C-reactive protein level predicts mortality in COPD: a systematic review and meta-analysis

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Baseline high CRP level is significantly associated with higher mortality in COPD patients
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ABSTRACT The prognostic role of baseline C-reactive protein (CRP) in chronic obstructive pulmonary disease (COPD) is controversial. In order to clarify this issue, we performed a systematic review and meta-analysis to assess the predictive effect of baseline CRP level in COPD patients. 15 eligible articles focusing on late mortality in COPD were included in our study. We performed a random-effects meta-analysis, and assessed heterogeneity and publication bias. We pooled hazard ratio (HR) estimates and their 95% confidence intervals on mortality for the comparison between the study-specific highest category of CRP level *versus* the lowest category. In overall analysis, elevated baseline CRP levels were significantly associated with higher mortality (HR 1.53, 95% CI 1.32–1.77, I^2=68.7%, p<0.001). Similar results were observed across subgroups. However, higher mortality risk was reported in studies using a cut-off value of 3 mg·L^{-1} (HR 1.61, 95% CI 1.12–2.30) and in those enrolling an Asiatic population (HR 3.51, 95% CI 1.69–7.31). Our analysis indicates that baseline high CRP level is significantly associated with higher late mortality in patients with COPD. Further prospective controlled studies are needed to confirm these data.

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) is ~10% in adults older than 40 years [1]. According to World Health Organization (WHO) estimates, 65 million people have moderate to severe COPD and more than 3 million people died of COPD in 2005, corresponding to 5% of all deaths globally [2]. This number is projected to rise by 30% during the next 10 years and estimates show that COPD will become the third leading cause of death worldwide in 2030 [2]. Approximately 50% of patients with COPD have at least one exacerbation per year and >20% are readmitted within 30 days, with a total of nearly 800 000 hospitalisations and USD50 billion in healthcare costs annually [3–5]. COPD is characterised by

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persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [6]. It is well established that COPD is a multifactorial disease composed of both modifiable (smoking, occupational exposures, pollution, *etc.*) and nonmodifiable (genetics, ageing, bronchial hyperreactivity, *etc.*) risk factors, with cigarette smoking being the most significant factor [7]. In particular, smokers with COPD have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in forced expiratory volume in 1 s (FEV_1), and a greater mortality rate compared with nonsmokers [8].

As a rule, the persistent damage related to risk factors causes mucus accumulation, bronchiolar fibrosis and local inflammation (development of lymphoid follicles and inflammatory cells infiltration) [9]. In addition to lung inflammation, it is well recognised that patients with moderate to severe stable COPD frequently demonstrate persistent low-grade systemic inflammation, with elevated levels of circulating molecules that are part of the inflammatory cascade (C-reactive protein (CRP), interleukin (IL)-6, tumour necrosis factor (TNF)-α and blood leukocytes) [10, 11]. This issue is of particular interest when considering that systemic inflammation is a significant risk factor for morbidity or mortality in the general population, especially related to cardiovascular events [12] or cancer onset [13]. Furthermore, the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study has recently defined different COPD subtypes, and reported an interesting association between COPD clinical course and systemic inflammation [14].

The search for an optimal prognostic marker in COPD patients is challenging. As defined by McShane *et al.* [15] and De Gruttola *et al.* [16], an ideal biomarker must possess several combined properties: 1) a biological role in pathogenesis of disease, 2) easy to measure accurately, 3) sensitive to change in order to be repeatedly evaluated, 4) modifiable by therapies or interventions, 5) a long half-life and 6) associated with outcome. As recently evidenced [17], CRP could be one of the ideal biomarkers available in common clinical practice.

The aim of this meta-analysis was to evaluate and discuss the association between baseline CRP level and mortality in the setting of COPD.

Methods

We retrieved studies from the PubMed database published up to May 2016 using a web-based search engine. Search terms or related MeSH terms included "CRP" or "C-reactive protein" or "C reactive protein" and "mortality" or "survival" and "COPD" or "chronic obstructive pulmonary disease" or "smoker" or "smokers" or "smoke". We also manually searched the reference lists of all articles retrieved. Relevant review articles were also cross-referenced.

Two investigators (G.L. and C.G.) independently identified all eligible articles. The first screen was based on article title and then on related abstracts. Subsequently, the full texts of potentially eligible papers were assessed for final inclusion. In order to avoid disagreement in search results, a third reviewer (U.P.) made the final decision in case of different results.

Inclusion criteria were: 1) study enrolling patients with COPD, 2) reported baseline CRP levels, 3) provided information on survival, 4) reported estimates of association between CRP levels and survival in patients with COPD, and 5) inclusion of the most recent article or the most complete article for publication data repeatedly reported by the same author.

Exclusion criteria were: 1) letters, case reports or editorials, 2) abstracts or unpublished studies, 3) animal research, 4) laboratory studies, 5) non-English language articles, 6) articles that measured CRP levels after treatment or discharge and 7) studies not providing all necessary data reported in the inclusion criteria. Review articles were consulted for discussion purposes only. No studies were excluded *a priori* because of weakness of design or data quality.

In case of incomplete data, we contacted the corresponding authors to acquire the unpublished results. Alternatively, these data were extracted from summary data or the Kaplan–Meier curve according to Tierney *et al.* [18]. If the necessary data were not provided or could not be acquired according to this method, these studies were finally excluded.

Data collected from these studies included first author, year of publication, country of origin, study design, number of institutions involved, recruitment period, sample size, sex, follow-up time, type of COPD (stable or with acute exacerbations), CRP combination with other variables, CRP study-specific cut-off values, outcome (late mortality and early mortality) and mortality risk estimates (hazard ratio (HR) or relative risk) of CRP for survival with their 95% confidence intervals. Due to the different and nonstandardised outcomes reported in each study, we empirically *a priori* defined late and early mortality as all causes of deaths occurring after at least and within 24 months, respectively.

As a rule, we acquired the mortality risk estimates and the corresponding 95% confidence intervals from results and tables. If a study reported more than one mortality risk estimate, we used the one adjusted for the larger number of available potential confounding factors. When a study reported the adjusted mortality risk estimates and the corresponding p-values, but not the corresponding adjusted 95% confidence intervals, we calculated the 95% confidence intervals for a ratio [19]. For studies that reported mortality risk estimates according to a continuous measure of CRP level, we calculated mortality risk estimates and 95% confidence intervals for an *a priori* defined cut-off of 10 mg·L^{-1} [20]. Different cut-off values (*i.e.* 5 and 15 mg·L^{-1}) were used for sensitivity analyses.

The systematic review and meta-analysis was performed and reported according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [21].

Statistical analysis

We pooled mortality risk estimates for the comparison between the study-specific highest category of CRP level *versus* the lowest category using the DerSimonian and Laird random-effects model. We used the Duval and Tweedie "trim and fill" method [22] to calculate the effect of potential data censoring or publication bias on the outcome of the meta-analysis. Heterogeneity among studies was assessed using the Chi-squared test and the I^2 statistic. Usually, I^2<25% is indicative of low heterogeneity, I^2=25–75% is indicative of moderate heterogeneity and I^2>75% is indicative of high heterogeneity. To identify sources of heterogeneity, subgroup analyses were performed according to geographic area (Asia, Europe, America) and CRP study-specific cut-off values (⩽3 *versus* >3 mg·L^{-1} and ⩽5 *versus* >5 mg·L^{-1}). Presence of publication bias was assessed by examination of funnel plot and by applying the tests proposed by Egger and Begg.

All the statistical analyses were performed using STATA version 11 (StataCorp, College Station, TX, USA).

Results

Study selection and characteristics

Figure 1 summarises the selection process adopted for the systematic review. Overall, 275 studies were identified. By excluding 26 duplicate publications and 147 studies not focusing on the main topics, 102 articles were fully examined. We found 38 studies focusing on CRP and COPD prognosis. 12 studies were excluded because of the following reasons: duplicated data [23, 24], no data on mortality [25–28], insufficient data to calculate 95% confidence intervals [29–31] and no data on CRP levels used for statistical analysis [32–34]. Finally, 26 articles on COPD mortality were eligible for the meta-analysis [35–60].

Study characteristics of all 26 articles are reported in table 1. Overall, 17 890 patients were collected from five retrospective studies [35, 50, 51, 54, 57] and 21 prospective studies [36–49, 52, 53, 55, 56, 58–60]. Two

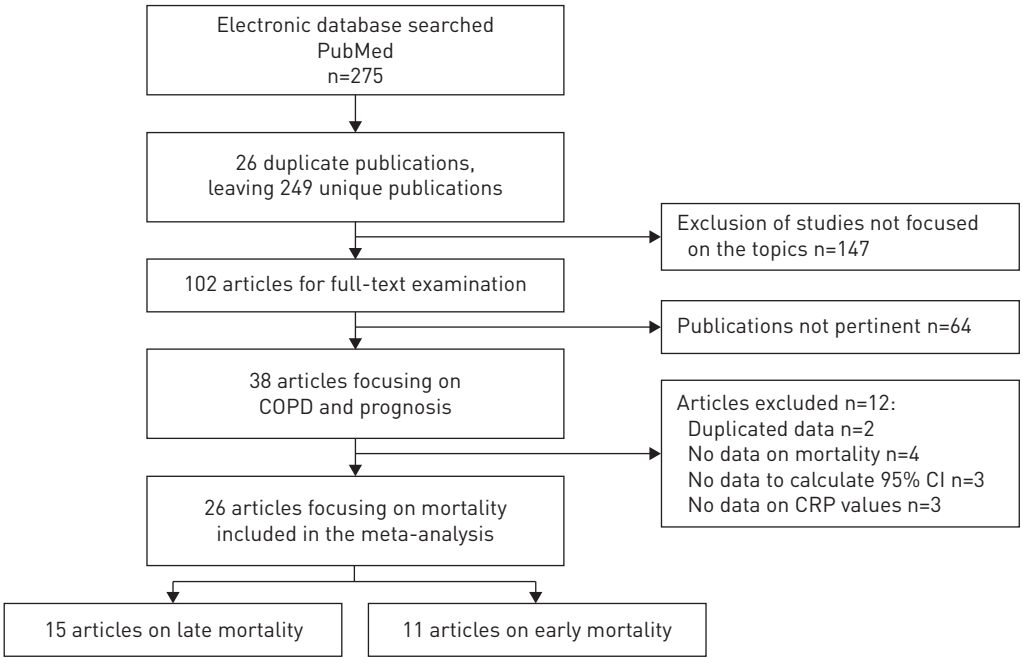

FIGURE 1 Flowchart of literature search and study selection. COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein.

TABLE 1 Characteristics of studies included in the meta-analysis of association between baseline C-reactive protein (CRP) level and mortality in chronic obstructive pulmonary disease (COPD) patients

First author [ref.]	Year	Study design; recruitment period; location	Patients n	Type of patients#	Main aim	Outcome	CRP¶	Prognostic value+	Cut-off mg·L^{-1}
Kuller [35]	1996	Retrospective, multicentric; 1973–1976; UK/USA	737	Smokers; stable	To investigate the relationship between CRP, α_1-acid glycoprotein and albumin and subsequent risk of myocardial infarction and coronary heart disease death in a nested case–control study among the Multiple Risk Factor Intervention Trial participants	Late mortality	Alone	Multivariate; 2.8 (1.4–5.4); age, tobacco dose, blood pressure, triglycerides, cholesterol levels	Not reported (fourth quartile)
Man [36]	2006	Prospective, multicentric; 5 years; USA/Canada	4803	COPD; stable	To determine whether serum CRP is associated with increased risk of all-cause and disease-specific causes of mortality, increased risk of fatal and nonfatal cardiovascular events, and an accelerated decline in lung function in COPD patients	Late mortality	Alone	Multivariate; 1.79 (1.25–2.56); age, sex, race, smoking status, pack-years, BMI, FEV_1	7.06
Dahl [37]	2007	Prospective, multicentric (epidemiological study); 1991–1994; Denmark	1302	COPD; stable	To determine whether increased serum CRP in individuals with airway obstruction predicts future hospitalisation and death from COPD	Late mortality	Alone	Multivariate; 1.4 (1.1–1.8); age, sex, tobacco consumption, FEV_1, cardiovascular disease	3
de Torres [38]	2008	Prospective, multicentric; 2000–2004; Spain/USA	218	COPD; stable	To determine if CRP levels are associated with survival in patients with moderate to very severe COPD in comparison with other well-known prognostic parameters	Late mortality	Alone	Multivariate; 1.00 (0.82–1.22); age, sex, pack-years, cardiovascular disease, corticosteroids	Not reported
Mehrotra [39]	2010	Prospective, community-based observational cohort (Pittsburgh, PA and Memphis, TN); 1997–1998; USA	268	COPD; stable	To identify significant covariates in addition to spirometry that predict mortality in elderly subjects with obstructive airway disease	Late mortality	Alone	Multivariate; 1.12 (0.90–1.30); age, sex, race, smoking status, cardiovascular disease	Not reported
Liu [40]	2011	Prospective, single-institution; 2005–2006; China	114	COPD; stable	To investigate the predictive value of combined serum CRP and BODE index score for mortality in COPD patients	Late mortality	Alone	Multivariate; 5.15 (1.65–16.60); BODE index	3

Continued

TABLE 1 Continued

First author [ref.]	Year	Study design; recruitment period; location	Patients n	Type of patients#	Main aim	Outcome	CRP¶	Prognostic value+	Cut-off mg·L^{-1}
Zhang [41]	2011	Prospective, single-institution; 2001–2003; the Netherlands	405	COPD; stable	To quantify the effect of cardiovascular determinants on mortality in patients with a diagnosis of COPD	Late mortality	Alone	Multivariate; 1.78 (1.15–2.82); age, FEV1, angina pectoris	3
Høiseth [42]	2012	Prospective, single-institution; 2005–2006; Norway	99	COPD; acute	To test the hypothesis that N-terminal pro-brain natriuretic peptide independently predicts long-term mortality following acute exacerbations of COPD	Late mortality	Alone	Multivariate; 2.4 (1.7–3.2); age, sex, comorbidity, BMI, S_{aO_2}, troponin level	50
Deng [43]	2014	Prospective, single-institution; 2009–2012; China	116	COPD; stable	To evaluate whether circulating CRP levels are a biomarker of systemic inflammation and a significant predictor of future COPD outcome	Late mortality	Alone	Univariate; 2.71 (1.05–6.99)	3
Moberg [44]	2014	Prospective, single-institution; 2005–2011; Denmark	423	COPD; stable	To investigate if leukocytes, CRP and vitamin D are independent predictors of mortality and hospitalisation after adjusting for disease severity with an integrative index (i-BODE index)	Late mortality	Alone	Multivariate; 1.50 (1.07–2.10); age, sex, i-BODE index	10
Cano [45]	2014	Prospective, multicentric; recruitment period 1 year; France	637	COPD; stable	To investigate predictors of long-term survival, including respiratory, nutritional and inflammatory dimensions, in a prospective cohort of home-treated patients with chronic respiratory failure	Late mortality	Alone	Multivariate; 1.51 (1.13–2.02); age, P_{aO_2}, P_{aCO_2}, BMI, FEV1/FVC, 6MWT distance, transthyretin	5
Ford [46]	2015	Prospective, multicentric; 1988–1994; USA	1144	COPD; stable	To examine the association between elevated inflammatory marker count (white blood cell count, CRP and fibrinogen) on all-cause mortality in a national sample of US adults with obstructive lung function	Late mortality	Alone/ combined (white blood cell count, fibrinogen)	Univariate for CRP alone; 1.26 (0.95–1.66)/multivariate for CRP combined; 2.08 (1.29–3.37); age, sex, race, education, smoking status, comorbidity, physical activity, alcohol use, BMI, FEV1/FVC, blood pressure, cholesterol level, urinary albumin/creatinine ratio, cancer history	3

Continued

TABLE 1 Continued

First author [ref.]	Year	Study design; recruitment period; location	Patients n	Type of patients#	Main aim	Outcome	CRP¶	Prognostic value+	Cut-off mg·L^{-1}
Kleber [47]	2015	Prospective, single-institution; 1997–2001; Germany	777	Smokers; stable	To characterise the diagnostic value of two independent risk factors for cardiovascular events (high-sensitivity CRP and lipoprotein-associated phospholipase A2), which provide information on inflammation and plaque stability in active smokers and never-smokers of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study	Late mortality	Combined (lipoprotein-associated phospholipase A2)	Multivariate; 1.94 (1.10–3.45); age, sex, comorbidity BMI, cholesterol level, triglycerides	3.6
Blumenthal [48]	2015	Prospective (randomised controlled trial), multicentric; 2009–2014; USA	326	COPD; stable	To examine the prognostic value of select biobehavioural factors in patients with COPD in a secondary analysis of participants from the INSPIRE-II trial	Late mortality	Alone	Multivariate; 2.25 (1.02–4.96); age, Charlson score, COPD duration, GOLD, corticosteroids, coping skills training	Not reported
Loprinzi [49]	2016	Retrospective, single-institution; 2003–2006; USA	385	COPD; stable	To examine the association between objectively measured physical activity and all-cause mortality among a national sample of COPD patients, with stratification by inflammatory status	Late mortality	Alone	Multivariate; 1.33 (1.02–1.72); age, sex, comorbidity, race, BMI, physical activity, poverty/income ratio, cotinine	Not reported
Saltürk [50]	2015	Retrospective, single-institution; 2013–2014; Turkey	647	COPD; acute	To assess whether eosinophilic COPD exacerbations have better outcomes than noneosinophilic COPD exacerbations in the intensive care unit	Early mortality	Alone	Multivariate; 1.78 (1.01–3.14); age, sex, BMI, NLR, eosinophilia, invasive mechanical ventilation, noninvasive mechanical ventilation, APACHE II score, septic shock, resistant pathogen	500
Murphy [51]	2010	Retrospective, single-institution; 2004–2007; UK	60	COPD; acute	To determine if routine clinical assessment could reliably predict in-hospital death in patients admitted with acute exacerbation of COPD	Early mortality	Alone	Multivariate; 1.22 (0.95–1.14); Charlson score, pH, urea	Not reported

Continued

TABLE 1 Continued

First author [ref.]	Year	Study design; recruitment period; location	Patients n	Type of patients#	Main aim	Outcome	CRP¶	Prognostic value+	Cut-off mg·L^{-1}
Zhao [52]	2014	Prospective, single-institution; 2010–2011; China	159	COPD; acute	To investigate the COPD assessment test, serum copeptin, procalcitonin and CRP levels as potential predictive factors for recurrence of acute exacerbation and all-cause mortality in 6 months in COPD inpatients	Early mortality	Alone	Univariate; 0.90 (0.82–1.01)	Not reported
Stolz [53]	2008	Prospective, single-institution; 2003–2005; Germany	167	COPD; acute	To investigate whether plasma pro-endothelin-1 and/or pro-adrenomedullin on admission to the hospital for acute exacerbation predict survival in patients with COPD	Early Survival	Alone	Multivariate; 1.02 (0.92–1.13); age, Charlson score, P_{aO_2}, P_{aCO_2}, pro-adrenomedullin, endothelin-1, BMI, FEV_1, leukocyte counts, procalcitonin, pulmonary arterial hypertension	Not reported
Duman [54]	2015	Retrospective, single-Institution; 2014 (1 year); Turkey	1704	COPD; acute	To evaluate mortality and outcomes of eosinophilic and noneosinophilic COPD exacerbations, and identify new biomarkers that predict survival	Early mortality	Alone	Multivariate; 1.32 (1.01–1.71); cardiovascular disease, corticosteroids, length of stay, readmission, NLR	19
Tofan [55]	2012	Prospective, single-institution; 1999–2010; Iran	60	COPD; acute	To assess the clinical utility of serum high-sensitivity CRP at admission in predicting outcome in hospitalised patients with acute exacerbation COPD	Early mortality	Alone	Univariate; 4.04 (1.32–12.33)	100
Zhang [56]	2014	Prospective, single-institution; 2007–2012; China	378	COPD; acute	To assess the association of high-sensitivity CRP with in-hospital outcomes in patients with COPD undergoing percutaneous coronary intervention	Early mortality	Alone	Multivariate; 1.78 (1.15–2.82); FEV_1, left ventricular ejection fraction, three-vessel disease, β-blocker use	3
Andreassen [57]	2014	Retrospective, multicentric; 2005; Norway/Sweden	731	COPD; acute	To find the proportion of patients with pneumonia among admissions due to acute exacerbations COPD and whether pneumonia has an impact on the length of stay, usage of noninvasive ventilation or in-hospital mortality	Early mortality	Alone	Multivariate; 0.71 (0.28–1.82); age, sex, GOLD	40

Continued

TABLE 1 Continued

First author [ref.]	Year	Study design; recruitment period; location	Patients n	Type of patients[#]	Main aim	Outcome	CRP[¶]	Prognostic value[+]	Cut-off mg·L^{-1}
Guertler [58]	2011	Prospective, multicentric; 2006–2008; Switzerland	877	COPD; acute	To investigate the long-term prognostic performance of the Pneumonia Severity Index score and the association of clinical parameters and different blood biomarkers with long-term mortality rate in a large cohort of patients with community-acquired pneumonia	Early mortality	Alone	Multivariate; 0.3 (0.2–0.5); age, sex, comorbidity, temperature, chills, pro-adrenomedullin	Not reported (fourth quartile)
Moghbeli [59]	2005	Prospective, multicentric; 1997–1999; USA	1862	Smokers; acute	To investigate the role of inflammation, as measured by high-sensitivity CRP levels, in cardiovascular risk in smokers who have acute coronary syndrome	Early mortality	Alone	Multivariate; 2.60 (1.42–4.79); age, comorbidity, previous treatment, troponin level	15
Haja Mydin [60]	2013	Prospective, single-institution; 2009–2010; 23 months; UK	65	COPD; acute	To identify factors associated with inpatient mortality from hypercapnic respiratory failure with respiratory acidosis due to COPD	Early mortality	Alone	Univariate; 3.43 (0.38–30.55)	3

HR: hazard ratio; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; BODE: BMI, airflow obstruction, dyspnoea and exercise capacity; S_{aO_2}: arterial oxygen saturation; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; FVC: forced vital capacity; 6MWT: 6-min walk test; GOLD: Global Initiative for Chronic Obstructive Lung Disease; NLR: neutrophil/lymphocyte ratio. [#]: COPD or smokers; stable or acute; [¶]: alone or combined; [+]: univariate or multivariate; HR (95% CI); adjusted covariables.

different subsets of COPD patients were identified: patients with stable COPD (n=11 081) and those with acute exacerbations (n=6809). Of these 26 articles, 15 studies with 11 180 patients focused on late mortality [35–49] and 11 studies with 6710 patients focused on early mortality [50–60]. Patients with acute COPD were enrolled in one [42] and all articles focusing on late and early mortality, respectively. The CRP cut-off values were based on study-specific categories reported in all studies. The CRP level was combined with another factor in two studies [46, 47]. Adjusted mortality risks estimates were available for 23 studies. The most common variables accounted for adjusting multivariable analyses in these studies were: age (n=18 articles) [35–39, 41, 42, 44–50, 53, 57–59], comorbidities (n=15 articles) [37–39, 41, 42, 46–49, 51, 53, 54, 56, 58, 59], COPD severity (n=10 articles) [36, 37, 41, 42, 45, 46, 48, 53, 56, 57], sex (n=9 articles) [36, 37, 42, 44, 46, 47, 50, 57, 58], body mass index (n=8 articles) [36, 42, 45–47, 49, 50, 53] and smoking (n=6 articles) [35–39, 46].

Meta-analysis on late mortality

The pooled analysis on 15 late mortality studies including 11 180 patients showed a significant positive association between elevated baseline CRP levels and increase in late mortality (HR 1.53, 95% CI 1.32–1.77), with a moderate level of heterogeneity (I^2=68.7%, p<0.001) (figure 2). The results were not driven by any single study as the exclusion of each study from the meta-analysis did not materially change the summary estimate.

Subgroup analysis was performed by stratifying for geographic areas and CRP cut-off values. No heterogeneity was observed across the strata considered (table 2). However, we found a higher risk for late mortality in four studies that used a study-specific CRP cut-off value of 3 mg·L^{-1} (HR 1.61, 95% CI 1.12–2.30) and in two studies focusing on Asiatic populations (HR 3.51, 95% CI 1.69–7.31). The presence of publication bias was evidenced by visual inspection of the funnel plot and by using Egger's (p=0.01) and Begg's (p=0.006) tests (online supplementary figure S1a). Adjustment for publication bias according to the "trim and fill" method resulted in HR 1.33 (95% CI 1.10–1.60), with six studies imputed (online supplementary figure S1b).

Meta-analysis on early mortality

According to the relationship between CRP level at baseline and early mortality, eight studies (based on 4943 patients) and three studies (based on 1767 patients) reported a relative risk >1 and <1, respectively. The pooled analysis revealed a nonsignificant association between CRP levels and early mortality (relative risk 1.15, 95% CI 0.94–1.42), with a high level of heterogeneity (I^2=86.7%, p<0.001) (figure 3).

No evidence of publication bias was reported by visual inspection of the funnel plot and by using Egger's (p=0.53) and Begg's (p=0.88) tests (online supplementary figure S2).

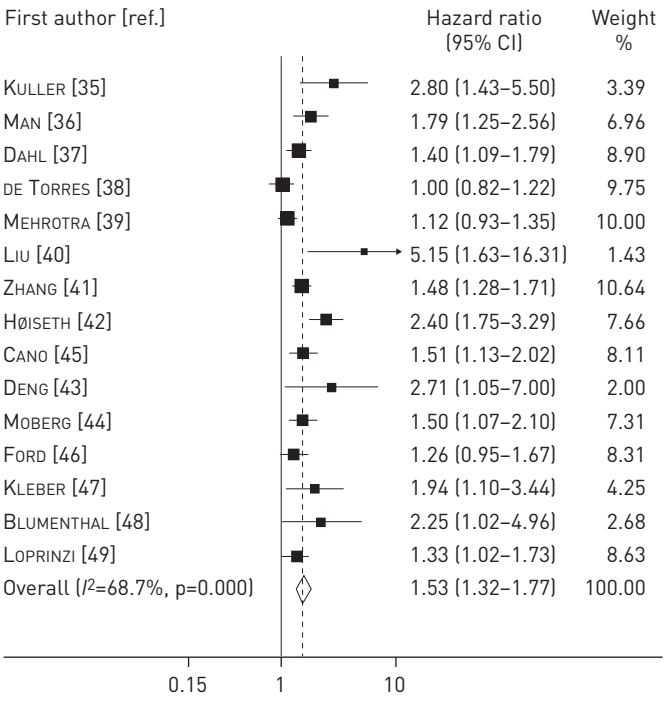

FIGURE 2 Forest plot for the association between C-reactive protein level and late mortality in chronic obstructive pulmonary disease patients. Studies are listed in chronological order (see table 1 for full study details).

TABLE 2 Pooled hazard ratio (HR) of mortality for highest *versus* lowest category of study-specific C-reactive protein (CRP) level, according to selected subgroups

	Studies n	HR (95% CI)	I^2 %	$p_{heterogeneity}$-value
Overall	15	1.53 (1.32–1.77)	68.7	
Geographic area				
Europe	6	1.61 (1.38–1.87)	46.8	0.06
USA and Canada	5	1.34 (1.12–1.61)	46.2	
Europe and USA (multicentric)	2	1.59 (0.58–4.33)	87.8	
China	2	3.51 (1.69–7.31)	0	
Study-specific CRP cut-off 3 mg·L^{-1}#				
⩽3 mg·L^{-1}	4	1.61 (1.12–2.30)	58.9	0.85
>3 mg·L^{-1}	9	1.55 (1.29–1.85)	70.7	
Study-specific CRP cut-off 5 mg·L^{-1}#				
⩽5 mg·L^{-1}	6	1.55 (1.25–1.93)	40.5	0.93
>5 mg·L^{-1}	7	1.53 (1.23–1.91)	77.0	

#: two studies did not report the cut-off value [35, 39].

Discussion

The prognostic role of baseline CRP level has been well established in the setting of cardiovascular disease [61, 62] as well as in cancer patients [17, 63], but the effect of CRP on COPD mortality is still unclear, and the association between baseline CRP levels and survival remains controversial in COPD patients [64, 65]. In this clinical setting, it has been suggested that elevated levels of CRP are related to the occurrence of cardiovascular events, rather than mortality from COPD itself [66]. However, other authors reported that CRP increase is secondary to serum concentration of other pro-inflammatory cytokines (TNF-α, IL-6, IL-8 or fibrinogen) [39].

The pooled estimates of the present meta-analysis revealed a consistent and significant association between elevated baseline CRP levels and mortality in patients with COPD. The only prior meta-analysis on this subject included four papers and 460 patients, showing a nonsignificant relative risk of 1.72 (95% CI 0.75–3.95) [67]. Although these data may appear controversial, our study pooled the results of 15 studies and 11 180 patients, thereby reaching solid statistical significance.

Two different mechanisms have been proposed to explain the association between CRP and COPD. The first hypothesis is related to the effect of lung inflammation itself in COPD patients. It is well known that prolonged exposure to cigarettes leads to lung injury and inflammation [9]. Once this process starts, lung inflammation persists even after smoking cessation [68], thus resulting in an exponential systemic reaction, related to the severity of COPD [69]. However, the parallel activation of systemic inflammation maintains

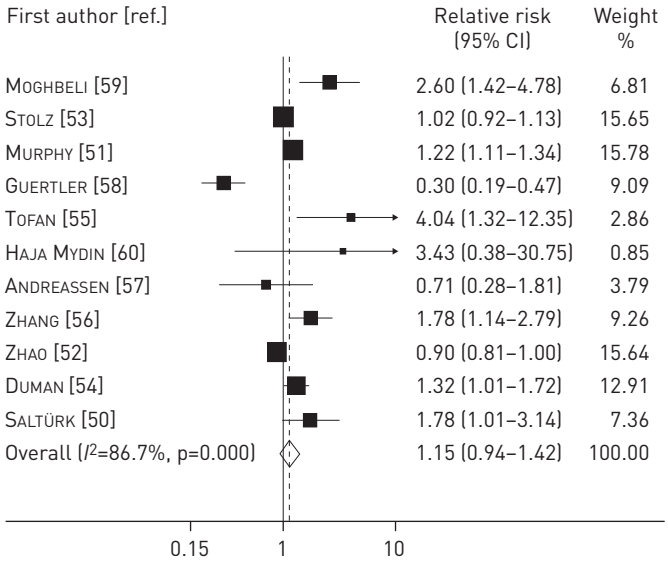

FIGURE 3 Forest plot for the association between C-reactive protein level and early mortality in chronic obstructive pulmonary disease patients. Studies are listed in chronological order (see table 1 for full study details).

and increases the local airway inflammation [68, 69], leading to COPD progression. The second hypothesis is linked to systemic inflammatory factors (*e.g.* CRP, fibrinogen, IL-6, leukocytes and platelets) that are major mediators for atherosclerosis and cardiovascular diseases. In this setting, Suwa *et al.* [70] studied the effect of air pollution and reported that the concentration of alveolar macrophages containing particulate matter was directly proportional to the extent of atherosclerosis. Similarly, the Tucson Epidemiologic Study of Airways Obstructive Disease reported that only 8% of patients with COPD died because of lung disease, whereas the majority of patients died either from cardiovascular diseases or cancer [71]. Furthermore, although respiratory failure represents a significant cause of mortality in severe COPD, cardiovascular events and lung cancer still account for a large proportion of deaths even in this group of patients [72]. The association with heart disease is further supported by other studies reporting increased levels of N-terminal pro-brain natriuretic peptide and troponin-T in such patients [73]. Thus, it is not surprising that CRP (related to immune status imbalance) could be used as a prognostic marker in COPD, as inflammation itself may lead both to lung damage persistence and cardiovascular events in these patients. However, we are aware that other possible mechanisms may be related to CRP increase in COPD patients (*e.g.* associated comorbidities, inactivity, *etc.*). Further data are needed to better investigate these associations.

An interesting issue that has not been properly explored in the literature is the optimal CRP cut-off value to predict the outcome in COPD patients. Although the discriminant values of other biomarkers have been investigated [74], no studies are available in the setting of CRP levels. Our analysis indicated different cut-off points among each study, ranging from 3 to 50 mg·L^{-1} and from 3 to 500 mg·L^{-1} in those focusing on late and early mortality, respectively. Considering late mortality, we performed a subgroup analysis according to different CRP cut-off points (3 and 5 mg·L^{-1}) in order to obtain an optimal stratification. We demonstrated a better discrimination for those studies adopting a cut-off point $\leqslant$3 mg·L^{-1}. These data are similar to the those reported in a previous meta-analysis on early-stage lung cancer [17], confirming an interesting dual role of CRP (a mirror of the underlying systemic inflammation) in predicting the prognosis of two different diseases (COPD and lung cancer) sharing the same risk factors (smoking, occupational exposures and chronic inflammation). However, the data on this issue are limited and we advocate the need for further studies to better investigate this association.

Considering the immune hyperactivity that characterises COPD, other prognostic biomarkers have already been evaluated in the literature. Reportedly, fibrinogen has been chosen by the Food and Drug Administration as the "gold standard" to assess systemic inflammation in COPD. In particular, fibrinogen levels >350 mg·dL^{-1} may help clinicians to identify COPD individuals at an increased risk of exacerbations and death [75]. Similarly, adrenomedullin [76] and copeptin [27, 52, 77] (both biomarkers reflecting different pathobiological pathways) have been recently reported as COPD prognostic biomarkers. In this setting, the use of drugs to modulate systemic inflammation (and also biomarkers) is an interesting issue that should be better assessed. Pharmacotherapies with bronchodilators such as β_2-agonists, anticholinergics and theophylline have been evaluated, although the effect of such local drugs on CRP level reduction is controversial [78]. However, the use of statins in such patients seems promising. In addition to their lipid-lowering effect, statins have anti-inflammatory and immunomodulating properties, reducing the levels of inflammatory markers such as CRP [79]. This effect was further confirmed in a randomised controlled trial performed by Lee *et al.* [80] reporting that pravastatin treatment significantly decreased CRP and IL-6 levels compared with placebo, and that the improvement of exercise tolerance was greater in those with a greater decrease of CRP levels and higher baseline CRP levels. Similarly, other authors suggest that patients with COPD treated with statins have an advantage in terms of morbidity and mortality, by reducing the rate of mortality from pneumonia or infective exacerbations, by slowing the decline in FEV_1, and by improving exercise tolerance [81]. It is noteworthy that the Rotterdam Study recently reported long-term statin use was associated with a 78% reduction in mortality if the CRP level was >3 mg·L^{-1} *versus* a nonsignificant 21% reduction if the CRP level was $\leqslant$3 mg·L^{-1} [25]. This interaction is of particular interest if one considers that the baseline CRP level (*e.g.* using a cut-off of 3 mg·L^{-1}) could be used to stratify COPD patients in low- and high-risk subsets. Such stratification might be useful to select which patients would benefit from immunomodulating therapies. In this setting, the use of widely available drugs such as aspirin seems beneficial, as reported in a recent meta-analysis showing a reduction of all-cause mortality in patients with COPD receiving anti-platelet treatment (relative risk 0.81, 95% CI 0.75–0.88) [82]. Probably, the preventive effect of aspirin may be linked to the reduction of both systemic inflammation and atherosclerosis in such patients. Further well-designed prospective studies are needed to better clarify the role of these combined therapies.

Another matter of debate is the prediction of early outcome in COPD patients, especially in those with acute exacerbations. This issue is of interest to physicians in daily clinical practice. Studies have shown that the early outcome of COPD is related mainly to exacerbations due to infection, either viral or bacterial, or both; these acute events are associated with high economic costs and accelerated lung function decline

[83]. It is widely established that CRP is a useful and sensitive indicator of infections and acute exacerbations in patients with COPD [84]. Some authors have reported that high CRP levels are associated with the need for intensive care unit transfer, intubation or mechanical ventilation, congestive heart failure onset, and higher in-hospital and after-discharge mortality [85]. Based on our pooled analysis on early mortality, we evidenced a weak association only between CRP and short-term outcome in COPD. However, the results on this issue may be influenced by the high heterogeneity reported in the 11 analysed studies. We advocate for further studies to better clarify these associations.

Study limitations and strengths

This meta-analysis has some limitations. First, although the majority of studies were prospective, no study was randomised. Thus, biases in treatment selection and covariate distribution cannot be excluded, resulting in difficult estimation of the real prognostic role of CRP. Furthermore, given the lack of data on the causes of mortality, the real cause of death was not properly explored in this meta-analysis, leaving the possibility that CRP level could actually be associated with increased deaths due to comorbidities. Second, several articles reported different CRP cut-off values, thus making study comparison difficult. Third, these studies were heterogeneous in terms of geographic area, age, sex and type of COPD. Fourth, there was publication bias, but the "trim and fill" method confirmed the main result. Finally, although the main results focused on late mortality, the pooled analysis on early mortality revealed a high level of heterogeneity, probably because different events (all-cause mortality within 24 months, in-hospital complications and hospitalisation) were accounted for in those studies focusing on this outcome.

The main strength of our study is the combination of all published data up to now using a meta-analytic approach. Furthermore, the systematic review and meta-analysis was strictly performed according to the MOOSE guidelines.

Conclusions

Systemic inflammation plays an important role in COPD pathogenesis, disease progression and mortality. Although CRP is associated with several conditions related to the natural history of COPD, its level may also be used to assess the outcome in COPD patients. Based on our analysis, CRP levels could be used, in combination with other biochemical markers, to target preventive and therapeutic strategies in this disease. Further prospective studies should be performed to confirm the clinical value of CRP.

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