Original research

Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England

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ABSTRACT

Background Identifying correlates of cause-specific mortality in patients with chronic obstructive pulmonary disease (COPD) may aid the targeting of therapies to reduce mortality. We determined factors associated with causes of death in a primary care COPD population.

Methods Clinical Practice Research Datalink Aurum was linked to Hospital Episode Statistics and death certificate data. People with COPD alive between 1 January 2010 and 1 January 2020 were included. Patient characteristics were defined before the start of follow-up: (a) frequency and severity of exacerbations; (b) emphysema or chronic bronchitis; (c) Global Obstructive Lung Disease (GOLD) groups A–D; and (d) airflow limitation. We used Cox Proportional Hazards regression and competing risks to investigate the association between patient characteristics and risk of all-cause, COPD and cardiovascular (CV) mortality.

Results 339 647 people with COPD were included of which 97 882 died during follow-up (25.7% COPD related and 23.3% CV related). Airflow limitation, GOLD group, exacerbation frequency and severity, and COPD phenotype were associated with all-cause mortality. Exacerbations, both increased frequency and severity, were associated with COPD-related mortality (≥2 exacerbations vs none adjusted HR: 1.64, 1.57–1.71; 1 severe vs none adjusted HR: 2.17, 2.04–2.31, respectively). Patients in GOLD groups B–D had a higher risk of COPD and CV mortality compared with GOLD group A (GOLD group D vs group A, adjusted HR for COPD mortality: 4.57, 4.23–4.93 and adjusted HR for CV mortality: 1.53, 1.41–1.65). Increasing airflow limitation was also associated with both COPD and CV mortality (GOLD 4 vs 1, adjusted HR: 12.63, 11.82–13.51 and adjusted HR: 1.75, 1.60–1.91, respectively).

Conclusion Poorer airflow limitation, worse functional status and exacerbations had substantial associations with risk of all-cause mortality. Differing results for CV and COPD-related mortality suggests interventions to prevent mortality may need to target particular characteristics or time points in the disease course.

INTRODUCTION

People with chronic obstructive pulmonary disease (COPD) are at increased risk of death compared with the general population and it is estimated that 30 000 people die each year in the UK of COPD, of which many are premature deaths. ¹² Globally, approximately one-third of patients with COPD die from respiratory-related causes and a further third from cardiovascular disease (CVD). ²³ In the UK, the proportion of COPD-related deaths in patients with COPD has remained constant over time, while cardiovascular-related deaths have declined, and deaths attributed to mental and behavioural disorders have increased. ² It is predicted that by 2030, a total of 1.3 million people in England will have COPD, an increase of 39% from 2011, due to growing populations and ageing. ⁴⁻⁵

Previous studies investigating COPD mortality have usually included populations of people with COPD with specific inclusion and exclusion criteria and are, therefore, not always generalisable of the wider COPD population. Given that COPD is an umbrella term covering a spectrum of diseases, mortality profiles are likely to differ in different subgroups. For example, patients with COPD and concomitant heart failure (HF) are at increased risk of death compared with people with HF alone and this has not improved over the last 10 years in the UK. ⁶ Approximately two-thirds of people with COPD in primary care in the UK will have exacerbations at some point in the course of their disease. ⁷ These events are associated with mortality not only from COPD itself (respiratory failure) but also cardiovascular events. ⁸⁻¹⁰ It is highly likely there are other characteristics of people with COPD that may increase the risk of cause specific mortality, both individually and in combinations. Understanding differences in the causes of death in different COPD subgroups will help us to better understand if there are certain subpopulations at higher risk than typical.
others who should be managed differently or more aggressively or screened for particular conditions.

Therefore, using de-identified electronic healthcare record data, we aimed to describe causes of death in a primary care population of people with COPD in the UK and determine factors that may be associated with specific causes of death, specifically exacerbation frequency and severity, emphysema and chronic bronchitis phenotypes, severity of airflow limitation and Global Obstructive Lung Disease (GOLD) groups A–D.

**METHODS**

Primary care electronic records from the Clinical Practice Research Datalink (CPRD) Aurum database were obtained. CPRD Aurum contains information on individuals registered at general practices in England and includes information on consultations, clinical diagnoses, therapies prescribed and referrals to secondary care. Patient identifiers are pseudonymised and date of birth, patient names and specific practice locations are not available to CPRD researchers. Linked data from Hospital Episode Statistics (HES) and mortality data from the Office of National Statistics (ONS) were provided for this study by CPRD/NHS Digital for patients in England.

Patients were included if they had: (a) a clinical diagnosis of COPD; (b) were over the age of 40 years at the time of COPD diagnosis; (c) were current or ex-smokers; (d) eligible for HES and ONS linkage; (e) had data recorded from 1 January 2010 onwards; (f) had at least 1 year of ‘research standard’ CPRD registration before their disease diagnosis and (g) had at least one pre-disease consultation in their CPRD history prior to their COPD diagnosis. Briefly, a clinical diagnosis of COPD was based on clinical diagnosis codes recorded in primary care. Patient’s start of follow-up (index date) was defined as the date by which all inclusion criteria were met. End of follow-up was 1 January 2020 or earlier if patient died or left the CPRD-contributing general practice.

**Mortality**

Our outcome of interest was mortality which was obtained from ONS mortality data. Specific cause of death was determined from death certificates using the International Classification of Diseases 10th revision (ICD10) codes that related to the patient’s underlying cause of death. We included all ICD10 codes to identify all-cause mortality and identified specific COPD-related and CVD-related ICD10 death codes (https://github.com/NHLI-Respiratory-Epi/Cause-specific-mortality-in-COPD-patients.git). COPD-related and CVD-related mortality were chosen as these events could be reduced by better COPD care or CVD management and are the main reasons for mortality in this patient population.11 12 (See supplementary material p 2 for further methodological detail.)

**Exposure groups**

We explored causes of death by six different baseline exposure groups:

1. Evidence of an exacerbation of COPD in the year prior to index date (none vs ≥1 exacerbation).
2. Frequency of exacerbations of COPD in the year prior to index date (none, 1 and ≥2).
3. Severity of exacerbations of COPD in the year prior to index date (none, ≥1 moderate and ≥1 severe).
4. COPD phenotype (emphysema vs chronic bronchitis);
5. Airflow limitation using forced expiratory volume in one second (FEV₁) per cent predicted in the year prior to index date.
6. GOLD stages A–D using exacerbation frequency and medical research council (MRC) grade in the year prior to index date.

Moderate exacerbations of COPD (ie, primary care treated exacerbations) were ascertained in CPRD Aurum using validated definitions.13 These included: (a) a diagnosed exacerbation of COPD or lower respiratory tract infection; (b) a prescribed course of respiratory-related antibiotics and oral corticosteroids for a duration of 5–14 days and (c) a combination of prescribed respiratory antibiotics and oral corticosteroids on the same day as two of the following symptoms, chronic cough, breathlessness and sputum. Severe exacerbations (ie, exacerbations that required hospitalisation) of COPD were identified using a validated definition in HES.14 These included a hospital admission for an exacerbation of COPD (https://github.com/NHLI-Respiratory-Epi/Cause-specific-mortality-in-COPD-patients.git). Chronic bronchitis and emphysema characteristics recorded prior to index date were used. The latest recorded FEV₁ per cent predicted in 2 years prior to index date to 3 months after index date was used to define airflow limitation. This time period was chosen to reduce missingness of values while maintaining a true representation of patient’s spirometry at the start of follow-up. Where recorded FEV₁ per cent predicted this was missing, FEV₁ per cent predicted was calculated using the latest record FEV₁, in 2 years prior to index date to 3 months after index date as well as age and sex using standard equations. Patient’s latest MRC value 5 years prior to index date was used to calculate GOLD groups A–D.

**Statistical analysis**

Baseline characteristics were described using summary statistics. Crude all-cause, COPD-related and CVD-related mortality rates were calculated by baseline exposure group by dividing the number of deaths due to each cause by the total person years of follow-up. Mortality rates adjusted for age, gender and smoking status were predicted from an adjusted Poisson model.

Cox Proportional Hazards regression was used to determine which exposures were associated with all-cause mortality and competing risks analysis was used for COPD-related and CVD-related mortality outcomes. The proportional hazards assumption was tested and models were not violated. Both models were adjusted for age at index date, gender, body mass index (BMI; underweight: <18.5 kg/m²; normal: 18.5–24.9 kg/m²; overweight: 25.0–29.9 kg/m² and obese: ≥30.0 kg/m²) within 5 years of index date, smoking status (current or ex-smoking) and a history of depression, anxiety, gastro-oesophageal reflux disorder, lung cancer, acute myocardial infarction, congestive HF, stroke, hypertension, diabetes mellitus, cholesterol level, current asthma (defined as a diagnosis within 3 years from 2 years prior to index date), socioeconomic deprivation (using linked Index of Multiple Deprivation data) and MRC dyspnoea grades 1–5. Depending on the outcome, models were also adjusted for airflow obstruction and history of exacerbations in the year prior to index date. Complete case analysis was performed, and all models were performed using STATA statistical software V17.

**Exploratory analyses**

To better understand how causes of death are linked to exacerbations of COPD, we also described the proportion of patients who died from all-cause, COPD-related and CVD-related causes 30 days after their last exacerbation of COPD in those who died and had at least one exacerbation during follow-up. This was also described by baseline FEV₁ per cent predicted.
RESULTS

A total of 339,647 people with COPD were included and mean follow-up was 5.5 years (SD: 3.6 years) (figure 1). Table 1 reports the proportion of patients in each exposure group.

Mean age was 67 years (SD: 11.7 years), slightly more men were included compared with women (53% vs 47%), slightly more ex-smokers were included compared with current smokers (53% vs 47%), and most patients had normal BMI or were overweight or obese. With respect to comorbidities, the most common was hypertension (43.3%), current asthma (35.6%) and depression (26.8%) (table 2). Online supplemental tables S1–S5 highlight patient characteristics within each exposure group.

Mortality rates

A total of 97,882 patients died during follow-up, of which 25,116 (25.7%) died of COPD-related causes and 22,793 (23.3%) of CVD-related causes. Table 3 illustrates crude and adjusted all-cause, COPD-related and CVD-related mortality rates by exposure groups. Patients with any number and increasing frequency of exacerbations at baseline had higher rates of adjusted all-cause and COPD-related mortality compared with patients with no baseline exacerbations; however, rates of CVD-related mortality were similar. Patients with at least one severe exacerbation at baseline had higher rates of all types of mortality.

Patients with chronic bronchitis had higher rates of all-cause and COPD-related mortality compared with patients with emphysema but similar rates of CVD-related mortality. Rates of all-cause, COPD-related and to a lesser degree CVD mortality were higher with increasing airflow obstruction but within patients with FEV₁ ≥80% predicted, rate of CVD-related mortality
mortality was higher than the rate of COPD-related mortality. In terms of GOLD groups A–D, groups B and D had higher rates of all-cause, COPD-related, and to a lesser extent CVD-related mortality, compared with groups A and C. Patients in group D also had slightly higher rates of all-cause and COPD-related mortality compared with patients in group B.

**Risk of mortality**

HRs for the risk of all-cause, COPD-related and CVD-related mortality by baseline exposure group are illustrated in figure 2. Overall, patients with any number of exacerbations of COPD in the year prior to index date had a higher risk of all-cause and COPD-related mortality (adjusted HR: 1.18, 95% CI 1.16 to 1.20, and adjusted HR: 1.42, 95% CI 1.37 to 1.46, respectively) compared with non-exacerbators. Increasing number of exacerbations at baseline was also associated with increased risk of all-cause and COPD-related mortality compared with non-exacerbators but only two or more exacerbations were associated with an increased risk of CVD-related mortality compared with no exacerbations. This was also seen for increasing severity of exacerbations. Specifically, patients with at least one severe exacerbation had a higher risk of all-cause, COPD-related and CVD-related mortality compared with patients with non-exacerbators at baseline (adjusted HR: 1.81, 95% CI 1.75 to 1.87, adjusted HR: 2.17, 95% CI 2.04 to 2.31, and adjusted HR: 1.16, 95% CI 1.08 to 1.26, respectively) (figure 2 and online supplemental table S6).

Compared with patients with chronic bronchitis, those with emphysema had a higher risk of all-cause and COPD-related mortality but a similar risk of CVD-related mortality (adjusted HR: 1.17, 95% CI 1.10 to 1.24, adjusted HR: 1.24, 95% CI 1.12 to 1.38 and adjusted HR: 0.94, 95% CI 0.83 to 1.06, respectively) (figure 2).

Compared with patients in GOLD group A, patients in GOLD groups B–D had a higher risk of all-cause mortality with the highest risk in GOLD groups D and B (adjusted HR: 2.43, 95% CI 2.34 to 2.52 and 1.65, 95% CI 1.60 to 1.69, respectively), followed by GOLD group C (adjusted HR: 1.30, 95% CI 1.21 to 1.39). A similar pattern of association was seen for COPD-related and CVD-related mortality (figure 2). Finally, compared with patients with FEV₁ ≥80% predicted, increasing airflow limitation was associated with increased risk of all-cause and COPD-related mortality (figure 2). Risk of CVD-related mortality was also higher with increasing airflow limitation but to a lesser extent than COPD-related mortality. Detailed estimates are described in online supplemental table S6.

**Exploratory analysis**

Overall, of 97882 patients who died during follow-up, 33819 patients died within 30 days of an exacerbation of COPD. Of
these patients, 43.1% died from COPD-related causes and 14.9% died of CVD-related causes. Of patients who died, but not within 30 days of an exacerbation of COPD (n=64063), 16.5% died from COPD-related causes, and 27.7% died of CVD-related causes (figure 3). In additional, a greater proportion of patients died from COPD-related causes within 30 days of an exacerbation with decreasing FEV₁ per cent predicted (online supplemental figure E1).

**DISCUSSION**

We investigated the relationship between patient characteristics and common causes of death in order to understand which patient groups might be more likely to die from particular causes. First, we found that increasing severity and frequency of COPD exacerbations, GOLD groups B and D and lower FEV₁ per cent predicted were associated with increased risk of all-cause mortality. Similarly, increasing severity and frequency of COPD exacerbations, patients in GOLD groups B and D and patients with lower FEV₁ per cent predicted were had higher COPD related mortality. However, those with emphysema had higher COPD-related mortality. Patients in GOLD groups B and D, and those with lower FEV₁ per cent predicted had higher CVD mortality, but we did not find evidence for a relationship between infrequent or moderate exacerbations and CVD mortality. Lastly, we found of patients who died within 30 days of an exacerbation, the majority died of COPD-related or CVD causes. Patients with lower baseline FEV₁ per cent predicted were also more likely to die within 30 days of an exacerbation and die from COPD-related causes.

**Exacerbations of COPD**

Our findings are in line with prior work which showed that exacerbations of COPD are associated with increased risk of all-cause and COPD-related mortality, including a single moderate exacerbation in symptomatic patients. Interestingly, we found that only frequent or severe exacerbations of COPD requiring hospitalisation at baseline were associated with an increased risk of CVD mortality. This is in line with previous literature that has shown that the odds of CVD-related mortality 1 year after an acute exacerbation of COPD was 33% higher than in those without an acute exacerbation in the year before. Further literature has also shown that exacerbations of COPD are associated with future CVD events, not limited to mortality in people with COPD. Although increasing frequency and severity of exacerbations were associated with all-cause and COPD-related mortality, the association was lower in magnitude compared

<table>
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**Figure 2** Risk of all-cause, COPD-related and CVD-related mortality by baseline exposure groups. Effect estimates are adjusted HR. N = 229928 for all exacerbation exposures and for GOLD FEV₁ % predicted exposure. N = 172114 for GOLD groups A–D exposure. N = 18528 for chronic bronchitis/emphysema exposure. Nb: different scale x-axes for all-cause, COPD and CVD mortality. Cox regression estimates can be found in online supplemental table S6. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; GOLD, Global Obstructive Lung Disease; ref, reference group.

**Figure 3** Proportion of patients dying from all-cause, COPD-related and CVD-related causes within 30 days of an exacerbation of COPD. Of those with at least one exacerbation during follow-up, COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.
with airflow limitation and poorer functional limitation (GOLD groups B and D), potentially reflecting those effective therapies exist to prevent exacerbations in those with a history of frequent or severe events.

We also found that in those with poorer lung function, a greater number of patients are more likely to die within 30 days of an exacerbation and of COPD-related causes. This suggests that in a subgroup of patients, there is a period at which patients have a higher risk of mortality following an exacerbation. This highlights the need to create disease-modifying therapies that prevent exacerbations and subsequently reduce risk of mortality.

**Airflow limitation**

Many previous studies have found that lower airflow limitation is associated with mortality, including COPD mortality. The literature on the association between airflow limitation and CVD-related mortality, however, is mixed. Whittaker et al found that in a primary care COPD population increasing baseline GOLD FEV₁ per cent predicted was not associated with increased risk of CVD-related events, including CVD mortality, over a mean follow-up of 3.6 years (IQR: 1.7–6.1 years). Similarly, a recent post-hoc analysis of the SUMMIT trial found that FEV₁ per cent predicted was not associated with CVD events in a population of people with COPD with a heightened risk of CVD. Despite this, other studies have found that increasing level of airflow limitation is associated with increased risk of CVD events. The ARIC study found that participants in the lowest quartile of airflow limitation had a higher risk of CVD-related hospitalisations and mortality compared with patients in the highest quartile of airflow limitation. In addition, the Health, Ageing and Body composition study and the CARDIA study found linear associations between baseline FEV₁ per cent predicted and hospitalisation for HF and stroke (including fatal events). While our study found a linear association between baseline FEV₁ per cent predicted and odds of CVD-related mortality, the increase in the odds between each group was marginal.

We also found that within patients with FEV₁ ≥80%, the rates of CVD-related mortality were higher than COPD-related mortality. However, within patients with FEV <50% the rate of COPD-related mortality was higher than CVD-related mortality. Patients with milder disease are less likely to die of their COPD and more likely to die of other causes, such as CVD, and interventions could be targeted toward this population to mitigate risk of non-COPD-related mortality. Conversely, any disease modifying therapy may need to target patients before decline in FEV₁ per cent predicted to prevent any mortality associated with poorer lung function.

**GOLD group**

In our study, we found that patients in GOLD groups B and D were more likely to die of any cause, (including COPD and CVD), compared with patients in group A. Patients in group C were more likely to die of any cause compared with group A; however, the magnitude of associations were lower than for groups B and D. Patients in groups B and D are those who have a higher burden of functional limitation (identified through MRC dyspnoea score) but for group B also have relatively few exacerbations of COPD. The higher estimates in mortality in GOLD group D compared with groups B and C compared with group A are expected due to higher frequency or severity of exacerbations in these groups and highlight the importance of considering multiple risk factors (exacerbations and functional limitation) in the same patient. This is in line with what we found for baseline exacerbation frequency whereby increasing number of exacerbations was associated with increased odds of all-cause and COPD-related mortality.

Previous studies have also found that GOLD group D had a higher risk of all-cause mortality compared with the three other groups. A previous study found that in patients with COPD, increasing baseline MRC score and increasing frequency of exacerbations of COPD were independently associated with risk of future CVD events and CVD mortality. Given the previous literature and results from our study, it is possible that there is an interaction between functional limitation and exacerbation frequency and severity as patients with higher functional limitation but with few exacerbations do worse than patients with lower functional limitation and fewer exacerbations (ie, GOLD group A vs group B and group C vs group D). This suggests a more complex relationship between exacerbations and mortality and other factors such as functional limitation may influence patient trajectory. Similarly, it is possible that other factors such as comorbidities also influence the relationship between exacerbations and mortality.

A number of post-hoc analyses from randomised controlled trials in COPD as well as observational studies have shown mixed mortality effects. The TORCH (Towards a Revolution in COPD Health) and the IMPACT (Informing the Pathway of COPD Treatment) studies showed a mortality benefit in people with COPD on inhaled corticosteroids, whereas the SUMMIT (Study to Understand Mortality and Morbidity in COPD) study showed no association between inhaled corticosteroids (ICS) and all-cause or cardiovascular mortality. The SUMMIT population included patients who were at a heightened risk for CVD, but these patients were those with mild COPD with moderate airflow limitation and a history of few exacerbations in the prior year. The implications of the findings of our study are that these mixed results may be due to the underlying population included in the RCTs and explain the reason that mortality benefits have been seen in studies which have not targeted more patients with severe COPD.

Overall, our study highlights the differences in cause-specific mortality between people with COPD. Understanding which patient characteristics are associated with cause-specific mortality provides information on which patients and at which time point in their disease course may benefit from targeted intervention or evaluation to reduce mortality.

**Limitations**

This is the first study to investigate COPD-specific patient characteristics associated with cause-specific mortality in a large population of people with COPD in England. We identified cause-specific mortality using ICD10 codes for underlying causes of death. It is possible that these may not be accurate for each individual; however, after exploring this further, we found that the majority of underlying causes were in the first position for causes of death and it did not change our findings. In addition, we found that very few patients had data on chronic bronchitis or emphysema recorded resulting in a small population of patients included in our analyses comparing causes of death in patients with chronic bronchitis and emphysema. While we found that patients with chronic bronchitis were more likely to die of CVD-related mortality compared with those with emphysema, our analyses were underpowered. Missing exposure variables were also seen for GOLD grades (both A–D and using FEV₁ per cent...
CONCLUSION

Lower lung function and GOLD groups B and D were associated with increased all-cause mortality; however, effect sizes were different between COPD-related and CVD-related mortality. Exacerbations of COPD were associated with increased all-cause and COPD-related mortality but not CVD-related mortality. This suggests that people with COPD are heterogeneous and more attention to the absence or presence of particular factors at particular time points in the disease course is needed to help prevent mortality.

Contributors JKK, KJR and HW planned and designed the study, interpreted the results and edited the manuscript. HW analysed the data and wrote the original draft. JKK is the guarantor of the paper.

Funding This study, 214667, is a supported collaborative study where GlaxoSmithKline provided support and collaborated with the research sponsor. No payment was made for manuscript development.

Competing interests This study, 214667, is a supported collaborative study where GlaxoSmithKline provided support and collaborated with the research sponsor. No payment was made for manuscript development. HW and JKK report grants from GlaxoSmithKline, during the conduct of this study. KJR is an employee of GlaxoSmithKline. 

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are available on request from the Clinical Practice Research DataLink (CPRD). Their provision requires the purchase of a license, and this license does not permit the authors to make them publicly available to all. This work used data from the version collected in May 2021 and have clearly specified the data selected within each Methods section. To allow identical data to be obtained by others, via the purchase of a license, the code lists will be provided upon request.

DATA SHARING DETAILS

Not applicable.

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