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Global mortality and readmission rates following COPD exacerbation-related hospitalisation: a meta-analysis of 65 945 individual patients

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In-hospital mortality, post-discharge mortality and hospital readmission rates after ECOPD-related hospitalisation remain poor in patients with COPD across the world, with high heterogeneity and noticeable variability between countries. https://bit.ly/3vo05pC

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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. The aims of the present study were to explore global in-hospital mortality, post-discharge mortality and hospital readmission rates after ECOPD-related hospitalisation 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 hospitalisation. 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 65 945 individual patients with COPD were analysed. The pooled in-hospital mortality rate was 6.2%, pooled 30-, 90- and 365-day post-discharge mortality rates were 1.8%, 5.5% and 10.9%, respectively, and pooled 30-, 90- and 365-day hospital readmission rates were 7.1%, 12.6% and 32.1%, respectively, with noticeable variability between studies and countries. Strongest predictors of mortality and hospital readmission included noninvasive mechanical ventilation and a history of two or more ECOPD-related hospitalisations <12 months prior to the index event.

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

Introduction

Exacerbations of chronic obstructive pulmonary disease (ECOPD) exert deleterious effects on patients and healthcare systems [1], and significantly increase resource utilisation and healthcare 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 hospitalisation [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, 9, 10, 12–21]. However, great heterogeneity exists between studies, hindering our understanding of the true, global

burden of ECOPD on healthcare 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 utilisation 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 hospitalisations, 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 recognised 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 hospitalisation for ECOPD, and/or subsequent ECOPD hospital readmission (online supplementary material). The search was conducted from database inception until 31 March 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 standardise 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 (M. Crutsen, S. Keene and K. Waeijen-Smit). Agreements upon inclusion were made in consensus with a fourth independent person (M.A. Spruit).

Study selection

Eligible studies needed to: 1) be conducted in patients with COPD aged ⩾18 years; 2) be conducted in patients hospitalised for ECOPD; and 3) 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 harmonisation

Original individual patient data were extracted in an anonymised and secure 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 hospitalisations <12 months prior to the index event (0, 1, ⩾2), noninvasive 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) dyspnoea grades (*i.e.* 0–4) during the index event and forced expiratory volume in 1 s (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 mean±standard deviation (SD) or median±interquartile 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 hospitalisation.

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 hospitalisation history, mMRC, use of NIMV or IMV and ICU stay). Effect estimates were presented as hazard rates 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 $\leqslant 0.05$ were considered statistically significant. Graphs were created in GraphPad Prism 9.3.1. (GraphPad Software, La Jolla, CA, USA).

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Results

The manual electronic database search identified 1400 potentially relevant records. After screening, 321 studies were eligible for inclusion and the authors were contacted for sharing of individual patient data. In total, 47 authors shared data of 65 945 individual patients (supplementary 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 supplementary tables S1 and S2.

In-hospital mortality

Results for in-hospital mortality were available for 62 022 patients from 35 studies [18, 32–62]. Baseline characteristics of the pooled data subset are displayed in supplementary 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, 3868 (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 hospitalisations in the year before index admission, spent more days in hospital, experienced more dyspnoea during hospitalisation and were more likely to receive (N)IMV or to be admitted to the ICU. Length of hospital stay was available in 1364 of the 3868 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 1 week of hospitalisation and 5.1% died after $\geqslant 40$ days of hospitalisation (figure 2).

In-hospital mortality rates and median length of hospital stay stratified by study are provided in supplementary 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=1421).

FIGURE 1 Countries included in the current individual patient data meta-analysis (IPDMA). Note: countries included in the IPDMA with IPD of n<90 (*i.e.* Mexico, Colombia, USA and Slovakia) are not coloured blue.

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 supplementary 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 [18, 32, 33, 36, 37, 39–44, 47–58, 60–75]. Baseline characteristics of the pooled data subset are displayed in supplementary table S5. Median follow-up time after hospital discharge in these studies was 365 days. In total, 4662 (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 hospitalisations in the year prior to the index event, spent more days in hospital during the index event, experienced more dyspnoea during the index event, and were more likely

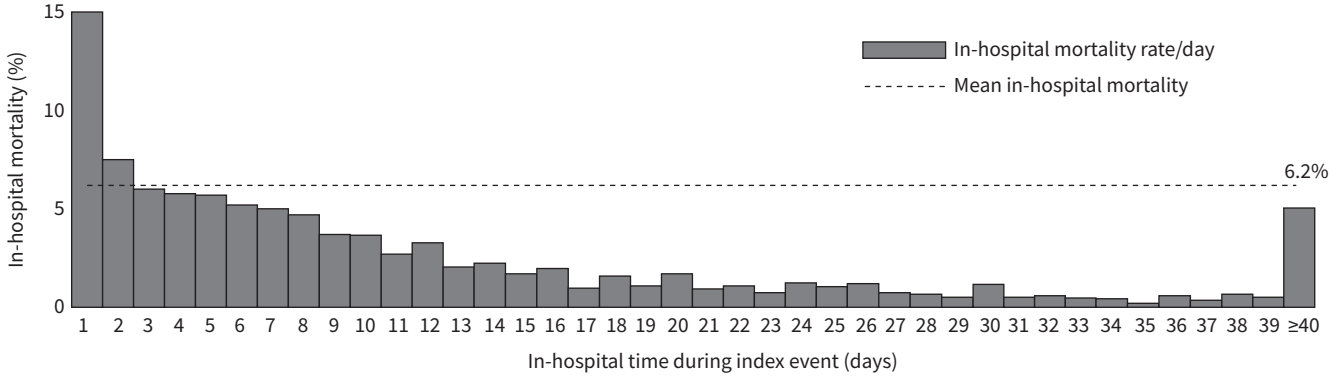

FIGURE 2 In-hospital mortality rates (%) by day for severe exacerbations of chronic obstructive pulmonary disease (n=1346).

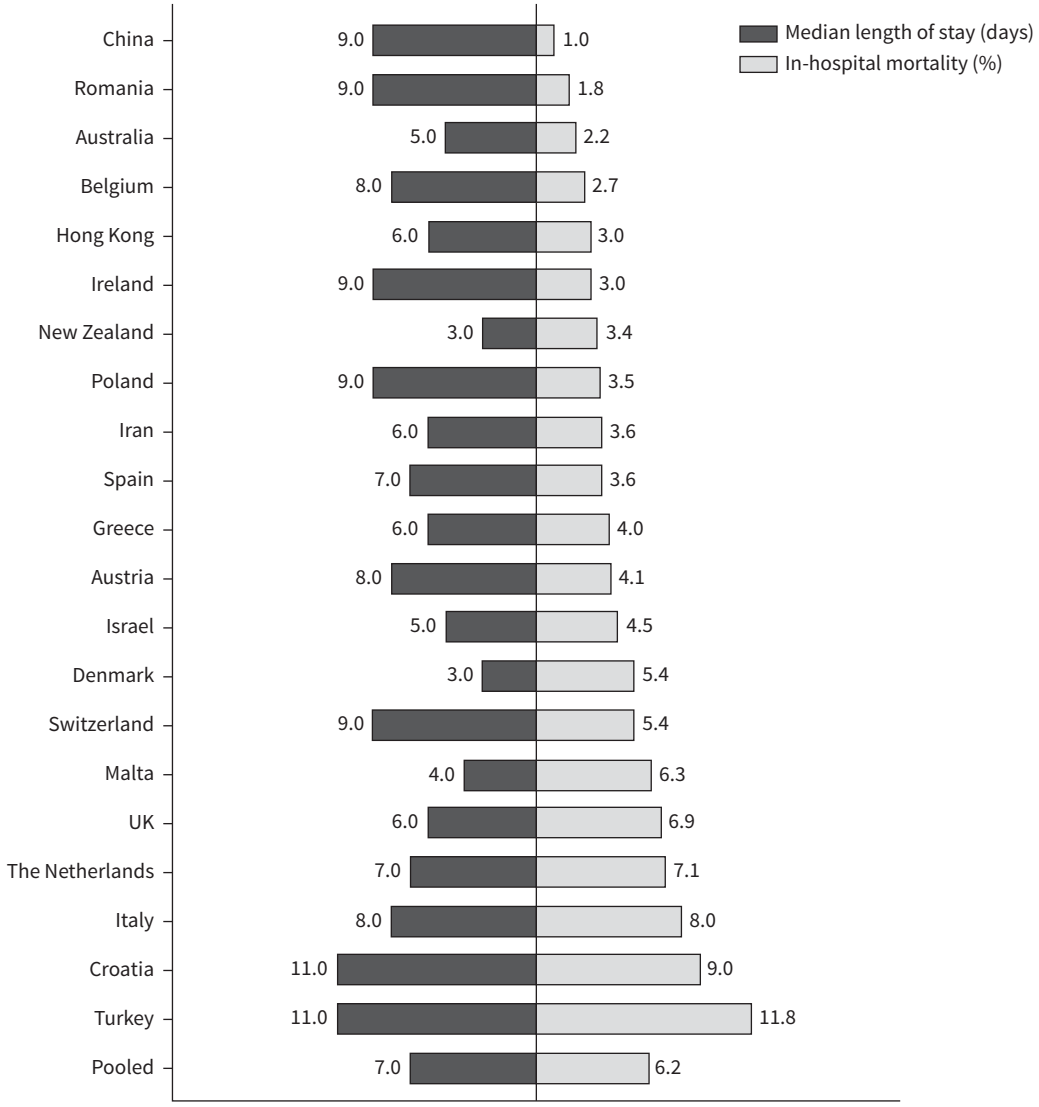

FIGURE 3 Pooled and stratified median length of hospital stay (left) and in-hospital mortality rates (right) during the index event per country. Relative percentages are displayed. Total number of patients included per country (percentage of the pooled population): China n=191 (0.3%), Romania n=718 (1.2%), Australia n=90 (0.1%), Belgium n=814 (1.3%), Hong Kong n=401 (0.6%), Ireland n=237 (0.4%), New Zealand n=1126 (1.8%), Poland n=734 (1.2%), Iran n=507 (0.8%), Spain n=8859 (14.3%), Greece n=1133 (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%), UK n=35 707 (57.6%), The Netherlands n=662 (1.1%), Italy n=7234 (11.7%), Croatia n=445 (0.7%), Turkey n=1421 (2.3%).

to receive (N)IMV or to be admitted to the ICU during the index event. >70% of the post-discharge deaths occurred in the first year of follow-up (71.4%, 3330 out of 4662) (supplementary 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 1.8% (95% CI 1.6–1.9), the pooled 90-day mortality rate was 5.5% (95% CI 5.2–5.8) and the pooled 365-day mortality rate was 10.9% (95% CI 10.5–11.2). The lowest stratified post-discharge mortality rates were observed in Norway (1.0%, n=99), whereas the highest 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 supplementary figure S4.

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)

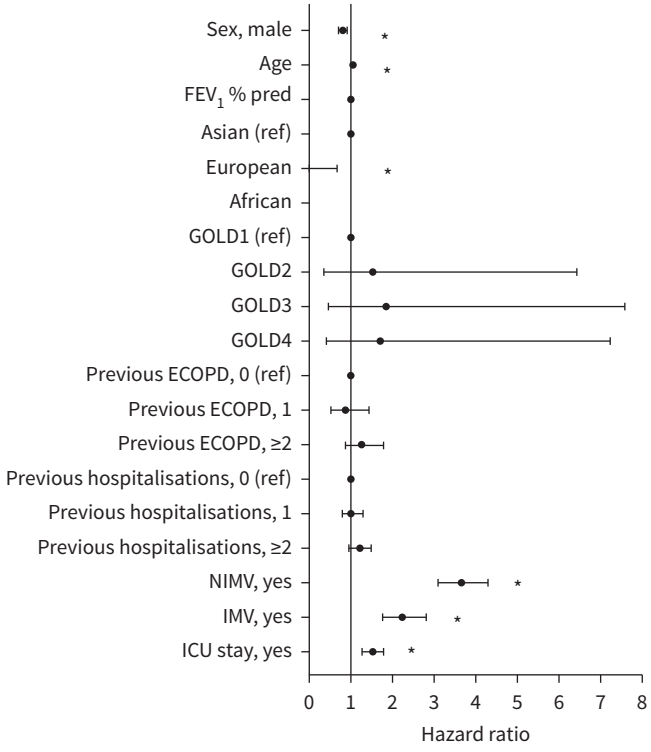

FIGURE 4 Forest plot displaying Cox proportional hazard ratios for in-hospital mortality in the pooled data subset. *p<0.05. Details are provided in supplementary table S4. FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ECOPD: exacerbations of COPD; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; ICU: intensive care unit.

(supplementary figure S5). Survival probability was significantly reduced in patients receiving (N)IMV during index hospitalisation: 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 Chi-squared (1)=194.08, p<0.001) (supplementary 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 Chi-squared (1)=59.23, p<0.001) (supplementary figure S6B).

Age, FEV_1, ethnicity, hospitalisation 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 supplementary table S6). The odds of post-discharge mortality was higher with older age, European ethnicity, higher number of previous hospitalisations, higher mMRC scores, use of (N)IMV and ICU admission during the index event, and lower FEV_1.

Hospital readmission

Results for hospital readmission were available in 46 297 patients from 30 studies [18, 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 supplementary table S7. Median follow-up time after hospital discharge in these studies was 365 days. In total, 15 195 (32.8%, 95% CI 32.4–33.3) 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 less often male, were younger, had more severe lung function impairment, had a higher symptom burden, experienced more ECOPD and hospitalisations prior to the index event, and more often needed ventilator support or ICU admission during the index event. Virtually all readmissions occurred in the first year of follow-up (97.7%, 14 846 out of 15 195) (supplementary 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 7.1% (95% CI 6.8–7.3), the pooled 90-day mortality rate was 12.6%

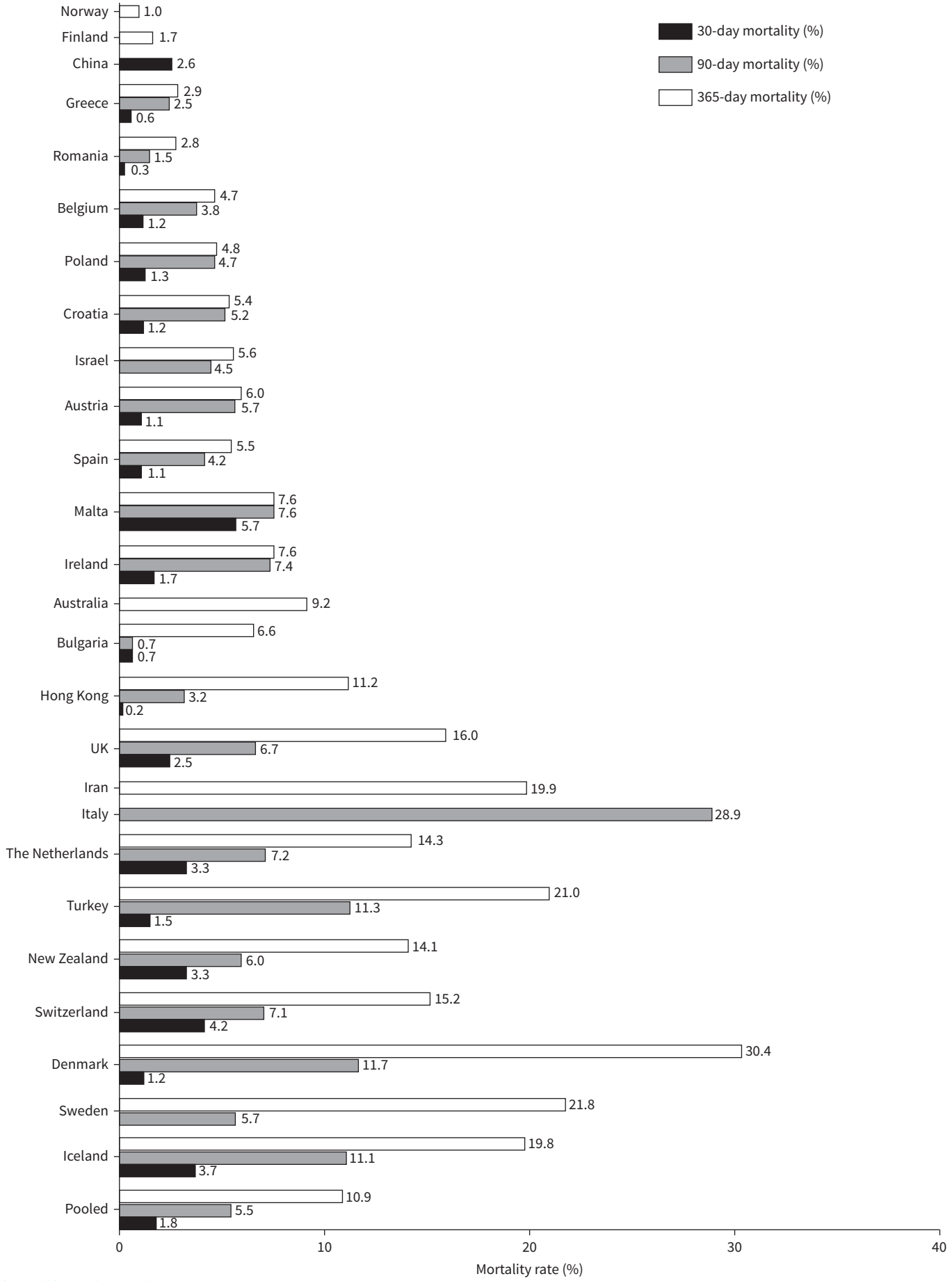
30-day mortality (%)
90-day mortality (%)
365-day mortality (%)
Norway 1.0
Finland 1.7
China 2.6
Greece 2.9 2.5 0.6
Romania 2.8 1.5 0.3
Belgium 4.7 3.8 1.2
Poland 4.8 4.7 1.3
Croatia 5.4 5.2 1.2
Israel 5.6 4.5
Austria 6.0 5.7 1.1
Spain 5.5 4.2 1.1
Malta 7.6 7.6 5.7
Ireland 7.6 7.4 1.7
Australia 9.2
Bulgaria 6.6 0.7 0.7
Hong Kong 11.2 3.2 0.2
UK 16.0 6.7 2.5
Iran 19.9
Italy 28.9
The Netherlands 14.3 7.2 3.3
Turkey 21.0 11.3 1.5
New Zealand 14.1 6.0 3.3
Switzerland 15.2 7.1 4.2
Denmark 30.4 11.7 1.2
Sweden 21.8 5.7
Iceland 19.8 11.1 3.7
Pooled 10.9 5.5 1.8
0
10
20
30
40
Mortality rate (%)

FIGURE 5 Pooled and stratified 30-day, 90-day and 365-day post-discharge mortality rates per country. Relative percentages are displayed. Total number of patients included per country (percentage of the pooled population): Norway n=99 (0.3%), Finland n=60 (0.2%), China n=189 (0.6%), Greece n=1088 (3.6%), Romania n=683 (2.2%), Belgium n=773 (2.5%), Poland n=708 (2.3%), Croatia n=405 (1.3%), Israel n=603 (2.0%), Austria n=788 (2.6%), Spain n=8934 (29.2%), Malta n=105 (0.3%), Ireland n=230 (0.8%), Australia n=87 (0.3%), Bulgaria n=151 (0.5%), Hong Kong n=819 (2.7%), UK

(95% CI 12.3–12.9) and the pooled 365-day mortality rate was 32.1% (95% CI 31.6–32.5). The lowest stratified readmission rates were observed in China (10.1%, n=189), whereas the highest 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 supplementary figure S8.

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) [18, 31, 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) (supplementary figure S9). Median time to hospital readmission was significantly reduced in patients receiving NIMV during index hospitalisation: 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 Chi-squared (1)=29.32, p<0.001) (supplementary figure S10A). Median time 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 Chi-squared (1)=0.50, p=0.478) (supplementary 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 hospitalisation history, mMRC score, use of NIMV and ICU admission during the index event were significantly associated with hospital readmission in the subset of

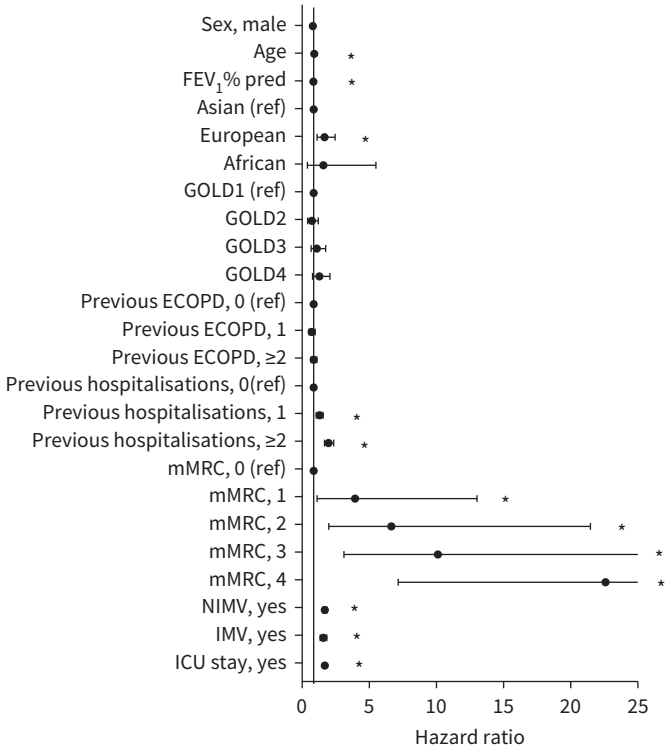

FIGURE 6 Forest plot displaying Cox proportional hazard ratios for post-discharge mortality in the pooled data subset. *p<0.05. Details are provided in supplementary table S6. FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ECOPD: exacerbations of COPD; mMRC: modified Medical Research Council; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; ICU: intensive care unit.

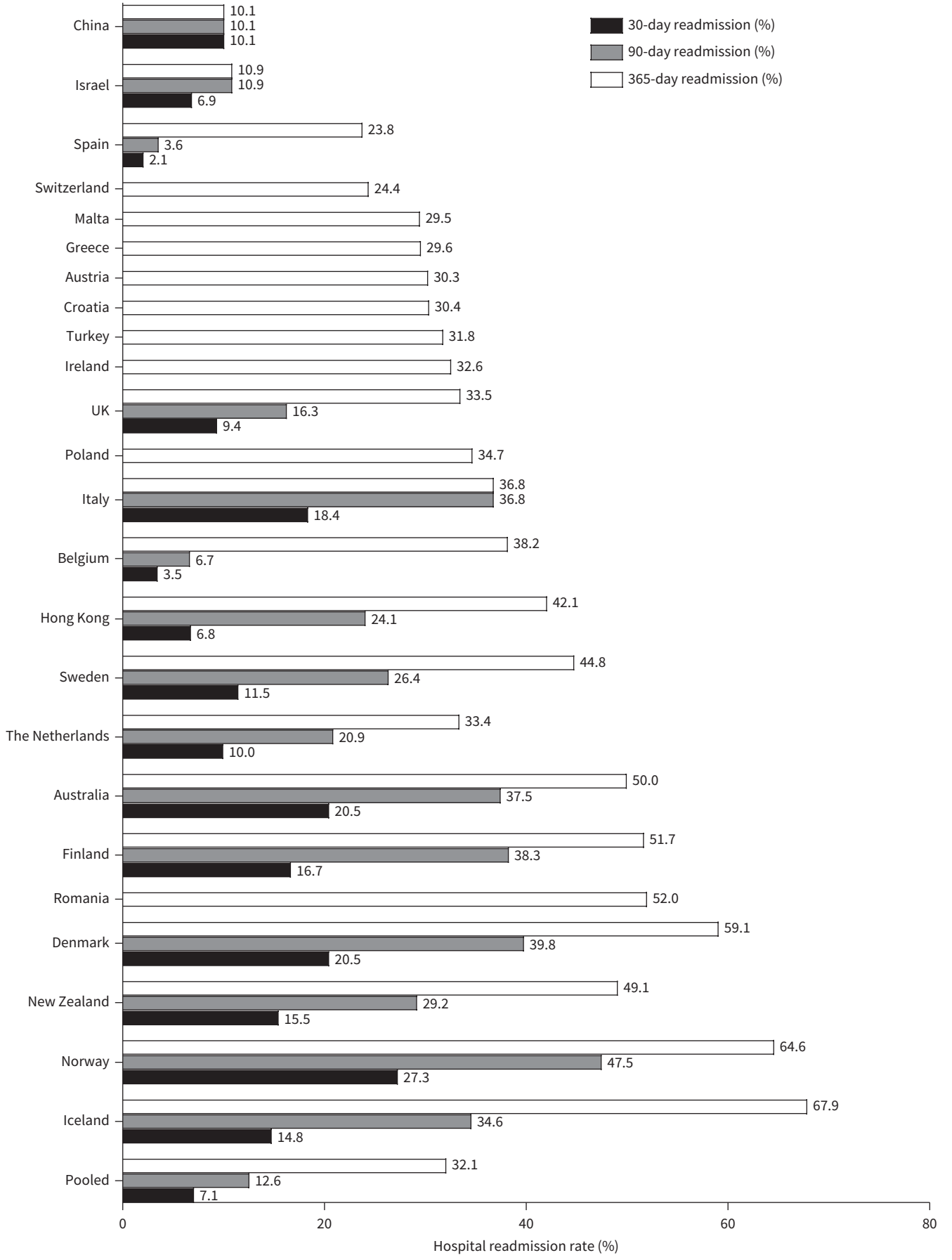
30-day readmission (%)
90-day readmission (%)
365-day readmission (%)
China 10.1 10.1 10.1
Israel 10.9 10.9 6.9
Spain 23.8 3.6 2.1
Switzerland 24.4
Malta 29.5
Greece 29.6
Austria 30.3
Croatia 30.4
Turkey 31.8
Ireland 32.6
UK 33.5 16.3 9.4
Poland 34.7
Italy 36.8 36.8 18.4
Belgium 38.2 6.7 3.5
Hong Kong 42.1 24.1 6.8
Sweden 44.8 26.4 11.5
The Netherlands 33.4 20.9 10.0
Australia 50.0 37.5 20.5
Finland 51.7 38.3 16.7
Romania 52.0
Denmark 59.1 39.8 20.5
New Zealand 49.1 29.2 15.5
Norway 64.6 47.5 27.3
Iceland 67.9 34.6 14.8
Pooled 32.1 12.6 7.1
0
20
40
60
80
Hospital readmission rate (%)

FIGURE 7 Pooled and stratified 30-day, 90-day and 365-day post-discharge hospital readmission rates per country. Relative percentages are displayed. Total number of patients included per country (percentage of the pooled population): China n=189 (0.4%), Israel n=539 (1.2%), Spain n=8770 (18.9%), Switzerland n=279 (0.6%), Malta n=105 (0.2%), Greece n=1088 (2.4%), Austria n=788 (1.7%), Croatia n=405 (0.9%), Turkey n=592 (1.3%), Ireland n=230 (0.5%), UK n=27 839 (60.1%), Poland n=708 (1.5%), Italy n=38 (0.1%), Belgium n=773 (1.7%), Hong Kong n=819 (1.8%), Sweden n=87 (0.2%), The Netherlands n=1127 (2.4%), Australia n=88 (0.2%), Finland n=60 (0.1%), Romania n=683 (1.5%), Denmark n=88 (0.2%), New Zealand n=782 (1.7%), Norway n=99 (0.2%), Iceland n=81 (0.2%).

patients with an exact time till readmission (n=27 401), both in the univariate- and age- and sex-adjusted model (figure 8 and supplementary table S8). The odds of hospital readmission was higher for male patients, higher GOLD grades, higher number of previous ECOPD and hospitalisations, 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.

Discussion

The current IPDMA summarises in-hospital mortality, post-discharge mortality and hospital readmission rates following ECOPD-related hospitalisation 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 1.8%, 5.5% and 10.9%, and 30-day, 90-day and 365-day hospital readmission rates of 7.1%, 12.6% and 32.1%, respectively, were observed. Most deaths (50.2%) occurred within the first week of hospitalisation. Furthermore, over 70% of the post-discharge deaths, and almost every readmission (97.7%) 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 hospitalisations, 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

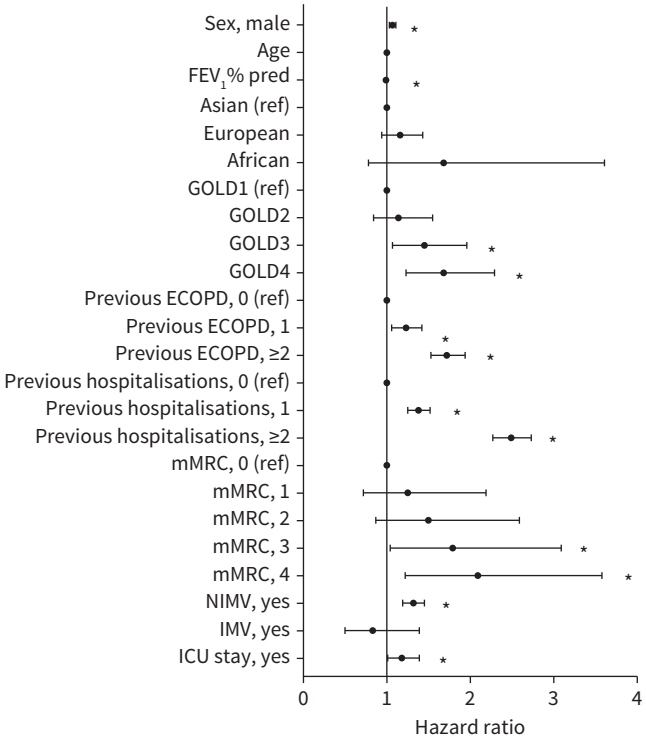

FIGURE 8 Forest plot displaying Cox proportional hazard ratios for hospital readmission in the pooled data subset. *p<0.05. Details are provided in supplementary table S8. FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ECOPD: exacerbations of COPD; mMRC: modified Medical Research Council; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; ICU: intensive care unit.

representation of mortality and readmission rates after ECOPD-related hospitalisation. The current findings highlight the poor outcomes and high heterogeneity of ECOPD-related hospitalisation, 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 it is expected to continue to increase, especially in developing countries [77]. Over time, the epidemiology of COPD has shifted from a disease mainly affecting white male smokers [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 hospitalisation.

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 healthcare 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 hospitalisation and/or post-discharge follow-up/monitoring of patients [82–84] and the subsequent clinical utilisation/implementation of such guidelines, or patient-specific traits such as ethnicity [85, 86] or socioeconomic 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 socioeconomic 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% *versus* 6.4%, p=0.738), significant differences were found for post-discharge mortality and hospital readmission (14.1% *versus* 22.0%, p<0.001, and 32.5% *versus* 38.2%, p<0.001, respectively).

Globally, several indications for hospitalisation 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, among healthcare facilities and systems, 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 standardised and guided post-discharge follow-up/monitoring of patients after ECOPD-related hospitalisation, especially in the first year post-discharge. Whilst the first attempts at the standardisation of the management and follow-up of ECOPD-related hospitalisations 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, 16, 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 USA 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 were 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 behaviour. 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 either in-hospital or 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 hospitalisation: survival probability was reduced by 2 years in patients receiving NIMV, and by 1 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 observation that the readmitted patients were less often male (*i.e.* 58% *versus* 62%) 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 younger 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 recognise an ECOPD than younger patients with COPD [103]. Superior self-management and healthcare-seeking behaviour, important pillars to improve the post-discharge prognosis of patients with COPD, might thus be a potential explanation for the younger 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 6 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 hospitalisation in over 65 000 patients with COPD from 47 individual studies. IPDMAs are recognised as the gold standard approach for evidence synthesis and therefore present a major methodological strength over using aggregate data from publications [29]. 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 hospitalisations, 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 standardised 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 were 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 hospitalisation. 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 minimised 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 (supplementary table S1).

In conclusion, the current IPDMA provides precise estimates of the outcomes and determinants of ECOPD-related hospitalisation in over 65 000 patients with COPD from across the world. With an overall in-hospital mortality rate of 6.2%, 1-year post-discharge mortality rate of 10.9% and 1-year hospital readmission rate of 32.1%, the impact of ECOPD-related hospitalisation 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 hospitalisation. More (funding of) research focusing on the standardisation of guidelines for post-discharge follow-up/monitoring of patients after ECOPD-related hospitalisation is needed. Moreover, policy makers should prioritise 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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Data sharing statement: Access to the extracted data, and/or the codes developed for this analysis, are possible upon reasonable request. Such queries may be directed towards the senior author.

Author contributions: K. Waeijen-Smit, M. Crutsen, S. Keene, S. Houben-Wilke, F.M.E. Franssen, S.O. Simons and M. A. Spruit contributed substantially to the conception, design and acquisition of the study, drafted the work, approved the final version to be published and agree to be accountable for all aspects of the work. M. Miravitlles, E. Crisafulli, A. Torres, C. Mueller, P. Shuetz, T.J. Ringbæk, F. Fabbian, E. Mekov, T.H. Harries, C-t. Lun, B. Ergan, C. Esteban, J.M. Quintana Lopez, J.L. López-Campos, C.L. Chang, R.J. Hancox, E. Shafuddin, H. Ellis, C. Janson, C.S. Ulrik, G. Gudmundsson, D. Epstein, J. Dominguez, A. Lacoma, C. Osadnik, I. Alia, F. Spannella, Z. Karakurt, H. Mehravaran, C. Utens, M.D. de Kruif, F.W.S. Ko, S.P. Trethewey, A.M. Turner, D. Bumbacea, P.B. Murphy, K. Vermeersch, S. Zilberman-Itskovich, J. Steer, C. Echevarria, S.C. Bourke, N. Lane, J. de Batlle, R.T.M. Sprooten, R. Russell, P. Faverio, J.L. Cross and H.J. Prins contributed substantially to the acquisition of the study, approved the final version to be published and agree to be accountable for all aspects of the work. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Conflict of interest: K. Waeijen-Smit, M. Crutsen, S. Keene, T.J. Ringbæk, F. Fabbian, C-t. Lun, B. Ergan, C. Estebam, J.M. Quintana Lopez, C.L. Chang, R.J. Hancox, E. Shafuddin, H. Ellis, C. Janson, G. Gudmundsson, D. Epstein, A. Lacoma, C. Osadnik, I. Alia, F. Spannella, Z. Karakurt, H. Mehravaran, C. Utens, M.D. de Kruif, F.W.S. Ko, S.P. Trethewey, K. Vermeersch, S. Zilberman-Itskovich, C. Echevarria, R.T.M. Sprooten, P. Faverio, H.J. Prins and S. Houben-Wilke have no grants or personal fees to report. M. Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Kamada, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Janssen, Grifols and Novartis, consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, ONO Pharma, Palobiofarma SL, Takeda, Novartis, Novo Nordisk, Sanofi and Grifols and research grants from

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References

1 May SM, Li JT, eds. Burden of chronic obstructive pulmonary disease: healthcare costs and beyond. *Allergy Asthma Proc* 2015; 36: 4–10.
2 Pasquale MK, Sun SX, Song F, *et al.* Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 757–764.
3 Hurst JR, Skolnik N, Hansen GJ, *et al.* Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. *Eur J Intern Med* 2020; 73: 1–6.
4 Demeyer H, Costilla-Frias M, Louvaris Z, *et al.* Both moderate and severe exacerbations accelerate physical activity decline in COPD patients. *Eur Respir J* 2018; 51: 1702110),
5 Spruit MA, Gosselink R, Troosters T, *et al.* Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003; 58: 752–756.
6 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2023 Report. https://goldcopd.org/2023-gold-report-2/
7 Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.
8 Suissa S, Dell’Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012; 67: 957–963.

9 de Miguel-Díez J, Jiménez-García R, Hernández-Barrera V, *et al.* Readmissions following an initial hospitalization by COPD exacerbation in Spain from 2006 to 2012. *Respirology* 2016; 21: 489–496.
10 Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003; 124: 459–467.
11 Lipson DA, Barnhart F, Brealey N, *et al.* Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018; 378: 1671–1680.
12 Serra-Picamal X, Roman R, Escarrabill J, *et al.* Hospitalizations due to exacerbations of COPD: a big data perspective. *Respir Med* 2018; 145: 219–225.
13 Patil SP, Krishnan JA, Lechtzin N, *et al.* In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 2003; 163: 1180–1186.
14 Asiimwe AC, Brims FJH, Andrews NP, *et al.* Routine laboratory tests can predict in-hospital mortality in acute exacerbations of COPD. *Lung* 2011; 189: 225–232.
15 Brown H, Dodic S, Goh SS, *et al.* Factors associated with hospital mortality in critically ill patients with exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 2361–2366.
16 Yamauchi Y, Yasunaga H, Matsui H, *et al.* Comparison of in-hospital mortality in patients with COPD, asthma and asthma–COPD overlap exacerbations. *Respirology* 2015; 20: 940–946.
17 Echevarria C, Steer J, Heslop-Marshall K, *et al.* Validation of the DECAF score to predict hospital mortality in acute exacerbations of COPD. *Thorax* 2016; 71: 133–140.
18 Morasert T, Jantarapootirat M, Phinyo P, *et al.* Prognostic indicators for in-hospital mortality in COPD with acute exacerbation in Thailand: a retrospective cohort study. *BMJ Open Respir Res* 2020; 7: e000488.
19 Alqahtani JS, Njoku CM, Bereznicki B, *et al.* Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis. *Eur Respir Rev* 2020; 29: 190166.
20 Steer J, Norman E, Afolabi O, *et al.* Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax* 2012; 67: 117–121.
21 Jo YS, Rhee CK, Kim KJ, *et al.* Risk factors for early readmission after acute exacerbation of chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2020; 14: 1753466620961688.
22 Cao Y, Xing Z, Long H, *et al.* Predictors of mortality in COPD exacerbation cases presenting to the respiratory intensive care unit. *Respir Res* 2021; 22: 77.
23 Esteban C, Garcia-Gutierrez S, Legarreta MJ, *et al.* One-year mortality in COPD after an exacerbation: the effect of physical activity changes during the event. *COPD* 2016; 13: 718–725.
24 Milne RJ, Beasley R. Hospital admissions for chronic obstructive pulmonary disease in New Zealand. *N Zealand Med J* 2015; 128: 23.
25 Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, *et al.* Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J* 2016; 47: 113–121.
26 Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013; 10: 81–89.
27 Alqahtani JS, Aldabayan YS, Aldhahir AM, *et al.* Predictors of 30- and 90-day COPD exacerbation readmission: a prospective cohort study. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 2769–2781.
28 Stewart LA, Clarke M, Rovers M, *et al.* Preferred reporting items for a systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement. *JAMA* 2015; 313: 1657–1665.
29 Pauwels RA, Buist AS, Calverley PM, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
30 Scotti L, Rea F, Corrao G. One-stage and two-stage meta-analysis of individual participant data led to consistent summarized evidence: lessons learned from combining multiple databases. *J Clin Epidemiol* 2018; 95: 19–27.
31 Zheng H, Wason JMS. Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy. *Biostatistics* 2020; 23: 120–135.
32 Guerrero M, Crisafulli E, Liapikou A, *et al.* Readmission for acute exacerbation within 30 days of discharge is associated with a subsequent progressive increase in mortality risk in COPD patients: a long-term observational study. *PloS One* 2016; 11: e0150737.
33 Ringbaek TJ, Terkelsen J, Lange P. Outcomes of acute exacerbations in COPD in relation to pre-hospital oxygen therapy. *Eur Clin Respir J* 2015; 2.
34 Fabbian F, De Giorgi A, Manfredini F, *et al.* Impact of renal dysfunction on in-hospital mortality of patients with severe chronic obstructive pulmonary disease: a single-center Italian study. *Int Urol Nephrol* 2016; 48: 1121–1127.
35 Harries TH, Thornton HV, Crichton S, *et al.* Length of stay of COPD hospital admissions between 2006 and 2010: a retrospective longitudinal study. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 603–611.
36 Wang J-X, Zhang S-M, Li X-H, *et al.* Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial. *Int J Infect Dis* 2016; 48: 40–45.

37 Ergan B, Ergun R. Impact of anemia on short-term survival in severe COPD exacerbations: a cohort study. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1775–1783.
38 Ergan B, Sahin AA, Topeli A. Serum procalcitonin as a biomarker for the prediction of bacterial exacerbation and mortality in severe COPD exacerbations requiring mechanical ventilation. *Respiration* 2016; 91: 316–324.
39 Quintana JM, Esteban C, Unzurrunzaga A, *et al.* Predictive score for mortality in patients with COPD exacerbations attending hospital emergency departments. *BMC Med* 2014; 12: 66.
40 López-Campos JL, Hartl S, Pozo-Rodriguez F, *et al.* European COPD Audit: design, organisation of work and methodology. *Eur Respir J* 2013; 41: 270–276.
41 Shafuddin E, Chang CL, Cooray M, *et al.* Changes in biomarkers of cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Respir Med* 2018; 145: 192–199.
42 Chang CL, Sullivan GD, Karalus NC, *et al.* Predicting early mortality in acute exacerbation of chronic obstructive pulmonary disease using the CURB65 score. *Respirology* 2011; 16: 146–151.
43 Lacoma A, Prat C, Andreo F, *et al.* Value of procalcitonin, C-reactive protein, and neopterin in exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2011; 6: 157–169.
44 Osadnik CR, McDonald CF, Miller BR, *et al.* The effect of positive expiratory pressure (PEP) therapy on symptoms, quality of life and incidence of re-exacerbation in patients with acute exacerbations of chronic obstructive pulmonary disease: a multicentre, randomised controlled trial. *Thorax* 2014; 69: 137–143.
45 Alía I, de la Cal MA, Esteban A, *et al.* Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. *Arch Intern Med* 2011; 171: 1939–1946.
46 Spannella F, Giulietti F, Cocci G, *et al.* Acute exacerbation of chronic obstructive pulmonary disease in oldest adults: predictors of in-hospital mortality and need for post-acute care. *J Am Med Dir Assoc* 2019; 20: 893–898.
47 Takir HB, Karakurt Z, Salturk C, *et al.* Reasons for ICU demand and long-term follow-up of a chronic obstructive pulmonary disease cohort. *COPD* 2014; 11: 627–638.
48 Aliyali M, Mehravaran H, Abedi S, *et al.* Impact of comorbid ischemic heart disease on short-term outcomes of patients hospitalized for acute exacerbations of COPD. *Tanaffos* 2015; 14: 165–171.
49 Ko FW, Chan PK, Chan RWY, *et al.* Molecular detection of respiratory pathogens and typing of human rhinovirus of adults hospitalized for exacerbation of asthma and chronic obstructive pulmonary disease. *Respir Res* 2019; 20: 210.
50 Trethewey SP, Edgar RG, Morlet J, *et al.* Temporal trends in survival following ward-based NIV for acute hypercapnic respiratory failure in patients with COPD. *Clin Respir J* 2019; 13: 184–188.
51 Steriade AT, Johari S, Sargarovschi N, *et al.* Predictors of outcome of noninvasive ventilation in severe COPD exacerbation. *BMC Pulm Med* 2019; 19: 131.
52 Vermeersch K, Gabrovska M, Aumann J, *et al.* Azithromycin during acute chronic obstructive pulmonary disease exacerbations requiring hospitalization (BACE). A multicenter, randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 2019; 200: 857–868.
53 Zilberman-Itskovich S, Rahamim E, Tsiporin-Havatinsky F, *et al.* Long QT and death in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease is not related to electrolyte disorders. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 1053–1061.
54 Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2012; 67: 970–976.
55 Hartley T, Lane ND, Steer J, *et al.* The Noninvasive Ventilation Outcomes (NIVO) score: prediction of in-hospital mortality in exacerbations of COPD requiring assisted ventilation. *Eur Respir J* 2021; 58: 2004042.
56 Sprooten RTM, Rohde GGU, Lawyer G, *et al.* Risk stratification for short-term mortality at hospital admission for acute exacerbations of COPD. *Respirology* 2019; 24: 765–776.
57 Medrano MJA, Torres OY, Robles IB, *et al.* Exacerbations of chronic obstructive pulmonary disease: an analysis of the care process in a regional hospital emergency department. *Medicine (Baltimore)* 2018; 97: e11601.
58 Sprooten RTM, Rohde GGU, Janssen M, *et al.* Predictors for long-term mortality in COPD patients requiring non-invasive positive pressure ventilation for the treatment of acute respiratory failure. *Clin Respir J* 2020; 14: 1144–1152.
59 Russell R, Beer S, Pavord ID, *et al.* The acute wheezy adult with airways disease in the emergency department: a retrospective case-note review of exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 971–977.
60 Faverio P, Stainer A, De Giacomi F, *et al.* Noninvasive ventilation weaning in acute hypercapnic respiratory failure due to COPD exacerbation: a real-life observational study. *Can Respir J* 2019; 2019: 3478968.
61 Cross JL, Elender F, Barton G, *et al.* Evaluation of the effectiveness of manual chest physiotherapy techniques on quality of life at six months post exacerbation of COPD (MATREX): a randomised controlled equivalence trial. *BMC Pulm Med* 2012; 12: 33.
62 Prins HJ, Duijkers R, van der Valk P, *et al.* CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. *Eur Respir J* 2019; 53: 1802014.

63 Stolz D, Breidthardt T, Christ-Crain M, *et al.* Use of B-type natriuretic peptide in the risk stratification of acute exacerbations of COPD. *Chest* 2008; 133: 1088–1094.
64 Grolimund E, Kutz A, Marlowe RJ, *et al.* Long-term prognosis in COPD exacerbation: role of biomarkers, clinical variables and exacerbation type. *COPD* 2015; 12: 295–305.
65 Mekov E, Slavova Y, Tsakova A, *et al.* One-year mortality after severe COPD exacerbation in Bulgaria. *PeerJ* 2016; 4: e2788.
66 Lun C-T, Tsui MSN, Cheng S-L, *et al.* Differences in baseline factors and survival between normocapnia, compensated respiratory acidosis and decompensated respiratory acidosis in COPD exacerbation: a pilot study. *Respirology* 2016; 21: 128–136.
67 Gudmundsson G, Gislason T, Lindberg E, *et al.* Mortality in COPD patients discharged from hospital: the role of treatment and co-morbidity. *Respir Res* 2006; 7: 109.
68 Almagro P, Salvado M, Garcia-Vidal C, *et al. Pseudomonas aeruginosa* and mortality after hospital admission for chronic obstructive pulmonary disease. *Respiration* 2012; 84: 36–43.
69 Epstein D, Nasser R, Mashiach T, *et al.* Increased red cell distribution width: a novel predictor of adverse outcome in patients hospitalized due to acute exacerbation of chronic obstructive pulmonary disease. *Respir Med* 2018; 136: 1–7.
70 Miravitlles M, García-Sidro P, Fernández-Nistal A, *et al.* The chronic obstructive pulmonary disease assessment test improves the predictive value of previous exacerbations for poor outcomes in COPD. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 2571–2579.
71 Utens CMA, Goossens LMA, Smeenk FWJM, *et al.* Early assisted discharge with generic community nursing for chronic obstructive pulmonary disease exacerbations: results of a randomised controlled trial. *BMJ Open* 2012; 2: e001684.
72 Smulders L, van der Aalst A, Neuhaus E, *et al.* Decreased risk of COPD exacerbations in obese patients. *COPD* 2020; 17: 485–491.
73 Ko FW, Cheung NK, Rainer TH, *et al.* Comprehensive care programme for patients with chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax* 2017; 72: 122–128.
74 Murphy PB, Rehal S, Arbane G, *et al.* Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017; 317: 2177–2186.
75 Matkovic Z, Huerta A, Soler N, *et al.* Predictors of adverse outcome in patients hospitalised for exacerbation of chronic obstructive pulmonary disease. *Respiration* 2012; 84: 17–26.
76 Soriano JB, Kendrick PJ, Paulson KR, *et al.* Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2020; 8: 585–596.
77 Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009; 374: 733–743.
78 Scanlon PD, Connett JE, Waller LA, *et al.* Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: the Lung Health Study. *Am J Respir Crit Care Med* 2000; 161: 381–390.
79 Li HY, Gao TY, Fang W, *et al.* Global, regional and national burden of chronic obstructive pulmonary disease over a 30-year period: estimates from the 1990 to 2019 Global Burden of Disease Study. *Respirology* 2023; 28: 29–36.
80 Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. *Lancet Respir Med* 2022; 10: 497–511.
81 Stolz D, Mkorombindo T, Schumann DM, *et al.* Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet* 2022; 400: 921–972.
82 Roberts CM, Lopez-Campos JL, Pozo-Rodriguez F. European hospital adherence to GOLD recommendations for chronic obstructive pulmonary disease (COPD) exacerbation admissions. *Thorax* 2013; 68: 1169–1171.
83 Miravitlles M, Vogelmeier C, Roche N, *et al.* A review of national guidelines for management of COPD in Europe. *Eur Respir J* 2016; 47: 625–637.
84 Cousins JL, Wood-Baker R, Wark PAB, *et al.* Management of acute COPD exacerbations in Australia: do we follow the guidelines? *ERJ Open Res* 2020; 6: 00270.
85 McGhan R, Radcliff T, Fish R, *et al.* Predictors of rehospitalization and death after a severe exacerbation of COPD. *Chest* 2007; 132: 1748–1755.
86 Maselli DJ, Bhatt SP, Anzueto A, *et al.* Clinical epidemiology of COPD: insights from 10 years of the COPDGene study. *Chest* 2019; 156: 228–238.
87 Eisner MD, Blanc PD, Omachi TA, *et al.* Socioeconomic status, race and COPD health outcomes. *J Epidemiol Community Health* 2011; 65: 26–34.
88 Hurst JR, Buist AS, Gaga M, *et al.* Challenges in the implementation of chronic obstructive pulmonary disease guidelines in low- and middle-income countries: an Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc* 2021; 18: 1269–1277.

89 Stolbrink M, Thomson H, Hadfield RM, *et al.* The availability, cost, and affordability of essential medicines for asthma and COPD in low-income and middle-income countries: a systematic review. *Lancet Glob Health* 2022; 10: e1423–e1e42.

90 Ramakrishnan S, Janssens W, Burgel PR, *et al.* Standardisation of clinical assessment, management and follow-up of acute hospitalised exacerbation of COPD: a Europe-wide consensus. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 321–332.

91 Dong F, Ren X, Huang K, *et al.* Development and validation of risk prediction model for in-hospital mortality among patients hospitalized with acute exacerbation chronic obstructive pulmonary disease between 2015 and 2019. *Front Med (Lausanne)* 2021; 8: 630870.

92 Esteban C, Castro-Acosta A, Alvarez-Martínez CJ, *et al.* Predictors of one-year mortality after hospitalization for an exacerbation of COPD. *BMC Pulm Med* 2018; 18: 18.

93 Abdelhalim M, Khan M, Paracha M. Prognosis after non-invasive ventilation (NIV) for chronic obstructive pulmonary disease (COPD). *Eur Respir Soc* 2011; 38: 3790.

94 Foreman MG, Zhang L, Murphy J, *et al.* Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. *Am J Respir Crit Care Med* 2011; 184: 414–420.

95 Almagro P, López García F, Cabrera FJ, *et al.* Comorbidity and gender-related differences in patients hospitalized for COPD. The ECCO study. *Respir Med* 2010; 104: 253–259.

96 Divo MJ, Marin JM, Casanova C, *et al.* Comorbidities and mortality risk in adults younger than 50 years of age with chronic obstructive pulmonary disease. *Respir Res* 2022; 23: 267.

97 Giezeman M, Sundh J, Athlin Å, *et al.* Comorbid heart disease in patients with COPD is associated with increased hospitalization and mortality: a 15-year follow-up. *Int J Chron Obstruct Pulmon Dis* 2023; 18: 11–21.

98 Stolz D, Kostikas K, Loefroth E, *et al.* Differences in COPD exacerbation risk between women and men: analysis from the UK clinical practice research datalink data. *Chest* 2019; 156: 674–684.

99 Cydulka RK, Rowe BH, Clark S, *et al.* Gender differences in emergency department patients with chronic obstructive pulmonary disease exacerbation. *Acad Emerg Med* 2005; 12: 1173–1179.

100 Whittaker H, Rubino A, Müllerová H, *et al.* Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 427–437.

101 Rhodes K, Jenkins M, de Nigris E, *et al.* Relationship between risk, cumulative burden of exacerbations and mortality in patients with COPD: modelling analysis using data from the ETHOS study. *BMC Med Res Methodol* 2022; 22: 150.

102 Soler-Cataluña J, Martinez-Garcia MA, Sánchez PR, *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931.

103 Stone RA, Lowe D, Potter JM, *et al.* Managing patients with COPD exacerbation: does age matter? *Age Ageing* 2012; 41: 461–468.