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Pneumonia Is Associated with Increased Mortality in Hospitalized COPD Patients: A Systematic Review and Meta-Analysis

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Keywords
Chronic obstructive pulmonary disease · Pneumonia · Mortality · Meta-analysis · Systematic review

Abstract
Background: Patients with chronic obstructive pulmonary disease (COPD) are at a heightened risk of pneumonia. Whether coexisting community-acquired pneumonia (CAP) can predict increased mortality in hospitalized COPD patients is still controversial. ***Objective:*** This systematic review and meta-analysis aims to assess the association between CAP and mortality and morbidity in COPD patients hospitalized for acute worsening of respiratory symptoms. ***Methods:*** In this review, cohort studies and case-control studies investigating the impact of CAP in hospitalized COPD patients were retrieved from 4 electronic databases from inception until December 2019. Methodological quality of included studies was assessed using Newcastle-Ottawa Quality Assessment Scale. The primary outcome was mortality. The secondary outcomes included length of hospital stay, need for mechanical ventilation, intensive care unit (ICU) admission, length of ICU stay, and readmission rate. The Mantel-Haenszel method and inverse variance method were used to calculate pooled relative risk (RR) and mean difference (MD), respectively. ***Results:*** A total of 18 studies were included. The presence of CAP was associated with higher mortality (RR = 1.85; 95% CI: 1.50–2.30; $p < 0.00001$), longer length of hospital stay (MD = 1.89; 95% CI: 1.19–2.59; $p < 0.00001$), more need for mechanical ventilation (RR = 1.48; 95% CI: 1.32–1.67; $p < 0.00001$), and more ICU admissions (RR = 1.58; 95% CI: 1.24–2.03; $p = 0.0002$) in hospitalized COPD patients. CAP was not associated with longer ICU stay (MD = 5.2; 95% CI: −2.35 to 12.74; $p = 0.18$) or higher readmission rate (RR = 1.02; 95% CI: 0.96–1.09; $p = 0.47$). ***Conclusion:*** Coexisting CAP may be associated with increased mortality and morbidity in hospitalized COPD patients, so radiological confirmation of CAP should be required and more attention should be paid to these patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease ranked as the fourth leading cause of death and has been estimated to become the third leading cause of death by 2030 [1]. Acute exacerbation of

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COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy. It is associated with poorer health status, accelerated lung function decline, faster disease progression, and worse prognosis with increased hospitalizations, readmissions, and mortality [2–5]. Community-acquired pneumonia (CAP) is also a major cause of hospital admission and death globally, and it is particularly problematic among COPD patients [6–8]. Use of inhaled corticosteroids (ICS), advanced age, prior severe exacerbations, comorbidities, and poor nutritional status may increase the risk of CAP in COPD patients [8–10]. Approximately, 8–36% of COPD patients requiring hospitalization for acute worsening of respiratory symptoms have radiographic confirmation of CAP [8, 11–13].

Although presence of CAP is associated with more intense inflammatory responses and different pathogen profiles in COPD patients [14, 15], whether CAP leads to poor clinical outcomes in hospitalized COPD patients remains controversial. Some studies found that mortality during hospitalization was similar between the patients with pneumonia and those without [15–17]. Nevertheless, other studies demonstrated that CAP was associated with higher in-hospital mortality (IHM), longer hospital stay, intensive use of mechanical ventilation (MV), and more ICU admissions in hospitalized COPD patients [11, 12, 18]. Therefore, we performed a systematic review and meta-analysis to assess whether CAP was associated with increased mortality and morbidity in hospitalized COPD patients.

Methods

Protocol and Registration

This systematic review has been registered in the PROSPERO (International Prospective Register of Systematic Reviews) (www.crd.york.ac.uk/prospero; Record No. CRD42019144549) and conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [19] and the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement [20].

Eligibility Criteria

Study Design

Only cohort studies (either prospective or retrospective) and case-control studies were considered. Reviews, editorials, letters, commentaries, unpublished papers, and conference reports with insufficient information regarding participant ascertainment, study design, and outcome data were excluded.

Participants

COPD patients hospitalized for acute worsening of respiratory symptoms with or without CAP were included, regardless of gender, age, ethnicity, disease duration, severity, and treatment. COPD was confirmed by spirometry or identified by medical records including previous diagnosis by respiratory specialists or International Classification of Diseases (ICD) code recordings. CAP was identified according to the radiological confirmation or ICD code. COPD patients who hospitalized for other identified causes such as cardiovascular disease, pulmonary embolism, and pleural effusion were excluded. In addition, patients with hospital-acquired pneumonia or ventilator-associated pneumonia were excluded.

Comparison

Comparison was made between hospitalized COPD patients with CAP (PCOPD) and those with acute exacerbation (ECOPD).

Outcomes

The primary outcome was mortality: (1) IHM: defined as the proportion of deaths during admission; (2) short-term mortality (STM): defined as the proportion of deaths in a ≤3-month follow-up after discharge; and (3) long-term mortality (LTM): defined as the proportion of deaths in a >3-month follow-up after discharge.

The secondary outcomes were as follows: (1) length of hospital stay (LOS): calculated as the number of days in hospital; (2) need for MV: calculated as the proportion of patients who used noninvasive mechanical ventilation or invasive mechanical ventilation; (3) ICU admission: calculated as the proportion of patients admitted to ICU; (4) length of ICU stay: calculated as the number of days hospitalized in ICU; and (5) readmission rate: calculated as the proportion of patients readmitted to the hospital for a COPD exacerbation within the follow-up period.

Search Strategy

Study searches were carried out in MEDLINE and EMBASE from inception until December 31, 2019. Separate searches were also conducted in the Web of Science and the Cochrane Library. Ongoing studies were searched on the clinicaltrials.gov website (http://www.clinicaltrials.gov/). Additional eligible studies were hand searched from the bibliographies of included studies, as well as previous systematic reviews. The search strategy was performed using a combination of Medical Subject Headings and text words for aforementioned databases, including "pulmonary disease, chronic obstructive" or "COPD" or "chronic obstructive pulmonary disease" and "pneumonia" or "community-acquired pneumonia" or "CAP" (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000510615). The search terms were appropriately modified to suit the instructions for individual databases. No language or date restrictions were imposed.

Study Selection

Two reviewers (Y.Y. and W.L.) worked independently to perform the study selection. Firstly, we carried out the initial search and removed duplicated studies by using the citation manager EndNote X9. Secondly, we checked the included titles and abstracts for eligibility and identified potential articles for further full-text screening. Lastly, we went through the full articles to determine the final inclusions according to the prespecified inclusion criteria. Disagreement was resolved by consensus or settled by the third reviewer (H.L.J.).

Data Extraction

Two investigators (Y.Y. and W.L.) independently extracted data from included studies on the name of the first author, year of publication, country of study, study duration, study design, participants' demographic characteristics (including sample size, age, and male ratio), diagnostic or screening criteria for COPD and CAP, severity of COPD, treatment (use of corticosteroids before or during hospitalization), and outcomes, according to a standardized data collection form. Where available, we recorded multivariate adjusted data regarding the outcomes together with adjusting confounders. When several adjusting models were adopted, we extracted data from the model where age and sex were adjusted as confounders as they were the most common confounding factors. The original investigators would be contacted for further information regarding study design, participant inclusion, and outcome definition. If required, study protocols would be requested. The reviewers cross- checked all extracted data, and any discrepancy was resolved by discussion until consensus was reached.

Quality Assessment

Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the risk of bias by 2 authors (Y.Y. and W.L.). NOS consisted of 8 items in 3 domains: selection (4 items, maximum 4 scores), comparability (1 item, maximum 2 scores), and outcome/exposure (3 items, maximum 3 scores) for cohort studies and case-control studies [21]. Similarly, disagreements were addressed through consensus. Quality of included studies was rated according to the following criteria by converting the NOS scores to Agency for Healthcare Research and Quality (AHRQ) standards [22–24]:

- *Good quality:* 3 or 4 scores in the selection domain AND 1 or 2 scores in the comparability domain AND 2 or 3 scores in the outcome/exposure domain.
- *Moderate quality:* 2 scores in the selection domain AND 1 or 2 scores in the comparability domain AND 2 or 3 scores in the outcome/exposure domain.
- *Poor quality:* 0 or 1 score in the selection domain OR 0 score in the comparability domain OR 0 or 1 score in the outcome/exposure domain.

Data Analysis

Data analysis was conducted by 2 reviewers (Y.Y. and W.L.) using RevMan 5.3 (Cochrane Collaboration) and Stata 15.1. For crude data, relative risk (RR) with 95% confidence interval (CI) was calculated using the Mantel-Haenszel method for dichotomous data (e.g., mortality, need for MV, ICU admission, and readmission rate), and mean difference (MD) with 95% CI was summarized using the inverse variance method for continuous data (e.g., LOS and length of ICU stay). For adjusted data, the pooled RR with 95% CI was estimated using the inverse variance method. Odds ratio (OR) was considered similar to RR when the outcome was uncommon [25]. Heterogeneity was quantified by I^2 statistic and the χ^2 test, with an I^2 value of 25–50% indicating low heterogeneity, 50–75% indicating moderate heterogeneity, and >75% indicating high heterogeneity, respectively [26]. Random-effects model was used for all analyses. $p < 0.05$ was considered statistically significant.

To further evaluate the robustness of meta-analysis, we performed sensitivity analyses by removing each individual study one by one or the studies with poor quality. Subgroup analyses were performed to explore sources of heterogeneity. All included studies were stratified into subgroups according to study design (retrospective or prospective), COPD diagnostic method (spirometry or ICD codes/others), baseline comparability of age, baseline comparability of sex, baseline comparability of age and sex, sample size (≥500 or <500), and quality of study (good or moderate/poor). Sensitivity analyses and subgroup analyses were conducted only for the outcome of IHM.

Publication bias was visually inspected by funnel plots, and Egger's and Begg's tests were conducted to determine the degree of funnel plot asymmetry with $p < 0.05$ representing significant publication bias [27]. When publication bias was found, trim and fill analysis was performed to find out the influence of missing studies on overall effects.

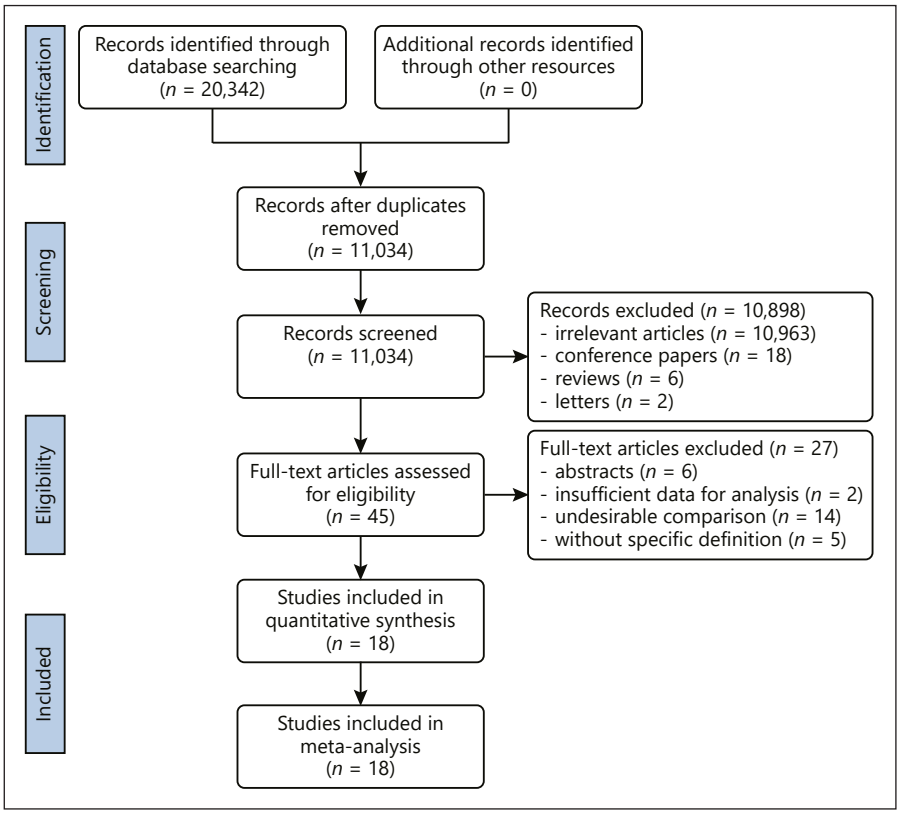
Results

Study Selection

The comprehensive search strategy identified 20,342 potentially relevant citations from database searches. No additional records were retrieved using the hand search strategy. After duplicates removal, 11,034 articles were screened for initial elimination. From these, 10,989 results were excluded for the following reasons: irrelevant articles (n = 10,963), conference papers (n = 18), reviews (n = 6), and letters (n = 2). From the remaining 45 records for full-text evaluation, 27 studies were excluded due to the following reasons: meeting abstracts (n = 6), insufficient data for analysis (n = 2), undesirable comparison (n = 14), and no COPD and/or CAP diagnostic criteria reported (n = 5). We tried to communicate with the authors through emails to access data for studies without enough details for assessment [28–32], but no response was received. Finally, 18 studies met the eligibility and were included for the final analysis. The process of study search and selection is shown in Figure 1.

Study Characteristics

A total of 18 studies including 17 cohort studies [11–18, 33–41] and 1 case-control study [42] were included with sample sizes ranging from 54 to 52,520. The final analysis included 91,209 participants in total, with 28,480 in the PCOPD group and 62,729 in the ECOPD group, respectively. Among cohort studies, 10 were retrospective in nature [11–14, 17, 35, 37–39, 41] and 7 were prospective in nature [15, 16, 18, 33, 34, 36, 40]. All studies were published in English except one [35]. Majority studies were conducted in Europe (10/18) [11–13, 15–18, 33, 34, 38], followed by Asia (7/18) [14, 35–37, 40–42] and North America (1/18) [39]. Study duration ranged from 3 months to 12 years. Males were predom-



Color version available online

Fig. 1. Flow diagram of study search and selection.

inant in both groups, with a slightly but significantly higher proportion in the PCOPD group (59.1 vs. 56.6%, $p < 0.0001$). An older age was found in PCOPD patients (74.0 ± 2.5 vs. 71.9 ± 2.0, $p < 0.05$). Less use of ICS therapy was reported in PCOPD patients (18.9 vs. 24.8%, $p < 0.0001$). Besides, the ratio of patients with GOLD stage III–IV was 36.1% in the PCOPD group (1,469/4,071) and 39.8% in the ECOPD group (5,217/13,115), respectively ($p < 0.0001$). In most studies, the diagnosis of COPD was reached according to the spirometric criteria based on the GOLD guideline (12/18) [14–16, 18, 33, 35–38, 40–42]. ICD-10 and ICD-9 codes were used for COPD ascertainment in 3 studies [11, 17, 39]. All studies confirmed the presence of pneumonia with chest radiological evidence except one, in which pneumonia was ascertained by ICD-10 codes [11]. Five studies [11–13, 17, 34] provided adjusted data for mortality analysis. In addition to age and sex, confounders such as COPD stage [17], use of antibiotics [34], comorbidities, and respiratory medications [11] were also adjusted. The characteristics of included studies are summarized in Table 1 and online suppl. Table 2.

Quality Assessment

Based on the NOS, 14 studies were considered good quality [11–17, 34–38, 40, 41] and 4 were poor quality (online suppl. Table 3) [18, 33, 39, 42]. The NOS scores ranged from 6 to 9, and the average score was 7.7. All studies fulfilled the outcome domain as they showed reliable assessment for outcomes, and the duration of follow-up was long enough to evaluate mortality with a loss to follow-up <20% in all studies. Retrospective studies got 0 score for the item of demonstration of outcome in the selection domain as outcomes of interest had already occurred at the time the study was initiated in these studies. Four studies failed to control the confounders such as age, sex, disease severity, or comorbidities that might impact the baseline comparability and were considered to be of poor quality.

Outcomes

Mortality

Sixteen [11, 13–18, 33, 35–42] studies reported patients' mortality. Among them, 11 [13–18, 35–37, 39, 41] studies reported in-hospital death and 6 [11, 13–15, 38, 39] and 5 [15, 33, 39, 40, 42] studies reported short-term and long-term death, respectively. In hospitalized COPD

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Table 1. Characteristics of included studies (PCOPD/ECOPD)

Study	Country	Study duration, mo or yr	Study design	Patient characteristics			Condition ascertainment		COPD severity, %	Treatment, %	Outcomes
				N	age, yr	male, %	COPD	CAP			
Andreassen et al. [17]	Norway, Sweden	12 mo	Retrospective study	709 (237/472)	75.3 (74.2–76.4)/ 71.7 (70.8–72.7)	60.8/47.5	ICD-10 codes	Pneumonic infiltrates on CXR and CRP ≥40 mg/L	GOLD stage: I–II, 23.6/17.8; III–IV, 43.9/57.8	ICS: 58/67	LOS; IHM; NIV
Boixeda et al. [16]	Spain	3 mo	Prospective, longitudinal, observational cohort study	124 (20/104)	69.7±10.2/ 71.8±10.1	100/91.3	GOLD criteria	New radiological condensation	FEV_1% predicted: 55.2±15.9/ 44.3±14.7; GOLD stage: I, 5.6/4; II, 66.7/26.7; III, 11.1/32.7; IV, 16.7/36.6	Cortico-steroids: 10/28.2	LOS; ICU admission; length of ICU stay; MV; IHM
Grolimund et al. [33]	Switzerland	nm	Prospective cohort study	469 (252/217)	74 (65–82)/ 74 (64–81)	61.9/60.8	Spirometric data or medical records	New chest radiographic infiltrate and clinical features	GOLD stage: I, 16.7/2.6; II, 31.6/42.2; III, 35.1/42.2; IV, 16.7/12.9	nm	LOS; LTM
Huerta et al. [15]	Spain	nm	Prospective cohort study	249 (116/133)	71.9±10.0/ 69.4±9.8	95.7/93.2	GOLD criteria	Chest radiological infiltrates	GOLD stage: I, 10/2; II, 46/37; III, 34/37; IV, 10/24	ICS: 53.4/56.3; SCS: 11.2/9.0	LOS; ICU admission; NIV; IHM; STM; LTM; readmission
Husebø et al. [34]	Norway	nm	Prospective cohort study	320 (98/222)	nm	nm	Clinical diagnosis	A lung infiltrate on CXR and clinical diagnosis made by a physician	nm	nm	LTM; readmission
Jeong et al. [35]	Korea	24 mo	Retrospective study	147 (65/82)	72±7.6/ 71±8.7	92.3/64.6	GOLD criteria	Chest radiograph with pulmonary infiltration with one or more clinical features of pneumonia	GOLD stage: I, 21.5/24.4; II, 47.7/32.9; III, 26.2/26.8; IV, 4.6/15.9	SCS: 12.3/23.2	ICU admission; NIV; IHM; LOS; readmission
Kim et al. [14]	Korea	36 mo	Retrospective cohort study	477 (236/241)	72.8±9.1/ 71.1±9.5	89.4/83.4	GOLD criteria	New radiographic pulmonary infiltration plus two or more clinical features of pneumonia	GOLD stage: I, 10.7/6.2; II, 43.8/36.6; III, 34.3/37.9; IV, 11.2/19.3	SCS: 5.1/12.8	ICU admission; MV; length of ICU stay; LOS; STM; IHM

Table 1 (continued)

Study	Country	Study duration, mo or yr	Study design	Patient characteristics			Condition ascertainment		COPD severity, %	Treatment, %	Outcomes
				N	age, yr	male, %	COPD	CAP			
Lieberman et al. [36]	Israel	16 mo	Prospective, observational study	213 (23/190)	66.4±9.6/ 67.2±8.7	78/85	Spirometric data	Experts reported pulmonary infiltrate in the acute-phase radiograph	FEV_1% predicted: 41.6±17.6/40.7±16.4	SCS: 13/31	IMV; ICU admission; IHM; LOS; readmission
Lu et al. [37]	China	36 mo	Retrospective observational study	80 (38/42)	74.11±8.02/ 75.36±8.23	73.7/71.4	GOLD criteria	Typical symptoms; new focal chest signs, at least 1 systemic feature; new radiographic shadowing; no other explanation for the illness	COPD categories: group B, 15.8/33.3; group C, 47.4/35.7; group D, 36.9/31.0	nm	LOS; IHM
Myint et al. [13]	UK	3 mo	Retrospective study	9,338 (1,505/7,833)	<65, 14%/24% 65–74, 28%/31% 75–84, 42%/34% ≥85, 16%/12%	53/50	Audit collected items	CXR shadow	FEV_1% predicted: <50%, 71/71; 50–74%, 23/23; ≥75%, 6/6	SCS: 84/87[§]	IHM; STM; MV; IMV; NIV; readmission
Pizzini et al. [38]	Austria	22 mo	Retrospective cohort study	54 (20/34)	75(15)/ 69(18)[‡]	60/61.8	GOLD criteria	Typical symptoms and a CXR or CT scan confirming a pneumonic infiltrate	GOLD stage: I, 0/8.9; II, 30/17.6; III, 60/50; IV, 10/23.5;	ICS, 55/73.5 SCS, 30/58.8	IHM; LOS; readmission
Saleh et al. [12]	Europe	12 mo	Retrospective cohort study	14,111 (2,714/11,397)	71.6±10.5/ 70.4±10.8	65.7/67.6	Medical records	With consolidation on the admission chest radiograph	GOLD stage: I, 1.2/1.2; II, 11.6/14.3; III, 21.4/24.2; IV, 11.6/13.7	ICS: 68.1/69.2; SCS: 18.7/19.2 ICS: 35.0/33.1[§] SCS: 78.6/84.8[§]	LOS; NIV; IMV
Sharafkhane et al. [39]	USA	12 yr	Retrospective cohort study	10,632 (3,478/7,154)	70.4±10.6/ 68.8±10.4	97.9/97.2	ICD-9 codes	ICD-9 codes and a chest imaging of X-ray or CT scan	nm	ICS: 25.2/18.7	IHM; STM; LTM; IMV
Shin et al. [41]	South Korea	11 yr	Retrospective study	374 (194/180)	74 (69–78)/ 73 (66–78)	86.6/84.4	GOLD criteria	A new pulmonary infiltration on a chest radiograph	GOLD stage: III–IV, 58.8/67.8	ICS: 47.7/38.8	NIV; ICU admission; LOS; IHM

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Table 1 (continued)

Study	Country	Study duration, mo or yr	Study design	Patient characteristics			Condition ascertainment		COPD severity, %	Treatment, %	Outcomes
				N	age, yr	male, %	COPD	CAP			
Shin et al. [40]	Korea	48 mo	Prospective cohort study	308 (134/174)	72.8±8.8/ 71.9±10.0	76.1/76.4	GOLD criteria	A new infiltrate on chest radiography and one or more of the criteria	GOLD stage: I, 2.2/2.9; II, 41.8/52.3; III, 19.4/16.1; IV, 36.6/28.7	ICS: 60.4/56.9 SCS: 20.1/10.3	LTM; readmission
Søgaard et al. [11]	Denmark	6 yr	Retrospective cohort study	52,520 (18,968/33,552)	75 (66–82)/ 73(64–80)	50.4/45.2	ICD-10 codes	ICD-10 codes	nm	ICS: 9.4/10.1 SCS: 20.7/26.8	STM; LOS; ICU admission; MV; NIV; readmission
Steer et al. [18]	UK	19 mo	Prospective observational cohort study	920 (299/621)	75.8±9.1/ 71.7±10.2	50.5/44	Spirometric data	Consolidation on admission chest radiograph	FEV_1% predicted: 46.2±17.7/43.2±18.0	nm	IHM; MV; readmission
Yu et al. [42]	China	37 mo	Retrospective case-control study	164 (83/81)	75.6±7.2/ 72.6±9.7	63.7/72.5	CTS criteria	Pulmonary exudation and consolidation on CT scan at admission	GOLD stage: I–II, 33.7/29.6; III–IV, 66.3/70.4	SCS: 1 6.9/23.5	NIV; IMV; LOS; LTM

Data are presented as absolute numbers (percentage) for categorical variables and mean±standard deviation or median (interquartile range) for continuous variables, unless indicated otherwise. PCOPD, chronic obstructive pulmonary disease with community-acquired pneumonia; ECOPD, chronic obstructive pulmonary disease with exacerbation; mo, month; yr, year; CAP, community-acquired pneumonia; CRP, C-reactive protein; IHM, in-hospital mortality; STM, short-term mortality; LTM, long-term mortality; LOS, Length of hospital stay; NIV, noninvasive ventilation; MV, mechanical ventilation; IMV, invasive mechanical ventilation; FEV_1, forced expiratory volume in 1 s; ICD, International Classification of Diseases; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CT, chest computed tomography; CXR, chest X-ray; ICS, inhaled corticosteroids; SCS, systemic corticosteroids; nm, not mentioned; CTS, Chinese Thoracic Society. ‡ Represents median and interquartile range. § Represents treatment during admission.

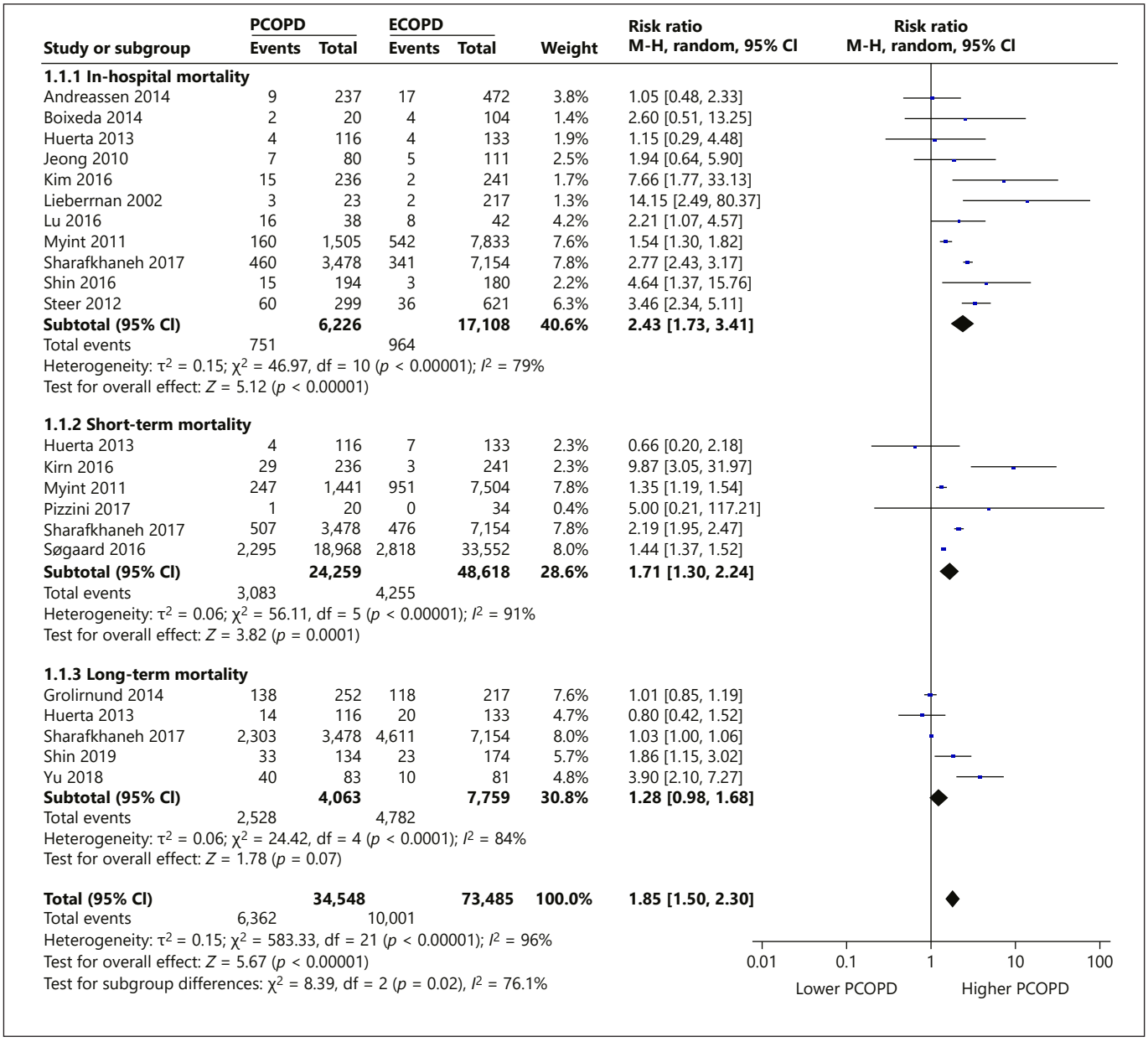

Fig. 2. Forest plot of mortality in PCOPD and ECOPD patients. PCOPD, COPD with community-acquired pneumonia; ECOPD, COPD with acute exacerbation; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel method; IHM, in-hospital mortality; STM, short-term mortality; LTM, long-term mortality.

patients, pneumonia was associated with increased mortality (RR = 1.85; 95% CI: 1.50–2.30; $p < 0.00001$; $I^2 = 96\%$). The pooled RR for IHM, STM, and LTM was 2.43 (95% CI: 1.73–3.41; $p < 0.00001$), 1.71 (95% CI: 1.30–2.24; $p = 0.0001$), and 1.28 (95% CI: 0.98–1.68; $p = 0.07$), respectively (Fig. 2). The pooled results for adjusted data showed a similar association between 2 groups (RR = 1.23; 95% CI: 1.15–1.31; $p < 0.00001$; $I^2 = 32\%$) (Fig. 3).

Subgroup Analysis of IHM

As presented in Table 2, all subgroup analyses yielded significant results that were consistent with the original analysis. We found a decreased value of I^2 in the subgroup of studies with prospective design, COPD diagnosis according to spriometric criteria, baseline comparability of age and sex, sample size <500, and poor study quality.

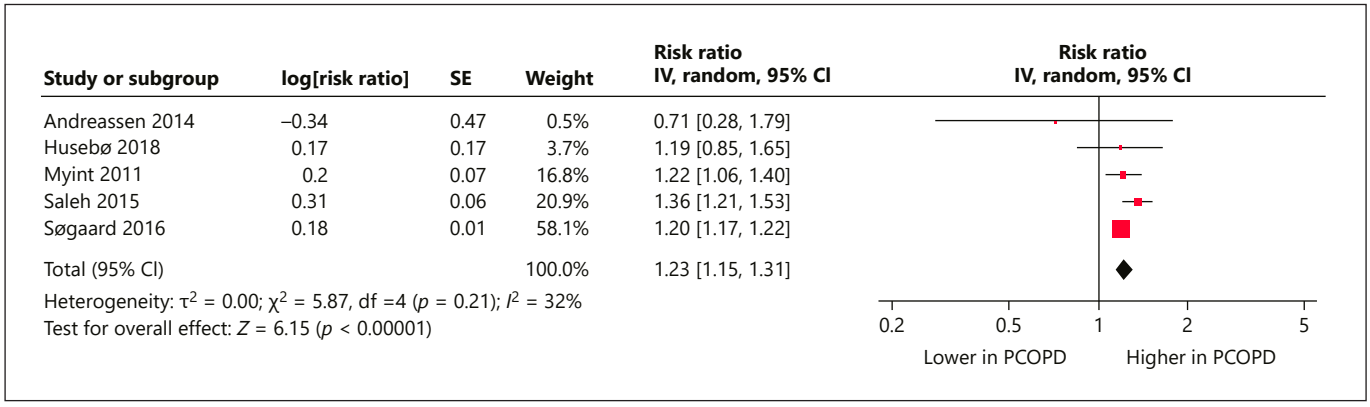

Fig. 3. Forest plot of mortality from adjusted data in PCOPD and ECOPD patients. PCOPD, COPD with community-acquired pneumonia; ECOPD, COPD with acute exacerbation; CI, confidence interval; df, degrees of freedom; SE, standard error; IV, inverse variance method.

Table 2. Subgroup analyses for IHM in included studies

Stratification	Studies	Patients, *n*	RR (95% CI)	*p* value	I^2, %
Study design					
Retrospective	7	21,801	2.18 (1.47–3.25)	0.0001	84
Prospective	4	1,533	3.24 (1.53–6.87)	0.002	42
COPD diagnostic method					
Spriometry	8	2,655	3.13 (2.13–4.60)	<0.00001	20
ICD codes or others	3	20,679	1.80 (1.07–3.02)	<0.00001	94
Baseline comparability of age					
No	4	21,599	2.12 (1.36–3.29)	0.0008	92
Yes	7	1,735	2.43 (1.75–5.26)	<0.0001	28
Baseline comparability of sex					
No	4	10,318	1.55 (1.32–1.81)	<0.00001	0
Yes	7	13,016	3.18 (2.36–4.27)	<0.00001	29
Baseline comparability of age and sex					
No	6	21,870	2.12 (1.46–3.08)	<0.0001	87
Yes	5	1,464	4.08 (1.79–9.13)	0.0008	37
Sample size					
≥500	4	21,599	2.12 (1.36–3.29)	0.0008	92
<500	7	1,735	3.03 (1.75–5.26)	<0.0001	28
Quality of study					
Good	9	11,782	2.18 (1.41–3.35)	0.0004	50
Moderate or poor	2	11,552	2.86 (2.46–3.34)	<0.00001	10

IHM, in-hospital mortality; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases; RR, relative risk; CI, confidence interval.

Sensitivity Analysis

As presented in online suppl. Table 4, the results had not been substantially changed by removing individual studies one by one. Similarly, the pooled recalculated results were steady after eliminating poor quality studies (RR = 2.18; 95% CI: 1.41–3.35; $p = 0.0004$; $I^2 = 50\%$) [18, 39].

Need for MV

Thirteen studies [11–18, 35, 36, 39, 41, 42] reported the use of MV. More need for MV was shown in the PCOPD group with a statistical heterogeneity across studies (RR = 1.48; 95% CI: 1.32–1.67; $p < 0.00001$; $I^2 = 67\%$) (online suppl. Fig. 1).

ICU Admission

A total of 7 studies [11, 14–16, 35, 36, 41] reported ICU admissions. PCOPD patients had a higher risk of ICU admission compared with ECOPD patients (RR = 1.58; 95% CI: 1.24–2.03; $p = 0.0002$; $I^2 = 30\%$) (online suppl. Fig. 2).

Length of Hospital Stay

Thirteen studies [11, 12, 14–17, 33, 35–38, 41, 42] presented data on LOS. The pooled analysis showed a significant difference between 2 groups with a longer hospitalization in PCOPD patients (MD = 1.89; 95% CI: 1.19–2.59; $p < 0.00001$; $I^2 = 88\%$) (online suppl. Fig. 3).

Length of ICU Stay

Length of ICU stay was reported in 2 studies [14, 16]. No significant difference was observed between groups (MD = 5.20; 95% CI: −2.35 to 12.74; $p = 0.18$; $I^2 = 98\%$) (online suppl. Fig. 4).

Readmission

There were 8 studies [11, 13, 15, 18, 35, 36, 38, 40] which provided data on readmissions. No significant difference in readmission rate was found between PCOPD and ECOPD patients (RR = 1.02; 95% CI: 0.96–1.09; $p = 0.47$; $I^2 = 22\%$) (online suppl. Fig. 5).

Publication Bias

Funnel plot was constructed to detect publication bias. An asymmetry was observed in visual conditions (online suppl. Fig. 6). Significant bias was found in Egger's test ($p = 0.018$) but not in Begg's test ($p = 0.367$). Therefore, a publication bias could not be ruled out in these studies. A total of 4 missing studies were identified in the trim and fill analysis. According to the aggregated analysis where the estimated missing effects were included, the trim and fill method still indicated similar effect (RR = 1.68; 95% CI: 1.38–2.04; $p < 0.0001$).

Discussion

In this systemic review and meta-analysis, we found that CAP was associated with higher mortality, longer hospital stay, more need of MV, and more ICU admissions in hospitalized COPD patients. The results were consistent and robust in subgroup analyses and sensitivity analyses.

COPD patients have increased risk of developing pneumonia. Exacerbations and pneumonia are two of the most common reasons for acute hospital admissions in these patients. They present with similar symptoms, representing a diagnostic challenge with a significant impact on patient outcomes. The pneumonic events have heightened inflammatory profiles, more intense inflammatory responses, and differing pathogen profiles. Pneumonic hospitalization presents a pattern that is more apparently associated with bacterial isolation, with *Streptococcus pneumoniae*, *Staphylococcus aureus,* and *Haemophilus influenzae* being the most frequently detected [43–45]. Moreover, bacterial pathogens *such as Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *Acinetobacter baumannii* that associated with poor clinical outcomes were more commonly detected in PCOPD patients [14, 46]. Besides, viral-bacterial coinfections are significantly more common in the PCOPD group compared to the ECOPD group [14]. As a consequence, the poorer outcomes in the PCOPD group might be partially explained by possible aetiological difference.

In the current review, we found that less ICS therapy was reported in PCOPD patients (18.9 vs. 24.8%, $p < 0.0001$). A retrospective cohort study with 15,768 COPD patients hospitalized for pneumonia showed that ICS therapy was significantly associated with decreased STM (30-day mortality: OR = 0.80, 95% CI: 0.72–0.89; 90-day mortality: OR = 0.83, 95% CI: 0.72–0.85) in multilevel regression analyses [47]. Therefore, less use of ICS in the PCOPD group could be one of the causes for increased mortality risk.

The proportion of patients with GOLD stage III–IV was 36.1% in the PCOPD group (1,469/4,071) and 39.8% in the ECOPD group (5,217/13,115) ($p < 0.0001$), respectively, which indicated that PCOPD patients might have less advanced airflow obstruction. Exacerbations among patients with COPD GOLD stage I–II were generally managed at home, and hospitalization was required primarily when symptoms of pneumonia were present [17].

High heterogeneity was detected in most outcomes in our review. Any inconsistency across individual studies might result in heterogeneity, which was inevitable. Based on the subgroup analyses, first, heterogeneity was low in prospective cohort studies (I^2: 42 vs. 84%), indicating that study design may be one source of heterogeneity. Second, the value of I^2 decreased to 20% in subgroup analysis where spirometric criteria were used to ascertain the presence of COPD, suggesting that spirometry might be a more reliable criterion for COPD diagnosis compared with ICD codes or physician-reported diagnosis. Third, we found a lower heterogeneity in studies with a baseline comparability between groups. Therefore, population

differences in age and sex contributed to potential source of heterogeneity. In addition, studies with a sample size <500 and poor quality showed lower I^2 values, implying that sample size and quality of studies might have an impact on heterogeneity. Li et al. [48] found that when the sample size of trials enrolled in the meta-analysis was substantially increased, the Q and I^2 values also increased steadily, which indicated that I^2 statistic and Q test might be more suitable for testing heterogeneity amongst small sample size trials. Within-study biases could lead to overestimation or underestimation of the true intervention effect in a study and were expected to contribute to between-study variation in meta-analyses [49]. For this reason, the studies judged to be of poorer quality were assumed to be at least as heterogeneous as those of higher quality. It might not be the case as the accuracy of the reported design characteristics might not well represent how a study was actually conducted, and studies that were conducted well could be poorly reported [50, 51]. Variability in ICS use, COPD severity, and comorbidities could also result in heterogeneity. However, due to the limited provided data, we could not make more detailed explanations.

A previous meta-analysis published in 2013 addressed similar issues [52], but some differences highlighted the necessity for this current review. Firstly, the previous meta-analysis included only 4 studies. More studies investigating related clinical outcomes that published after 2013 were supplemented in our up-to-date review to strengthen the results. Secondly, as the quality assessment was important for systemic review and was always recommended by the MOOSE guideline [20], we performed a comprehensive methodological quality assessment for included studies, which was absent in the previous one. Thirdly, we additionally reported important clinical outcomes including LOS, ICU admission, length of ICU stay, need for MV, and readmission to make a comprehensive assessment of the effect of CAP in hospitalized COPD patients. Fourthly, although the previous review showed a higher mortality in COPD patients with concomitant CAP, statistical difference was not detected between groups. Our review strengthened the result and confirmed the difference, which might be attributed to the increased sample size.

Our meta-analysis has several limitations which should be noted. Most pooled effects were based on raw data with adjusted data presented in only 5 studies. Confounders including age, sex, comorbidities, or severity of disease might have some potential influence on primary outcomes. However, the pooled analyses of mortality based on the adjusted or crude data were consistent. Furthermore, most studies were implemented in Europe and Asia, weakening the patients' representativeness.

In conclusion, coexisting CAP may be a predictor of higher mortality, longer hospital stay, more need for MV, and more ICU admissions in hospitalized COPD patients. Our result highlights the necessity of radiological confirmation of CAP in hospitalized COPD patients, and more attention should be paid to these patients.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, supervision, and validation: W.L. and H.L.J. Data curation, formal analysis, and writing – original draft: Y.Y. and W.L. Writing – review and editing: W.L., H.L.J., and B.M. W.L. and Y.Y. are co-first authors and contributed equally to this work.

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