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# Prevalence and Impact of Chronic Obstructive Pulmonary Disease in Ischemic Heart Disease: A Systematic Review and Meta-Analysis of 18 Million Patients

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**Background:** The prevalence of chronic obstructive pulmonary disease (COPD) in patients with ischemic heart disease (IHD) remains uncertain, and its association with adverse outcomes is frequently overlooked. This study aimed to estimate the prevalence of COPD, and its impact on pharmacological treatment, and clinical outcomes in patients with IHD.

**Methods:** A systematic literature search was conducted in Web of Science, Embase, and PubMed until November 20, 2023. All studies that reported the prevalence of COPD in IHD patients were included, and a random-effects model was employed to calculate the pooled prevalence. Data on cardiovascular risk factors/comorbidities, beta-blockers (BBs) prescription, acute phase outcomes [in-hospital mortality, major adverse cardiovascular events (MACE), acute heart failure (AHF), and cardiogenic shock], and long-term mortality were compared according to COPD status.

**Results:** A total of 82 eligible studies that reported the prevalence of COPD in 18 million IHD patients were included. The pooled prevalence of COPD was 12.0% [95% confidence intervals (CI): 9.9%–14.1%] in patients with IHD. In subgroup analysis, the prevalence of COPD was highest in North America (15.3%), followed by Europe (10.0%), and Asia (8.8%). In addition, COPD was associated with a higher burden of cardiovascular risk factors/comorbidities, but lower BBs prescription [odds ratio (OR) 0.50, 95% CI 0.38–0.66]. Moreover, COPD was linked to an increased risk of in-hospital mortality (OR 1.47, 95% CI 1.37–1.58), MACE (OR 1.81, 95% CI 1.44–2.27), AHF (OR 2.14, 95% CI 1.86–2.46), cardiogenic shock (OR 1.30, 95% CI 1.01–1.68), as well as long-term mortality (OR 1.99, 95% CI 1.80–2.20).

**Conclusion:** This meta-analysis demonstrated that COPD is prevalent in IHD, involving 12.0% of IHD patients, and is linked to a lower prescription of BBs, an increased burden of comorbidities, and worse acute phase outcomes and long-term mortality.

**Keywords:** ischemic heart disease, chronic obstructive pulmonary disease, prevalence, beta-blockers, outcomes

## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by persistent, usually progressive airflow limitation and airway inflammation, along with systemic manifestations.[1,2] As the third leading cause of mortality, COPD's annual toll is expected to reach 4.4 million by 2040, imposing substantial and growing economic and social burdens.[3] Ischemic heart disease (IHD), sharing primary risk factors with COPD like aging, smoking, and systemic inflammation, is another leading cause of death, accounting for over 9 million fatalities in

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2016.[4,5] These two diseases often coexist in the same individual and have become issues of great concern, making diagnosis, management, and outcomes more complex than each comorbidity exists separately.[6] Despite the reciprocal association between these two conditions, whether COPD contributes to cardiovascular disease (CVD) or vice versa was still uncertain because of the cross-sectional nature of the present evidence.[7] Compared with the general population, many studies have concluded that patients with COPD are more susceptible to IHD, increasing more than 2-fold, contributing substantially to clinical outcomes, mortality, and resource use.[6–13] However, less attention has been paid to COPD as a comorbid condition of IHD, potentially resulting in the overlook of its possible adverse effects.[14–16]

Recognizing the connection between IHD and COPD has significant consequences for disease management, such as target "case finding" in IHD patients, risk factors intervention, drug usage like beta-blockers (BBs), and the application of an integrated care approach. Studies have demonstrated a substantially increased risk of concomitant COPD and its adverse impact on outcomes in patients with IHD,[17–21] and this was recapitulated in previous narrative reviews.[5,8] Yet, no prior study has formally quantified the clinical relationship between these two conditions using quantitative evidence synthesis. Considering these factors, the primary aim of this study was to determine the prevalence of COPD in IHD patients. Additionally, we aimed to evaluate the relationship between cardiovascular risk factors/comorbidities and COPD in patients with IHD, analyse the prescription of BBs in IHD patients comorbid with COPD, and assess the impact of COPD on clinical outcomes.

# Methods

## Study Design

This systematic review and meta-analysis followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[22] The study was registered on PROSPERO (CRD42023483569) and reported by the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA),[23] and the PRISMA Checklist was also provided.

## Search Strategy and Selection Criteria

After identifying relevant Medical Subject Headings (Mesh), a systematic search was performed in Web of Science, Embase, and PubMed until November 20, 2023. Details regarding the search strategy are reported in Table S1. After removing duplicates, 2 reviewers (M.K. and Z.X.) independently and systematically screened titles and abstracts, and then reviewed full texts. Studies were included if they reported the prevalence of COPD in IHD patients with a sample size of more than 400, irrespective of study design. We excluded the studies which had one of the following characteristics: 1) the study population were highly selected cohorts of patients with IHD (such as cohorts based only on patients with IHD and atrial fibrillation (AF); 2) the language used in the article was not English; 3) article type was conference abstracts, letters, editorials, and review articles. If two or more studies were based on the same cohort, only the study with the largest sample size was included.

## Data Extraction

Two independent reviewers (MK and ZX) extracted data from the included studies, with discrepancies resolved by a third reviewer (DH) when necessary. The following data were extracted: author, publication year, geographical regions, study design, sample size, number of patients with COPD, mean age, the proportion of males, risk factors/comorbidities [including smoking history, hypertension, diabetes mellitus (DM), chronic heart failure (CHF), AF, chronic kidney disease (CKD)]. In addition, available data on BBs prescription, acute phase outcomes [in-hospital mortality, major adverse cardiovascular events (MACE), acute heart failure (AHF), and cardiogenic shock], and long-term mortality were also extracted.

## Quality Assessment

After extracted data from eligible studies, 2 independent reviewers (MK and ZX) critically analysed all studies to evaluate the risk of bias. A modified Newcastle–Ottawa Scale (NOS),[24,25] consisting of five elements across the areas of selection, comparability, and outcome, was employed for the evaluation of COPD prevalence, given a score out of five

(Table S2). Studies with a score less than 3 points were classified as having a high likelihood of bias. Additionally, in the studies that grouped IHD patients based on the diagnosis of COPD, a modified NOS was employed, which consists of eight elements across three domains (Table S3). Studies with a score of modified NOS less than 6 points was considered at high risk of bias. All discrepancies were discussed with a third reviewer (DH).

## Outcomes Definition

The primary outcome of this study was the prevalence of COPD among individuals with IHD. Furthermore, the odds ratios (OR) for baseline cardiovascular risk factor/comorbidities, the prescription of BBs, and the acute phase outcomes (in-hospital mortality, MACE, AHF, and cardiogenic shock) and long-term mortality were also investigated in IHD patients according to the diagnosis of COPD.

## Statistical Analysis

Prevalence estimates were extracted as raw proportions. Pooled estimates were determined through a random-effects model, applying the Freeman-Tukey double arcsine transformation for variance stabilization. Point estimates of proportions along with 95% confidence intervals (CI) were computed and presented in forest plots. For pooled estimates, $tau^2$ was utilized for estimating variance across studies, while the $I^2$ served to assess heterogeneity. The jackknife sensitivity analyses were conducted with a "leave-one-out" method, which sequentially excluded each study to evaluate its impact on pooled estimate and heterogeneity. Furthermore, we calculated COPD prevalence by progressively excluding studies that had sample sizes below defined cut-offs. To identify possible sources of heterogeneity in COPD prevalence, multiple subgroup analyses were conducted based on geographical location, study design, definition of COPD, age cutoffs, and year of data source (1980s, 1990s, 2000s, 2010s). In order to further clarify the possible factors contributing to the heterogeneity of COPD prevalence, meta-regressions were performed. Initially, univariable meta-regressions were conducted based on factors like study design, mean age, male proportions, definition of COPD, and proportion of relevant comorbidities. Subsequently, a multivariable meta-regression was conducted incorporating factors that showed significant associations with COPD prevalence at univariable meta-regression. The studies with AF data were limited, so AF will not be included in the multivariable regression analysis, even if it showed statistical significance in the univariable analysis.

In the comparisons based on COPD status, we calculated weighted-pooled summary estimates of OR with a random effects model. The jackknife sensitivity analyses were also conducted. In addition, Meta-regressions for the prescription of BBs, and long-term mortality were performed. Funnel plots and Begg's test were employed to evaluate potential publication bias in comparisons based on COPD status, with at least 10 studies included. All statistical analyses were performed using Stata 17.0 software.

# Results

## Characteristics of Included Studies

The search in databases yielded 23374 publications (12213 from Web of Science, 6336 from Embase, 4822 from PubMed, and 3 from other sources). After removing duplicates and conducting title and abstract screening, 308 full texts were reviewed for eligibility. Finally, a total of 82 studies, with a combined sample of 18 million subjects, which reported the prevalence of COPD in IHD patients were included for quantitative synthesis (Figure 1, Table S4). Among 82 studies, 35 were from North America, 27 from Europe, 15 from Asia, and 5 from other geographical regions. According to the study designs, 33 studies were from administrative databases, 23 studies were from observational multicentre studies, 21 studies were from observational single centre studies, and the remaining 5 studies were from secondary analysis of randomized controlled trials (RCTs). As for the classifications based on the non-pharmacological interventions, 20 studies were from the coronary artery bypass grafting (CABG) cohorts, 18 were from percutaneous coronary intervention (PCI) cohorts, and the remaining 44 studies were from other cohorts. According to the definition of COPD, 43 studies were based on ICD/Spirometry, while 39 studies were based on patients' self-reports. Assessment of bias in the prevalence of COPD was provided in Table S5, and 17 studies were considered at high risk of bias.

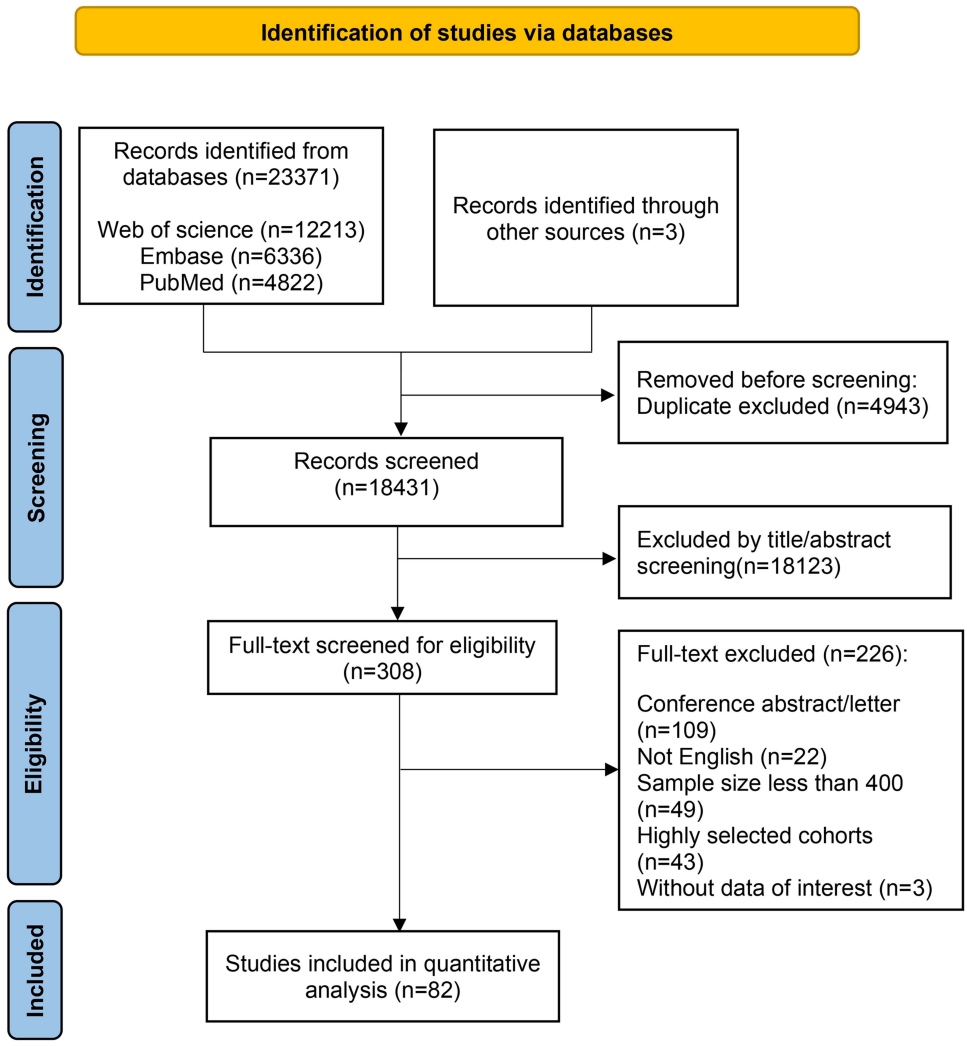


**Figure 1** PRISMA flowchart of this study.

## The Prevalence of COPD in IHD Patients

From the random-effects meta-analysis, the pooled prevalence of COPD was 12.0% (95% CI 9.9%–14.1%), with a high heterogeneity across different studies (Figure 2). Sensitivity analyses were performed with the use of the "leave-one-out" approach, and we did not observe substantial effects of individual studies on the pooled estimates or on heterogeneity (Table S6). Further sensitivity analyses were conducted by progressively excluding studies with sample sizes below increasing cutoff values (cut-off values were 1000, 10,000, 20,000,100,000). Similar results were observed, with all figures falling within the 95% CI of the pooled prevalence of COPD (Table S7).

Subgroup analyses were performed to assess the potential sources of heterogeneity (Table 1). Among the different geographical locations, the prevalence of COPD was highest in North America (15.3%, 95% CI 13.0%–17.6%), followed by Europe (10.0%, 95% CI 8.6%–11.3%), and Asia (8.8%, 95% CI 5.3%–12.3%). Across most settings, administrative databases had higher COPD prevalence (16.0%, 95% CI 12.9%–19.2%) than observational single centre/multicentre studies or RCTs. An analysis according to the mean age showed that the prevalence of COPD was higher in patients ≥70 years (18.3%, 95% CI 14.6%–22.0%, $p < 0.001$) compared with those <70 years. The prevalence of COPD, when defined based on self-reported, was lower compared to that defined by ICD/spirometry criteria (10.2% vs 13.1%), though the difference was not statistically significant. In addition, the prevalence of COPD showed an upward trend over time, with the highest prevalence of 13.1% in 2010s. Finally, no statistical differences in the prevalence of COPD were found among different non-pharmacological intervention cohorts.

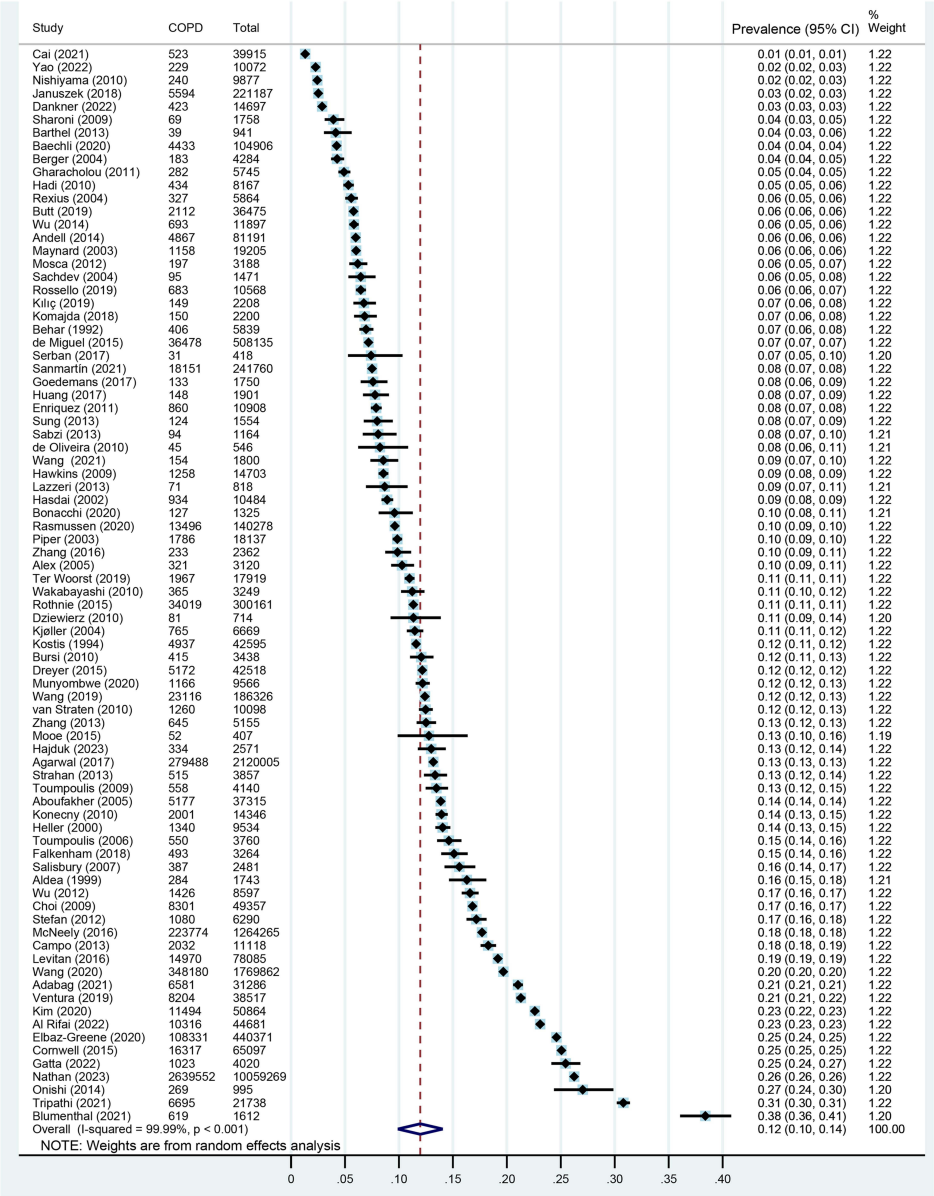


**Figure 2** Pooled prevalence of COPD in patients with ischemic heart disease.
**Abbreviations**: COPD, chronic obstructive pulmonary disease; CI, confidence interval; ES, effect size.

The initial univariable meta-regression analysis indicated that mean age, study design, the proportion of hypertension, DM, CHF, as well as AF, were related to a higher prevalence of COPD (Table 2). Graphical representations of the univariable meta-regressions for mean age, hypertension, DM, CHF, and AF were documented in Figure S1. The multivariable meta-regression model, including mean age, hypertension, HF, and study design accounted for the most proportion of the heterogeneity reported ($R^2$ = 42.8%, $p < 0.001$) (Table 2).

## Association Between Cardiovascular Risk Factors/Comorbidities and COPD in IHD Patients

To investigate the relationship between cardiovascular risk factors/comorbidities and COPD in IHD patients, the included studies, which were grouped according to COPD status, were further analysed. Overall, 28 studies provided data on hypertension and DM, 16 studies on CHF, 13 studies on CKD, and 5 studies on AF. In addition, 27 studies reported data

**Table 1** Subgroup Analysis for the Pooled Prevalence (%) of COPD in Patients with Ischemic Heart Disease

| Subgroups | Number of Studies | Pooled Prevalence | Lower 95% CI | Upper 95% CI | $I^2$ | p-value |
|---|---|---|---|---|---|---|
| **Geographical location** | | | | | | <0.001 |
| North America | 35 | 15.3 | 13.0 | 17.6 | 100.0 | |
| Europe | 27 | 10.0 | 8.6 | 11.3 | 99.9 | |
| Asia | 15 | 8.8 | 5.3 | 12.3 | 100.0 | |
| Others | 5 | 9.0 | 7.0 | 11.1 | 97.2 | |
| **Study design** | | | | | | <0.001 |
| Administrative databases | 33 | 16.0 | 12.9 | 19.2 | 100.0 | |
| Observational single centre | 21 | 9.7 | 7.5 | 11.8 | 88.4 | |
| Observational multicentre | 23 | 9.2 | 6.9 | 11.5 | 99.8 | |
| RCT | 5 | 7.3 | 5.7 | 8.9 | 96.2 | |
| **COPD definition** | | | | | | 0.285 |
| ICD/Spirometry | 43 | 13.1 | 10.4 | 15.9 | 100.0 | |
| Self-reported | 39 | 10.2 | 8.4 | 13.4 | 99.9 | |
| **Age class** | | | | | | 0.001 |
| <70 years | 58 | 10.6 | 8.8 | 12.5 | 100.0 | |
| ≥70 years | 13 | 18.3 | 14.6 | 22.0 | 100.0 | |
| **Non-pharmacological intervention** | | | | | | 0.460 |
| CABG | 20 | 13.7 | 11.0 | 16.4 | 100.0 | |
| PCI | 18 | 10.3 | 3.1 | 17.6 | 100.0 | |
| Other cohorts | 44 | 11.8 | 10.1 | 13.6 | 99.9 | |
| **Year of data source** | | | | | | 0.374 |
| 1980s | 3 | 8.4 | 4.6 | 12.1 | 98.0 | |
| 1990s | 10 | 9.8 | 7.2 | 12.4 | 99.6 | |
| 2000s | 18 | 11.4 | 10.0 | 12.9 | 99.9 | |
| 2010s | 36 | 13.1 | 6.4 | 17.8 | 100.0 | |

**Abbreviations**: RCT, randomized controlled trial; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CI, confidence interval; $I^2$, inconsistency index.

**Table 2** Meta-Regression Analysis for COPD Prevalence in Patients with Ischemic Heart Disease

| Variable | Coefficient | Standard Error | Lower 95% CI | Upper 95% CI | p-value | $R^2$ |
|---|---|---|---|---|---|---|
| **Univariable analysis** | | | | | | |
| Age (years) | 0.005 | 0.002 | 0.002 | 0.008 | 0.004 | 0.103 |
| Male | −0.087 | 0.066 | −0.219 | 0.044 | 0.190 | 0.010 |
| Hypertension | 0.128 | 0.051 | 0.026 | 0.229 | 0.015 | 0.072 |
| Smoking history | 0.029 | 0.053 | −0.077 | 0.135 | 0.590 | 0.000 |
| DM | 0.301 | 0.093 | 0.116 | 0.485 | 0.002 | 0.112 |
| CKD | 0.084 | 0.075 | −0.070 | 0.237 | 0.275 | 0.008 |
| CHF | 0.211 | 0.064 | 0.066 | 0.121 | 0.002 | 0.152 |
| AF | 0.487 | 0.210 | 0.038 | 0.937 | 0.036 | 0.228 |
| Study design | | | | | <0.001 | 0.202 |
| Administrative databases | Ref | Ref | Ref | Ref | | |
| Observational multicentre | −0.063 | 0.018 | −0.099 | −0.028 | 0.001 | |
| Observational single centre | 0.068 | 0.017 | −0.103 | −0.034 | <0.001 | |
| RCT | −0.087 | 0.031 | −0.148 | −0.026 | 0.006 | |

(*Continued*)

**Table 2** (Continued).

| Variable | Coefficient | Standard Error | Lower 95% CI | Upper 95% CI | p-value | $R^2$ |
|---|---|---|---|---|---|---|
| COPD definition | | | | | 0.863 | 0.000 |
| ICD/Spirometry | Ref | Ref | Ref | Ref | | |
| Self-reported | −0.003 | 0.016 | −0.035 | 0.029 | | |
| **Multivariable analysis** | | | | | <0.001 | 0.428 |
| Age (years) | 0.004 | 0.001 | −0.003 | 0.007 | 0.440 | |
| Male | 0.023 | 0.014 | −0.015 | 0.048 | 0.422 | |
| Hypertension | 0.106 | 0.032 | 0.012 | 0.188 | 0.045 | |
| DM | 0.208 | 0.054 | 0.068 | 0.442 | 0.038 | |
| CHF | 0.156 | 0.040 | 0.065 | 0.225 | 0.006 | |
| Study design | | | | | | |
| Administrative databases | Ref | Ref | Ref | Ref | | |
| Observational multicentre | −0.075 | 0.024 | −0.152 | −0.045 | 0.008 | |
| Observational single centre | −0.084 | 0.016 | −0.122 | −0.037 | <0.001 | |
| RCT | 0.023 | 0.022 | −0.115 | 0.064 | 0.125 | |

**Note**: Multivariable meta-regression that included factors showing significant associations with COPD prevalence in the univariable analysis.
**Abbreviations**: DM, diabetes mellitus; CKD, chronic kidney disease; CHF, chronic heart failure; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; RCT, randomized controlled trial; CI, confidence interval; ICD, International Classification of Diseases.

on male sex, 23 studies on mean age, 17 studies on smoking history, and 16 studies on mean BMI in IHD patients with and without COPD. Among these risk factors, DM, hypertension, CHF, CKD, and AF were more prevalent in IHD patients comorbid with COPD than in those with IHD alone (Table 3, Figures S2-S6). In addition, COPD patients were less likely to be male sex but were more likely to be smokers (Table 3, Figures S7 and S8). Moreover, higher mean age was observed in IHD patients with COPD compared with no-COPD patients (4.24, 95 CI 3.86–4.63) (Table 3, Figure S9).

## Association Between BBs Prescription and COPD in IHD Patients

Among the 17 studies that provided data on BBs prescriptions, the probability of COPD patients being prescribed BBs was only half that of the non-COPD patients (OR 0.50, 95% CI 0.38–0.66) (Figure 3), with a high degree of heterogeneity. Sensitivity analysis showed that all the estimated ORs were ≤0.66 after sequentially excluding each study at a time, which confirmed the high stability of the present findings (Figure S10). To explain the possible sources of heterogeneity in the pooled estimates for BBs prescription, univariable meta-regressions were conducted based on baseline characteristics, and no significant associations were observed except for male sex (p = 0.004, $R^2$ = 49.38%)

**Table 3** Association Between Risk Factors/Comorbidities and Comorbid COPD in Patients with Ischemic Heart Disease

| Conditions | Number of Studies | OR/WMD | 95% CI | p-value | $Tau^2$ | $x^2$ | $I^2$ |
|---|---|---|---|---|---|---|---|
| DM | 28 | 1.17 | 1.07–1.29 | 0.001 | 0.051 | 596.19 | 95.5% |
| Hypertension | 28 | 1.23 | 1.08–1.41 | <0.001 | 0.111 | 1454.21 | 98.1% |
| CHF | 16 | 2.27 | 1.96–2.64 | <0.001 | 0.067 | 318.94 | 95.3% |
| AF | 5 | 1.66 | 1.37–2.02 | <0.001 | 0.040 | 159.26 | 97.5% |
| Male | 27 | 0.89 | 0.81–0.98 | 0.018 | 0.049 | 719.26 | 96.4% |
| Smoking history | 17 | 2.39 | 1.98–2.88 | <0.001 | 0.135 | 928.42 | 98.3% |
| CKD | 13 | 1.67 | 1.46–1.91 | <0.001 | 0.038 | 105.69 | 88.6% |
| Age (years) | 23 | 4.24 | 3.86–4.63 | <0.001 | 0.537 | 219.59 | 90.0% |
| BMI | 16 | −0.34 | −0.74–0.05 | 0.125 | 0.534 | 209.81 | 92.9% |

**Abbreviations**: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CHF, chronic heart failure; AF, atrial fibrillation; CKD, chronic kidney disease; BMI, body mass index; OR, odds ratio; WMD, weighted mean difference; CI, confidence interval.

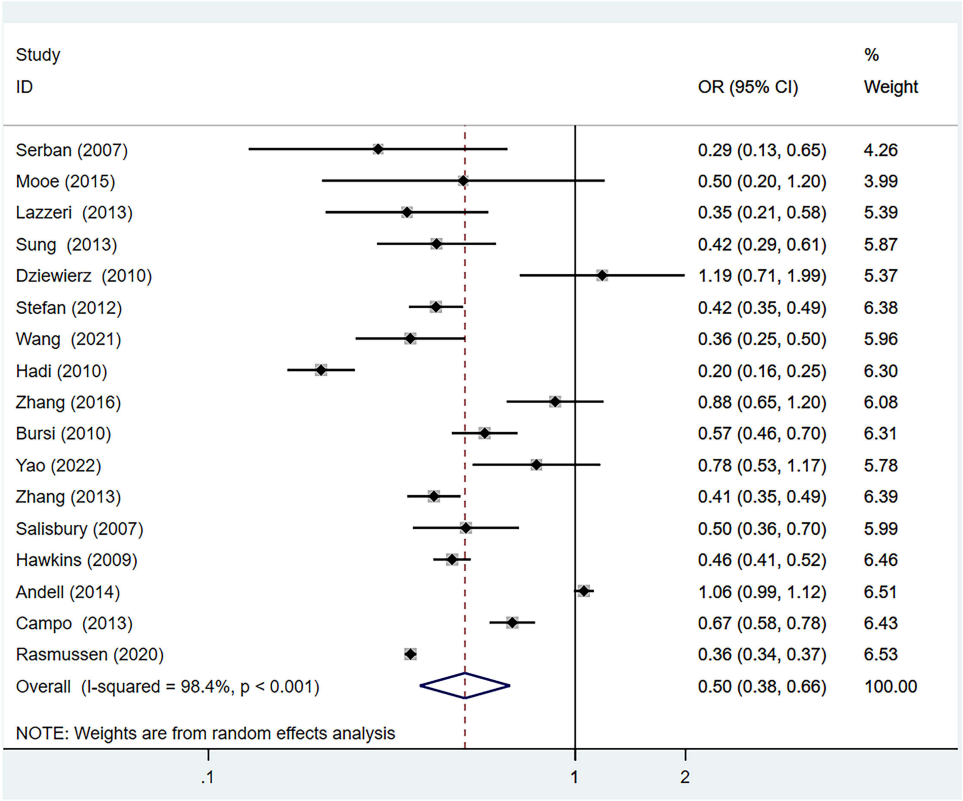


**Figure 3** Associations of comorbid COPD with pooled prescription of beta-blockers in patients with ischemic heart disease.
**Abbreviations**: COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

(Table S8, Figure S11). Intriguingly, a multivariable meta-regression model that combines male sex and geographical locations was able to explain most of the heterogeneity ($R^2$ = 62.7%, p = 0.022, Table S8).

## Outcomes According to COPD Diagnosis

A total of 26 studies described data on outcomes based on the status of COPD. In the acute phase, 17 studies provided data on in-hospital mortality, 8 studies on MACE, 5 studies on acute heart failure (AHF), and 4 studies on cardiogenic shock. Furthermore, 17 studies with no less than 1 year of follow-up presented data on long-term mortality. Assessment of bias in studies reporting outcomes was provided in Table S9. The scores showed consistency across various outcomes, and only 5 studies were identified as having a high risk of bias.

In the acute phase, increased risks of in-hospital mortality (OR 1.47, 95% CI 1.37–1.58) (Figure 4A), MACE (OR 1.81, 95% CI 1.44–2.27), AHF (OR 2.14, 95% CI 1.86–2.46), cardiogenic shock (OR 1.30, 95% CI 1.01–1.68) were observed in COPD compared with non-COPD patients (Figure S12). Similarly, the risk of long-term mortality was also higher in COPD patients, with a nearly 2 times of odds (OR 1.99, 95% CI 1.80–2.20) (Figure 4B). Subsequently, univariable meta-regressions were performed to explain the heterogeneity in the pooled estimates for long-term mortality, and no significant associations were observed between corresponding variable and long-term mortality (Table S10).

In the sensitivity analyses of acute phase outcomes (in-hospital mortality, MACE, AHF, and cardiogenic shock) and long-term mortality, as shown in Figure S13, both the ORs and the corresponding 95% CIs remained above 1 after sequentially excluding each study at a time.

## Publication Bias

The distributions in the funnel plots for the data points for BBs prescription, risk factors/comorbidities, and clinical outcomes were largely symmetric and indicated no clear evidence of systematic disparities, except for hypertension.

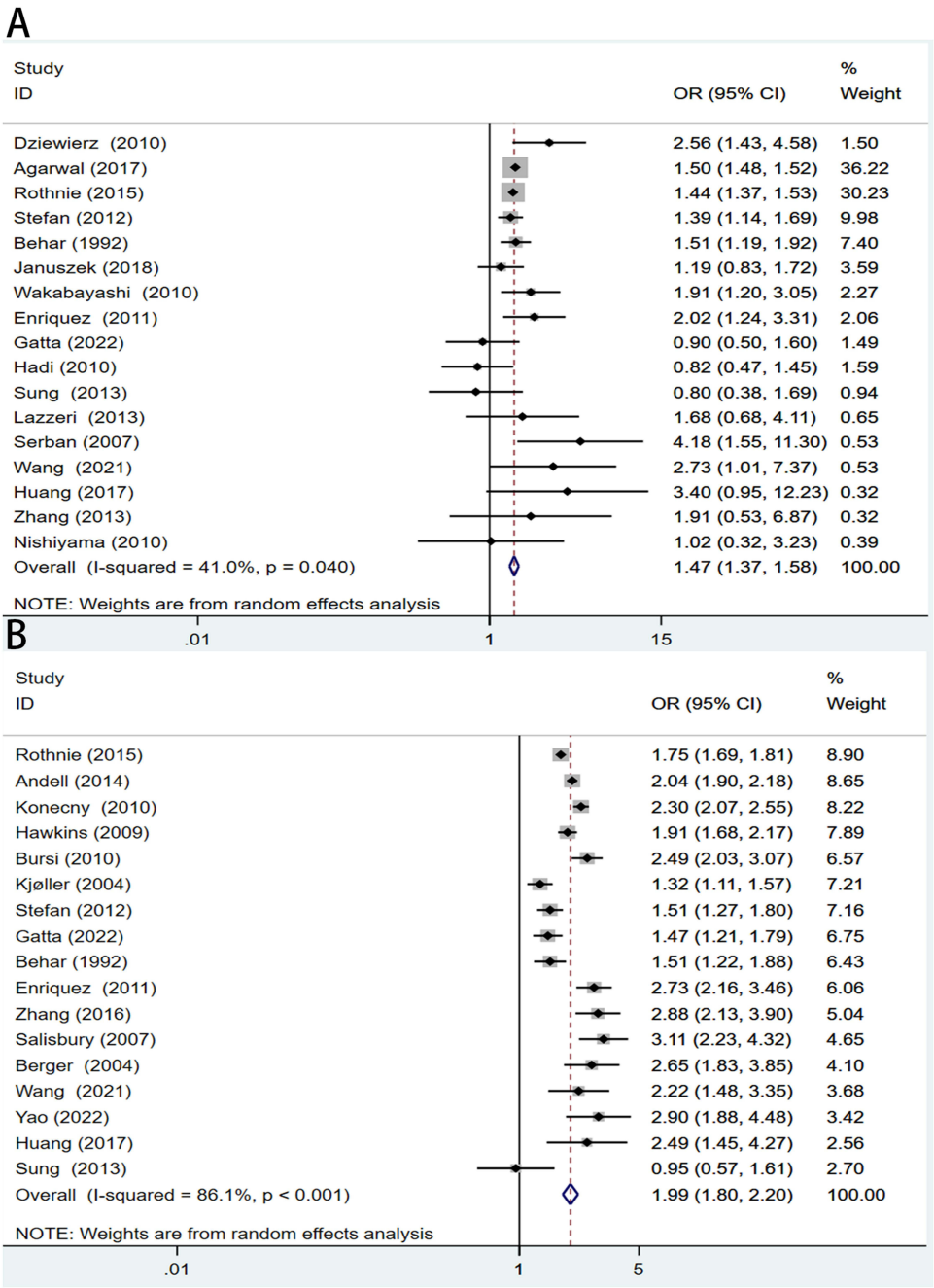


**Figure 4** Associations of comorbid COPD with clinical outcomes in patients with ischemic heart disease. (**A**) In-hospital mortality and (**B**) long-term mortality.
**Abbreviations**: COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

Consistently, the Begg's test found no substantial bias in meta-analyses that involved a minimum of ten studies (BBs (p = 0.537), DM (p = 0.128), CHF (p = 0.079), smoking history (p = 0.303), in-hospital mortality (p = 0.387), and long-term mortality (p = 0.837)), except for hypertension (p = 0.002) (Figure S14).

## Discussion

To update and extend the qualitative review,[5,8] we quantified the prevalence of COPD in 82 studies covering 18 million patients with IHD, showing a pooled prevalence of 12.0%, which indicated that COPD is a significant comorbidity in IHD. The prevalence of COPD, influenced by geographic location, study design, age class, and its definition, was notably

higher in North America, in older age classes (≥70 years), in datasets derived from administrative data, and in those identified using ICD/spirometry. In addition, the increased mean age, proportion of females, and risk factors/comorbidities (smoking history, hypertension, DM, CHF, CKD, AF) were observed in IHD patients with concomitant COPD. Intriguingly, IHD patients with concomitant COPD were still less often prescribed BBs, despite having a higher burden of risk factors/comorbidities. As expected, our findings indicated a nearly 2 times increased risk of long-term mortality and a 1.3 to 2.1 times higher risk of acute phase outcomes (in-hospital mortality, MACE, AHF, cardiogenic shock).

Subgroup analyses showed that nearly half of the studies were conducted in North America, where the prevalence of COPD escalates to 15.30% in IHD. Additionally, subgroup analyses by study design reported the highest prevalence in administrative databases. For example, the National Inpatient Sample (NIS) database reported a prevalence of 26%, covering more than 10 million IHD patients.[26] Typically, the lowest prevalence estimates in populations are derived from self-reported data regarding a physician-diagnosed COPD, and most national data indicate that less than 6% of the adult population have received a COPD diagnosis.[27] In our meta-analysis, nearly half of the studies utilized self-reported criteria to define COPD. Furthermore, almost all these epidemiologic studies defined COPD solely based on spirometry, without considering clinical context.[2] However, in the present meta-analysis, the diagnostic criteria employed in certain studies were more stringent than epidemiologic diagnosis. The above-mentioned implies that the actual prevalence could be higher than the results found in the current meta-analysis.

The significant variation in COPD prevalence among studies is expected and aligns with previous meta-analyses that estimated COPD prevalence in both general and specific populations.[25,27,28] Moreover, substantial variations in the prevalence of COPD were also observed in large-scale surveys, even in different spots within the same geographical zone.[2,29] The variable prevalence of COPD in IHD could be attributed to differences in exposure to risk factors, variations in analytical approaches and diagnostic criteria, as well as the population from which these patients originate.[25,30] In addition, gender is an important demographic factor that influences the prevalence of COPD, with males typically exhibiting higher rates.[31] However, our results revealed that women with IHD exhibit a higher frequency of comorbid COPD compared to males, in line with previous meta-analyses of COPD in AF cohorts.[25] Interestingly, patients with IHD undergoing CABG appeared to have a higher prevalence of COPD compared to those receiving PCI, indicating a potential association between IHD severity and COPD prevalence.

Both conditions exhibit parallel epidemiological characteristics, typically more prevalent among men, older adults, and individuals with a smoking history, either current or former.[5,8] In the context of IHD, Soriano et al[14] reported the highest prevalence of airflow limitation of 33.6% in coronary artery disease (CAD), compared with CVD patients and the general population, with an underdiagnosis rate as high as 87.2%. A large cross-sectional study included 2730 smokers with confirmed IHD and found that 30.5% met the spirometry criteria for COPD, yet 70.6% of them had never undergone spirometry testing before.[15] Similarly, our findings indicated that COPD was common in patients with IHD, especially in North America. The above emphasizes the feasibility of case-finding in patients with IHD. Furthermore, the case-finding of COPD in IHD is more meaningful than in the general population, given a twofold risk of long-term mortality in IHD patients with comorbid COPD. Of note, COPD identified through targeted case-finding in IHD based on spirometry was mainly with less symptom burden and lower grade.[14–16] This implies that implementing case-finding for COPD in IHD cohorts could induce a "stage shift", possibly enabling early action before significant burdens of comorbidities and clinical outcomes arise.

Our quantitative results showed that the prescription of BBs in IHD patients with comorbid COPD was only half compared with IHD alone. In addition, meta-regression indicated that male IHD patients were less likely to be prescribed BBs, which may be related to more severe COPD in men due to smoking habits. BBs are standard drugs for IHD. Since COPD management typically involves long-term bronchodilator therapy, including $\beta_2$-agonists, the use of BBs in COPD patients has sparked widespread discussion.[32] Both the 2016 European Society of Cardiology (ESC) guidelines and Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 recommend that the management of IHD should adhere to established protocols irrespective of the coexistence of COPD, and vice versa.[2,33] Despite the safety of BBs in COPD patients, the prescription of BBs in IHD patients with COPD was still insufficient, especially in males, which highlights an urgent need for measures to address this issue.

Our analysis systematically investigated and demonstrated that COPD is linked to an increased burden of cardiovascular risk factors and comorbidities in IHD patients. Elevated risks of hypertension, DM, CHF, and AF in COPD are particularly significant, and evidence suggests that they may have substantial implications on prognosis.[7,34,35] The association between COPD and CKD is not common,[34] possibly because of the influence of more common DM and hypertension in patients with COPD. These results prompt us to contemplate the impact of multimorbidity when these two conditions coexist in the same individual.

Meta-analyses of long-term mortality were based on studies with a follow-up period exceeding 1 year, all studies included reported higher risk in IHD patients with comorbid COPD, except for Sung et al.[36] IHD patients with comorbid COPD might experience worse outcomes attributable to impaired lung function, elevated inflammation, more burden of comorbidities, and a more extensive atherosclerotic disease.[18,37,38] In addition, these patients are less likely to be treated with crucial interventions, such as BBs therapy, which may make sense to the enhanced mortality in COPD patients.[39] Previous studies have also found that IHD patients with comorbid COPD are at an elevated risk for the onset of acute phase complications, such as AHF[17,18,40–42] and cardiogenic shock,[17,18,41,43] which are associated with increased in-hospital mortality in IHD patients.[18,44] In addition, individuals with COPD might struggle more to overcome physiological stressors like pulmonary edema and hypoxemia, which are frequently seen during myocardial infarction.[45] Therefore, these individuals are more prone to airway deterioration compared to those without COPD.

The major strength of this systematic review was the comprehensive literature search, which yielded a sufficient number of studies measuring the prevalence of COPD in patients with IHD. In addition, multiple subgroup analyses and meta-regressions were performed to investigate potential sources of heterogeneity for the prevalence of COPD. This study has several limitations. Firstly, although a substantial number of studies were identified for this review, some studies may not have been included due to limitations in our selection criteria. Moreover, the geographic distribution of the studies included was not proportionate, predominantly from North America and Europe, potentially limiting the generalizability of the findings to the global population. The second is the quality and consistency of available data due to the heterogeneity of included studies. For example, this meta-analysis utilized diverse COPD definitions ranging from self-reported to ICD/spirometry-based diagnoses, enhancing heterogeneity and impacting the estimated prevalence in our study. Some IHD cohorts were selected based on specific populations, such as studies that only included ST-segment elevation myocardial infarction (STEMI),[18,43,46,47] or the IHD in veterans,[48,49] though highly selected IHD cohorts were excluded. In addition, the pooled risk estimates of long-term mortality were from studies with different follow-up durations and thus increased the heterogeneity. Thirdly, it was limited by its cross-sectional nature. The pooled risk estimates including BBs prescription, cardiovascular risk factors, and comorbidities were assessed only at a single time point, leaving the chronological relationships among them ambiguous. Due to all these considerations, the interpretations of these findings should be treated with prudence.

## Conclusion

In conclusion, this comprehensive analysis demonstrated that the prevalence of COPD in IHD patients is 12%, and COPD is associated with a lower prescription of BBs, an increased burden of comorbidities, and worse acute phase outcomes and long-term mortality. Considering these results, our research highlights the need for systematic respiratory evaluations in IHD patients and the implementation of a comprehensive care strategy for their management.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

## References


1. Agusti A, Celli BR, Criner GJ, et al. Global initiative for chronic obstructive lung disease 2023 report: gold executive summary. *Eur Respir J*. 2023;207:61.
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for prevention, diagnosis and management of COPD: 2023 report. *Global Initiative for Chronic Obstructive Lung Disease* 2023: Available from: https://goldcopd.org/2023-gold-report-2/. Accessed October 17, 2024.
3. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381(13):1257–1266. doi:10.1056/NEJMra1900500
4. Collaborators GBDCo D. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the GLOBAL BURDEN OF DISEASE STUDY 2016. *Lancet*. 2017;390:1151–1210.
5. Roversi S, Fabbri LM, Sin DD, et al. Chronic obstructive pulmonary disease and cardiac diseases. an urgent need for integrated care. *Am J Respir Crit Care Med*. 2016;194(11):1319–1336. doi:10.1164/rccm.201604-0690SO
6. Shrikrishna D, Taylor CJ, Stonham C, et al. Exacerbating the burden of cardiovascular disease: how can we address cardiopulmonary risk in individuals with chronic obstructive pulmonary disease? *Eur Heart J*. 2023.
7. Chen W, Thomas J, Sadatsafavi M, et al. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3(8):631–639. doi:10.1016/S2213-2600(15)00241-6
8. Campo G, Pavasini R, Malagù M, et al. Chronic obstructive pulmonary disease and ischemic heart disease comorbidity: overview of mechanisms and clinical management. *Cardiovasc Drugs Ther*. 2015;29(2):147–157. doi:10.1007/s10557-014-6569-y
9. Deshmukh K, Khanna A. Implications of managing chronic obstructive pulmonary disease in cardiovascular diseases. *Tubersis Respir Dis*. 2021;84 (1):35–45. doi:10.4046/trd.2020.0088
10. Groenewegen A, Zwartkruis VW, Smit LJ, et al. Sex-specific and age-specific incidence of ischaemic heart disease, atrial fibrillation and heart failure in community patients with chronic obstructive pulmonary disease. *BMJ Open Resp Res*. 2022;9(1):e001307. doi:10.1136/bmjresp-2022-001307
11. Schneider C, Bothner U, Jick SS, et al. Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. *Eur J Epidemiol*. 2010;25 (4):253–260. doi:10.1007/s10654-010-9435-7
12. Feary JR, Rodrigues LC, Smith CJ, et al. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax*. 2010;65(11):956–962. doi:10.1136/thx.2009.128082
13. Finkelstein J, Cha E, Scharf SM. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *Int J Chron Obstruct Pulmon Dis*. 2009;4:337–349. doi:10.2147/COPD.S6400
14. Soriano JB, Rigo F, Guerrero D, et al. High prevalence of undiagnosed airflow limitation in patients with cardiovascular disease. *Chest*. 2010;137 (2):333–340. doi:10.1378/chest.09-1264
15. Franssen FM, Soriano JB, Roche N, et al. Lung Function Abnormalities in Smokers with Ischemic Heart Disease. *Am J Respir Crit Care Med*. 2016;194(5):568–576. doi:10.1164/rccm.201512-2480OC
16. Yangui F, Touil A, Antit S, et al. COPD prevalence in smokers with stable ischemic heart disease: a cross-sectional study in Tunisia. *Respir Med*. 2021;179: 106335.
17. Stefan MS, Bannuru RR, Lessard D, et al. The impact of COPD on management and outcomes of patients hospitalized with acute myocardial infarction: a 10-year retrospective observational study. *Chest*. 2012;141(6):1441–1448. doi:10.1378/chest.11-2032
18. Agarwal M, Agrawal S, Garg L, et al. Effect of chronic obstructive pulmonary disease on in-hospital mortality and clinical outcomes after ST-segment elevation myocardial infarction. *Am j Cardiol*. 2017;119(10):1555–1559. doi:10.1016/j.amjcard.2017.02.024
19. Rothnie KJ, Smeeth L, Herrett E, et al. Closing the mortality gap after a myocardial infarction in people with and without chronic obstructive pulmonary disease. *Heart*. 2015;101:1103–1110.
20. Enriquez JR, Parikh SV, Selzer F, et al. Increased adverse events after percutaneous coronary intervention in patients with COPD: insights from the National Heart, Lung, and Blood Institute dynamic registry. *Chest*. 2011;140(3):604–610. doi:10.1378/chest.10-2644
21. Januszek R, Siudak Z, Dziewierz A, et al. Chronic obstructive pulmonary disease affects the angiographic presentation and outcomes of patients with coronary artery disease treated with percutaneous coronary interventions. *Polish Arch Internal Med*. 2018;128(3):24–34. doi:10.20452/pamw.4237
22. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology a proposal for reporting. *JAMA*. 2000;283 (15):2008–2012. doi:10.1001/jama.283.15.2008
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
24. Wells G, Shea B, O'Connell D The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2023. Aavialable from: http://www.Ohri.Ca/programs/clinical_epidemiology/oxford.Asp. Accessed October 17, 2024.
25. Romiti GF, Corica B, Pipitone E, et al. Prevalence, management and impact of chronic obstructive pulmonary disease in atrial fibrillation: a systematic review and meta-analysis of 4,200,000 patients. *Eur Heart J*. 2021;42(35):3541–3554. doi:10.1093/eurheartj/ehab453
26. Nathan A, Hashemzadeh M, Movahed MR. Percutaneous coronary intervention of chronic total occlusion associated with higher inpatient mortality and complications compared with non-CTO lesions. *Am j Med*. 2023;136:994–999. doi:10.1016/j.amjmed.2023.06.004
27. Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J*. 2006;28(3):523–532. doi:10.1183/09031936.06.00124605
28. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: systematic review and meta-analysis. *J Glob Health*. 2015;5 (2):020415. doi:10.7189/jogh.05.020415
29. Menezes AM, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet*. 2005;366(9500):1875–1881. doi:10.1016/S0140-6736(05)67632-5
30. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442. doi:10.1371/journal.pmed.0030442

31. Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *BMJ*. 2022;378:e069679. doi:10.1136/bmj-2021-069679
32. Minor DS, Meyer AM, Long RC, et al. beta-blockers and chronic obstructive pulmonary disease: inappropriate avoidance? *J Clin Hypertens (Greenwich)*. 2013;15(12):925–930. doi:10.1111/jch.12204
33. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
34. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(2):155–161. doi:10.1164/rccm.201201-0034OC
35. Mannino DM, Thorn D, Swensen A, et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Europ resp J*. 2008;32(4):962–969. doi:10.1183/09031936.00012408
36. Sung PH, Chung SY, Sun CK, et al. Impact of chronic obstructive pulmonary disease on patient with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Biomedical Journal*. 2013;36(6):274–281. doi:10.4103/2319-4170.113373
37. Bursi F, Vassallo R, Weston SA, et al. Chronic obstructive pulmonary disease after myocardial infarction in the community. *Am Heart J*. 2010;160 (1):95–101. doi:10.1016/j.ahj.2010.05.004
38. Maclay JD, MacNee W. Cardiovascular disease in COPD: mechanisms. *Chest*. 2013;143(3):798–807. doi:10.1378/chest.12-0938
39. Yang YL, Xiang ZJ, Yang JH, et al. Association of beta-blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J*. 2020;41(46):4415–4422. doi:10.1093/eurheartj/ehaa793
40. Andell P, Koul S, Martinsson A, et al. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. *Open Heart*. 2014;1(1):e000002. doi:10.1136/openhrt-2013-000002
41. Hadi HA, Zubaid M, Mahmeed WA, et al. Prevalence and prognosis of chronic obstructive pulmonary disease among 8167 middle-eastern patients with acute coronary syndrome in the current era. *Circulation*. 2010;122:e48.
42. Zhang M, Cheng YJ, Zheng WP, et al. Impact of chronic obstructive pulmonary disease on long-term outcome in patients with coronary artery disease undergoing percutaneous coronary intervention. *Biomed Res Int* 2016;2016:8212459. doi:10.1155/2016/8212459
43. Wakabayashi K, Gonzalez MA, Delhaye C, et al. Impact of chronic obstructive pulmonary disease on acute-phase outcome of myocardial infarction. *Am j Cardiol*. 2010;106(3):305–309. doi:10.1016/j.amjcard.2010.03.026
44. Velazquez EJ, Francis GS, Armstrong PW, et al. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. *Eur Heart J*. 2004;25(21):1911–1919. doi:10.1016/j.ehj.2004.08.006
45. Schmidt GA, Hall JB. Acute or chronic respiratory failure. Assessment and management of patients with COPD in the emergency setting. *JAMA*. 1989;261(23):3444–3453. doi:10.1001/jama.261.23.3444.
46. Şerban RC, Hadadi L, Şuş I, et al. Impact of chronic obstructive pulmonary disease on in-hospital morbidity and mortality in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention. *Int J Cardiol*. 2017;243:437–442. doi:10.1016/j.ijcard.2017.05.044
47. Lazzeri C, Valente S, Attanà P, et al. The prognostic role of chronic obstructive pulmonary disease in ST-elevation myocardial infarction after primary angioplasty. *Eur J Prev Cardiol*. 2013;20(3):392–398. doi:10.1177/1741826711428243
48. Cornwell LD, Omer S, Rosengart T, et al. Changes over time in risk profiles of patients who undergo coronary artery bypass graft surgery: the Veterans Affairs Surgical Quality Improvement Program (VASQIP). *JAMA Surgery*. 2015;150(4):308–315. doi:10.1001/jamasurg.2014.1700
49. Choi JC, Bakaeen FG, Huh J, et al. Outcomes of coronary surgery at a veterans affairs hospital versus other hospitals. *J Surg Res*. 2009;156 (1):150–154. doi:10.1016/j.jss.2009.03.041