic glucocorticoids, antibiotics or both.[24] Severe AECOPD were defined as AECOPD necessitating treatment with (enhanced) oxygen therapy, intensification of long-term home non-invasive ventilation (NIV), or escalation to hospital care facilities >24 hours for care not available in Ciro such as need for intravenous treatment, mechanical ventilation, initiation of acute NIV or continuous monitoring.

Baseline characteristics included age, sex, smoking status (current, former and never-smoker), pack years, body weight (kg), height (m) and body mass index (BMI [kg/m^2]). Disease-specific measures included lung function (FEV_1, FVC and FEV_1/FVC [absolute and % predicted), GOLD grade (I-IV) and the total number of moderate AECOPD and AECOPD-related hospitalizations in the year prior to admission for PR. Furthermore, the modified Medical Research Council (mMRC) scale (0-4 points), and the COPD Assessment Test (CAT [0-40 points]) were assessed. Equivalent cut-off scores of ≥2 for mMRC, and ≥10 for CAT were used to stratify patients based on dyspnea severity or health status, respectively.[24] The use of maintenance therapies (inhalation therapy, systemic antibiotics, systemic corticosteroids, long-term oxygen therapy and home-based NIV) were recorded. These outcomes were collected during the 2.5 day baseline pre-rehabilitation assessment.[19]

COVID-19-related IPC measures

COVID-19-related IPC measures were introduced in Ciro during March-May of 2020 (during/after the first national COVID-19 wave[25]) and included social distancing (i.e. 1.5 meter), strictly using single-patient rooms, enhanced hygiene measures and indoor ventilation, as well as training group size limits and introduction of eating meals in shifts. Furthermore, all newly admitted patients were tested for SARS-CoV-2 using SARS-CoV-2 antigen tests (Abbott Panbio™). Patients could only commence PR after having obtained a negative test result. In addition, patients were isolated during PR when a SARS-CoV-2 infection was suspected, and remained in isolation if confirmed by PCR testing. During these events, patients were also tested for influenza. During the early stages of the second national COVID-19 wave[25], further COVID-19-related IPC measures (in addition to the previously administered COVID-19-related IPC measures) were introduced at Ciro as of October 1, 2020. These measures included wearing surgical IIR face masks in public areas and weekly routine testing using SARS-CoV-2 RT-PCR tests. Hence, October 2020 to March 2021 marks the first winter season with full COVID-19-related IPC measures in place. Some IPC measures had already been established at Ciro as part of routine clinical care before the COVID-19 pandemic. These included aerogenic isolation (i.e. patient-isolation and wearing surgical IIR face masks) in case an influenza or human metapneumovirus infection was suspected and/or confirmed. Moreover, a no handshaking policy was introduced in January 2018 in response to the national influenza epidemic.[26]

Statistical analysis

Baseline characteristics were reported as mean and standard deviation (SD) or as median and interquartile range (IQR) for continuous variables, as appropriate, and as count and percentage for categorical characteristics. The primary outcome of interest was the occurrence of AECOPD during each observational period. The Pearson's Chi-squared test was performed to compare the number of patients experiencing an AECOPD (yes/no) between the different periods. The one-way analysis of variance (ANOVA) was performed to compare the number and severity of AECOPD between the different periods. The Pearson's Chi-squared test, ANOVA and Kruskal-Wallis test were performed to assess differences between patient characteristics, as appropriate. Post-hoc pairwise comparisons were performed and adjusted

by the Bonferroni correction for multiple tests. Statistical analyses and visualization were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA) and Excel (Microsoft Excel 2007, Redmond, WA, USA). A priori, *p*-values ≤0.05 were considered statistically significant.

Results

A total of 526 patients with COPD were admitted for inpatient PR at Ciro between October 1st and March 1st during the years 2017-2021. A total of 501 patients were included for analyses (Figure 1). Patient characteristics were comparable between the different periods (Table 1). Briefly, the median age of the total population was 67 years and 43% was male. The majority of patients was classified as GOLD III-IV (73%), and most patients reported a moderate to very severe breathlessness (mMRC ≥2). 71% of the patients had experienced at least two moderate AECOPD, and 54% of the patients was admitted to the hospital at least once for an AECOPD in the year before admission for PR. The use of maintenance therapies is shown in table 2. Apart from long-term oxygen therapy, no significant differences were observed between the different periods. Long-term oxygen therapy use was significantly higher in 2017-2018 vs. 2018-2019 (Chi-square, *p*=0.013) and in 2019-2020 vs. 2018-2019 (Chi-square, *p*=0.014). No differences in drop-out and mortality rates were observed (Online Data Supplement).

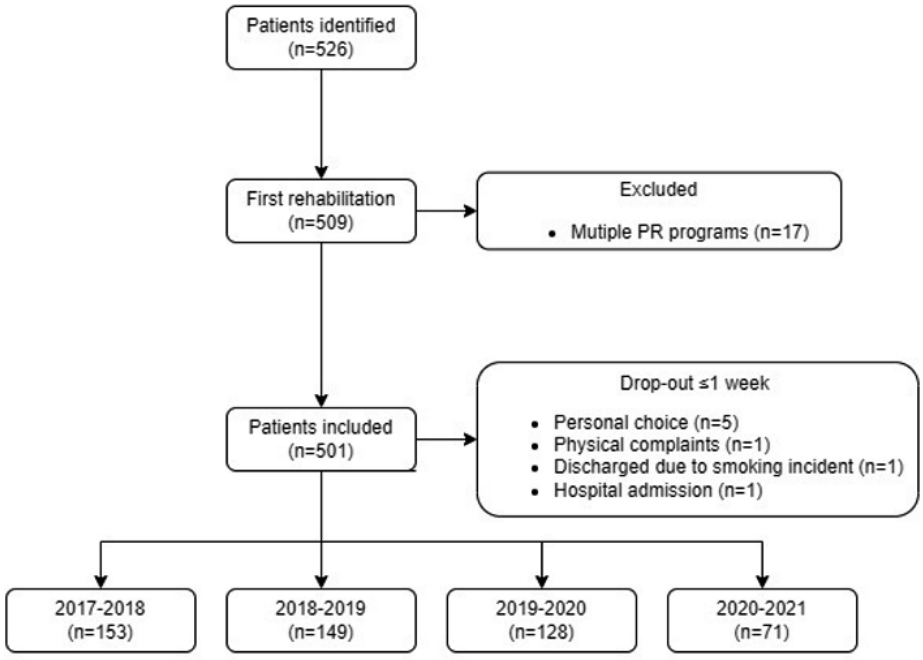


Fig 1. Flowchart of the study population.

Table 1. Patient characteristics stratified for the different periods

	Total (n=501)	**2017-2018 (n=153)**	**2018-2019 (n=149)**	**2019-2020 (n=128)**	**2020-2021 (n=71)**	***p*-value**
Age, years	66.6 [60.3-71.9]	66.5 [60.3-72.0]	67.2 [61.1-71.8]	66.3 [59.8-71.7]	66.2 [58.9-73.5]	0.761
Sex, male	216 (43.1)	63 (41.2)	67 (45.0)	54 (42.2)	32 (45.1)	0.897
FEV_1, % predicted	35.9 [26.8-50.6]	35.9 [26.1-52.3]	33.9 [26.8-50.5]	38.6 [26.4-51.7]	37.7 [28.3-49.8]	0.769
FEV_1/FVC, %	32.6 [26.4-42.0]	32.6 [26.6-43.0]	30.6 [25.7-42.5]	33.1 [26.6-41.5]	33.2 [28.5-44.0]	0.728
GOLD						
I	19 (3.8)	5 (3.3)	8 (5.4)	6 (4.7)	0 (0)	0.807
II	114 (22.8)	37 (24.2)	31 (20.8)	30 (23.4)	16 (22.5)	
III	196 (39.1)	56 (36.6)	59 (39.6)	50 (39.1)	31 (43.7)	
IV	172 (34.3)	55 (35.9)	51 (34.2)	42 (32.8)	24 (33.8)	
Moderate AECOPD ≤1 year,						
0	57 (11.5)	14 (9.3)	14 (9.5)	17 (13.4)	12 (17.1)	0.293
1	87 (17.5)	27 (17.9)	35 (23.4)	18 (14.2)	7 (10.0)	
≥2	352 (71.0)	110 (72.8)	99 (66.9)	92 (72.4)	51 (72.9)	
AECOPD-related hospitalizations ≤1 year,						
0	227 (46.0)	72 (47.1)	59 (39.9)	63 (51.2)	33 (47.1)	0.130
1	130 (26.3)	41 (26.8)	46 (31.1)	28 (22.8)	15 (21.4)	
≥2	137 (27.7)	40 (26.1)	43 (29.0)	32 (26.0)	22 (31.5)	
Other hospitalizations ≤1 year,						
0	403 (86.3)	134 (88.2)	127 (88.8)	91 (81.3)	51 (85.0)	0.339
1	52 (11.1)	14 (9.2)	13 (9.0)	19 (17.0)	6 (10.0)	
≥2	12 (2.6)	4 (2.6)	3 (2.1)	2 (1.7)	3 (5.0)	
mMRC						
0	1 (0.2)	0 (0)	1 (0.7)	0 (0)	0 (0)	0.042[a,b]
1	14 (2.8)	2 (1.3)	6 (4.0)	3 (2.4)	3 (4.2)	
2	128 (25.8)	48 (31.4)	33 (22.1)	30 (24.2)	17 (23.9)	
3	154 (31.0)	39 (25.5)	63 (42.3)	34 (27.4)	18 (25.4)	
4	200 (40.2)	64 (41.8)	46 (30.9)	57 (46.0)	33 (46.5)	
CAT, total score	23.0 (19.0-27.0)	24.0 (20.0-28.0)	23.0 (19.0-27.0)	23.0 (19.0-26.0)	21.0 (16.0-25.0)	0.010[c,d]

CAT ≥10	445 (97.2)	145 (97.3)	136 (97.8)	109 (97.3)	55 (94.8)	0.705
BMI, kg/m^2	25.6 [21.4-30.2]	26.2 [22.5-30.9]	24.5 [20.1-29.3]	25.6 [21.3-30.8]	25.6 [20.8-31.0]	0.079
Smoking status, current smoker	84 (17.4)	27 (17.9)	19 (14.1)	26 (20.6)	12 (16.9)	0.574
Smoking history, yes	475 (95.8)	144 (94.1)	136 (93.2)	125 (99.2)	70 (98.6)	0.036[b,e]
Pack years	42.0 [30.0-55.0]	40.0 [30.0-50.0]	40.0 [30.0-55.0]	45.5 [35.0-60.8]	42.5 [30.0-57.8]	0.044[b,e]
SARS-CoV-2 infection	3 (0.19)	-	-	2 (1.6)	1 (1.4)	-

Data presented as absolute (%), mean ± SD or median [IQR]. Abbreviations: AECOPD; acute exacerbation of chronic obstructive pulmonary disease, BMI; body mass index, CAT; COPD Assessment Test, FEV_1; forced expiratory volume in the first second, FVC; forced vital capacity, GOLD; Global Initiative for Chronic Obstructive Lung Disease, mMRC; modified Medical Research Council, SARS-CoV-2; severe acute respiratory syndrome corona virus 2. Post-hoc pairwise comparisons $p<0.05$ between [a] period 2017-2018 and 2018-2019, [b] between period 2018-2019 and 2019-2020, [c] between period 2017-2018 and 2020-2021, [d] between period 2018-2019 and 2020-2021 and [e] between period 2017-2018 and 2019-2020.

Table 2. Baseline maintenance therapy stratified for the different periods

	Total (n=501)	**2017-2018 (n=153)**	**2018-2019 (n=149)**	**2019-2020 (n=128)**	**2020-2021 (n=71)**	***p*-value**
Inhalation therapy						
SABA and/or SAMA	422 (84.2)	125 (81.7)	127 (85.2)	110 (85.9)	60 (84.5)	0.768
LABA and/or LAMA and/or ICS	487 (97.2)	146 (95.4)	148 (99.3)	126 (98.4)	67 (94.4)	0.069
Systemic therapy						
Corticosteroids	111 (22.2)	36 (23.5)	31 (20.8)	26 (20.3)	18 (25.4)	0.802
Antibiotics	125 (25.0)	38 (24.8)	39 (26.2)	27 (21.1)	21 (29.6)	0.583
Respiratory support						
Long-term oxygen therapy	163 (34.4)	59 (39.3)	37 (25.7)	45 (40.2)	22 (32.4)	0.041[a,b]
BiPAP	29 (6.3)	13 (8.6)	8 (5.7)	6 (5.8)	2 (3.2)	0.480
CPAP	43 (9.4)	13 (8.6)	10 (7.1)	11 (10.6)	9 (14.3)	0.398

Data presented as absolute (%). Abbreviations: BiPAP; bilevel positive airway pressure, CPAP; continuous positive airway pressure, ICS; inhaled corticosteroids, LABA; long-acting beta agonist, LAMA; long-acting muscarinic antagonist, SABA; short-acting beta agonist, SAMA; short-acting muscarinic antagonist. Post-hoc pairwise comparisons $p<0.05$ [a] between period 2017-2018 and 2018-2019 and [b] between period 2018-2019 and 2019-2020.

SARS-CoV-2 infections

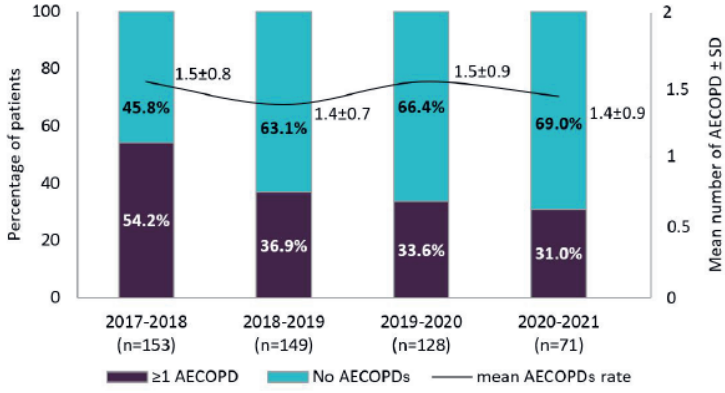
One patient (1.4%) admitted during 2020-2021, and two patients (1.6%) admitted during 2019-2020 got infected with SARS-CoV-2. Two out of the three patients experienced mild COVID-19 and restarted PR after a negative SARS-CoV-2 RT-PCR test result was shown. One patient was admitted to the hospital and died of the consequences of COVID-19. Of note, as a direct consequence of the COVID-19-related IPC measures a 50.5% reduction was seen in the total number of admissions for inpatient PR during October 1st 2020 and March 1st 2021 compared to the average of the previous three periods. This was mainly related to the introduction of single-patient rooms, and thus a reduction in the overall number of available beds.

AECOPD rates during inpatient PR

During 2020-2021, 22 patients (31.0%) experienced at least one AECOPD during inpatient PR compared to 43 patients (33.6%) in 2019-2020, 55 patients (36.9%) in 2018-2019 and 83 patients (54.2%) in 2017-2018, Figure 2A. This represents a non-significant reduction of 25.4% in the number of patients experiencing at least one AECOPD during 2020-2021 (31.0%) compared to the average of the previous three periods (41.6%) (Chi-square, p=0.077).Significant differences were however found in the number of patients experiencing an inpatient AECOPD between 2017-2018 vs. 2018-2019 (Chi-square, p=0.002), 2017-2018 vs. 2019-2020 (Chi-square, p=0.001) and 2017-2018 vs. 2020-2021 (Chi-square, p=0.001).

No significant differences were observed in the mean AECOPD rate per patient between the different periods (Figure 2A): 1.51 ± 0.80, 1.35 ± 0.67, 1.51 ± 0.88, 1.41 ± 0.91 in 2017-2018, 2018-2019, 2019-200 and 2020-2021, respectively (ANOVA (F (3,199)=0.552, p=0.647). Moreover, no significant differences were observed between the relative number of moderate (ANOVA (F (3,199)=0.129, p=0.943) and severe AECOPD (ANOVA (F (3,199)=0.475, p=0.700) in the different time periods (Figure 2B).

A.



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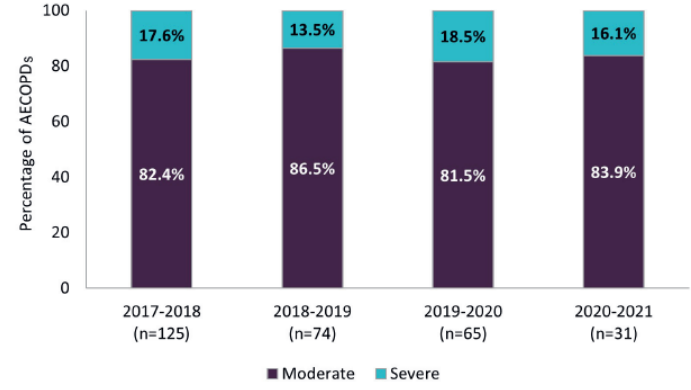

Fig 2. Occurrence of AECOPD during inpatient PR across the different time periods. A: Percentage of patients experiencing ≥1 versus no AECOPD during inpatient PR. N= total number of patients. The mean AECOPD rate ± SD is shown on the secondary vertical axis. B: Percentage of moderate versus severe AECOPD during inpatient PR. N= total number of AECOPD.

The majority of patients with a history of two or more AECOPD in the year before admission for PR experienced no or one AECOPD during inpatient PR (Figure 3).

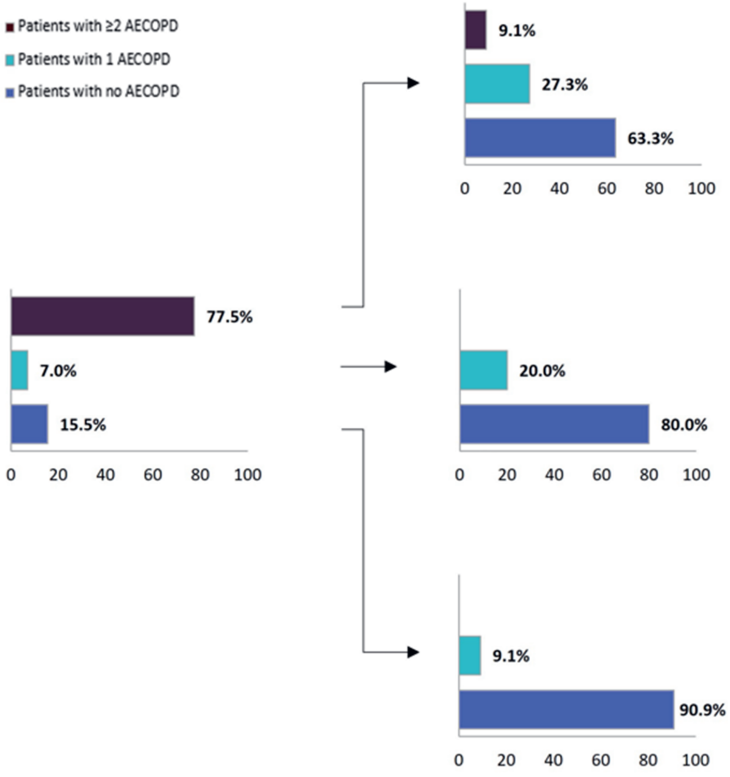

Fig 3. Percentage of patients with no (indigo) , 1 (turquois) or ≥2 (purple) AECOPD in the year before (left), and during the eight-week inpatient PR program (right). A: Patients admitted during 2020-2021 with no, 1 or ≥2 AECOPD in the year before (left), and during the eight-week inpatient PR program (right). B: Patients admitted during 2017-2018, 2018-2019 and 2019-2020 with no, 1 or ≥2 AECOPD in the year before (left), and during the eight-week inpatient PR program (right).

Discussion

This single-center, real-life, retrospective study showed that COVID-19-related IPC measures did not significantly reduce the occurrence of AECOPD in patients with COPD admitted for inpatient PR. This could not be explained by differences in AECOPD severity, drop-out, or mortality between the COVID-19-related IPC measures period (2020-2021) and previous years (2017-2020). These results lend credence to the hypothesis that the reduction in AECOPD hospitalizations during the COVID-19 pandemic previously observed might have been driven, at least in part, by altered healthcare seeking behavior of patients rather than the installation of IPC measures.

The worldwide reduction in the number of hospital-admitted AECOPD during the COVID-19 pandemic[1-8] was not observed in the present study. However, in contrast to previous studies, the current study was not restricted to AECOPD-related hospital admissions. Indeed, both moderate AECOPD (events necessitating treatment with systemic glucocorticoids, antibiotics or both) and severe AECOPD (events necessitating treatment with [enhanced] oxygen therapy, intensification of long-term home NIV, or escalation to hospital care facilities >24 hours) were studied. It was hypothesized that, regardless of the severity, the underlying mechanism of AECOPD starts with presentation to a healthcare provider. Patients included in this study received daily nursing during the eight-week PR program. As such, medical care was constantly available. The unique real-life inpatient setting of this study therefore precluded the potential effect of healthcare avoidance. Moreover, the large time window and the comparability of patient characteristics between the different time periods resulted in a relatively homogenous study cohort enabling us to study AECOPD rates during the COVID-19-related IPC measures period and previous years. Also, the severity of disease and high proportion of frequently exacerbating patients makes this setting particularly suitable to address the aims of this study.

Whilst IPC measures were effective in contributing to a decrease in COVID-19 cases in the community, and whilst we do not argue the effectiveness of these measures, the current findings suggest that healthcare avoidance of patients rather than COVID-19-related IPC measures has been driving the previously observed reduction in AECOPD during the COVID-19 pandemic. An argument against healthcare avoidance in previous studies has been the absence of increased mortality rates in patients with COPD during the pandemic.[27-30] Whilst hospital-admitted AECOPD exert a direct and independent negative effect on survival, the risk of mortality increases with the frequency of severe AECOPD.[31] Hence, it may be too soon to conclude that the COVID-19 pandemic has had a protective effect on the occurrence of (severe) AECOPD. Moreover, this argument includes the assumption that hospital admission is purely defined by the severity of physiological distress, and that mortality is equally correlated with the severity of presentation. It can be argued that reasons for hospitalization are highly variable throughout different healthcare systems, and that mortality due to AECOPD may not purely be linked to the severity of the initial presentation. Thus, the absence of increased mortality does not necessarily mean that the number of severe AECOPD has declined. What's more, the confounding effects of altered healthcare seeking behavior by

patients, such as increased at home use of rescue medication[5, 15], cannot be precluded and may have decreased the number of hospital admissions, but not the number of AECOPD per se.

To date, only a few studies investigated the occurrence of moderate AECOPD during the COVID-19 pandemic. Two studies demonstrated a significant reduction in the number of moderate AECOPD during 2020.[32, 33] These studies were however conducted in an outpatient setting including patients with a less severe disease status[32], or were based on national medication prescription data[33] which hampers the comparison of results. The current study predominantly included patients with moderate to very severe COPD. Susceptibility to AECOPD is related to disease severity[34], and may therefore explain the current lack of reduction in the occurrence of AECOPD. Indeed, despite the overall reduced number of AECOPD-related hospital admissions, the proportion of patients being admitted to the hospital for an AECOPD with GOLD stage 4 was shown to be higher during the COVID-19 pandemic compared to previous years.[6] That said, COVID-19-related IPC measures were shown to reduce the risk of AECOPD-related hospital admission even when adjusted for the level of airflow obstruction and a history of severe AECOPD.[8] In this view, we noted a significant decline in the number of AECOPD since the national influenza epidemic of 2017-2018 and the establishment of the no handshaking policy in Ciro since 2018 (Chi-square, p<0.001). This suggests that some protective IPC measures might have been in place before COVID-19, providing an additional explanation as to why the current study could not show a significant reduction in the number of AECOPD during the COVID-19 pandemic compared to previous years.

There are some limitations to the current study. First, its single-center study design, and limited sample size should be considered when interpreting the results. Moreover, although the potential effect of healthcare avoidance was precluded, the current cohort was unavoidably limited to a group of patients who did not avoid inpatient PR during the COVID-19 pandemic. In addition, the microbiological origin of AECOPD was not systematically recorded in the electronic medical records and could therefore not be explored in the present study. Previous studies showed that the COVID-19-related reduction in hospital admissions for COPD correlated with a reduced community viral burden.[35] In this view, the national

influenza rates were substantially reduced in the Netherlands during 2020-2021 compared to previous years.[26] This reduction was however not reflected in the AECOPD rates of the present study. This suggests that the AECOPD seen in the current study might not have had a predominate (viral) infectious origin[36, 37], and that endogenous triggers (e.g. bacterial burden[11] and eosinophilic inflammation[36]) drive these AECOPD during PR. Data regarding vaccination status (against influenza, pneumococci, tetanus, diphtheria and pertussis, herpes zoster and later also SARS-CoV-2), comorbidities as well as mild AECOPD (defined by the use of additional inhalation therapy) were not systematically recorded in the electronic medical records. As a result, the relation between vaccination status, comorbidities, and changes in healthcare seeking behavior such as additional use of inhalation therapy during the pandemic and the AECOPD rate could unfortunately not be assessed in the current study. Finally, other respiratory diseases in medical history were not considered exclusion criteria. However, all included patients had a diagnosis of COPD established by a chest physician and confirmed by spirometry. Moreover, the median age of 66.6 years (60.3-71.9) and median number of pack years of 42.0 (30.0-55.0) of the current study population are inherent to a typical COPD population.[24]

Conclusions

Taken together, this study showed that COVID-19-related IPC measures did not significantly reduce the occurrence of AECOPD in patients with COPD admitted for inpatient PR. These findings suggest that avoidance of healthcare may be an important factor in the observed reduction of AECOPD-related hospitalizations during the pandemic. Whilst the post-pandemic maintenance of COVID-19-related IPC measures to reduce the risk of AECOPD in patients with COPD is increasingly advised[27, 38], some caution may need to be taken as many questions remain. Indeed, further research is needed to explore the value of the strict COVID-19-related IPC measures for the prevention of AECOPD. Specifically, there is a need to assess whether, which, when and to what extent IPC measures can prevent (the different types of) AECOPD. Moreover, patients with varying degrees of COPD disease severity should be included to unravel which patients could benefit from such measures. As such, the current findings may indicate that the impact of (COVID-19-related) IPC measures may be more pronounced in patients with a less severe overall clinical presentation.[35]

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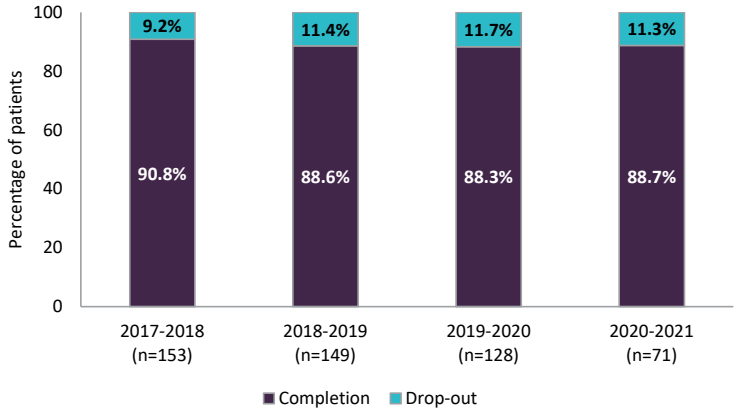
Online Supplement

Results

Drop-out and mortality rates

During 2020-2021, 8 patients (11.3%) dropped-out compared to 15 patients (11.7%) in 2019-2020, 17 patients (11.4%) in 2018-2019 and 14 patients (9.2%) in 2017-2018 (Figure S1A). Drop-out rates did not differ significantly between the different periods (Chi-square, *p*=0.892). The majority of drop-outs was related to physical complaints and non-COPD related hospitalizations (Figure S1B). Drop-out due to AECOPD-related hospital admission occurred in 7.4% of the cases. No significant differences were observed between the total number of deaths between the different periods: 1 patient (1.4%) died during inpatient PR in 2020-2021 compared to 4 patients (3.1%) in 2019-2020, 1 patient (0.7%) in 2018-2019 and 2 patients (1.3%) in 2017-2018 (Chi-square, *p*=0.421).

A.



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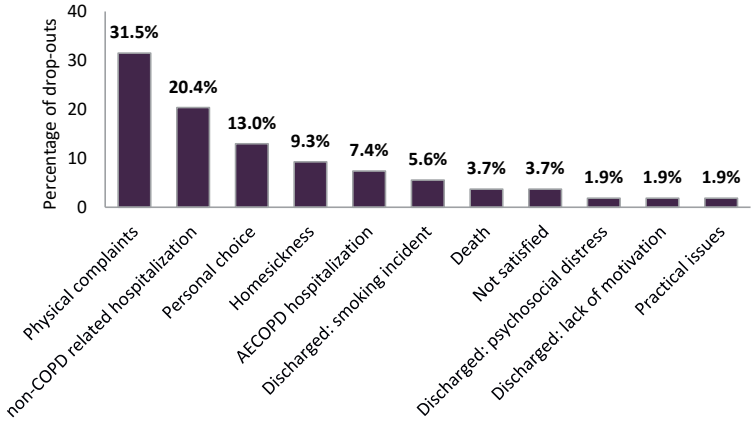

Fig S1. Drop-out during the eight-week inpatient PR program. A: Drop-out rates (%) across the different time periods. B: Reasons for drop-out.

CHAPTER 7

General discussion

Prediction of the occurrence and outcomes of exacerbations of COPD (ECOPD) currently remains challenging, which hinders clinical management for people living with COPD. Therefore, the central aims of this thesis were to predict the occurrence and outcomes of ECOPD. In this chapter the results of this thesis will be put in perspective, and directions for future research will be provided.

Outcomes of exacerbations

Currently, about one in ten ECOPD result in hospital admission.[1] Major outcomes of interest in relation to ECOPD-related hospitalization are in-hospital mortality, post-discharge mortality and hospital readmission. Although numerous studies have reported on the rates and determinants of these outcomes over the past 20 years, great heterogeneity exists between studies and countries. This hinders our understanding of the true, global burden of ECOPD-related hospitalizations on healthcare systems. **Chapter 2** provided more precise estimates of the global in-hospital mortality, post-discharge mortality, and hospital readmission rates following ECOPD-related hospitalization. This study, including data of 65,945 individual patients with COPD from 30 different countries, highlighted the poor outcomes of ECOPD-related hospitalization around the globe.[2] Furthermore, routinely available predictors of mortality and hospital readmission were identified, including a history of frequent previous ECOPD-related hospitalizations, and markers of disease severity such as the need for (non)invasive mechanical ventilation and admission to an intensive care unit.

Another important finding of this study was the irregular availability of clinical data in the studies, which underlines the need for collecting standardized data around ECOPD. A consensus-based core outcome set for clinical trials evaluating the management of ECOPD was recently developed by an international expert panel.[3] According to this European Respiratory Society (ERS) statement, the minimum set of outcomes included in future trials should be: survival, treatment success, breathlessness, quality of life, activities of daily living, the need for a higher level of care, arterial blood gases, disease progression, future ECOPD and hospital admissions, and treatment safety and adherence.[3] Whilst this is an important step towards improving the consistency, quality and comparability of future studies, the results in **Chapter 2** stressed, in line with others[4, 5], that previous ECOPD and hospitalizations are also important determinants of future ECOPD. As such, these too should be included as

core outcomes in future studies. Indeed, assessing ECOPD history during hospital admission is considered crucial according to further European-wide efforts to standardize the assessment and management of hospitalized ECOPD.[6, 7]

Importantly, a paucity of data from non-European countries was noted. This lack of outcome data is of particular importance given the high, or even higher, prevalence and impact, i.e. morbidity and mortality, of COPD in non-European countries.[8, 9] Indeed, low- and middle income countries (LMIC), such as South Asia, Southeast Asia, East Asia and Oceania, account for more than three-quarters of global COPD cases[9], and mortality and disability rates from COPD are most frequent in these LMIC, irrespective of sex.[8] Challenges related to the management of COPD in these regions include, in addition to cigarette smoking, exposure to ambient and household air pollution and occupational hazards.[8] Furthermore, availability and (correct) use of spirometry and the subsequent underdiagnosis of COPD[10], as well as limited access to treatment are important in these regions, negatively affecting disease outcomes.[11] Taken together, these results underline the necessity of future strategies that focus on strengthening and improving ECOPD prevention strategies, as well as global standardization of guidelines for post-discharge follow-up and monitoring of patients after ECOPD-related hospitalization. This is essential to improve the current poor prognostic rates associated with ECOPD-related hospitalization.

Besides the importance of respiratory outcomes, the results presented in **Chapter 3** underline the need for a heightened vigilance of non-respiratory outcomes following ECOPD. In this study, including data of 82,964 patients with COPD from the Danish national patient registry, non-respiratory admissions accounted for more than half of the subsequent hospital admissions following a first ever exacerbation-related hospitalization, both on the short- and long-term.[12] Cardiac events, including myocardial ischemia, myocarditis, cardiomyopathy and arrhythmias, were most common. These findings substantiate the previously identified increased risk of cardiovascular events following, even a first ever, ECOPD.[13-22] This increased risk is dependent on the severity of the ECOPD, and is not constant over time; cardiovascular risk is higher following a severe ECOPD compared to a moderate event, and peaks at the onset (day 1-7) following an ECOPD.[19, 21] More importantly, the increased risk of cardiovascular events persists up to one year post-ECOPD, irrespective of ECOPD severity, underlying the

importance of preventing these events.[13, 19-22] Several mechanisms have previously been suggested to play a role, including increased systemic inflammation and oxidative stress, hypercoagulability and increased platelet activation, endothelial dysfunction, hypoxemia, hypercapnia, increased airway resistance and hyperinflation, and coronary ischemia.[23-25] Targeting these factors may therefore not only contribute to improving outcomes of ECOPD, but also decrease stress upon the cardiovascular system. Hence, a key challenge for future studies is to further increase our understanding on how these different mechanisms contribute to the development of adverse cardiovascular events, thereby identifying therapeutic targets.

Given the importance of cardiovascular outcomes after an ECOPD, the prevention of such non-respiratory events following a first-ever ECOPD should be given more attention as a target to decrease the disease burden. At present, the provision of a management plan for comorbidities is part of a list of recommendations for follow-up after ECOPD-related hospital discharge.[26] However, several concerns exist with this recommendation. First, this recommendation deserves to be extended to ECOPD managed outpatient. Since 80-90% of ECOPD is managed in outpatient settings[1, 26], it is presumable that the largest impact can be made here. Indeed, early identification allows more amenable reversal of pathological changes.[11] Furthermore, according to expert recommendations, patients are advised to check their comorbidities with their primary care physician at their next appointment following hospital discharge.[27] This underpins the crucial role of primary healthcare professionals in managing and monitoring comorbidities. Second, this recommendation lacks clear screening or diagnostic modalities. Provided that cardiac events are the most common cause of non-respiratory admissions following ECOPD-related hospitalization, there is an evident rational to integrate such screening modalities in hospital discharge planning. However, currently, no guidelines exist on cardiovascular screening in respiratory patients.[28] Validated scores such as the Framingham general cardiovascular risk profile prediction are available for the estimation of cardiovascular disease risk.[29] However, such risk scores tend to underestimate cardiac risk in people living with COPD.[30] In cases where there is a need for more detailed individual testing, several diagnostic tests are available. For instance, electrocardiography, echocardiography and blood biomarkers such as amino-terminal pro B-type natriuretic peptide (NT-proBNP) and troponin are available to screen for acute cardiac dysfunction during

ECOPD.[25] A recent study in primary care showed that such proactive strategies improved the yield of undiagnosed cardiovascular disease in stable COPD, although the effects on patient outcomes warrant further research.[31] Finally, whilst acknowledging that still too little is known about the mechanisms between ECOPD and subsequent non-respiratory events, this recommendation lacks specific therapeutic guidelines. Research has shown that some treatments for COPD may decrease cardiovascular risk. Inhaled corticosteroids (ICS) in combination with dual long-acting bronchodilators have for instance been shown to reduce mortality, and putatively cardiovascular mortality in COPD.[32-34] One of the suggested mechanisms behind this is the reduction in hyperinflation, subsequently improving cardiac function and pulmonary vasoconstriction.[35, 36] Such interactions warrant further investigation, though carefully minding potential side-effects, such as increased risk of pneumonia and osteoporosis.[37, 38] Taken together, more extensive and specific guidelines with a focus on prevention and early intervention are warranted to improve the burden and outcomes of exacerbation-related hospitalization.

Occurrence of exacerbations

Notwithstanding existing risk factors for ECOPD, such as a history of ECOPD and cigarette smoking[26], the susceptibility of an individual patient to exacerbate remains largely unknown. As such, timely individualized prediction of the occurrence of ECOPD remains unsuccessful to date. Accurate prediction of ECOPD and timely initiation of treatment are pivotal to reduce their negative impact on individual patients. Indeed, early recognition and treatment of ECOPD are associated with a faster recovery and reduced risk of hospitalization.[39] For over a decade, a history of ECOPD has remained the single best predictor of frequent ECOPD.[40] Accordingly, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document states that having had two or more moderate ECOPD in the preceding year predicts high future ECOPD risk.[26, 41] In addition, given the significance of hospital admission, previous hospitalization(s) has also been considered an indicator of high future ECOPD risk by GOLD.[26] Accumulating evidence suggests that having had two or more prior moderate ECOPD may not be on a par with prior hospitalization(s) in terms of future risk of ECOPD, hospitalization and mortality.[42-45] Results of the study presented in **Chapter 4** confirm the limited predictive performance of the current COPD future risk assessment by GOLD, based on these cutoffs. This study, including 2,291 patients with COPD from the German COSYCONET cohort, found

that one previous ECOPD instead of ≥2 revealed the most optimal cutoff value, while one previous hospitalization was validated as the most optimal cutoff value to predict future ECOPD and hospitalization risk. This has recently also been shown in GOLD A and B patients with COPD.[46] Hence, patients may need to be referred to as non-exacerbators and high-risk exacerbators as opposed to patients with a moderate and severe ECOPD history. Nevertheless, whilst these cutoffs showed a slight improvement from the current GOLD model, the models' predictive performance still remained limited. Thus, the prediction of future COPD outcomes cannot solely be predicted by ECOPD history, and other factors should be explored and incorporated to improve the accuracy of risk status prediction in COPD. For instance, gastroesophageal reflux disease, chronic bronchitis, a higher symptom burden and lower lung function demonstrated an elevated risk of ECOPD in patients with COPD who do not have a recent history of ECOPD[47], presenting potential utility in refining predictive models.

As described in **Chapter 1**, the lack of biomarkers predicting ECOPD susceptibility forms an important unmet need in the management of COPD, and might provide a helpful tool for clinicians to improve targeted treatment of ECOPD.[48] For example, previously, an eosinophil-predominant biologic cluster of ECOPD was identified.[49] It has been shown that blood eosinophil count can be used as a biomarker to identify individuals whom will benefit from a corticosteroid treatment for an ECOPD.[50, 51] Blood eosinophil-guided treatment with corticosteroids during ECOPD was non-inferior compared with standard care in terms of outcomes including length of hospital stay and mortality, and reduced overall corticosteroid use.[52-54] Accordingly, in the most recent Dutch COPD guideline, as published by the Dutch Association of Physicians for Pulmonary Diseases and Tuberculosis (NVALT)/the Dutch Federation for Medical Specialists (FMS), taking blood eosinophil levels into consideration is recommended when contemplating treatment of ECOPD with systemic corticosteroids[55], although consensus on the cutoff value is yet to be reached. To date, there are no other ECOPD biomarkers aside from the Food and Drug Administration (FDA) qualified prognostic biomarker for ECOPD and all-cause mortality, plasma fibrinogen.[56, 57] However, it is noteworthy that this biomarker is not currently utilized in clinical practice. Biomarkers such as C-reactive protein (CRP) and procalcitonin have been suggested to differentiate bacterial from non-bacterial ECOPD[58], and have shown promising results to help guide the prescription of antibiotics with more precision.[59-61] Hyaluronic acid (HA), a major component of the

extracellular matrix in lung tissues[62], is gaining attention to serve as a biomarker of COPD disease severity and/or disease progression.[63] In **Chapter 5** it was shown that plasma HA did not differ significantly between 192 patients with clinically stable COPD and 191 (non)smoking controls, although there was a trend towards higher levels in patients with a recent, i.e. <12 months, hospitalization history.[64] Furthermore, expression levels of the HA degrading enzyme hyaluronidase-2 (HYAL-2) were significantly elevated, and positively associated with plasma HA, in patients with COPD. These results challenge the utility of HA as potential biomarker in COPD, but methodological shortcomings in this study should be acknowledged. Further research into the potential role of alterations in HA levels and HYAL activity in COPD is needed before statements on their potential use for clinical recommendations in respiratory health and disease can be made.

Chapter 1 furthermore pointed out that microbial composition and host-microbe interactions are increasingly recognized for their role in affecting the susceptibility to ECOPD, and may steer towards another novel promising direction in ECOPD biomarker research. For instance, patients with a neutrophilic inflammatory endotype at a stable disease state have been shown to exhibit increased proportions of the bacterial phylum Proteobacteria, in particular *Haemophilus influenzae*, whereas patients characterized by an eosinophilic inflammatory endotype exhibit a decreased proportion of Proteobacteria and a higher abundance of Firmicutes.[65, 66] While there is some degree of temporal stability of an individual's lung microbiome[67], accumulating evidence has shown that there may be temporal variability during ECOPD[68-71], with amplification of the underlying inflammatory profile.[70, 72] Indeed, increased levels of proinflammatory mediators such as IL-1β and TNF-α have been shown during neutrophilic/Proteobacteria predominant ECOPD, whereas increased levels of type 2 and type 1 inflammatory mediators were shown during eosinophilic/Bacteroidetes, and viral/Firmicutes predominant ECOPD, respectively.[72] Still, many questions remain. Since the design of most studies was cross-sectional[67-72], temporal changes and causal relations remain to be elucidated. Further research is needed to explore the causality of microbial changes in relation to inflammation and the onset of ECOPD. Therefore, microbial composition and host-microbe interactions should be explored in the stable state, in the days leading up to an ECOPD, during ECOPD and at a convalescent disease state. Furthermore, most studies focused

on the sputum microbiome[65-72], neglecting evidence of a distinct gut microbiome in (E)COPD.[73, 74] Indeed, alterations and dysbiosis of the gut microbiota have been linked to lung immunity and respiratory diseases including COPD.[75, 76] Moreover, enterocyte damage and intestinal hyperpermeability have been observed in stable COPD[77], as well as during severe ECOPD.[78] Importantly, the lung microbiota differs in function, colonization, and individual microbes from the gut microbiota.[79] Therefore, including gut microbiome samples in addition to lung microbiome samples could shed light on the gut-lung axis and its bidirectional relationship in COPD.[80]

Results from this thesis underline the urgency for strengthened and improved ECOPD prevention strategies to decrease the burden of ECOPD on healthcare systems, and the more than 480 million individuals currently living with COPD around the globe.[81] In the 2023 update of the GOLD strategy document, shielding measures were added to a list of interventions that may reduce the frequency of ECOPD.[82] This addition was the result of the major reduction in the number of ECOPD-related hospitalizations observed around the world during the Coronavirus Disease 2019 (COVID-19) pandemic.[83-95] Indeed, it is presumable that the COVID-19-related infection prevention and control (IPC) measures, including social distancing, wearing face masks, and overall enhanced hygiene measures were responsible for this reduction by also affecting the transmission of respiratory viruses other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[96] An alternative explanation, however, could be the avoidance of hospital care by patients during ECOPD due to fear of contracting a SARS-CoV-2 infection. The results provided in **Chapter 6** favor the latter hypothesis since a non-significant reduction of 25.4% was observed in the number of ECOPD during the COVID-19 pandemic compared to previous years in a real-life inpatient pulmonary rehabilitation setting.[97] Importantly, this study included 501 patients with severe COPD, with many patients (71.0%) exhibiting the frequent exacerbating phenotype. Although pulmonary rehabilitation is beneficial irrespective of the underlying COPD disease severity, frequent ECOPD are a common indication for referral to pulmonary rehabilitation.[98] These findings may thus indicate that the protective effects of IPC measures for the prevention of ECOPD may be more pronounced in patients with a less severe overall clinical presentation, and/or that these effects may be different for the different types of ECOPD.[99] Future studies are indicated to elaborate further on this. Nevertheless, the prevention of every single ECOPD matters, and

the majority of patients with COPD expressed to be supportive of maintaining COVID-19-related IPC measures to reduce the risk of ECOPD.[100] As such, these measures could be considered during high-risk months, in patients at high-risk of ECOPD.

Conclusions

Taken together, this thesis has shown that readmissions and mortality rates following ECOPD-related hospitalizations remain poor around the world, and that the impact of these events extends beyond the lungs. Moreover, this thesis has shown that it remains a challenge to accurately predict and prevent the occurrence of ECOPD.

Despite the availability of several pharmacological and non-pharmacological interventions, a significant number of patients with COPD continues to experience (recurrent) ECOPD. This thesis underpins the need for a heightened vigilance of non-respiratory outcomes following ECOPD, in particular of the independent increased risk of subsequent cardiovascular events. This knowledge should be integrated into post-ECOPD care, irrespective of the severity of the ECOPD, and calls for proactive screening and risk management, as well as strengthening interdisciplinary partnerships with cardiologists.

This thesis has also demonstrated that predicting the occurrence of ECOPD cannot solely be determined by a history of ECOPD, and that other determinants of ECOPD should be explored and integrated in COPD risk status assessment tools. Furthermore, this thesis underscores the challenges associated with preventing ECOPD. As such, although many questions remain, the value of COVID-19-related IPC measures for the prevention of ECOPD may not be evident in every patient, or for every ECOPD. Nonetheless, each single ECOPD has a detrimental effect on a patient's life. Therefore, clinicians should be encouraged to implement such measures for the prevention of ECOPD during high-risk ECOPD seasons, especially in patients at high-risk for ECOPD.

Future directions

This thesis gives rise to several questions that could be addressed in future studies. First, the poor and heterogeneous readmission and mortality rates associated with ECOPD-related hospitalizations, and the high heterogeneity of available data between studies and countries stress the need for global standardization of the management and follow-up of these events. The collection of such data should be at the heart of future implementation research. In light of this, policy makers and future studies should focus on identifying novel evidence-based strategies that decrease (recurrent) ECOPD. Second, the high occurrence of cardiovascular and other non-respiratory events following ECOPD, and the largely unknown relation between ECOPD and such all-cause future events, prompt further research into the mechanistic pathways involved to provide new preventive and therapeutic targets. Third, while continuing to search for improved ECOPD prevention strategies, future studies should further assess whether, which, when, and to what extent COVID-19-related IPC measures can prevent (the different types of) ECOPD, as well as which patients might benefit from such measures. At last, studies are needed to improve the discriminative accuracy of COPD future risk assessment classification tools, by exploring and integrating other determinants besides a history of ECOPD. Indeed, the identification of early and accurate biomarkers to predict ECOPD should be prioritized in future research. Markers of extracellular remodeling, and alterations in the respiratory and gut microbial composition and host-microbiome interactions are increasingly recognized for their role in affecting the susceptibility to ECOPD, and might be useful in the development of more accurate prediction models. Studies that longitudinally assess multiple biological sample types could provide valuable information on the intra- and intervariability of biomarkers, and microbial composition and host–microbiome interactions within and across individuals over time. These studies, including the ongoing exploratory, prospective, longitudinal, single-center, observational MARKED study[101], will provide a deeper understanding of the clinical, laboratory and microbial factors associated with ECOPD. They involve comprehensive and longitudinal patient and ECOPD characterization, incorporating a broad spectrum of inflammatory parameters and multi-omics, which will allow the identification of causal relationships between biomarkers and other determinants of ECOPD. This knowledge is essential to improve the management and personalized treatment of ECOPD.

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ADDENDA

A

Summary

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by persistent respiratory symptoms and airflow limitation, resulting from abnormalities of the airways and lung parenchyma. Following ischemic heart disease and stroke, COPD ranks as the third leading cause of death worldwide, imposing a substantial burden on public health and economic resources. Most patients with COPD will suffer from exacerbations (ECOPD) at some point during the disease course. ECOPD are characterized by increased respiratory symptoms, such as dyspnea and/or cough and sputum, that worsen within 14 days, and are often associated with increased local and systemic inflammation caused by infection, pollution or other insult to the airways. Even a single ECOPD may significantly enhance the rate of lung function decline, reduce the patient's overall health status, and increase the risk of further ECOPD, cardiovascular comorbidities, hospital admissions and mortality. Despite their great impact, specific predictors of the occurrence and outcomes of ECOPD currently remain largely unknown, leading to a great challenge for their clinical management. Therefore, the central aims of this thesis were to predict the occurrence and outcomes of ECOPD (**Chapter 1**).

Increasing our understanding of the outcomes of ECOPD is essential while striving to improve their clinical management. ECOPD resulting in healthcare contact, especially those requiring visits to the emergency service and hospital admission, are associated with a more severe prognosis, and are the main driver of global COPD-related healthcare expenses. **Chapters 2** and **3** aimed to assess the outcomes of ECOPD-related hospitalization. **Chapter 2** studied in-hospital mortality, post-discharge mortality and hospital readmission rates following ECOPD-related hospitalization in 65,945 patients with COPD from 30 different countries around the world. This meta-analysis of individual patient data revealed poor pooled outcome rates for in-hospital mortality, 1-year post-discharge mortality and 1-year hospital readmission (6.2%, 12.2% and 38.2%, respectively), with noticeable variability between studies and countries. Furthermore, routinely available predictors of mortality and hospital readmission were identified, including a history of previous ECOPD-related hospitalizations, and markers of disease severity such as the need for (non)invasive mechanical ventilation and admission to

an intensive care unit. These outcomes can be used in clinical decision-making, with the overall aim of enhancing the prognosis of patients with COPD.

Whilst mortality and ECOPD-related hospital readmission are pivotal outcomes of ECOPD, the results of **Chapter 3** indicated that there is also a need for a heightened vigilance of non-respiratory events following ECOPD. In this study, including 82,964 patients with COPD from the Danish national patient registry, it was shown that more than half of the hospital admissions following a patient's first ever ECOPD-related hospital admission are driven by non-respiratory causes, both on the short- (30-days) and long-term (five years). Cardiac admissions were most frequent, and predominantly caused by myocardial ischemia, pulmonary heart disease and diseases of pulmonary circulation, myocarditis, cardiomyopathy and arrhythmias. Other frequent non-respiratory admissions were related to cancer and digestive-, endocrine-, nutritional- and metabolic disorders. Identification of the causal pathways between ECOPD and subsequent non-respiratory events, in particular cardiovascular events, may provide directions for therapeutic targets to decrease the burden of hospitalizations in COPD. **Chapter 3** furthermore indicated that, irrespective of the number of admissions, the patients not surviving the five-year follow-up period were older, had more comorbidities and a longer hospital stay during the index ECOPD. Altogether, these chapters underline the poor outcomes and widespread consequences of ECOPD-related hospitalization, and the importance of strengthening and improving the prevention and early intervention of ECOPD. Key to this is a timely individualized prediction of their occurrence.

Chapters 4, **5** and **6** aimed to assess (predictors of) the occurrence of ECOPD. **Chapter 4** studied the predictive performance of the current COPD future risk assessment tool by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2,291 patients with COPD from the German prospective, observational, multicenter COSYCONET cohort. According to GOLD, patients with ≥2 moderate ECOPD and/or ≥1 hospitalization <12 months are at high risk of ECOPD. The results presented in **Chapter 4** demonstrated that the current GOLD model has a limited discriminative accuracy to predict future ECOPD, hospitalizations and all-cause mortality. One previous ECOPD instead of ≥2 ECOPD was found to be the most optimal cutoff value, whereas one previous hospitalization was validated as the most optimal cutoff value to predict risk of ECOPD and hospitalizations. Importantly, while these cutoffs showed a slight

improvement from the current GOLD model, the models still had a low predictive performance. Taken together, these results indicated that the prediction of future COPD outcomes such as ECOPD, hospitalizations and all-cause mortality may not be solely dependent on ECOPD history, and that other determinants should be explored and incorporated to improve the accuracy of risk status prediction in COPD.

Recent studies suggest a potential relationship between hyaluronic acid (HA) and COPD, highlighting its role in inflammation, tissue remodeling and disease progression. HA is one of the key components of the extracellular matrix of the lungs, affecting airway wall structure, elasticity and resistance. In **Chapter 5**, levels of systemic HA and its metabolic regulators were assessed in 192 patients with clinically stable COPD and 191 (non)smoking controls from the Dutch single-center, longitudinal, observational ICE-Age study. This study showed that while plasma HA and expression levels of the HA synthesizing enzyme HA synthase-3 (HAS-3) did not differ significantly between patients with clinically stable COPD and (non)smoking controls, expression of the HA degrading enzyme hyaluronidase-2 (HYAL-2) was significantly higher in patients with COPD. No significant associations with ECOPD and hospitalization history were found. However, there was a trend towards higher plasma HA levels in patients with a recent hospitalization history. These results challenge the utility of HA to serve as a biomarker of COPD disease severity and/or disease progression, as previously suggested. Interestingly, a positive association between cardiovascular risk, assessed by arterial pulse wave velocity, and systemic HA was observed. These results indicated that cardiovascular risk might be involved in the systemic regulation of HA in stable COPD. Taken together, it was concluded that further research into the potential role, and origin of alterations in HA levels and HYAL activity in COPD is needed before statements on their potential use for clinical recommendations in respiratory health and disease can be made.

During the Coronavirus Disease 2019 (COVID-19) pandemic, a worldwide 50% reduction in the number of ECOPD-related hospitalizations was observed. In response to this significant reduction, shielding measures, e.g. social distancing, wearing face masks and overall enhanced hygiene, were added to a list of interventions that may reduce the frequency of ECOPD in the 2023 update of the GOLD strategy document. However, avoidance of healthcare by patients provides an alternative, plausible explanation for this observed reduction in hospitalizations.

In **Chapter 6**, the impact of the COVID-19-related infection prevention and control (IPC) measures on the occurrence of ECOPD was evaluated in a single-center pulmonary rehabilitation setting. This study, including a total of 501 Dutch patients with COPD, predominantly exhibiting the frequent exacerbator phenotype, demonstrated a 25.4% non-significant reduction in the number of ECOPD during the COVID-19 pandemic compared to previous years. These findings lend credence to the hypothesis that the reduction in ECOPD-related hospitalizations observed during the COVID-19 pandemic might have been driven, at least in part, by altered healthcare seeking behavior of patients rather than the installation of COVID-19-related IPC measures, and that the impact of such measures for the prevention of ECOPD may not be universal for every patient or for every type of ECOPD. Nevertheless, as the prevention of each single ECOPD matters, it was concluded that administering IPC measures should not be discouraged in patients at high ECOPD risk, during high-risk months.

And lastly, **Chapter 7** discussed the main findings and clinical implications of this thesis, and provided directions for future research. In conclusion, this thesis demonstrated that predicting and targeting the occurrence of ECOPD remains challenging. This is reflected by poor hospital readmission and mortality rates in patients with COPD around the world. Further research into the causal relations between ECOPD and subsequent non-respiratory events, as well as the identification of more accurate, timely, and individualized predictors of ECOPD, should be prioritized. This will lead to the development of superior ECOPD prediction models, strengthened and improved ECOPD prevention strategies, and more effectively reduce the burden of hospitalization in COPD.

Samenvatting

Chronisch obstructief longlijden (COPD) is een heterogene longaandoening gekenmerkt door aanhoudende ademhalingssymptomen en luchtwegvernauwing, voortkomend uit afwijkingen van de luchtwegen en het longweefsel. Na ischemische hartziekten en beroertes vormt COPD de derde belangrijkste doodsoorzaak wereldwijd, met een aanzienlijke last voor de volksgezondheid en zorgkosten. De meeste patiënten met COPD zullen op enig moment tijdens het ziektebeloop te maken krijgen met exacerbaties (ECOPD). ECOPD worden gekenmerkt door verhoogde ademhalingssymptomen, zoals kortademigheid en/of hoesten en het opgeven van slijm, welke verslechteren binnen 14 dagen en vaak geassocieerd zijn met verhoogde lokale en systemische ontstekingen veroorzaakt door infectie, vervuiling of andere prikkels voor de luchtwegen. Zelfs één enkele ECOPD kan zorgen voor een significante versnelde afname van longfunctie, de algehele gezondheidstoestand van de patiënt verminderen, en het risico op verdere ECOPD, cardiovasculaire comorbiditeiten, ziekenhuisopnames en sterfte verhogen. Ondanks hun grote impact blijven specifieke voorspellers van het optreden en de uitkomsten van ECOPD momenteel grotendeels onbekend, dit vormt een grote uitdaging voor hun klinische management. Daarom waren de centrale doelstellingen van dit proefschrift het voorspellen van het optreden en de uitkomsten van ECOPD (**Hoofdstuk 1**).

Een beter begrip van de uitkomsten van ECOPD is essentieel bij het streven naar verbetering van hun klinische management. ECOPD die resulteren in contact met de gezondheidszorg, in het bijzonder ECOPD die een bezoek aan de spoedeisende hulp en ziekenhuisopname vereisen, zijn geassocieerd met een ernstigere prognose en vormen de belangrijkste aandrijver voor de wereldwijde COPD-gerelateerde zorgkosten. **Hoofdstukken 2** en **3** beoogden de uitkomsten van ECOPD-gerelateerde ziekenhuisopnames te beoordelen. **Hoofdstuk 2** bestudeerde sterfte tijdens en na ziekenhuisopname, alsook ziekenhuisheropname cijfers na een ECOPD-gerelateerde ziekenhuisopname bij 65.945 patiënten met COPD uit 30 verschillende landen over de hele wereld. Deze meta-analyse van individuele patiëntengegevens onthulde dat het slecht gesteld is met deze uitkomsten: sterfte tijdens ziekenhuisopname, 1-jaar na ziekenhuisopname en ziekenhuisheropname 1-jaar na ontslag waren respectievelijk 6,2%, 12.2% en 38.2%, met aanzienlijke verschillen tussen

studies en landen. Daarnaast werden routinematig beschikbare voorspellers van sterfte en ziekenhuisheropname geïdentificeerd, waaronder een voorgeschiedenis van eerdere ECOPD-gerelateerde ziekenhuisopnames, en markers van de ernst van de ziekte zoals de behoefte aan (niet-)invasieve mechanische beademing en opname op een intensive care afdeling. Deze uitkomsten kunnen worden gebruikt bij klinische besluitvorming, met als algemeen doel het verbeteren van de prognose van patiënten met COPD.

Hoewel sterfte en ECOPD-gerelateerde ziekenhuisopnames belangrijke uitkomsten zijn van ECOPD lieten de resultaten van **Hoofdstuk 3** zien dat er ook meer aandacht voor niet-respiratoire gebeurtenissen na ECOPD zou moeten zijn. In deze studie, waarbij 82.964 patiënten met COPD uit het Deense nationale patiënten register werden geïncludeerd, werd aangetoond dat meer dan de helft van de ziekenhuisopnames na een allereerste ECOPD-gerelateerde ziekenhuisopname veroorzaakt wordt door niet-respiratoire oorzaken, zowel op de korte (30 dagen) als op de lange termijn (vijf jaar). Opnames voor cardiovasculaire aandoeningen kwamen het vaakst voor en werden voornamelijk veroorzaakt door myocardiale ischemie, pulmonale hartaandoeningen en aandoeningen van de pulmonale circulatie, myocarditis, cardiomyopathie en hartritmestoornissen. Andere frequente niet-respiratoire opnames waren gerelateerd aan kanker en spijsverterings-, hormonale-, voedings- en stofwisselingsstoornissen. Identificatie van de causale verbanden tussen ECOPD en daaropvolgende niet-respiratoire gebeurtenissen, in het bijzonder cardiovasculaire gebeurtenissen, kan aanwijzingen geven voor therapeutische doelen om de ziekenhuisopnamelast bij patiënten met COPD te verminderen. **Hoofdstuk 3** gaf bovendien aan dat, ongeacht het aantal heropnames, de patiënten die de vijfjarige follow-up periode niet overleefden ouder waren, meer comorbiditeiten en een langere opnameduur hadden tijdens de index ECOPD. Al met al onderstrepen deze hoofdstukken de slechte uitkomsten en wijdverspreide gevolgen van ECOPD-gerelateerde ziekenhuisopnames, en het belang van het versterken en verbeteren van de preventie en vroegtijdige interventie van ECOPD. Belangrijk hierbij is een tijdige, geïndividualiseerde voorspelling van het optreden hiervan.

Hoofdstukken 4, **5** en **6** waren gericht op het beoordelen van (voorspellers van) het optreden van ECOPD. **Hoofdstuk 4** onderzocht de voorspellende prestatie van het huidige COPD toekomstig risico voorspellingsmodel van het Global Initiative for Chronic Obstructive Lung

Disease (GOLD) bij 2.291 patiënten met COPD uit de Duitse prospectieve, observationele, multicenter COSYCONET cohort. Volgens GOLD lopen patiënten met ≥2 matige ECOPD en/of ≥1 ziekenhuisopname <12 maanden een hoog risico op het ontwikkelen van ECOPD. De resultaten gepresenteerd in **Hoofdstuk 4** toonden aan dat het huidige GOLD model een beperkte discriminerende nauwkeurigheid heeft om toekomstige matige en ernstige ECOPD en sterfte te voorspellen. Eén eerdere matige ECOPD in plaats van ≥2 matige ECOPD bleek de meest optimale afkapwaarde te zijn, terwijl één eerdere ernstige ECOPD werd gevalideerd als de meest optimale afkapwaarde om het risico op matige en ernstige ECOPD te voorspellen. Belangrijk is dat, hoewel deze afkapwaarden een lichte verbetering vertoonden ten opzichte van het huidige GOLD model, de modellen nog steeds een lage voorspellende waarde hadden. Concluderend suggereren deze resultaten dat de voorspelling van toekomstige uitkomsten van COPD, zoals ECOPD en sterfte mogelijk niet uitsluitend afhankelijk zijn van ECOPD-geschiedenis, en dat andere determinanten onderzocht en geïntegreerd moeten worden om de nauwkeurigheid van risicostatus voorspelling bij COPD te verbeteren.

Recente studies suggereren een mogelijk verband tussen hyaluronzuur (HA) en COPD, waarbij de rol van HA bij ontstekingen, hermodellering van weefsel en ziekteprogressie wordt benadrukt. HA is een van de belangrijkste componenten van de extracellulaire matrix van de longen, die de structuur, elasticiteit en weerstand van de luchtwegwand beïnvloedt. In **Hoofdstuk 5** werden de waardes van systemisch HA en zijn metabole regulatoren bestudeerd bij 192 patiënten met klinisch stabiele COPD en 191 (niet)rokende controles uit de Nederlandse single-center, longitudinale, observationele ICE-Age studie. Deze studie toonde aan dat hoewel plasma HA en expressieniveaus van het HA synthetiserende enzym HA synthase-3 (HAS-3) niet significant verschilden tussen patiënten met klinisch stabiele COPD en (niet)rokende controles, de expressie van het HA afbrekende enzym hyaluronidase-2 (HYAL-2) significant hoger was bij patiënten met COPD. Er werden geen significante associaties met ECOPD en ziekenhuisopnamegeschiedenis gevonden. Er werd echter wel een trend naar hogere plasma HA waardes geconstateerd bij patiënten met een recente ziekenhuisopnamegeschiedenis. Deze resultaten stellen de bruikbaarheid van HA als biomarker voor de ernst van COPD en/of ziekteprogressie, zoals eerder gesuggereerd, ter discussie. Interessant genoeg werd een positieve associatie waargenomen tussen cardiovasculair risico, beoordeeld aan de hand van de arteriële polsgolfsnelheid, en

systemisch HA. Deze resultaten suggereren dat cardiovasculair risico betrokken zou kunnen zijn bij de systemische regulatie van HA bij stabiele COPD. Al met al werd geconcludeerd dat verder onderzoek naar de mogelijke rol en oorsprong van veranderingen in HA waardes en HYAL-activiteit bij COPD nodig is voordat er uitspraken gedaan kunnen worden over hun mogelijke gebruik voor klinische aanbevelingen bij respiratoire gezondheid en ziekte.

Tijdens de Coronavirus disease 2019 (COVID-19) pandemie werd wereldwijd een afname van 50% in het aantal ECOPD-gerelateerde ziekenhuisopnames waargenomen. Als reactie op deze significante afname werden COVID-19-gerelateerde beschermende maatregelen, zoals het bewaren van afstand, het dragen van mondkapjes en algehele verbeterde hygiëne toegevoegd aan een lijst van interventies die de frequentie van ECOPD zouden kunnen verminderen in de update van 2023 van het GOLD-strategiedocument. Echter, het vermijden van gezondheidszorg door patiënten biedt een alternatieve, plausibele verklaring voor deze waargenomen daling in het aantal ziekenhuisopnames. In **Hoofdstuk 6** werd de impact van de COVID-19-gerelateerde infectiepreventie- en controlemaatregelen (IPC) op het optreden van ECOPD geëvalueerd in een single-center longrevalidatiesetting. Deze studie, die in totaal 501 Nederlandse patiënten met COPD includeerde die voornamelijk het frequente exacerbator fenotype vertoonden, liet een niet-significante afname van 25,4% zien in het aantal ECOPD tijdens de COVID-19 pandemie in vergelijking met voorgaande jaren. Deze bevindingen ondersteunen de hypothese dat de afname in het aantal ECOPD-gerelateerde ziekenhuisopnames tijdens de COVID-19 pandemie mogelijk deels veroorzaakt werd door veranderd gedrag van patiënten ten aanzien van het benaderen van gezondheidszorginstanties in tegenstelling tot de invoering van COVID-19-gerelateerde IPC-maatregelen, en dat het effect van dergelijke maatregelen voor de preventie van ECOPD mogelijk niet universeel is voor elke patiënt of voor elk type ECOPD. Desondanks werd geconcludeerd dat, aangezien de preventie van elke afzonderlijke ECOPD van belang is, het toepassen van IPC-maatregelen niet moet worden ontmoedigd bij patiënten met een hoog risico op ECOPD, tijdens hoog risico perioden.

Tot slot werden in **Hoofdstuk 7** de belangrijkste bevindingen en klinische implicaties van dit proefschrift besproken, en werden aanwijzingen gegeven voor toekomstig onderzoek. Concluderend toonde dit proefschrift aan dat het voorspellen en beïnvloeden van het

optreden van ECOPD uitdagend blijft. Dit wordt weerspiegeld door hoge ziekenhuisopname- en sterftecijfers bij patiënten met COPD over de hele wereld. Verder onderzoek naar de causale relaties tussen ECOPD en daaropvolgende niet-respiratoire gebeurtenissen, evenals de identificatie van nauwkeurigere, tijdige en geïndividualiseerde voorspellers van ECOPD moet worden geprioriteerd. Dit zal leiden tot de ontwikkeling van superieure ECOPD voorspellingsmodellen, versterkte en verbeterde ECOPD preventiestrategieën, en een effectievere vermindering van de last van ziekenhuisopnames bij COPD.

Impact paragraph

This thesis has provided a deeper understanding of the occurrence and outcomes of exacerbations of COPD (ECOPD). The current chapter aims to reflect on the scientific and social impact of the findings presented in this thesis, by elaborating on the following four questions: (1) What is the main objective of the research described in the thesis and what are the most important results and conclusions? (2) Wat is the (potential) contribution of the results from this research to science and social sectors, and social challenges? (3) To whom are the research results relevant, and why? (4) In what way can these target groups be involved in and informed about the research results, so that the knowledge gained can be used in the future?

Main objectives, findings and conclusions

The disease course of most patients with COPD is punctuated by ECOPD. These events are characterized by a worsening of respiratory symptoms such as dyspnea and/or cough and sputum, and are often associated with increased local and systemic inflammation caused by airway infection, pollution or other insult to the airways. However, clear evidence of a cause may be lacking in a significant proportion of cases. The treatment of ECOPD may range from increased use of bronchodilators, to oral corticosteroids and/or antibiotics, or to hospital admission in severe cases. Even a single ECOPD may result in a significant decline in lung function, muscle strength, exercise capacity, mental health, and quality of life. Furthermore, each ECOPD increases the risk of future ECOPD, cardiovascular comorbidities and mortality. Despite their great impact, specific predictors of the occurrence and outcomes of ECOPD currently remain largely unknown, imposing a great challenge for their clinical management. The main objectives of this thesis were to predict the occurrence and outcomes of ECOPD.

Chapters 2 and 3 of this thesis confirm the devastating impact of ECOPD-related hospitalizations on hospital readmission and mortality rates in patients with COPD around the world. In Chapter 2, great heterogeneity in outcome rates between studies and countries were noted, as well as significant differences in availability of clinical data, and a paucity of data from non-European countries. Chapter 3 demonstrates that more than half of the hospital admissions following ECOPD-related hospitalization concern non-respiratory events. Cardiovascular causes, such as myocardial ischemia, pulmonary heart disease and diseases of

pulmonary circulation, and arrhythmias are the most important drivers of non-respiratory hospital admissions. Taken together, these findings highlight the importance of global (standardization of) data collection, and the need for guidelines for post-discharge follow-up as well as monitoring of patients after ECOPD-related hospitalization. In addition, these results indicate that targeting the non-respiratory causes of hospital readmission will likely be key to effectively decrease the burden of hospitalization in COPD. Chapter 4 of this thesis demonstrates that predicting the occurrence of ECOPD based solely on a ECOPD history is not sufficiently accurate, and that other determinants of ECOPD risk should be explored and integrated in COPD risk status assessment tools. Moreover, Chapters 5 and 6 of this thesis challenge the utility of hyaluronic acid (HA) as potential biomarker in COPD, and indicate that the impact of the COVID-19-related infection prevention and control (IPC) measures for the prevention of ECOPD may not be universal for every patient, or for every ECOPD. Altogether, these results underline the need for improved ECOPD prediction models, as well as strengthened and improved ECOPD prevention strategies.

Potential contribution to science and social sectors and challenges

Individuals living with COPD and their caregivers have recently prioritized research into understanding ECOPD risk, recurrence and prevention as their most important unmet need. The results of this thesis contribute to this need in terms of providing comprehensive insights into the impact ECOPD have on outcomes such as hospital readmission and mortality. This knowledge can be utilized to study innovative targets for modifying risk factors associated with these adverse outcomes. The limited knowledge of such underlying mechanisms calls for allocation of research funding to understand these mechanisms and putatively the burden of disease, particularly in low- and middle income countries. Moreover, this thesis highlights the importance of heightened vigilance of non-respiratory events following ECOPD-related hospitalization. For clinical practice this implies routinely evaluating comorbidities in patients with COPD, especially during and following ECOPD. Such proactive screening and risk management calls for interdisciplinary partnerships with cardiologists, and other healthcare professionals depending on the patient's individual risk profile. This knowledge is furthermore of importance for policymakers and guideline developers as they prompt a paradigm shift in the management of COPD, in which the importance of preventing non-respiratory events should receive as much attention as the prevention of ECOPD.

In addition, this thesis informs clinicians that current COPD risk status assessment tools based solely on ECOPD history are limited at predicting the risk of ECOPD, hospitalizations and mortality. For scientists, this implies that future studies should be aimed at identifying and integrating other determinants besides ECOPD history to improve the discriminative accuracy of such tools. The narrative review included in Chapter 1 of this thesis suggests that alterations in the respiratory and gut microbial composition, and host-microbiome interactions might prove useful in the development of more accurate prediction models as they provide a hidden link between ECOPD and the stable disease state. Moreover, findings of ongoing studies, such as the MARKED study, will provide important insights into the clinical, laboratory and microbial factors associated with ECOPD. This thesis furthermore informs clinicians, patients and policymakers that the impact of COVID-19-related IPC measures for the prevention of ECOPD may not be evident for every patient, or for every ECOPD. For scientists, this study provided important questions to be addressed in future research, including the identification of whether, which, when, and to what extent COVID-19-related IPC measures can prevent (the different types of) ECOPD, as well as which patients might benefit from such measures.

Target groups

The results of this thesis are relevant to multiple target groups including patients with COPD and their caregivers, lung health organizations and patient associations, researchers and various healthcare professionals, in particular respiratory physicians, cardiologists, physician assistants, nurses and general practitioners. For patients and caregivers, this thesis provides insights in the far-reaching outcomes as well as predictors of ECOPD. Moreover, it emphasizes the importance of preventing ECOPD. Non-profit health organizations, such as the Dutch Lung Foundation (Longfonds in Dutch), may use this knowledge to set up novel national media campaigns to raise awareness of the importance of preventing each single ECOPD. Reaching a national audience of patients, healthcare professionals and policymakers, this may spark discussions between patients and their healthcare providers to (re)assess the patient's individual ECOPD risk, and to review their current COPD management plan. Accordingly, this may help improve disease management in their home environment. Improving self-management strategies not only enhances health outcomes of individual patients, but also has the potential to contribute to reducing health disparities across patients and regions. The latter is one of the primary objectives of the Dutch Research Agenda (Nationale

Wetenschapsagenda in Dutch), realized by ZonMw and NWO, and co-funded by the Ministry of Health, Welfare and Sport. In addition to fostering behavioral changes among patients, and actions by lung health organizations and patient associations, this thesis aims to raise awareness of the poor and extra-pulmonary outcomes of ECOPD among healthcare professionals, and the need to look beyond ECOPD history to determine ECOPD risk. Furthermore, healthcare professionals may be faced with the question whether COVID-19-related IPC measures may be useful for the prevention of ECOPD in the post COVID-19 era. This thesis concludes that the COVID-19-related IPC measures may prevent some, but not every ECOPD. Further research is needed to elaborate further on this, and the other research questions raised in this thesis. Furthermore, the results of this thesis may be relevant to pharmaceutical companies since targeting the non-respiratory causes of hospital admission as well as alterations in the respiratory and gut microbiome were pointed out as important topics for future COPD care and research, and might lead to the development of novel treatments. At last, the results of this thesis are of relevance to policymakers and guideline developers as they underscore the necessity of prioritizing the prevention of ECOPD and associated non-respiratory events. Moreover, they advocate for the standardization of data collection, as well as of guidelines for post-discharge follow-up and monitoring of patients following ECOPD-related hospitalization. This will be essential to improve COPD care.

Activities

Several activities were undertaken to disseminate the results of this thesis. The results presented in Chapters 1 to 6, as well as the protocol of the MARKED study (not included as a chapter in this thesis), have been published or submitted in different scientific, international, peer-reviewed journals. The results of Chapters 2, 3, 5 and 6 have been presented at international congresses including the annual European Respiratory Society (ERS) Congress in 2021 (online, due to the COVID-19 pandemic), 2022 (Barcelona, Spain), and 2023 (Milan, Italy), at national congresses including the Dutch Lung Congress in 2021 (online, due to the COVID-19 pandemic), and 2022 (Utrecht, the Netherlands), and at local congresses including the annual symposium of the School of Nutrition and Translational Research in Metabolism (NUTRIM) of Maastricht University (Maastricht, the Netherlands) in 2021 and 2022, and research meetings organized by Ciro (Horn, the Netherlands) in 2021 and 2022. The results of Chapters 3 and 5 were furthermore presented at meetings organized by pharmaceutical

companies, including the Novartis Breath Online ERS Highlights Event, in Utrecht, the Netherlands (2021), and the GlaxoSmithKline (GSK) Specialists in Training Access to Relevant Research Overseas and Worldwide (SPARROW) meeting in Amersfoort, the Netherlands and Barcelona, Spain (2022). The presentation of the results of Chapter 3 at the GSK SPARROW meeting in Barcelona was selected as the Best Scientific Presentation by expert panel Prof. Walter Canonica (Italy), Prof. Florence Schleich (Belgium), Prof. Dave Singh (UK) and Dr. Hans In 't Veen (the Netherlands), and was awarded with a travel grant. The results of Chapter 4 will furthermore be presented at the ERS Congress in Vienna, Austria in 2024. As a result, the findings of this thesis were broadly disseminated, and will hopefully inspire clinicians and researchers to explore novel research questions and innovative studies addressing the unresolved challenges associated with ECOPD.

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Curriculum Vitae

Kiki was born on June 20, 1997, in Roermond, the Netherlands. After completing secondary school at Lyceum Schöndeln in Roermond in 2015, she studied Health Sciences with a specialization in Biology and Health at Maastricht University. After obtaining her bachelor's degree in 2018, she commenced with the master Biomedical Sciences with a specialization in Inflammation and Pathophysiology. In 2020, she obtained her master's degree.

During her studies at Maastricht University she had a parttime job at the Department of Planning and Patient Contact at Ciro (Horn, the Netherlands). Amazed by the excellent and holistic care provided at Ciro, she was fortunate to conduct her graduation internship of the master Biomedical Sciences there, supervised by prof. dr. Frits Franssen (Ciro, Maastricht University Medical Centre) and dr. Rosanne Beijers (Maastricht University). The results of this internship formed the foundation of one of the publications of her doctoral thesis (chapter 5).

In the summer of 2020, she started her PhD candidacy at Ciro in collaboration with the Department of Respiratory Medicine of the Research Institute of Nutrition and Translational Research in Metabolism (NUTRIM) of Maastricht University, supervised by prof. dr. Frits Franssen (Ciro, Maastricht University Medical Centre), dr. Sarah Houben-Wilke (Ciro) and dr. Sami Simons (Maastricht University Medical Centre). Her research focused on the prediction of the occurrence and outcomes of exacerbations of Chronic Obstructive Pulmonary Disease (ECOPD). In 2021, she visited the Department of Respiratory Diseases at the Aalborg University Hospital in Aalborg, Denmark. Supervised by prof. dr. Ulla Weinreich, and in close collaboration with dr. Peter Jacobsen, she analyzed data of the Danish national patient registry which resulted in the publication presented in chapter 3. In Ciro, she coordinated the Early diagnostic BioMARKers in Exacerbations of COPD (MARKED) study, a comprehensive study to longitudinally characterize ECOPD and biomarkers in patients with COPD admitted for pulmonary rehabilitation.

The results of her research have been published in different scientific, international, peer-reviewed journals and have been presented at national and international congresses and meetings. In 2022, Kiki won the Best Scientific Presentation at the GlaxoSmithKline (GSK) Specialists in Training Access to Relevant Research Overseas and Worldwide (SPARROW) meeting in Barcelona, Spain, for her presentation of the results presented in chapter 3, which had earned her a travel grant. She will be using this travel grant to attend the European Respiratory Society (ERS) Congress 2024 in Vienna, Austria. During her PhD she was a (co)host and member of the Netherlands Respiratory Society (NRS) Webinar Committee, organizing and (co)hosting webinars aiming to inform, highlight and promote pulmonary research from fundamental up to a translational and clinical level.

Currently, Kiki is employed as a postdoctoral researcher at the Department of Respiratory Medicine at Maastricht University where she is involved in research aimed at developing a digital companion for patients with COPD with the goal of enhancing lifestyle and reducing the burden of ECOPD. Kiki is married to Kyle Waeijen, and together with their daughter Lore they live in Beegden.

List of scientific publications

Scientific articles in international journals

Waeijen-Smit K, Houben-Wilke S, DiGiandomenico A, Gehrmann U, Franssen FME. Unmet needs in the management of exacerbations of chronic obstructive pulmonary disease. Internal and Emergency Medicine. 2021 Apr;16(3):559-569. doi: 10.1007/s11739-020-02612-9. Epub 2021 Feb 22. PMID: 33616876; PMCID: PMC7897880.

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Waeijen-Smit K, Reynaert NL, Beijers RJHCG, Houben-Wilke S, Simons SO, Spruit MA, Franssen FME. Alterations in plasma hyaluronic acid in patients with clinically stable COPD versus (non)smoking controls. Poster presentation, European Respiratory Society (ERS) International Congress 2021, virtual congress.

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Waeijen-Smit K, Jacobsen PA, Houben-Wilke S, Simons SO, Franssen FME, Spruit MA, Pedersen CT, Kragholm KH, Weinreich UM. All-cause admissions following a first ever

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Waeijen-Smit K, Houben-Wilke S, Posthuma R, de Jong F, Janssen DJA, van Loon NPH, Hajian B, Simons SO, Spruit MA, Franssen FME. Impact of Coronavirus Disease 2019-Related Infection Prevention and Control Measures on the Occurrence of COPD Exacerbations During Inpatient Pulmonary Rehabilitation. Oral presentation, Ciro Research meeting 2022, Ciro, Horn, the Netherlands.

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