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META-ANALYSIS



Pre-existing COPD is associated with an increased risk of mortality and severity in COVID-19: a rapid systematic review and meta-analysis

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ABSTRACT

Objectives: The objective of this systematic review and meta-analysis was to investigate COVID-19 mortality and severity among patients with pre-existing COPD.

Methods: We performed systematic searches in Ovid Medline, Embase via Ovid, PubMed, and Scopus from 15 December 2019 to 7 July 2020. Studies which reported the association and presented data on risk estimate (Hazard Ratio [HR]) with 95% confidence intervals (95% CIs) were extracted. A random-effects model was used to obtain the pooled estimates, and a pooled Risk Ratio (RR) was calculated. Study quality was assessed using a modified version of the Newcastle–Ottawa Scale.

Results: Our meta-analysis showed an increased likelihood of mortality in COVID-19 patients with pre-existing COPD (RR 3.18, 95% CI 2.11–4.80, HR 1.90, 95% CI 1.11–3.26). Furthermore, the pooled estimate for the association between pre-existing COPD and severity due to COVID-19 was also significant (RR 3.63, 95% CI 2.48–5.31). Males had an increased risk of mortality (RR 1.20, 95% CI 1.12–1.29) compared to females.

Conclusion: We found that patients with pre-existing COPD had more than 3 times higher risk of mortality and severe COVID-19. There is a need to identify patients with pre-existing COPD during the pandemic so that early interventions can be aimed at this group of patients.

ARTICLE HISTORY

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KEYWORDS

COPD; COVID-19; co-morbidity

1. Introduction

As the novel coronavirus disease 2019 (COVID-19) pandemic has spread rapidly around the globe, there has been a growing concern that persons with underlying comorbidities may be affected excessively [1]. A large multicentre retrospective study from China reported that 23.7% of the patients had at least one pre-existing chronic disease or comorbidity, and in severe cases, the rate increased to 40% [2]. Due to high infectivity, the prevalence of new COVID-19 infection has proliferated with an overall case fatality rate of 2.3%–9.9% and 49% in critical cases [3]. Several recent studies found that underlying comorbidities such as coronary heart disease (CHD), cardiovascular disease (CVD), chronic kidney disease (CKD), cancer, hypertension, diabetes, and Chronic Obstructive Pulmonary Disease (COPD) were associated with a higher risk of mortality and severity due to COVID-19 [2,4–7].


COPD is the most common chronic respiratory disease, which is characterized by airflow limitation and not fully reversible [8]. With the 9–10% global prevalence [9], COPD is the third leading cause of mortality worldwide [8,10]. The

Global Burden of Disease study estimated that total mortality from COPD increased by 17.5% between 2007 and 2017, and mortality rates increased from 40.0 to 44.2 per 100,000 populations [10]. Despite the strong link between smoking and COPD, it is well known that not all smokers develop COPD, and not all COPD patients have a history of smoking [11]. The burden of COPD is predicted to increase over the next few decades due to an increased risk of exposure to nonsmoking, air pollution, workplace exposure to noxious gases/fumes, and continued aging of the global population [11,12].

The severity and progression of COPD increase with age and are driven by the systematic inflammatory responses to inhalation injury, frequency of exacerbations, and containment of other chronic diseases, which accelerates the airflow limitation [8]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily invades the pulmonary alveolar epithelial cells causing severe pneumonia with an increase in viral load, resulting in respiratory obstruction and failure [13]. The impact of pre-existing COPD on the course of SARS-CoV-2 infection is uncertain, as the recent studies have not delineated how the diagnosis of COPD has been performed. The diagnosis of COPD

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Article highlights

- Patients with various comorbidities had a higher incidence and prevalence of disease severity and mortality in COVID-19.
- The role of COPD on the progression of disease severity in COVID-19 was not well understood.
- This meta-analysis is based on 27 studies that showed that COVID-19 patients with pre-existing COPD significantly increased the risk of mortality and severity.
- Stratified analysis was conducted and found that males had a potentially higher risk of mortality compared to females in COVID-19.
- The causal relationship between male sex and the risk of mortality and severity in COVID-19 was not well illustrated in the literature.

is difficult in already overburdened hospitals due to COVID-19, where the pre-existing conditions may be overlooked, and spirometry cannot be performed [14]. Despite that limitation, several studies, including systematic review and meta-analysis, suggested that COPD is a risk factor for patients with COVID-19 and exacerbate the disease severity [15,16].

However, previous systematic reviews and meta-analyses have mostly focussed on COPD prevalence in smokers [9,14], resulting in inconclusive evidence [9]. Furthermore, earlier systematic reviews have focussed on the prevalence of all comorbidities in patients with severe COVID-19 rather than exclusively focusing on the risk of mortality and severity of COVID-19 in pre-existing COPD patients without adjusting the results for potential confounders. Keeping those limitations in mind, we aimed to conduct a systematic review and meta-analysis to investigate the risk of mortality and severity of COVID-19 amongst pre-existing COPD patients.

2. Materials and methods

2.1. Search strategy

This systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and MOOSE (Meta-analysis of the Observational Studies in Epidemiology) guidelines (Figure 1) [17,18]. The review was registered in the 'International Prospective Register of Systematic Reviews' (PROSPERO), number CRD42020190991. A comprehensive search strategy was developed to retrieve all articles published from 15 December 2019 to 7 July 2020, combining the three sets of keywords in Ovid Medline, Embase via Ovid, PubMed, and Scopus electronic databases. Search results were compiled using the bibliographic software Endnote™ X9.2. Based on the criteria of different databases, we used the following search terms:

COVID-19 (keyword) OR 2019-nCoV (keyword) OR SARS CoV-2 (keyword) OR coronavirus infection (MeSH) OR coronavirus (MeSH) OR novel coronavirus (Keyword)

AND

Pulmonary Disease (MeSH) OR Chronic Obstructive (MeSH) OR Obstructive (MeSH) OR Lung disease (MeSH)

AND

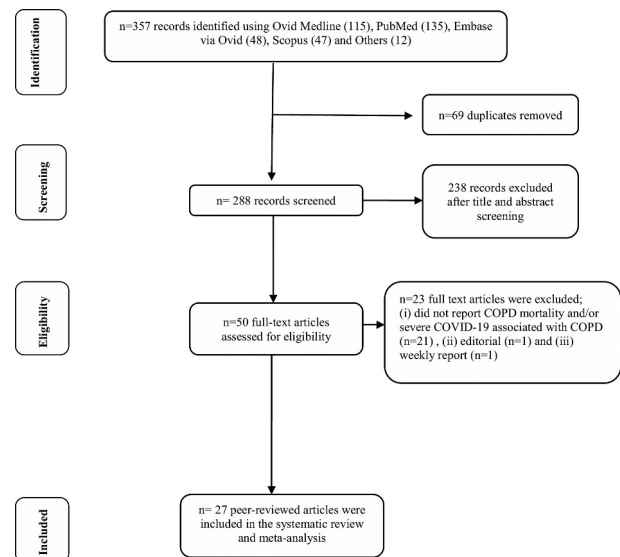


Figure 1. PRISMA flow chart of the studies selection process.

Severity (keyword) OR severe COVID-19 (keyword) OR clinical characteristics (keyword) OR clinical features (Keyword) OR clinical course (keyword)

AND

Hospital mortality (MeSH) OR Mortality (MeSH) or Death (MeSH)

Additionally, we searched the list of references for each selected article to identify any article that might have been missed during the initial search. In keeping with the MOOSE reporting guidelines, two independent researchers (GR and RCR) conducted the preliminary searches and screened the retrieved articles. The same investigators independently assessed the full texts of records deemed eligible for inclusion. Any discrepancy was resolved by discussion and consensus with a third researcher (SMA).

2.2. Inclusion and exclusion criteria

We included English language peer-reviewed publications that reported epidemiological, clinical characteristics and features of COVID-19, and mortality, and/or severe COVID-19 due to pre-existing COPD in adults, with laboratory-confirmed COVID-19. All the included studies reported hospitalized cases of COVID-19, confirmed by Real-Time Reverse Transcription Polymerase Chain Reaction Assay.

We followed the **Population, Exposure, Comparator** group, and **Outcome** criteria defined by Morgana et al. [19]. We defined laboratory-confirmed COVID-19 patients, aged more than 18 or more as population, history of pre-existing COPD as exposure, patients without the history of pre-existing COPD as comparator, and mortality, and/or severe COVID-19 associated with pre-existing COPD as the outcome of interest. We excluded studies that did not report mortality and/or severe COVID-19 with pre-existing COPD or chronic lung diseases, studies conducted on children, duplicate publications, clinical guidelines, consensus documents, single case reports, clinical trials, reviews, editorials, letters, and conference proceedings.

2.3. Definitions

The selected studies reported either COPD or chronic pulmonary disease or chronic respiratory disease as a comorbidity of COVID-19 patients. We included those terms and defined as pre-existing COPD. COPD mortality was defined as the deaths of COVID-19 patients with pre-existing COPD. According to the World Health Organization (WHO), clinical management of COVID-19 guideline, severity was defined as patients 1) who had clinical signs of severe pneumonia with respiratory rate >30 breaths/min or pulse oximeter oxygen saturation (SpO₂) <90 on room air, and 2) those with critical illness defined as patients who had respiratory failure and received mechanical ventilation or in shock or combined with a failure of other organs and received care in the intensive care unit (ICU) [20]. In this review, severe COVID-19 with pre-existing COPD was defined as COVID-19 patients who had above criteria 1 and 2 of the disease severity along with pre-existing COPD.

2.4. Quality assessment of included studies

The risk of bias for the included observational studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [21]. The methodological quality of the included studies was assessed using a modified version of the Newcastle–Ottawa Scale (NOS) (Table 2) [22]. We used three domains (selection, comparability, and outcome) to evaluate the quality of the included studies. The NOS summarized eight aspects of the studies including representativeness of the exposed group, selection of nonexposed group, ascertainment of the exposure, comparability of the cohort based on study design or statistical analysis, assessment of outcomes, and length of follow-up. The scale grants a maximum of nine points for each cohort, and scores of five or more were considered as high-quality studies [23].

2.5. Data extraction and analysis

Two reviewers (GR and SMA) extracted data from the eligible studies using a data extraction sheet. Any disagreement was resolved through discussion between the reviewers. The following information was extracted first author, study location, sample size, study design, age, sex, the prevalence of pre-existing COPD, mortality of COVID-19 with pre-existing COPD, the prevalence of overall mortality, the prevalence of severe COVID-19 case with a pre-existing COPD, and prevalence of overall severe COVID-19 case. Studies were grouped by the mortality of COVID-19 with pre-existing COPD, severe COVID-19 with pre-existing COPD, and sex. We calculated the RR by applying the following formula [24]:

$$\text{Risk ratio (RR)} = \frac{\text{Case number in exposed group}}{\text{Case number in unexposed group}}$$

To investigate the association between pre-existing COPD and the risk of mortality and severity of COVID-19, a pooled RR, and 95% CI was calculated for each study. The association between the risk of mortality due to COVID-19 and sex was

also calculated using the formula stated above. Studies reported the risk estimates as hazard ratio (HR) with 95% CI was also reported. The pooled data were displayed using forest plots, and the publication bias was assessed using the funnel plot [25] and Egger's test ($p < 0.05$ considered representative of statistical significance) [26]. We examined study heterogeneity using the Higgins I^2 statistic and computed using the following formula:

$$I^2 = 100\% \times \frac{Q - df}{Q}$$

where Q represents Cochran's heterogeneity statistic, and df is the degree of freedom. I^2 values ranged from <25% (no heterogeneity), 25–50% (moderate heterogeneity), 50–75% (large heterogeneity) and >75% (extreme heterogeneity) [27,28]. Due to moderate to extreme heterogeneity between the selected studies, random-effect modeling was used to ascertain the association between pre-existing COPD of the COVID-19 patients and the risk of mortality and severe COVID-19. This model was also used to determine the association between males and the risk of mortality due to COVID-19. We used Stata V.16.1 (Stata Corporation, College Station, Texas, USA) to perform the statistical analyses.

3. Results

An initial search retrieved 357 publications. After removing 69 duplicates, 288 articles were screened based on title and abstract, leading to the exclusion of 238 articles. The remaining 50 articles were selected for full-text review. Of them, 27 articles met the inclusion criteria and were analyzed for the systematic review, and 23 articles were excluded (Figure 1).

3.1. Study characteristics and demographic features

The characteristics of the included studies are presented in Table 1 that summarized 39312 laboratory-confirmed COVID-19 patients of whom about 58% were male, and 9.5% had a previous history of COPD. The sample size of the included studies was ranged from 25 to 20133 patients with median age 38 to 73 years. Out of 27 articles [1–3,7,13,29–50], 22 reported mortality [1–3,7,13,29–43,46,47] which referred 16.8% (6591/39312) prevalence of mortality. Further, 23 articles presented the results of overall severe COVID-19 [2,3,7,13–7,13,29–31,34–38,40–50], which referred 15.7% (6182/39312) prevalence of the severity. Of the total 27 studies, four studies reported both mortality and severe COVID-19 [2,7,29,30], 11 studies reported only mortality [1,31–40] and 12 studies reported only severe COVID-19 [3,13,41–50]. Most studies were retrospective and conducted in China except three studies, which were performed in the UK, the USA, and a multicenter study [1,31,32]. The baseline characteristics (e.g. age, smoking status, or severity) and respiratory conditions (e.g. asthma, bronchiectasis, or interstitial lung disease) of the 3729 COPD patients were not documented in the included studies. The methodological quality assessment through NOS is presented in Table 2. The overall quality of

Table 1. Characteristics of the included studies.

First author	Location	Study design	Sample size (male)	Age: median(IQR) or mean±SD or median, range	COPD patients n (%)	Overall mortality of the study n (%)	COPD mortality		Overall severe COVID-19 case for study n (%)	Severe COVID-19 case with COPD n (%)	Summary findings
							n (%)	n (%)			
Mortality and severe COVID-19											
Wu F et al. [2]	China	Retrospective	1048 (591)	71, (66–78) #	50 (4.8)	52 (5.0)	12 (24.0)	215 (20.5)	27 (12.6)	27 (12.6)	Patients with pre-existing COPD had higher risk of mortality due to shortness of breath, hypoxemia, abnormal laboratory, imaging findings and increase risk of admission to ICU
Guan W-j et al. [7]	China	Retrospective	1590 (904)	48.9 ± 16.3	24 (1.5)	50 (3.1)	6(25.0)	254 (16.0)	15 (5.9)	15 (5.9)	Patients with multiple comorbidities are a risk factor for poorer clinical outcomes in COVID-19
Xu PP et al. [29]	China	Retrospective	703 (382)	46.1 ± 15.2	13 (2)	33 (4.7)	4 (30.8)	55 (7.8)	4 (7.3)	4 (7.3)	Multiple comorbidities are the risk factor for severity or mortality in COVID-19
Li Y-K et al. [30]	China	Retrospective	25 (13)	61, 51–69	5 (20)	5 (20.0)	3(60.0)	9(36.0)	4 (44.4)	4 (44.4)	COVID-19 patients with COPD in perioperative period have higher risk of mortality
Mortality											
Docherty AB et al. [31]	UK	Prospective	20133 (12068)	73, (58–82)	3128* (17.7)	5165 (25.7)	1137 (22.0)	3001 (17.0)	-	-	Older age, male sex, obesity and comorbidities are the risk factors for mortality
Okoh AK et al. [32]	USA	Retrospective	251 (129)	62, (49–74)	23 (9.2)	97 (38.6)	10 (43.5)	-	-	-	Older age is associated with mortality in COVID-19
Li K et al. [33]	China	Retrospective	102 (58)	57, (45–70)	2 (2)	15 (14.7)	1(50)	-	-	-	Older age is a risk factor for mortality in adults with COVID-19
Shi Q et al. [34]	China	Retrospective	306 (150)	64, (56–72)	21* (6.9)	47 (15.4)	7(33.3)	39 (12.7)	-	-	Older age, and comorbidities are the risk factor for mortality in COVID-19
Shi S et al. [35]	China	Retrospective	671 (322)	63, (50–72)	23 (3.4)	62 (9.2)	2(8.7)	671 (31.9)	-	-	Older age and cardiovascular comorbidities are the risk factor for mortality in COVID-19
Wang L et al. [36]	China	Retrospective	339 (166)	69, (65–76)	21 (6.2)	65 (19.2)	11(52.4)	239 (70.5)	-	-	Older age and comorbidities including cardiovascular disease, COPD and ARDS are the risk factor for mortality in COVID-19
Yan Y et al. [37]	China	Retrospective	193 (114)	64, (49–73)	14* (7.3)	108 (56.0)	11(78.6)	193 (100.0)	-	-	Diabetes is a risk factor for death in severe COVID-19
Mehra MR et al. [1]	Multi-countries	Retrospective	8910 (5339)	49 ± 16	225 (2.5)	515 (5.8)	32(14.2)	-	-	-	Cardiovascular disease is independently associated with increased risk of mortality in COVID-19
Yang X et al. [38]	China	Retrospective	52 (35)	59.7 ± 13.3	4* (7.7)	32 (61.5)	2(50.0)	52 (100.0)	-	-	Older patients with comorbidities and ARDS are increased risk of mortality in COVID-19
Li X et al. [39]	China	Retrospective	25 (10)	73, 55–100	2 (8)	25 (100.0)	2(100.0)	-	-	-	Age and comorbidities are the most important risk factor for mortality of COVID-19
Zhou F et al. [40]	China	Retrospective	191 (119)	56, 18–87	6 (3.1)	54(28.2)	4(66.6)	119(62.3)	-	-	Older age is a risk factor for mortality in COVID-19
Severe COVID-19											
Cai Q et al. [41]	China	Retrospective	383 (183)	61, (52–65) Å	32 (8.4)	3 (0.8)	-	91 (23.8)	13 (14.3)	13 (14.3)	Obese patients had increased odds of progressing to severe COVID-19
Feng Y et al. [42]	China	Retrospective	476 (271)	53, (40–63)	22 (4.6)	38 (8.0)	-	124 (26.0)	14 (11.3)	14 (11.3)	Patients with severe COVID-19 were older and had more comorbidities
Guan W-j et al. [13]	China	Retrospective	1099 (640)	47, (35–58)	12 (1.1)	15 (1.4)	-	173 (15.7)	6 (3.4)	6 (3.4)	Compromised respiratory status on admission (the primary driver of disease severity) was associated with worse outcomes
Huang C et al. [43]	China	Prospective	41 (30)	49, (41–58)	1 (2.4)	6 (14.6)	-	13 (31.7)	1 (7.7)	1 (7.7)	The cytokine storm could be associated with disease severity and patients have a high likelihood of admission to intensive care, and might die

(Continued)

Table 1. (Continued).

First author	Location	Study design	Sample size (male)	Age: median(IQR) or mean±SD or median, range	COPD patients		Overall mortality of the study		COPD mortality		Overall severe COVID-19 case for study		Severe COVID-19 case with COPD		Summary findings
					n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)			
Liu W et al. [44]	China	Prospective	78 (39)	38, (33–57)	2(2.6)	-	-	-	-	-	11(14.1)	1 (9.1)	Several factors including age, history of smoking, maximum body temperature at admission, respiratory failure, and comorbidities that led to the progression of COVID-19.		
Mo P et al. [45]	China	Retrospective	155 (86)	54, (42–66)	5 (3.2)	-	-	-	-	85 (54.8)	4 (4.7)	Despite of a similar proportion of male and female patients in COVID-19, male patients had a higher incidence of disease refractoriness.			
Wang D et al. [46]	China	Retrospective	138 (75)	56, (42–68)	4 (2.9)	6 (4.3)	-	-	-	36(26.0)	3 (8.3)	Most critically ill patients were older and had more underlying conditions than those not admitted to the ICU			
Wu J et al. [3]	China	Retrospective	2041 (1006)	62, (50–70)	73 (3.6)	193 (9.5)	-	-	-	697 (34.1)	34 (4.9)	Blood glucose level is independent risk factor for severity or mortality in COVID-19			
Wang Z et al. [47]	China	Retrospective	69 (32)	42, (35–62)	4 (5.8)	5 (7.5)	-	-	-	14 (20.3)	2 (14.3)	Older patients and underlying comorbidities are at high risk of death in COVID-19			
Zhang J et al. [48]	China	Retrospective	111 (46)	38 (32–57)	3 (2.7)	-	-	-	-	18 (16.2)	1 (5.6)	Male sex and comorbidities are the risk factors for the poor prognosis in COVID-19			
Gao Y et al. [49]	China	Retrospective	43 (26)	43.7 ± 12.12	8 (18.6)	-	-	-	-	15 (34.9)	3 (20.0)	Most patients had mild symptoms, but a few patients have developed severe pneumonia, resulted deaths			
Zhang J-j et al. [50]	China	Retrospective	140 (71)	57, 25–87	2 (1.4)	-	-	-	-	58 (41.4)	2 (3.4)	Older age and multiple comorbidities are associated with severe COVID-19			

(n = number of cases, IQR = interquartile range, COPD = Chronic Obstructive Pulmonary Disease, RR = Risk Ratio, ARDS = Acute respiratory distress syndrome * = chronic pulmonary disease, † = COPD group, λ = Severe COVID-19 group)
 Severe COVID-19 = at least one of the following items: (i) breathing rate ≥30/min; (ii) hypoxia, i.e. pulse oximeter oxygen saturation (SpO2) ≤93% at rest; (iii) ratio of partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) ≤300 mmHg (1 mmHg = 0.133kPa), or at least one of the following items: (i) respiratory failure occurred and received mechanical ventilation; (ii) shock; (iii) combined with failure of other organs; and received care in the intensive care unit (ICU).

Table 2. The methodological quality score of included studies based on Newcastle–Ottawa quality assessment score.

First author	Representativeness of the exposed group		Selection		Comparability		Outcome		Total score	
	1	0	Selection of the nonexposed group	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of study on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur		Adequacy of follow up of the groups
Wu F et al. [2]	1	1	1	1	0	2	1	1	1	8
Guan W-J et al. [7]	1	1	1	1	0	2	1	1	0	7
Xu PP et al. [29]	1	1	1	1	0	2	1	1	1	8
Li Y-K et al. [30]	1	1	1	1	0	1	1	1	0	6
Docherty AB et al. [31]	1	0	1	1	0	2	1	1	1	7
Okoh AK et al. [32]	0	1	1	1	0	2	1	1	1	7
Li K et al. [33]	1	1	1	1	0	2	1	1	1	8
Shi Q et al. [34]	1	1	1	1	0	2	1	1	0	7
Shi S et al. [35]	1	1	1	1	0	2	1	1	0	7
Wang L et al. [36]	0	1	1	1	0	2	1	1	1	7
Yan Y et al. [37]	1	1	1	1	0	2	1	1	1	8
Mehra MR et al. [1]	1	0	1	1	0	2	1	1	1	7
Yang X et al. [38]	1	1	1	1	0	1	1	1	0	6
Li X et al. [39]	1	0	1	1	0	1	1	1	0	5
Zhou F et al. [40]	1	1	1	1	0	2	1	1	0	7
Cai Q et al. [41]	1	1	1	1	0	2	1	1	1	8
Feng Y et al. [42]	1	1	1	1	0	2	1	1	1	8
Guan W-J et al. [13]	1	1	1	1	0	2	1	1	0	7
Huang C et al. [43]	1	1	1	1	0	1	1	0	1	6
Liu W et al. [44]	1	0	1	1	0	1	1	0	1	5

(Continued)

Table 2. (Continued).

First author	1	0	1	0	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	Total score	
			Selection			Comparability				Outcome													
Mo P et al. [45]	1	0	1	0	0	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	7	
Wang D et al. [46]	1	0	1	0	0	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	7	
Wu J et al. [3]	1	0	1	0	0	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	7	
Wang Z et al. [47]	1	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	5	
Zhang J et al. [48]	1	0	1	0	0	2	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	7	
Gao Y et al. [49]	1	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	5	
Zhang J-j et al. [50]	1	1	1	1	0	2	1	1	0	0	2	1	1	1	0	1	1	1	1	1	1	7	

the included studies with NOS score ranging from 5 to 8 out of a scale of 9 (details in the online supplement, Table S1).

3.2. Pre-existing COPD and risk of mortality in COVID-19

Fifteen studies reported mortality in COVID-19 because of pre-existing COPD (Table 1) [1,2,7,29–40]. Among them, we included 14 studies for the meta-analysis to determine the effect estimate for the risk of mortality in COVID-19 because one study included only all death cases in the analysis [39].

A total of 3561 patients had pre-existing COPD while 1244 death cases were reported due to COVID-19. The prevalence of mortality in COVID-19 with pre-existing COPD was 35% (1244/3561) which attributed 19% (1244/6591) of the overall mortality. Figure 2 represents the associations between COVID-19 patients with pre-existing COPD and the risk of mortality. Overall, the heterogeneity between the included studies was high ($I^2 = 78.8\%$); therefore, we ran a random-effect model to estimate the pooled RR. Pre-existing COPD presented significant evidence of an increased risk of mortality due to COVID-19.

Sensitivity analysis showed that the results were not affected by any individual study (data not shown). Publication bias was assessed by visualizing the funnel plot (online supplement, Figure S1A) and Egger's test for small-study effects shows no publication bias in the analysis ($p = 0.016$). In addition, we also performed a random-effect meta-analysis for four studies that reported multivariate-adjusted HR for the risk of mortality and preexisting COPD [7,31,34,36]. The pooled HR provides evidence of increased risk of mortality associated with pre-existing COPD (Figure 3).

3.3. Pre-existing COPD and risk of severe COVID-19

Severe COVID-19 with pre-existing COPD was reported in 16 studies (Table 1) [2,3,7,13,29,30,41–50]. We included 14 studies in the meta-analysis as two studies were excluded because all the COPD cases were transformed into severe COVID-19 during the follow-up [43,50]. The prevalence of severity in COVID-19 with pre-existing COPD was 52% (134/260), which attributed only 2% (134/6182) of the overall severity. There was moderate heterogeneity in the analysis ($I^2 = 43.9\%$,

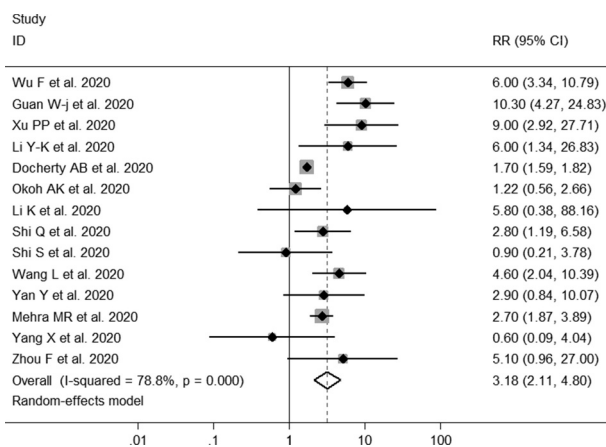


Figure 2. Forest plot displaying RR (crude) and 95% CI for the association between pre-existing COPD and risk of mortality in COVID-19.

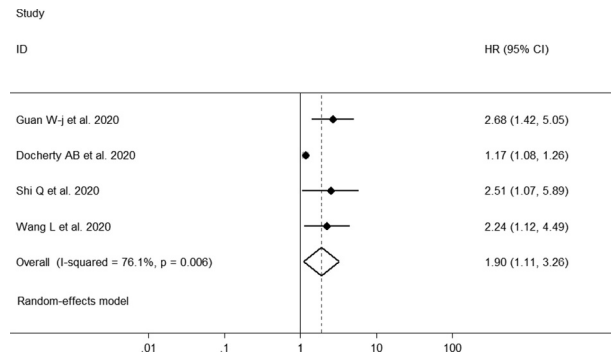


Figure 3. Forest plot displaying HR and 95% CI for the association between pre-existing COPD and risk of mortality in COVID-19.

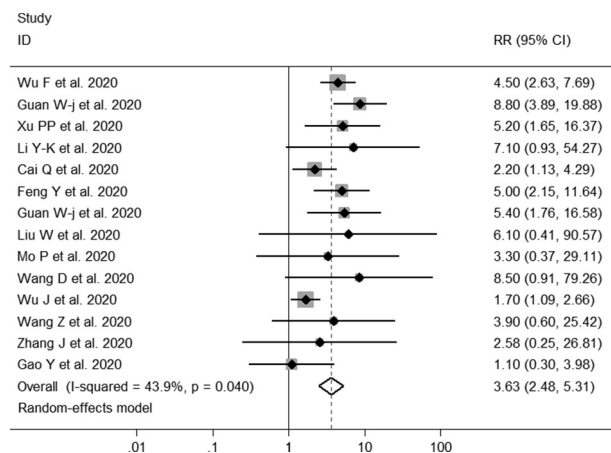


Figure 4. Forest plot displaying RR (crude) and 95% CI for the association between pre-existing COPD and risk of severe COVID-19.

$p = 0.040$) and random-effects model found evidence of the risk of developing severe COVID-19 due to pre-existing COPD (Figure 4). Sensitivity analysis showed that the results were not affected by any individual study (data not shown). Publication bias was assessed by visualizing the funnel plot (online supplement, Figure S1B) and Egger's test for small-study effects showed no publication bias ($p = 0.23$).

3.4. Pre-existing COPD and risk of mortality among male in COVID-19

Thirteen studies have reported deaths in male separately [1,–29–40]. Among them, we included 12 studies for the meta-analysis. One study was excluded because it included only death cases in the analysis [39]. The total COVID-19 deaths for males were 3951, which referred 21% (3951/18935) of mortality, and attributed almost 60% (3951/6591) of the overall mortality. The results of the random effects ($I^2 = 52.7\%$) meta-analysis (Figure 5) showed that males with pre-existing COPD had a higher risk of mortality in COVID-19 compared to females. Publication bias was assessed by visualizing the funnel plot (online supplement, Figure S1C) and Egger's test for small-study effects showed no publication bias ($p = 0.001$).

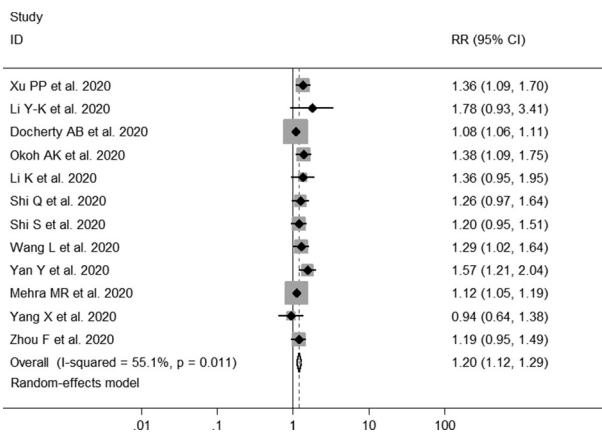


Figure 5. Forest plot displaying RR (crude) and 95% CI for the association between male and risk of mortality in COVID-19.

4. Discussion

To our knowledge, this is the most updated epidemiological and clinical assessment for the mortality and severity of COVID-19 patients with pre-existing COPD. The pooled analysis showed an overall increased risk of pre-existing COPD on developing severe COVID-19 and mortality. Furthermore, we also found that males had an increased risk of mortality in COVID-19 compared to females.

We found that patients with pre-existing COPD have a 3 times higher risk of mortality due to COVID-19. Our findings are consistent with a recent systematic review and meta-analysis that reported the risk of mortality in COVID-19 was 3.5 times higher in patients with COPD compared to those without COPD [4]. Furthermore, two meta-analyses also reported the risks of mortality in COVID-19 were 1.5 and 2 times higher for COPD patients with slightly lower pooled estimates [6,16]. Additionally, we also found 35% mortality in COVID-19 patients who had pre-existing COPD, while the previous reviews found it was 60% [9,16]. The variation in the prevalence was due to the small number of studies and the limited sample size in previous reviews.

The increased risk of mortality due to COVID-19 with pre-existing COPD could be attributed to several factors. The underlying clinical explanation could be, COPD patients had breathing difficulty along with lower lung function, abnormal lung structure, and dysfunctional immunity [2,51]. Pathogenic infections are common causes of acute exacerbation of COPD, which may lead to respiratory failure in many patients [16]. Therefore, COVID-19 patients combined with COPD increased the risk of severe acute exacerbation of COPD, which resulted in respiratory failure and deaths. Besides, the majority of COPD patients have various comorbidities that may also be associated with mortality. An observational study from China reported that COVID-19 patients with COPD were more likely to have comorbidities, including hypertension, CHD, CVD, CKD, and cancer than non-COPD patients [2].

Consequently, findings from previous systematic review and meta-analysis also supported the hypothesis that hypertension, CVD, CKD, diabetes, COPD, and cancer were associated with a higher risk of mortality from COVID-19 [2,4–7]. However, the pathophysiological explanation of how these diseases influenced

the COVID-19 outcomes remains unclear. Another reason would be limited access to respiratory support as part of already overwhelmed COVID-19 hospitals. A recent report from Italy mentioned that more than 12% of the positive cases in COVID-19 required ICU admission, which was a significant surge of patients to the ICU, making clinical management difficult [52]. As a consequence, a large number of patients died due to the shortage of mechanical ventilators [53,54].

We found a significant association between pre-existing COPD and severe COVID-19. This is consistent with a previous systematic review that found the risk of developing severe COVID-19 was higher in patients with pre-existing COPD [55]. Previous studies reported that the comorbidities, including COPD, diabetes, malignancy, and hypertension in COVID-19 were significantly associated with severe COVID-19 [6,7,55,56]. It was also reported that COVID-19 patients with COPD were more likely to develop bacterial or fungal coinfection (20% vs 5.9%) [2]. Pathogenic infection in COPD exacerbates the condition, which may cause respiratory failure in many cases [57]. The clinical symptoms of COVID-19 and acute exacerbation of COPD is difficult to differentiate, which may potentially result in a delayed intervention that leading to a worse prognosis of COVID-19 in patients with COPD [16]. Another explanation for the severity in COVID-19 might be the results of cytokine storm, which is considered to play an essential role in the disease severity [4,58]. Neutrophils are the primary source of cytokines and the severity of lung damage is correlated with a higher number of neutrophils and macrophages which was found in the peripheral blood of the patients with SARS and Middle East Respiratory Syndrome (MERS) [4,59]. This cytokine storm can lead to acute respiratory distress syndrome (ARDS), which was the leading cause of severity or death in patients with SARS and MERS [4,59]. A multicentred retrospective study on 1048 patients in China reported that COVID-19 patients with COPD were more likely to develop ARDS (20.0% vs 7.3%) [2]. This could explain the biological plausibility of the association between pre-existing COPD and severe COVID-19.

We found that male COVID-19 patients had consistently more severe outcomes than females. In our study, the prevalence of mortality for males was 21%, whereas it was 16% for females. The results from our meta-analysis revealed that males had a 20% increased risk of mortality in COVID-19 compared to females. Several studies reported the positive correlation between male sex and severity in COVID-19 [55,60,61]. However, none of the previous systematic reviews and meta-analysis reported the association between males and the risk of mortality in COVID-19. Previous coronavirus outbreak exhibited similar evidence of male predominance. For example, the SARS-CoV outbreak in Hong Kong reported the case fatality for males was 21.9%, whereas it was 13.2% for females [62]. The MERS-CoV in Saudi Arabia reported the mortality was higher in males than females (52% vs 23%) [63]. The observed association between male sex and mortality could be due to the heightened innate and adaptive immune response to viral infection in females compared to males [6,60,64]. There are multiple biological reasons why females have a more robust immune response against infectious diseases compared to males, including a genetic variant in immune-response genes and the presence of female sex hormones [60]. Males exhibit a predominant visceral adipose tissue distribution

compared to females, which is associated with a more pro-inflammatory circulating cytokine profile that induces increased inflammatory immune responses [60]. The previous study suggested that inflammatory immune responses to SARS-CoV-2 are more elevated in males and associated with more fatal outcomes than females [60]. It was also recommended that angiotensin-converting enzyme 2 (ACE2) be used as a receptor for cell entry in SARS-CoV-2 and also required the transmembrane serine protease TMPRSS2 for S protein priming in the cell [65]. ACE2 was located on the X chromosome, and the female has two copies compared with a male, which may be facilitated to regulated ACE2 in an alternative way [65]. Additionally, TMPSS2 is a direct androgen receptor target gene, and its expression is increased by androgens [65]. Together, ACE2 and TMPSS2 in the males are likely to be the reason influencing the virus entry and pathogenicity.

A key strength of our review included an extensive systematic search strategy and the absence of population bias as all the patients were tested positive for SARS-CoV-2. This study also has several limitations. First, we calculated unadjusted estimates which may overestimate the pooled estimated for mortality or severe COVID-19. Second, most of the included studies used retrospective design where data were collected from electronic medical records and history of comorbidities were self-reported, which may introduce information bias. Third, the definition of severe COVID-19 was not consistent across the studies. Fourth, moderate to extreme heterogeneity was observed in the meta-analysis, which may limit the generalizability of the results. Finally, the included studies did not report the smoking history of COPD patients with COVID-19; therefore, we were unable to include smoking in our analysis.

5. Conclusions

This systematic review and meta-analysis suggested that patients with pre-existing COPD had more than 3 times higher risk of mortality and severity in COVID-19 with the risk of mortality is more among males compared to females. These findings contribute to understanding a comorbid condition for severe COVID-19 which is valuable to support the ongoing clinical care as well as improve the diagnosis and management of critically ill patients. These findings will help in developing better hospital diagnosis strategies for COVID-19 patients with pre-existing COPD and associated comorbidities by implementing more rigorous preventative measures and targeted prevention.

6. Expert opinion

Given the rapid spread and high hospitalization rate of COVID-19, it is necessary to evaluate the possible risk factors affecting the progression of disease in confirmed hospitalized COVID-19 patients. It is widely discussed that pre-existing comorbidities are the leading cause of severity and mortality in confirmed COVID-19 patients. The common pre-existing conditions are associated with the high risk of severity and mortality in COVID-19 are CHD, CVD, CKD, cancer, hypertension, diabetes, and COPD. Pre-existing COPD is an important chronic respiratory condition that

not only increased the risk of mortality in hospitalized COVID-19 patients but also increases breathing difficulty that may lead to further airflow obstruction lead to death. Furthermore, in hospitalized COVID-19 patients, it is challenging to diagnose COPD using spirometry and to provide necessary treatment.

The definition of severity in COVID-19 is not consistent and does vary according to countries' clinical settings and available health facilities. For the better clinical management of COVID-19 patients with COPD, a consistent definition is required. This will result in the standardized clinical management of severity in COVID-19 as well as consistent data for further research. In published literature on COVID-19, there is limited evidence on the management of associated comorbidities such as COPD. Identification of severity and high-risk patients with associated COPD during the admission process will reduce the risk of mortality, and the patient can be isolated and treated according to the clinical management protocol of COVID-19 and COPD. Currently, the number of COVID-19 patients are increasing worldwide, and a better understanding of high-risk comorbidities may be helpful for the clinicians.

Until now, there is evidence from studies that smoking history significantly attributes to the worse progression and outcome of COVID-19. Smoking is a risk factor for COPD, but none of the studies specifically reported the association between smoking history, COPD, and severity, and/or mortality in COVID-19. So further research is needed to fine-tune the association of how smoking contributes to exacerbating the severe COVID-19 in COPD or it is solely affecting the severity of the disease. From our point of view, a prospective study with adequate follow-up should be adopted to untangle this association.

Author contributions

GR, RCR, NA, BM, and SMA were involved in the concept, design and development of the study and the instruments. GR, RCR, and SMA screened the articles, GR extracted the data and performed the meta-analysis. GR and SMA drafted the manuscript, and all authors provided critical conceptual input and interpreted the data. All authors read and approved the final version of the manuscript.

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