Targeted Literature Review (TLR) on the Mortality in Patients With Moderate-to-Severe Chronic Obstructive Pulmonary Disease (COPD) in the USA

COPD

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Introduction

- Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory condition that affects the respiratory system, resulting in airflow obstruction and tissue damage. With 3.23 million deaths in 2019, COPD is the third leading cause of mortality globally.[1]
- In 2020, COPD caused approximately 150,000 deaths in the United States (US) alone.[2] Though real-world studies have assessed COPD mortality rates in the US, there is a lack of a comprehensive review evaluating these mortality rates in relation to patient characteristics and disease severity.

Methods

Study design

- A targeted literature search was conducted following the Population, Intervention, Comparator and Outcome (PICO) framework. The pre-defined inclusion criteria are provided in **Table 1**.
- Electronic databases (Embase and Medline) were searched for observational and real-world studies published from inception until November 2023. A manual search was conducted for studies published between November 2023 and January 2024.

Outcomes

- Primary outcomes: mortality by disease severity, gender and smoking status (all-cause and COPD-related).
- Secondary outcomes: non-mortality-related outcomes, including treatment patterns and disease/exacerbation severity as per GOLD guideline.

Table 1. Pre-defined study inclusion criteria

PICO+ Component	Description
Population	Patients with moderate-to-severe COPD
Interventions and comparators	No restriction
Outcomes	**Mortality by age, gender and smoking status:** All-cause mortality, COPD-related mortality; **Treatment patterns:** Number of patients on treatments with LABA + LAMA vs LABA + ICS vs LABA + LAMA + ICS, escalation and de-escalation; **Patient characteristics:** Demographics (age and sex), COPD-related and cardiovascular disease outcomes (exacerbations, major adverse cardiac events and pneumonia), eosinophil level, GOLD stage[a], disease severity.
Study types	Observational studies/real-world evidence studies/systematic literature reviews/meta-analyses
Time frame	No restriction
Geography	United States
Language	English

Key search terms included chronic obstructive lung disease, chronic bronchitis, mortality, morbidity, death, exacerbation, retrospective study, prospective study, cohort analysis, real-world evidence, and United States.
[a]GOLD grades the severity of COPD based on airflow limitation and other factors- GOLD 1: Mild, with an FEV1 of at least 80% of predicted; GOLD 2: Moderate, with an FEV_1 between 50% and 80% of predicted; GOLD 3: Severe, with an FEV1 between 30% and 50% of predicted; GOLD 4: Very severe, with an FEV_1 of less than 30% of predicted.
COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonists; LAMA, long-acting muscarinic antagonist; PICO, Population Intervention Comparator and Outcome.

Objective

- **This targeted literature review (TLR) aimed to summarise the available observational and real-world studies for all-cause and disease-related mortality rates in patients with moderate-to-severe COPD, with a focus on the US.**

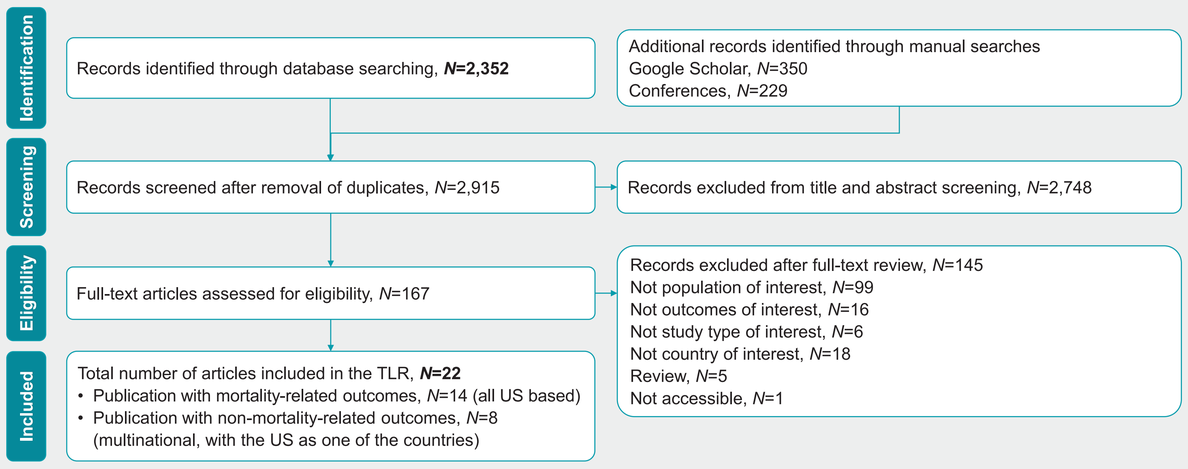
Conclusions

- **This TLR highlighted that the overall mortality rates are high in patients with moderate-to-severe COPD than those without lung disease. Higher mortality rates were also observed in patients with increasing GOLD stages (GOLD 3/4 vs. GOLD 1/2), male (vs. female), current smoking status (vs. former/never smoker) and the severity of disease.**
- **Future studies are needed to better understand treatment patterns and COPD-related mortality rates.**
- **These findings are subject to several limitations, including heterogeneity in data sources, study periods/follow-up and limited generalisability of smaller cohorts.**

Results

- The search yielded 2,352 records through electronic databases and 579 through manual searching, of which 22 publications were included in the TLR.
- Of the included publications, 14 reported mortality data[3–16] (primary outcome) and eight reported data on secondary outcomes[17–24] (**Figure 1**).

Figure 1. Flow chart for the selection of studies



TLR, targeted literature search; US, United States.

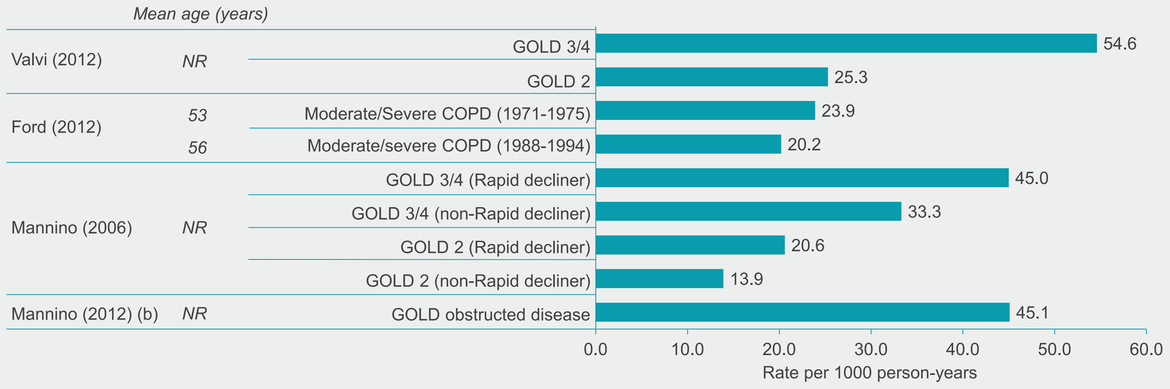
- At baseline, the studies reported a mean age range of 40.7 to 72.8 years, with the proportion of male patients ranging from 2.2% to 100.0%, the proportion of current smokers ranging from 2.5% to 59.3% and GOLD stages B–D or 2–4 representing 8.8% to 87.3% of the study population.[3–10, 12–24]

Mortality-related outcomes

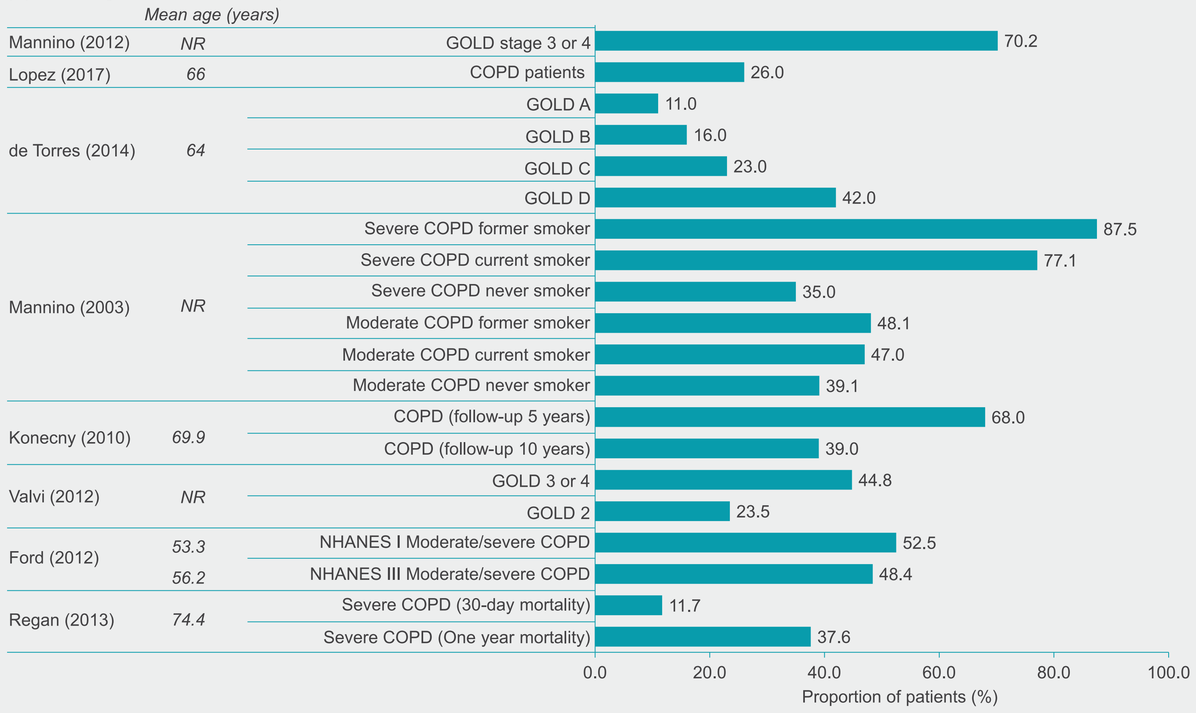
- In the US population, the mortality outcomes were reported in 14 out of the 22 publications, which provided data on either the mortality rate or the proportion of patients who experienced the event.[3–16]
- All-cause mortality ranged from 13.9 to 54.6 per 1000 person-years, varying with disease severity (**Figure 2A**)[8, 10,12, 13] with 11.0% to 87.5% of patients experiencing a mortality event (**Figure 2B**).[5–10, 15, 16] In the COPD-related mortality cohort, 0% to 29.7% of patients experienced a mortality event.[6]

Figure 2. All-cause mortality rates by disease severity/GOLD stage

(A) Mortality rate per 1000 person-years [8, 10,12, 13]



(B) Percentage of deaths in COPD patients [5–10, 15, 16]



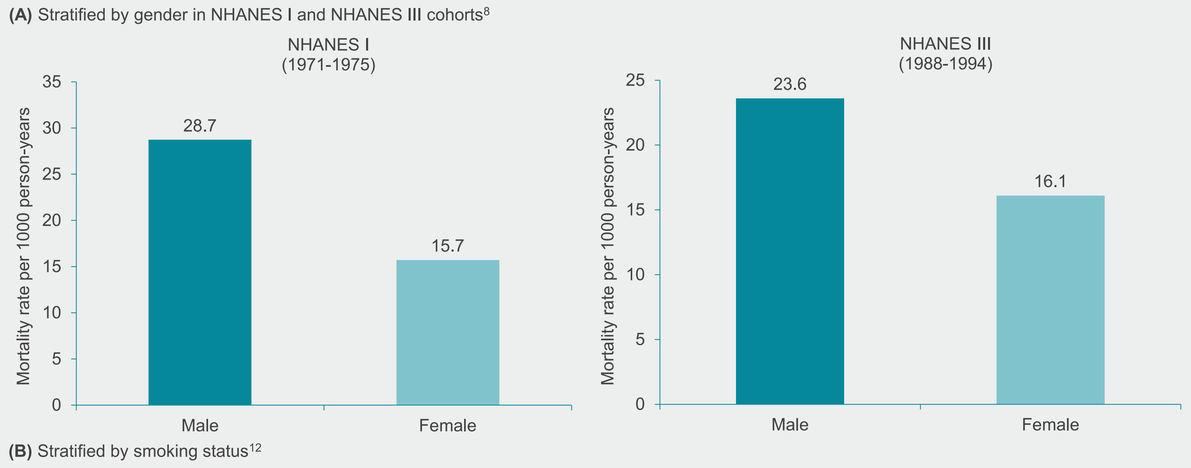
COPD, chronic obstructive pulmonary disease; FEV_1 forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; NHANES, National Health and Nutrition Examination Survey; NR, not reported.

Mortality rates stratified by age, gender, and smoking status

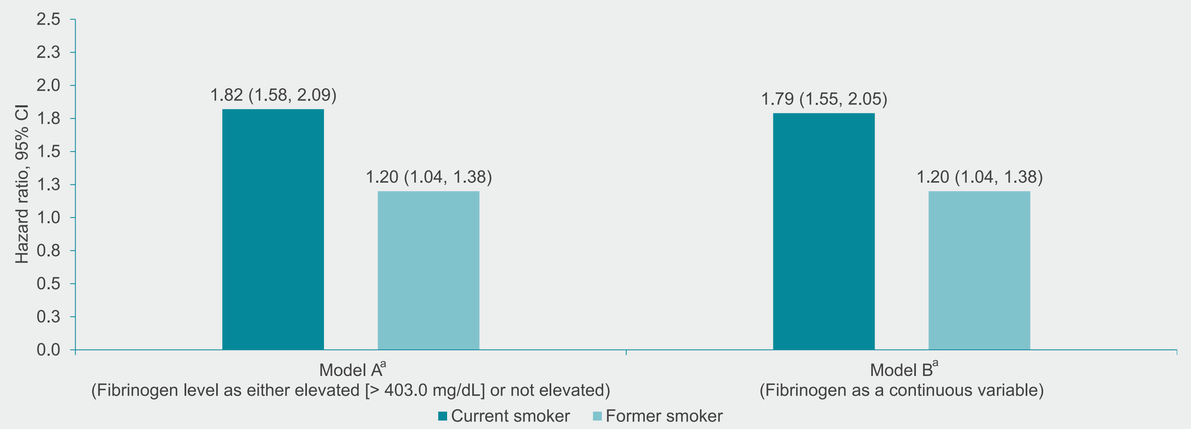
- A study analysing the National Health and Nutrition Examination Surveys (NHANES) I and III cohorts found that male patients with moderate-to-severe COPD had a higher age-adjusted mortality rate than women (**Figure 3A**).[8]
- Mannino et al. 2012 (b) reported higher COPD-related mortality rates in current smokers than in former/never smokers with moderate-to-severe COPD, with Cox proportional hazard models adjusted for all covariates.(**Figure 3B**).[12]
- Smokers with severe COPD had a higher risk of mortality, with a proportional hazards ratio (HR) of 8.0(5.6–11.5), than smokers with moderate COPD (HR: 3.9 [3.1–4.9]).[6]

Figure 3. Mortality in patients with moderate-to-severe COPD

(A) Stratified by gender in NHANES **I** and NHANES **III** cohorts[8]



(B) Stratified by smoking status[12]

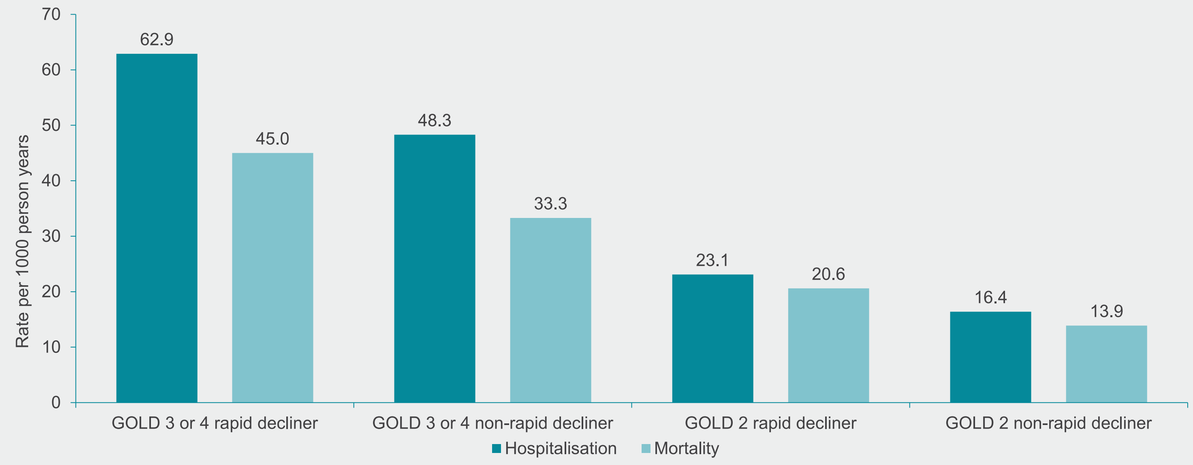


[a]The HR (95%CI) from multiple cox proportional hazard model adjusting for several covariates (e.g., age, sex, etc) while for the smoking status, "never smoke" was set as the reference group for comparison.
CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey.

Mortality rates by disease severity

- Patients with severe/very severe COPD were more likely to require hospitalisation (46.5% vs. 19.6%) and had higher mortality rates (44.8% vs. 23.5%) compared to those with moderate COPD.[10]
- Mannino et al. (2006) reported that a rapid decline in lung function is a predictor of time to COPD-related hospitalisation (HR: 1.4, 95% CI: [1.2, 1.8]) and mortality (HR:1.4, 95% CI [1.2, 1.7]) than those with a non-rapid decline.[13] The COPD-related hospitalisation and mortality rates are illustrated in **Figure 4**.

Figure 4. COPD-related hospitalisation and mortality rates[13]



COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease.

Non-mortality related outcomes

- One study (Schabert et al., 2021) reported deviations from the GOLD guidelines for the use of triple therapy. Two studies (Bogart et al., 2023 and Schabert et al., 2021) reported underutilisation of controller medications (ICS/LABA, LAMA, leukotriene modifiers, multiple-inhaler triple therapy, LAMA/LABA, ICS, fluticasone furoate/umeclidinium/vilanterol, LABA, methylxanthine, phosphodiesterase-4 inhibitor and Biologics), with over 50% of patients not on these medications.[19, 22] One study (Mannino et al., 2022) reported the proportion of patients utilizing controlled medications, highlighting that patients were managed with different controlling medication regimens.[20]
- Eight studies provided definitions of exacerbations, which included treatment and healthcare resource use. While 14 studies reported disease severity definition, with nine of them using GOLD criteria.

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CONFLICTS OF INTEREST
EMH, TQ and **VA** – Sanofi – employees, may hold stocks and/or stock options in the company;
EZ, SNB and **VL** – Amaris Consulting – employees, may hold stocks and/or stock options in the company;
JW – Regeneron Pharmaceuticals Inc. – employee, may hold stocks and/or stock options in the company.

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