

# Impact of chronic obstructive pulmonary disease on mortality in community acquired pneumonia: a meta-analysis

Journal of **Comparative Effectiveness Research**

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**Background:** The aim of the present study was to systematically review the exiting literature and to proceed a meta-analysis to determine the impact of chronic obstructive pulmonary disease (COPD) on mortality in patients with community acquired pneumonia. **Materials & methods:** Eligible studies were searched from PubMed, Cochrane Library and EMBASE. Odds ratios (ORs) with 95% CIs were used as effect estimates. **Results:** Twenty cohort studies were included. Analysis of unadjusted data revealed nonsignificant short- and long-term mortality associated with COPD. Analysis of adjusted 30-days mortality showed similarly no association between COPD and increased 30-days mortality (OR: 1.06, [0.68, 1.44]) but a positive association when COPD was confirmed spirometrically (OR: 1.84, [1.06, 2.62]). **Conclusion:** There is still no evidence to clear the impact of COPD on mortality in patients with community acquired pneumonia. More prospective studies with spirometrically-defined COPD and adequate adjustment for confounders are needed.

First draft submitted: 22 April 2020; Accepted for publication: 24 June 2020; Published online: 4 September 2020

**Keywords:** chronic obstructive pulmonary disease • COPD • meta-analysis • mortality • pneumonia

Currently, community acquired pneumonia (CAP) is one of the most common infectious diseases that contributes to substantial health and economic burden in the world [1]. In the general adult population, CAP affects about 2 to 13 cases per 1000 persons each year and remains a major cause of hospitalization and mortality, with a hospitalization rate of 22–51% and a mortality rate of 3–24% [2,3]. Chronic obstructive pulmonary disease (COPD) is featured by long-term worsening airflow, resulting in shortness of breath, cough and sputum production. COPD is one of the most common comorbidities and risk factors in patients with CAP, which is ranked as the third leading cause of death worldwide [4–6].

There are many studies analyzing whether the coexistence of COPD and CAP may cause an increased mortality rate, but to date their findings are still inconsistent and controversial. Some studies concluded that the presence of COPD as a comorbid condition was associated with increased mortality, whereas some other studies held the view that no significant link exists between presence or absence of COPD and mortality rate [7–11]. Two meta-analysis combining 13 and 11 studies, respectively demonstrated that evidence on associated mortality risk with concomitant CAP and COPD is underpowered and heterogeneous, and that additional information is needed [12,13].

Therefore, the aim of the present study was to systematically review the exiting literature and to proceed a meta-analysis to determine the impact of COPD on mortality in patients with CAP, focusing on the difference in mortality rate between COPD and non-COPD patients and whether COPD is a risk factor for mortality in CAP.

## Materials & methods

This study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [14].

### Literature search

Eligible papers were identified through computerized searching of the databases PubMed, Cochrane Library and EMBASE using the terms ‘community acquired pneumonia’ and ‘chronic obstructive pulmonary disease’, or their abbreviations, limited to English language papers until March 2020. Two independent reviewers identified possibly related studies based on titles and abstracts, and subsequently screened the articles by reading full texts to complete the literature search. In the event of any disagreement, a third reviewer was involved.

### Inclusion & exclusion criteria

To minimize the influence of variation in study design, we only included cohort studies for this meta-analysis. Cohort studies were included, if they reported the mortality in COPD and non-COPD patients with CAP or addressed COPD as a factor associated with mortality in CAP in univariate or multivariate analysis; the included patients were hospitalized for CAP as primary diagnosis established by medical records or radiographic confirmation. Except for original studies, other publications such as reviews, letters, case reports or conference abstracts were excluded. If there were two studies or more enrolled overlapping participants, the one with the most sufficient data were included.

### Data collection

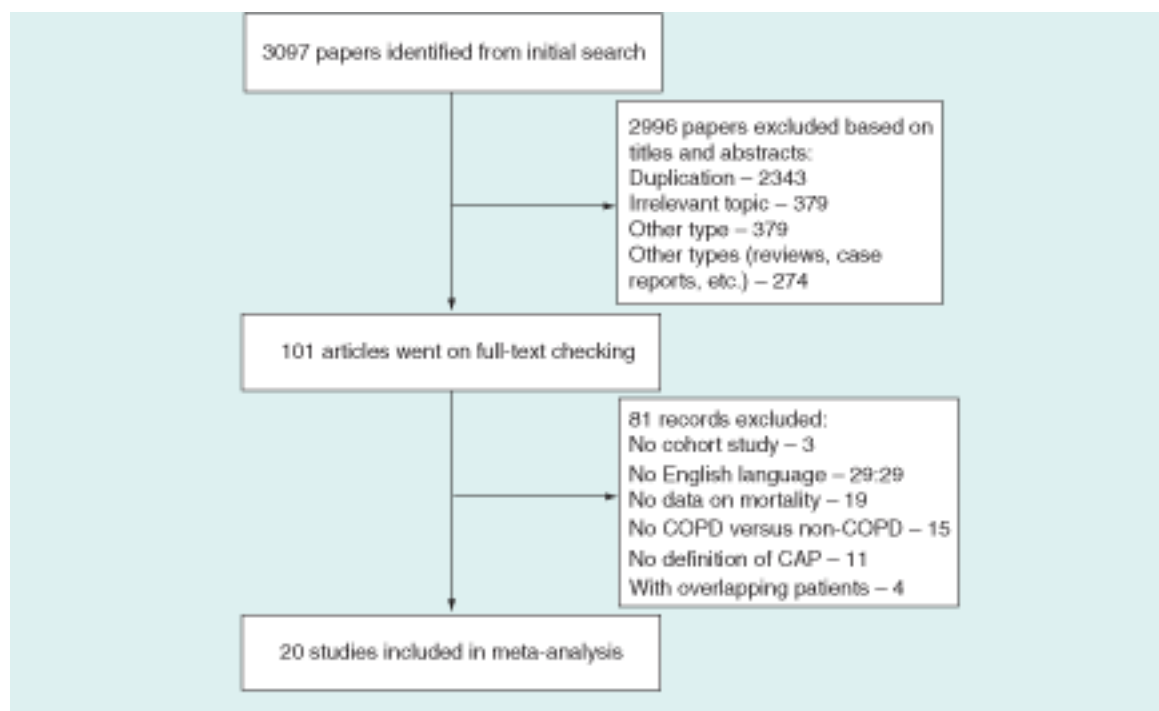
Two reviewers independently extracted data from included papers into a predefined data collection form. The following data were collected: the name of first author, year of publication, region, study design (prospective or retrospective), subjects inclusion and exclusion criteria, type of patients source (inpatients or intensive care unit [ICU] patients), year of entry for patients, patient characteristics (sample size, age and gender) and definition of CAP and COPD. The outcomes were in-hospital, 30-days, 90-days and long-term mortality (long-term mortality was defined as death in the follow-up duration of  $\geq 1$  year). Both raw unadjusted and adjusted data on mortality in COPD versus non-COPD patients were extracted. For the study of Braeken *et al.* [15] reporting the results of hospitalized and outpatient cohorts, we only extracted the data on hospitalized patients. Discrepancies were resolved by consultation with a third reviewer.

### Quality assessment

The critical appraisal of included studies were conducted using the Newcastle-Ottawa Scale [16]. The Newcastle-Ottawa Scale specific for cohort design consists of three domains (selection of the study groups, comparability of the groups and ascertainment of either the exposure or outcome of interest). Two authors performed the quality assessment independently, and discrepancies were resolved by discussion with a third author.

### Statistical analysis

For dichotomous data, odds ratios (OR) with 95% CI were used as effect estimates. CIs are used for statistical test, with a 95% CI excluding the point of no effect indicating statistical significance. Statistical heterogeneity across studies was assessed using  $I^2$  test, with  $I^2 > 50\%$  indicating significant heterogeneity. In data synthesis, pooled results were calculated by using a random-effects model based on Mantel–Haenszel method in the case of significant heterogeneity, while a fixed-effects model was used when no significant heterogeneity was found. Unadjusted and multivariate adjusted data were pooled and analyzed separately. For primary outcomes, subgroup analysis was performed based on study design (prospective vs retrospective), study quality (studies that met the comparability criteria vs those that did not) and sample size ( $> 1000$  vs  $< 1000$ ); we also performed sensitivity analysis by sequentially dropping one study at a time to determine whether removal of any one study would substantially change the effect size and the heterogeneity, and by restricting the meta-analysis to studies with spirometric definition of COPD. Begg’s and Egger’s test were performed to test publication bias, if ten studies or more were included in the meta-analysis, using a p-value  $< 0.05$  as the threshold to indicate significant risk of publication bias [17]. We used Stata software version 15.0 (Stata Corporation, College Station, TX, USA) to proceed our data analysis.



**Figure 1. The search process and study identification.**

CAP: Community acquired pneumonia; COPD: Chronic obstructive pulmonary disease.

## Results

### Study identification

The systematic search yielded 3097 papers, resulting in 101 potentially eligible studies. After reviewing the full text of these relevant articles, a total of 20 studies met the inclusion criteria and provided data to the meta-analysis. The search process and study identification are shown in Figure 1.

### Study characteristics & quality

All the included studies were published between 2006 and 2019, involving 918,449 patients hospitalized with CAP over a period of 22 years (1995–2016). A total of 304,222 and 614,227 patients were included in the COPD and non-COPD group, respectively. The mean age of the patients included varied from 54.2 to 82 years, with proportions of males ranging from 40 to 95%. Among the 20 cohort studies, 11 were prospective design [7,10,11,15,18–24], and 9 were retrospective design [8,9,25–31]. All studies were conducted in general inpatients population, except two [24,28] in ICU admissions only. Radiographically confirmed that pneumonia was reported in 18 studies, while one study [28] identified CAP according to symptoms or signs of pneumonia and medical records, and one study [29] according to the International Classification of Diseases–Ninth Revision. The definition of COPD was less certain, with only ten studies confirming COPD cases by spirometric evidence in ten studies [7,9–11,15,19,23,26,27,30]. The detailed study characteristics are presented in Table 1.

The methodological quality of the 20 included studies was overall acceptable. All of the included studies met the quality criteria with the exception of comparability, in which nine studies [9,18,20–23,27,29,31] did not, because patient baseline comparability were not controlled.

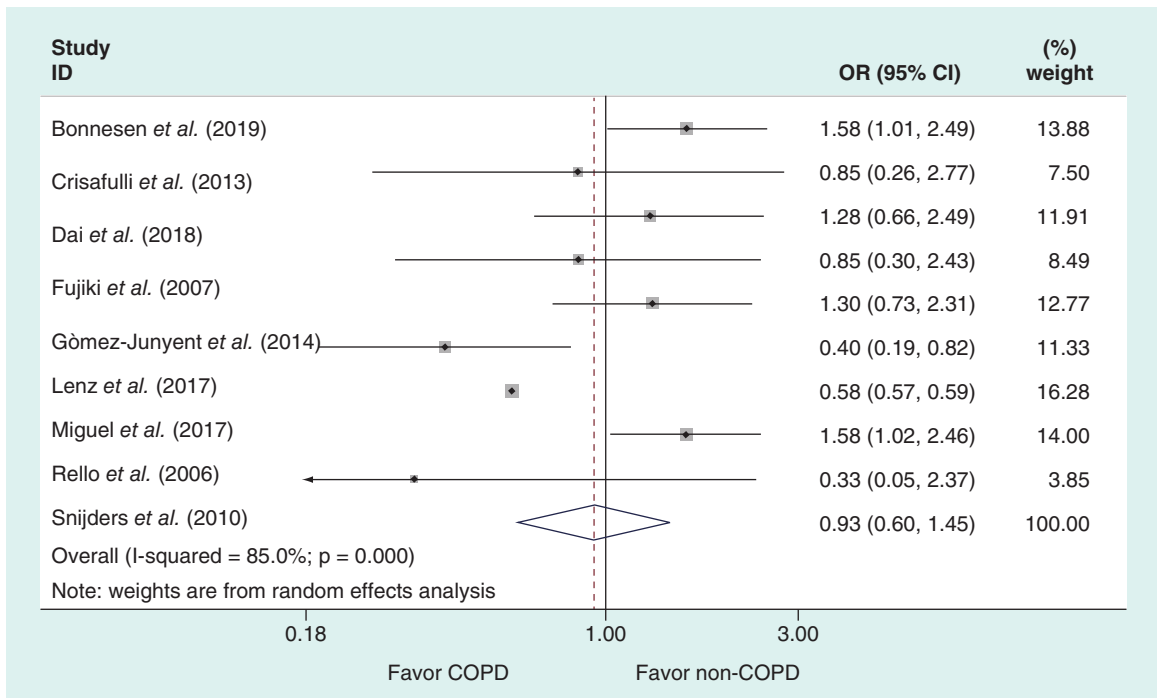
### Impact of COPD on mortality in patients with CAP

When analyzing unadjusted data on in-hospital and 30-days mortality, the pooled results from the meta-analysis of nine and 14 studies did not show any clear or consistent association between the presence of COPD and mortality in CAP (OR: 0.93 [95% CI: 0.60–1.45] and 1.06 [95% CI: 0.72–1.58], respectively) (Figures 2 & 3). Inter-study heterogeneity was high, with  $I^2 = 85\%$  in both in-hospital and 30-days mortality. Data synthesis found no statistically significant increase in 90-days and long-term mortality with COPD versus without COPD

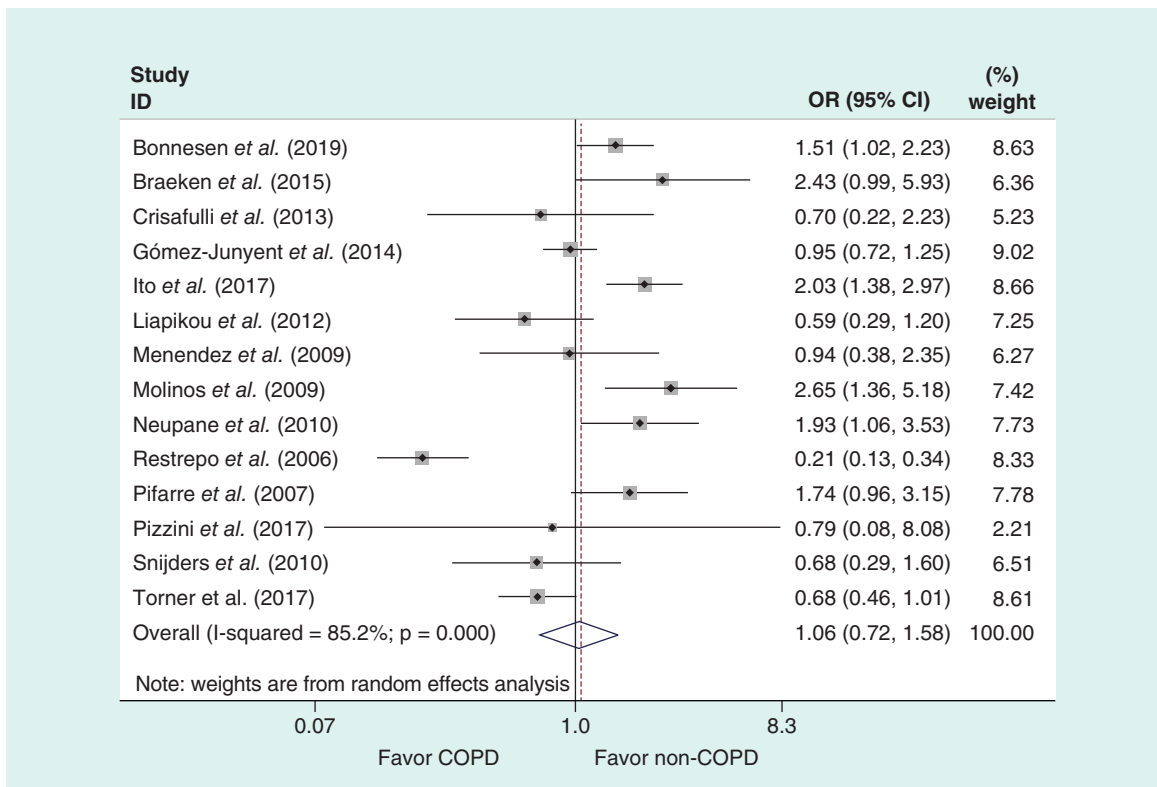
Table 1. Study characteristics.

Study (year)	Region	Study design	Sample size	Population (COPD/non-COPD)		CAP definition	CAP severity	COPD definition	Mortality
				n	Mean age (years)				
Bonnesen et al. (2019)	Denmark	Retrospective, multi-center	1309	243/1066	76/71	48/47	CURB-65 scores 3-5: 24%/13%	Patient self-report	In-hospital, 30-days mortality
Braeken et al. (2015)	European	Prospective, multi-center	1307	264/1043	71/57	64/55	CURB scores 2-4: 20%/9%	Spirometric evidence	30-days, 90-days mortality
Crisafulli et al. (2013)	Spain	Prospective, multi-center	367	117/250	72/64	95/60	PSI class IV-V: 61%/43%	Spirometric evidence	In-hospital, 30-days, 90-days, 1-year mortality
Dai et al. (2018)	China	Retrospective, multi-center	520	230/290	82/79	74/40	PSI >130: 24%/10%	Spirometric evidence	In-hospital, 60-days mortality
Fujiki et al. (2007)	Japan	Prospective, single-center	105	30/75	81.8	62	Pneumonia score >6: p <0.01	Not reported	In-hospital mortality
Gómez-Junyent et al. (2014)	Spain	Prospective, single-center	4121	983/3138	74/67	91/61	PSI class IV-V: 74%/54%	Spirometric evidence	In-hospital, 30-days mortality
Holter et al. (2016)	Norway	Prospective, single-center	259	60/199	66	51	CURB-65 scores 3-5: 37%	Medical records and clinical symptoms	5-years mortality
Ito et al. (2017)	Japan	Retrospective, single-center	1834	440/1394	73.5	70	PSI class IV-V: 72%	Spirometric evidence	30-days mortality
Lenz et al. (2017)	Norway	Retrospective, single-center	173	67/106	64.9/57.2	49	SAPS II: 12%/13%	Medical records	In-hospital, 5-years mortality
Liapikou et al. (2012)	Spain	Prospective, single-center	1379	212/1167	73.4/69.4	90/54	PSI class IV-V: 75%/66%	Spirometric evidence	30-days mortality
Menendez et al. (2009)	Spain	Prospective, multi-center	453	79/374	67.3	62	PSI class IV-V: 72%	Not reported	30-days mortality
Miguel et al. (2017)	Spain	Retrospective, national database	901136	295713/601423	75.9/75.3	76/53	Not reported	ICD-9 codes	In-hospital mortality
Molinos et al. (2009)	Spain	Prospective, multi-center	710	244/466	73.7/63.6	85/59	PSI class IV-V: 56%/34%	Spirometric evidence	30-days mortality
Neupane et al. (2010)	Canada	Prospective, multi-center	652	315/337	79.2	62.5	CRB-65 scores: 1.53 ± 0.7	Not reported	30-days mortality
Restrepo et al. (2006)	USA	Retrospective, multi-center	744	215/529	69.4/58.2	92/73	PSI scores: 105 ± 32/87 ± 34	Medical records	30-days, 90-days mortality
Pifarre et al. (2007)	Spain	Prospective, single-center	707	132/575	70.3/54.2	82/60	Not reported	Spirometric evidence	30-days mortality
Pizzini et al. (2017)	Austria	Retrospective, single-center	68	20/48	75/68	60/63	Not reported	Spirometric evidence	30-days mortality
Rello et al. (2006)	Spain	Prospective, multi-center	428	176/252	67.1/57.1	85/64	APs: 12.6 ± 10.1/12.4 ± 7.0	Medical records	In-hospital mortality
Snijders et al. (2010)	The Netherlands	Retrospective, single-center	262	95/167	70.4/60.8	64/46	PSI class IV-V: p < 0.05	Spirometric evidence	In-hospital, 30-days mortality
Torner et al. (2017)	Spain	Retrospective, multi-center	1915	587/1328	≥65	61	PSI class IV-V: 68%	Not reported	30-days mortality

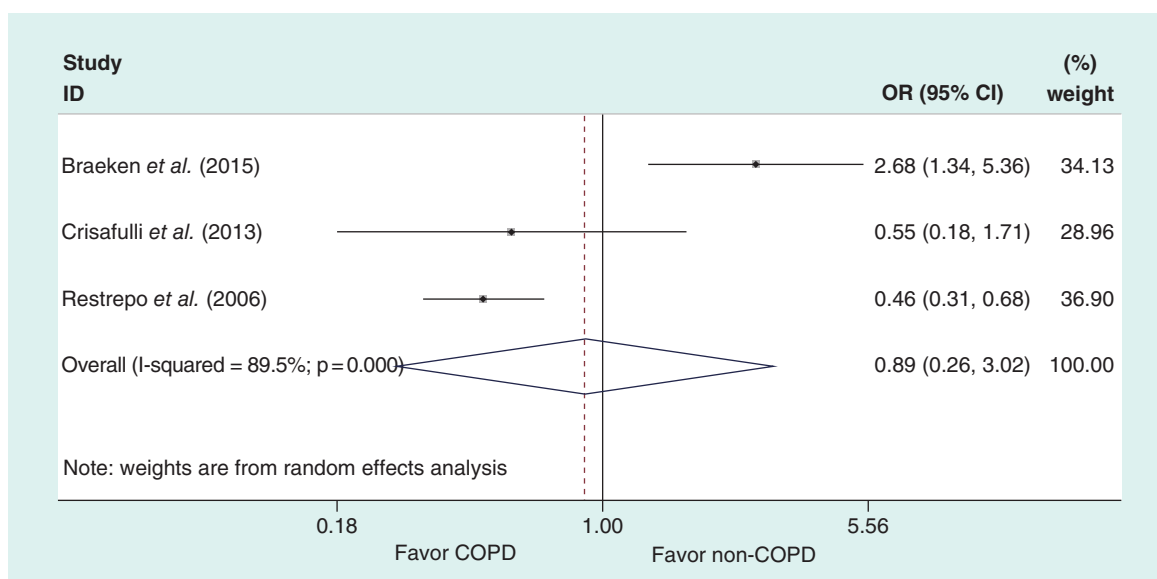
APs: Acute physiological score of Acute Physiology And Chronic Health Evaluation II score; CAP: Community acquired pneumonia; COPD: Chronic obstructive pulmonary disease; CURB: Confusion, urea, respiratory rate and blood pressure; ICD-9: The International Classification of Diseases-Ninth Revision; PSI: Pneumonia Severity Index; SAPs: Simplified Acute Physiology Score.



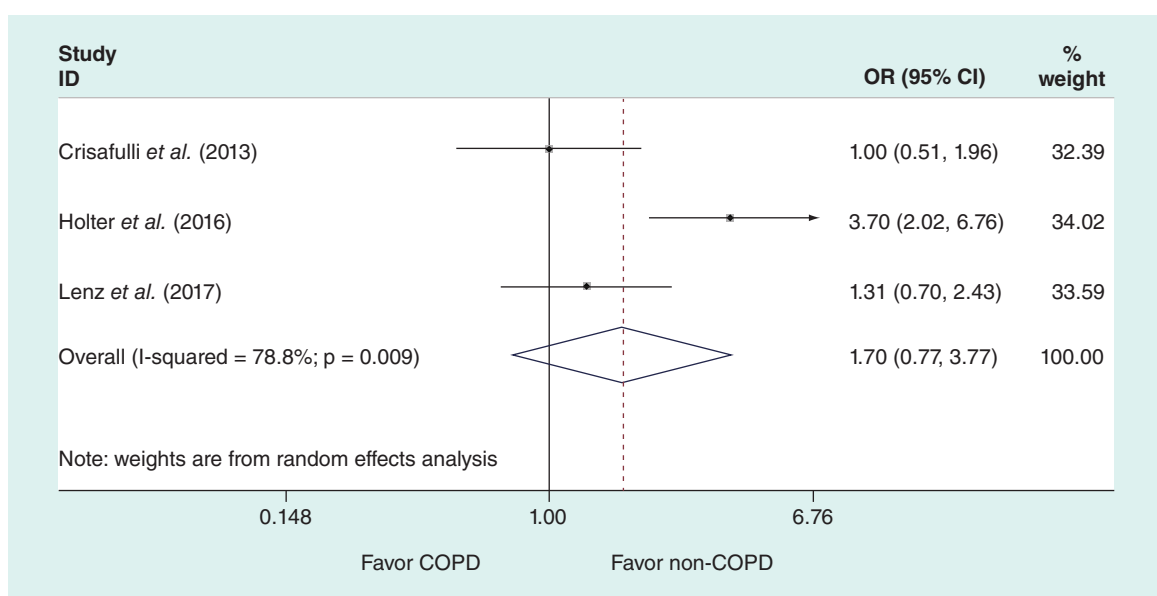
**Figure 2. Meta-analysis of in-hospital mortality in patients with COPD and non-COPD.** COPD: Chronic obstructive pulmonary disease; OR: Odds ratio.



**Figure 3. Meta-analysis of 30-days mortality in patients with COPD and non-COPD.** COPD: Chronic obstructive pulmonary disease; OR: Odds ratio.



**Figure 4. Meta-analysis of 90-days mortality in patients with COPD and non-COPD.** COPD: Chronic obstructive pulmonary disease; OR: Odds ratio.

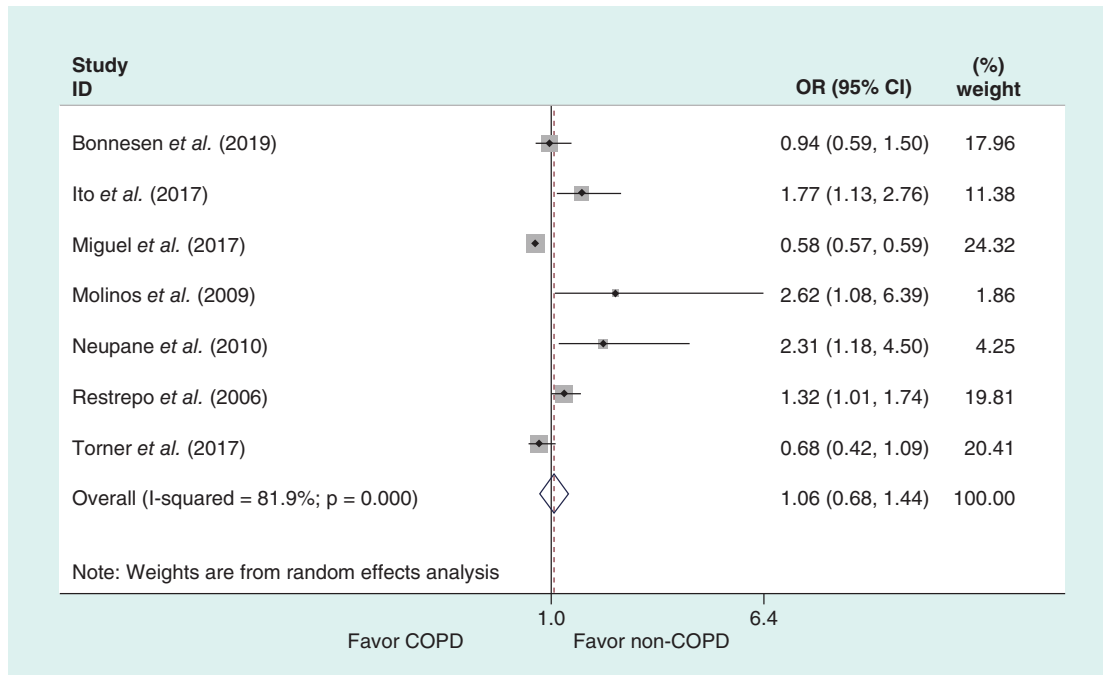


**Figure 5. Meta-analysis of long-term mortality in patients with COPD and non-COPD.**

(OR: 0.89 [95% CI: 0.26–3.02];  $I^2 = 90\%$  and 1.70 [95% CI: 0.77–3.77];  $I^2 = 79\%$ , respectively; Figures 4 & 5). After adjustment, meta-analysis of seven studies with the adjusted data on 30-days mortality showed similarly no significant association between COPD and increased 30-days mortality, and the heterogeneity was high (OR: 1.06 [95% CI: 0.68–1.44];  $I^2 = 82\%$ ) (Figure 6). No analysis of adjusted data were available for other time-point mortality due to insufficient data.

### Additional analysis

Additional analyses were only performed in in-hospital and 30-days mortality based on data adequacy. The subgroup analysis overall did not substantially alter the pooled estimates, except for prospective subgroup in-hospital mortality, indicating a trend toward higher mortality rate associated with COPD (OR: 1.34 [95% CI: 0.98–1.85];  $I^2 = 0\%$ ).



**Figure 6. Meta-analysis of adjusted 30-days mortality in patients with COPD and non-COPD.**  
COPD: Chronic obstructive pulmonary disease; OR: Odds ratio.

The sensitivity analysis showed that no individual study had an impact on the pooled effects and heterogeneity. Restricting the meta-analysis to studies with spirometric confirmation of COPD did not cause great changes for the unadjusted in-hospital and 30-days mortality, but materially increased the overall effect size of adjusted 30-days mortality, indicating COPD was significantly associated with 30-days mortality, if confounders were controlled (OR: 1.84; 95% CI: 1.06–2.62;  $I^2 = 0\%$ ).

### Publication bias

Begg's and Egger's test were performed based on studies with data on the unadjusted 30-days mortality, which detected no publication bias among the included studies ( $p = 0.89$ ).

### Discussion

Since it is always a matter of debate whether the co-existence of COPD increased mortality in patients with CAP, we tried to draw a conclusion through combining the existing evidence. In the present meta-analysis including 20 cohort studies, we found CAP patients comorbid with COPD had the same mortality rate as patients without COPD, no matter in short-term or long-term periods. However, evident inconsistency was found among the included studies to which we should pay more attention. Results from two studies with spirometrically-defined COPD indicated higher 30-days mortality in patients with COPD and CAP compared with patients without COPD, while this evidence was weak and underpowered owing to small sample size.

In this meta-analysis, CAP patients identified with COPD were reported more likely to be males, older, associated with additional comorbidities and categorized as severe pneumonia. Incomparability of baseline characteristics may be the major reason for the divergent findings of individual studies and lead to substantial heterogeneity across studies. Although COPD patients with CAP usually develop more severe pneumonia than non-COPD patients which may suggest their poorer outcomes, the pooled effects did not demonstrate the significant association between comorbid COPD and increased mortality. To reduce confounders, multivariate adjusted data were analyzed and still failed to provide evidence of increased mortality related to the presence of COPD.

Our findings regarding mortality should be taken as hypothesis generating to help further exploration, with different possible explanations for the conflicting results. First, the use of inhaled corticosteroid were reported in several included studies, which has been shown to be a protective factor and associated with lower mortality [32–34];

but possible influence of inhaled corticosteroid therapy in our results was unknown because no clear information was given and further analysis was unavailable. Second, there was an evident association between COPD and higher CAP mortality when examining only patients with COPD and excluding other pulmonary conditions, thus the diagnosis of COPD combined with other pulmonary diseases may bias the overall impact of COPD on mortality and further investigation should minimize this bias [8,35]. Furthermore, future studies should investigate severe-to-very severe patients with COPD and comorbidities (e.g., arrhythmias) at an increased risk of exacerbations, as this population is at a higher risk of future exacerbations, hospitalizations and death [36]. Third, variation in diagnostic criteria may cause misclassification of COPD and bring difficulties to measure any association consistently. Interestingly, while considering adjustment for confounders, we used spirometrically criteria to establish the diagnosis of COPD and found that COPD population exhibited significantly higher 30-days mortality as compared with non-COPD population. However, small sample size limited the strength and validity of the result and future studies are encouraged to verify this issue.

The current meta-analysis is more critical concerning the study design, study quality and sample size than any other previous meta-analyses on this topic [12,13]. Subgroup analysis of prospective studies and studies with moderate patient comparability or with more than 1000 participants may improve our result validity and be useful for planning future studies. There was an included study by Miguel *et al.* having a terribly larger sample size relative to other included studies, with 901,136 patients from national database [29], and it may be worrying that it may have caused some bias; however, we found elimination of this study did not bring any changes to our findings. Overall, the meta-analysis was robust to subgroup and sensitivity analyses. On the other hand, prior published meta-analyses of COPD versus non-COPD on pneumonia mortality are less comprehensive than our current meta-analysis, as they did not include more recent cohort studies, and generally did not evaluate mortality in different time points [12,13].

This meta-analysis represents the most complete analysis for this clinical question to date. However, some limitations should be acknowledged. First, significant inconsistency was present among studies and no clear source of heterogeneity was identified, thus the interpretation of the results should be careful. Additionally, multivariate analysis adjusted by various confounders like age, sex, processes of care, other comorbidities or severity of illness could cause some bias in the adjusted 30-days mortality. Second, as a major factor, COPD severity is not well addressed by any of the currently available research. It is reasonable to expect that COPD patients with the Global initiative for chronic Obstructive Lung Disease (GOLD) stage 'D' or  $FEV_1 < 30\%$  predicted have a much poorer chance of surviving a pneumonia than those with milder disease. The inability to see any impact on survival could be due to selection biases and classification errors introduced by including a high proportion of COPD cases with mild disease. Third, study population only included inpatients and ICU patients and generation to other patients should be done with caution; the included studies were conducted predominantly in Europe, therefore, geographical factor could bring some bias in the final analysis. Finally, data on 90-days and long-term mortality are sparse and more clinical evidences are required until we can draw a definite conclusion.

## Conclusion

The current available evidence suggests that there is still not enough evidence to clear the impact of COPD on mortality in patients hospitalized with CAP. Future studies should prospectively assess whether clinically differences exist in pneumonia mortality between COPD and non-COPD patients by conducting adequately powered cohort studies, with adequate adjustment for confounders, spirometric confirmation of COPD and sufficient duration of follow-up to provide valid estimates.

## Author contributions

H Ma was responsible for study conception and data interpretation and was the corresponding author. T Liu and Y Zhang were responsible for literature search and data collection. Z Ye and W Jia made contribution to statistical analysis using software and the draft of manuscript. Y Li contributed to manuscript revision. All authors have read and approved the manuscript.

## Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

## Summary points

- Community acquired pneumonia (CAP) is one of the most common infectious diseases that contributes to substantial health and economic burden in the world.
- Chronic obstructive pulmonary disease (COPD) is one of the most common comorbidities and risk factors in patients with CAP.
- This study reviewed the most recent literature and aimed to determine the impact of COPD on mortality in patients with CAP.
- In total, 20 cohort studies were included and the pooled results showed that CAP patients comorbid with COPD had similar short- and long-term mortality rate as patients without COPD.
- Subgroup analysis on prospective studies indicated a trend toward higher in-hospital mortality rate associated with COPD.
- COPD was significantly associated with 30-days mortality in studies with spirometric confirmation of COPD if confounders were controlled.
- Given high inter-study heterogeneity, the evidence in this meta-analysis is still not strong enough to clear the impact of COPD on mortality in patients hospitalized with CAP.
- More prospective studies with spirometrically-defined COPD and adequate adjustment for confounders are needed.

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