



# Clinical significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbations of COPD: present and future

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A review of the relationship between neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios and several adverse outcomes in AECOPD. NLR emerges as a useful predictor of mortality in these patients; the prognostic value of PLR is less clear. <https://bit.ly/3Jo6XGs>

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## Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a leading cause of hospitalisation and death in COPD patients. In addition to the identification of better strategies to prevent AECOPD, there is an intense focus on discovering novel markers of disease severity that enhance risk stratification on hospital admission for the targeted institution of aggressive *versus* supportive treatments. In the quest for such biomarkers, an increasing body of evidence suggests that specific indexes derived from routine complete blood counts, *i.e.* the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), can significantly predict adverse outcomes in AECOPD. This narrative review discusses the current evidence regarding the association between the NLR and the PLR on admission and several clinical end-points (need for invasive ventilation, noninvasive mechanical ventilation failure, admission to an intensive care unit, pulmonary hypertension, length of hospitalisation, and mortality) in AECOPD. Future research directions and potential clinical applications of these haematological indexes in this patient group are also discussed.

## Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD), a clinical state that is characterised by the rapid worsening in airway function and respiratory symptoms, represents the leading cause of hospitalisation and death in COPD patients and a significant financial burden to healthcare systems [1, 2]. Between 22–40% and 9–16% of patients with COPD suffer at least one or more than one episode of AECOPD annually, respectively [3]. Although a wide range of infectious and noninfectious factors trigger AECOPD, pharmacological management is standard and includes  $\beta_2$ -agonists, glucocorticoids and antibiotics [1, 4]. The lack of objective measures of AECOPD has prompted the search for novel, easily measurable prognostic biomarkers to develop more effective, patient-centred, management strategies [5–7]. Epidemiological studies have reported that circulating biomarkers of inflammation, *e.g.* C-reactive protein (CRP), fibrinogen, cytokines and white blood cell differentiation, do not significantly enhance risk prediction over clinical assessment, including history of previous AECOPD [8, 9]. Other studies, however, have shown that the combination of high CRP concentrations, neutrophils and laboured breathing is effective in discriminating between AECOPD and stable COPD [10].



Haematological indexes of inflammation, *e.g.* the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), have been investigated in several disease states, *e.g.* solid tumours, systemic lupus erythematosus, coronary artery disease, retinal artery occlusion, chronic kidney disease and stable COPD [11–24].

This narrative review critically appraises recent developments in the capacity of the NLR and the PLR on admission to predict several clinical end-points specifically in AECOPD and discusses future research directions and potential clinical applications of these haematological indexes in this group.

## Methods

We searched PubMed from inception to May 2022 for articles reporting retrospective or prospective studies investigating the associations between the NLR and/or the PLR assessed within 24–48 h of hospital admission and pre-defined clinical end-points (all-cause mortality, admission to the intensive care unit (ICU), length of hospital stay, noninvasive mechanical ventilation failure, need for invasive ventilation, pulmonary hypertension and composite outcomes) in adult patients hospitalised with a clinical diagnosis of AECOPD. The following data were extracted from each study: study design, sample size, specific in-hospital setting, outcome(s) investigated and relevant odds ratio (OR), area under the curve, cut-off used for NLR and PLR, sensitivity, specificity, and any other between-group comparisons of the NLR and/or the PLR. Plots of estimates weighted by power were also generated to provide an overall quantitative assessment of the association between the NLR and the PLR and clinical outcomes. Analyses were performed using Stata 14 (StataCorp LLC, College Station, TX, USA).

## Results

18 studies investigated associations between the NLR and clinical outcomes (table 1) whereas 10 studies investigated associations between the PLR and clinical outcomes (table 2). The following paragraphs describe the main characteristics and results of individual studies.

### NLR

Studies describing the association between the NLR and clinical outcomes in AECOPD have been published between 2017 and 2022. Outcomes investigated included mortality (12 studies) [25–36], ICU transfer (one study) [30], need for invasive ventilation (one study) [30], noninvasive ventilation failure (one study) [37], pulmonary hypertension (one study) [38], length of hospitalisation (one study) [39] and composite end-points (three studies) [40–42]. One study investigated three outcomes separately [30]. Three studies were prospective [39–41]. 15 studies reported independent associations between the NLR and clinical outcomes using multivariate logistic regression [25, 27, 28, 30–35, 38–42], and in 12 receiver operating characteristic (ROC) analysis was conducted to evaluate the prediction performance of specific cut-off values (table 1) [26, 27, 30, 31, 33–38, 40, 42]. All reported cut-off values were calculated by ROC analysis in each study. All studies described the use of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, barring two [27, 33]. A plot of the associations (ORs) between the NLR and adverse outcomes is described in figure 1.

### Mortality

KUMAR *et al.* [25] reported that the NLR was not independently associated with mortality after adjusting for age, haemoglobin, neutrophil count, urea and PLR. YAO *et al.* [26] reported that the NLR was significantly higher in nonsurvivors than survivors, and a significant positive correlation was observed between the NLR and CRP concentrations. Notably, combining the NLR with other parameters did not significantly improve the predictive capacity, suggesting that the NLR *per se* may be a useful prognostic marker. RAHMIRAD *et al.* [27] reported that the NLR was independently associated with in-hospital mortality after adjusting for age, sex, anaemia and thrombocytopenia. AKSOY *et al.* [28] reported that in multivariate analysis the NLR was not significantly associated with mortality after adjusting for age, CRP, albumin, platelet count/mean platelet volume ratio, use of steroids, hospital stay >7 days and eosinophilia. Similarly, ERGUN *et al.* [29] failed to observe significant differences in NLR values between survivors and nonsurvivors. In this study, significant associations were reported between the NLR and white blood cell count ( $r=0.397$ ,  $p<0.001$ ) and CRP concentrations ( $r=0.190$ ,  $p=0.028$ ). TENG *et al.* [30] reported that, in multivariate logistic regression, the NLR was independently associated with mortality, together with renal failure, heart failure and upper gastrointestinal bleeding. LIU *et al.* [31] reported that the NLR was independently associated with mortality at 90 days after adjusting for smoking, blood pressure, haemoglobin, CRP and pH. Similarly, YILMAZ *et al.* [32] and ARDESTANI *et al.* [33] reported independent associations between the NLR and in-hospital mortality, and LUO *et al.* [34] reported independent associations between the NLR and 28-day mortality. ROC analysis showed that, of all the variables considered, the NLR had the highest area under the curve. Notably, combining NLR values with the PLR and CRP concentrations

**TABLE 1** Characteristics of studies investigating the association between neutrophil-to-lymphocyte ratio (NLR) on admission and adverse outcomes in acute exacerbations of chronic obstructive pulmonary disease

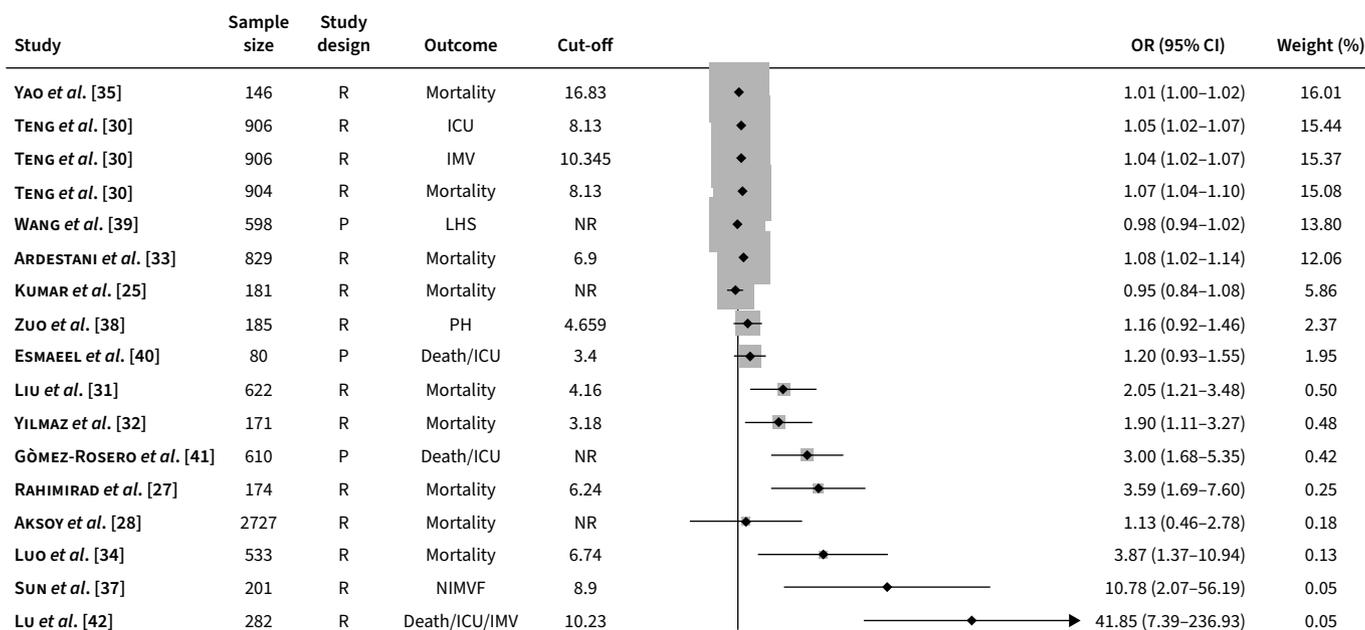
First author, year, country	Study design	Sample size	Setting	Outcome	OR (95% CI)	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	Additional findings
KUMAR, 2017, Australia [25]	R	181	ED	Mortality	0.95 <sup>#</sup> (0.84–1.08)	NR	NR	NR	NR	NLR in survivors <i>versus</i> nonsurvivors: 7±8 <i>versus</i> 13±10, p=0.004
YAO, 2017, China [26]	R	303	Ward	Mortality	NR	0.803 (NR)	6.24	0.81	0.69	NLR in survivors <i>versus</i> nonsurvivors: 7±8 <i>versus</i> 15±10, p<0.001
RAHIMIRAD, 2017, Iran [27]	R	174	Ward	Mortality	3.586 <sup>#</sup> (1.69–7.60)	0.717 (0.623–0.811)	4	0.87	0.4	NLR in survivors <i>versus</i> nonsurvivors: 8±8 <i>versus</i> 17±18, p<0.001
AKSOY, 2018, Turkey [28]	R	2727	Ward	Mortality	1.13 <sup>#</sup> (0.46–2.78)	NR	NR	NR	NR	NLR <sup>¶</sup> in survivors <i>versus</i> nonsurvivors: 7 (4–12) <i>versus</i> 10 (4–19), p=0.07
ERGUN, 2018, Turkey [29]	P	132	ICU	Mortality	NR	NR	NR	NR	NR	NLR in survivors <i>versus</i> nonsurvivors: 18±23 <i>versus</i> 24±32, p=0.65
TENG, 2018, China [30]	R	904	Ward	Mortality	1.067 <sup>#</sup> (1.039–1.095)	0.737 (0.661–0.814)	8.13	0.61	0.75	NLR significantly higher in nonsurvivors, p<0.001
LIU, 2019, China [31]	R	622	ED	Mortality	2.05 <sup>#</sup> (1.21–3.48)	0.742 (0.554–0.881)	4.19	0.71	0.74	NLR in survivors <i>versus</i> nonsurvivors: 3±7 <i>versus</i> 8±10, p<0.001
YILMAZ, 2019, Turkey [32]	R	171	ICU	Mortality	1.902 <sup>#</sup> (1.108–3.266)	NR	3.18	0.71	0.72	NLR in survivors <i>versus</i> nonsurvivors: 2.8±1.4 <i>versus</i> 3.5±1.9, p=0.037
ARDESTANI, 2020, Iran [33]	R	829	NR	Mortality	1.08 <sup>#</sup> (1.02–1.14)	0.7 (0.67–0.73)	6.9	0.61	0.73	NLR in survivors <i>versus</i> nonsurvivors: 6±5 <i>versus</i> 11±10, p<0.001
LUO, 2021, China [34]	R	533	Ward	Mortality	3.87 <sup>#</sup> (1.29–10.3)	0.801 (NR)	6.74	0.83	0.71	NLR in survivors <i>versus</i> nonsurvivors: 8±6 <i>versus</i> 15±13, p<0.001
YAO, 2021, China [35]	R	146	Ward	Mortality	1.01 <sup>#</sup> (0.999–1.022)	0.83 (0.761–0.899)	16.83	0.69	0.65	NLR <sup>¶</sup> in survivors <i>versus</i> nonsurvivors: 12 (6–25) <i>versus</i> 22 (11–40), p<0.001
KARAUDA, 2021, Poland [36]	R	275	Ward	Mortality	NR	0.96 (0.93–0.99)	13.2	1.00	0.93	NR
TENG, 2018, China [30]	R	906	Ward	ICU	1.046 <sup>#</sup> (1.023–1.068)	0.676 (0.607–0.744)	8.13	0.54	0.77	NLR significantly higher in patients admitted to ICU, p<0.001
TENG, 2018, China [30]	R	906	Ward	IMV	1.042 <sup>#</sup> (1.019–1.066)	0.732 (0.656–0.807)	10.345	0.54	0.85	NLR significantly higher in patients requiring IMV, p<0.001
SUN, 2021, China [37]	R	212	Ward	NIMVF	10.783 <sup>#</sup> (2.069–56.194)	0.858 (0.785–0.931)	8.9	0.69	0.88	NLR <sup>¶</sup> in NIMV success <i>versus</i> failure: 4 (3–6) <i>versus</i> 14 (7–17), p<0.001
Zuo, 2019, China [38]	R	185	NR	PH	1.161 <sup>#</sup> (0.924–1.458)	0.701 (0.629–0.766)	4.659	0.81	0.6	NLR <sup>¶</sup> in patients without <i>versus</i> with PH: 4 (3–6) <i>versus</i> 6 (5–12), p<0.001
WANG, 2022, China [39]	P	598	Ward	LHS	0.981 <sup>#</sup> (0.963–0.999)	NR	NR	NR	NR	NLR in patients with normal, mildly prolonged and significantly prolonged hospital stay: 4.6±6.0, 6.0±8.1 and 5.5±5.3, p=0.006
ESMAEL, 2017, Egypt [40]	P	80	Ward	Death/ICU	1.2 <sup>#</sup> (0.9–1.5)	0.642 (0.526–0.746)	3.4	0.89	0.49	NR
GÓMEZ-ROSETO, 2021, Colombia [41]	P	610	Ward	Death/ICU	3.0 <sup>#</sup> (1.7–5.4)	NR	NR	NR	NR	NLR <sup>¶</sup> in survivors/non-ICU admitted <i>versus</i> nonsurvivors/ICU admitted: 5 (3–10) <i>versus</i> 8 (5–14), p<0.001
Lu, 2021, China [42]	R	282	Ward	Death/ICU/IMV	41.85 <sup>#</sup> (9.57–306.74)	0.883 (0.771–0.894)	10.23	0.62	0.92	NLR <sup>¶</sup> in survivors/non-ICU admitted/not requiring IMV <i>versus</i> nonsurvivors/ICU admitted/requiring IMV: 5 (3–8) <i>versus</i> 11 (8–16), p<0.001

AUC: area under the curve; CI: confidence interval; ED: emergency department; ICU: intensive care unit; IMV: invasive mechanical ventilation; LHS: length of hospital stay; OR: odds ratio; NIMV: noninvasive mechanical ventilation; NIMVF: noninvasive mechanical ventilation failure; NR: not reported; P: prospective; PH: pulmonary hypertension; R: retrospective. <sup>#</sup>: from multivariate analysis. <sup>¶</sup>: median and interquartile range.

**TABLE 2** Characteristics of studies investigating the association between platelet-to-lymphocyte ratio (PLR) on admission and adverse outcomes in acute exacerbations of chronic obstructive pulmonary disease

First author, year, country	Study design	Sample size	Setting	Outcome	OR (95% CI)	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	Additional findings
KUMAR, 2017, Australia [25]	R	181	ED	Mortality	1.15 <sup>#</sup> (1.02–1.30)	0.695 (0.551–0.840)	235	63	74	PLR in survivors <i>versus</i> nonsurvivors: 208±164 <i>versus</i> 348±228, p=0.01
YAO, 2017, China [26]	R	303	Ward	Mortality	NR	0.639 (NR)	182.68	64.86	58.27	PLR in survivors <i>versus</i> nonsurvivors: 198±141 <i>versus</i> 273±184, p=0.004
RAHIMIRAD, 2017, Iran [27]	R	174	Ward	Mortality	NR	0.576 (0.465–0.686)	150	59	46	PLR in survivors <i>versus</i> nonsurvivors: 207±192 <i>versus</i> 241±224, p=0.15
AKSOY, 2018, Turkey [28]	R	2,727	Ward	Mortality	NR	NR	NR	NR	NR	PLR <sup>¶</sup> in survivors <i>versus</i> nonsurvivors: 225 (147–354) <i>versus</i> 224 (123–391), p=0.75
ERGUN, 2018, Turkey [29]	P	132	ICU	Mortality	NR	NR	NR	NR	NR	PLR in survivors <i>versus</i> nonsurvivors: 308±260 <i>versus</i> 405±414, p=0.26
YILMAZ, 2019, Turkey [32]	R	171	ICU	Mortality	1.004 <sup>#</sup> (0.994–1.014)	NR	NR	NR	NR	PLR in survivors <i>versus</i> nonsurvivors: 98±57 <i>versus</i> 128±82, p=0.021
ARDESTANI, 2020, Iran [33]	R	829	NR	Mortality	1.00 <sup>#</sup> (0.99–1.01)	0.56 (0.52–0.59)	213	58	82	PLR in survivors <i>versus</i> nonsurvivors: 153±105 <i>versus</i> 196±154, p=0.11
LUO, 2021, China [34]	R	533	Ward	Mortality	3.45 <sup>#</sup> (1.43–12.62)	0.750 (NR)	203.60	76.86	65.27	PLR in survivors <i>versus</i> nonsurvivors: 212±90 <i>versus</i> 284±132, p<0.001
YAO, 2021, China [35]	R	146	Ward	Mortality	NR	NR	NR	NR	NR	PLR <sup>¶</sup> in survivors <i>versus</i> nonsurvivors: 257 (160–417) <i>versus</i> 270 (162–408), p=0.47
ZUO, 2019, China [38]	R	185	NR	PH	1.003 <sup>#</sup> (0.993–1.013)	0.669 (0.596–0.736)	150	77.2	53.6	PLR <sup>¶</sup> in patients without <i>versus</i> with PH: 157 (123–227) <i>versus</i> 221 (161–291), p<0.001

AUC: area under the curve; CI: confidence interval; ED: emergency department; ICU: intensive care unit; OR: odds ratio; NR: not reported; P: prospective; PH: pulmonary hypertension; R: retrospective. <sup>#</sup>: from multivariate analysis. <sup>¶</sup>: median and interquartile range.



**FIGURE 1** Odds ratios (ORs) obtained from forest plots, squares (proportional to weights) and associated confidence intervals (CIs) describing the association between the neutrophil-to-lymphocyte ratio and adverse outcomes. The vertical line represents the value of no effect. All ORs were from multivariate analysis. ICU: intensive care unit; IMV: invasive mechanical ventilation; LHS: length of hospital stay; NIMVF: noninvasive mechanical ventilation failure; NR: not reported; P: prospective; PH: pulmonary hypertension; R: retrospective.

further increased the predictive performance [31]. YAO *et al.* [35] reported that, in AECOPD patients with heart failure, 28-day mortality was independently associated with brain natriuretic peptide (NT-proBNP) and the NLR. In line with the study by LUO *et al.* [34], combining NLR values with CRP/albumin and NT-proBNP increased the predictive performance. Finally, KARAUDA *et al.* [36] reported a relatively high area under the curve (AUC), 0.96, for the NLR in regard to in-hospital mortality.

*Other adverse outcomes*

TENG *et al.* [30] reported that the NLR was significantly associated with the risk of transfer to ICU and the need for invasive mechanical ventilation after adjusting for diabetes mellitus, osteoarthritis, reflux esophagitis, renal failure, hyperlipidaemia and upper gastrointestinal bleeding. SUN *et al.* [37] reported that the capacity of the NLR to predict noninvasive mechanical ventilation failure was superior to that of leukocyte count, CRP and procalcitonin. The NLR was also independently associated with noninvasive mechanical ventilation failure in multivariate logistic regression after adjusting for leukocyte count, procalcitonin, and CRP. ZUO *et al.* [38] observed that AECOPD patients with pulmonary hypertension had significantly higher median NLR values than patients without it. However, in multivariate analysis, the association between the NLR and pulmonary hypertension was no longer significant. WANG *et al.* [39] reported significant differences in the NLR between AECOPD patients with normal (<7 days), mildly prolonged (between 7 and 10 days) and significantly prolonged (≥11 days) hospitalisation. In particular, the NLR and erythrocyte sedimentation rate (ESR) were significantly higher in those with mild and prolonged hospitalisation compared to the reference group. However, no significant differences in NLR and ESR were observed between the mild and the significantly prolonged hospitalisation group. In logistic regression, NLR, ESR, hypertension and chronic cor pulmonale remained independently associated with length of stay. ESMAEEL *et al.* [40] reported that thrombocytopenia, renal function and GOLD group, but not the NLR, were independently associated with a composite outcome of ICU transfer and/or death in multivariate logistic regression. GÓMEZ-ROSETO *et al.* [41] reported that the NLR was independently associated with a composite outcome of ICU transfer and death in multivariate analysis. In this study, NLR values >5 decreased the probability of being discharged alive by 27% and increased the length of stay by 37% compared to values ≤5. Similarly, LU *et al.* [42] reported that NLR values were significantly associated with a composite outcome of death, ICU transfer or need for invasive mechanical ventilation after adjusting for age, sex, body mass index, smoking status, comorbidities, GOLD grade and therapy.

**PLR**

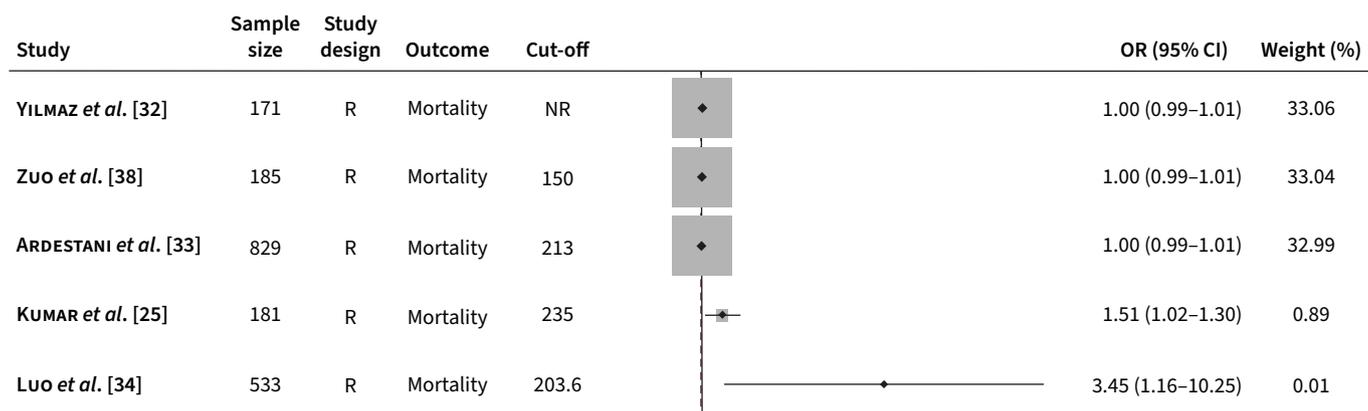
10 studies, published between 2017 and 2021, have investigated the association between the PLR and clinical outcomes in AECOPD. Outcomes investigated were limited to mortality (nine studies) [25–29, 32–35] and pulmonary hypertension (one study) [38]. All studies were retrospective [25–29, 32–35, 38]. Four studies reported independent associations between the NLR and clinical outcomes in multivariate logistic regression [25, 33, 34, 38], and in six ROC analysis was conducted to evaluate the prediction performance of specific cut-off values (table 2) [25–27, 33, 34, 38]. All reported cut-off values were calculated by ROC analysis in each study. All studies described the use of the GOLD guidelines, barring two [27, 33]. A plot of the associations (ORs) between the PLR and adverse outcomes is described in figure 2.

**Mortality and pulmonary hypertension**

KUMAR *et al.* [25] reported, in multivariate logistic regression, that the PLR was independently associated with mortality after adjusting for age, haemoglobin, neutrophil count, urea concentration and NLR. In the study by YAO *et al.* [26], in-hospital nonsurvivors had higher PLR values than survivors. ROC analysis revealed that, using a cut-off value of 182.68, PLR predicted in-hospital mortality with an AUC of 0.639. Combining the PLR with other markers, particularly the NLR, increased the AUC to 0.800. RAHIMIRAD *et al.* [27] reported nonsignificant differences in PLR values between nonsurvivors and survivors. The poor predictive performance in this study was further confirmed by ROC curve analysis (AUC=0.576). These results are similar to those by AKSOY *et al.* [28], ERGUN *et al.* [29] and YAO *et al.* [35] reporting nonsignificant differences in PLR between AECOPD survivors and nonsurvivors. ARDESTANI *et al.* [33] also reported a nonsignificant difference in PLR values between AECOPD patients who died during hospitalisation and those who were alive on discharge. Accordingly, the PLR was not significantly associated with mortality in multivariate regression. YILMAZ *et al.* [32] reported significant differences in the PLR between survivors and nonsurvivors; however, no independent associations were observed in multivariate analysis. LUO *et al.* [34] reported an independent association between PLR values and mortality in multivariate logistic regression. Finally, ZUO *et al.* [38] reported that the PLR values in AECOPD patients with pulmonary hypertension were significantly higher than those without. However, there was no independent association between the PLR and pulmonary hypertension in multivariate analysis.

**Discussion**

Despite the relatively high prevalence of AECOPD in patients with COPD and the significant burden of disease exacerbations to patients, relatives, caregivers and healthcare systems, the identification of the exact mechanisms triggering this state as well as objective markers of severity and response to treatment remain an unaddressed issue. There is very good evidence that a heterogeneous group of factors ultimately favours the development of acute bursts of inflammation in the airways. This phenomenon appears to be part of the natural progression of COPD in most patients, which is typically characterised by a state of chronic local and systemic inflammation [1, 43]. It is widely reported that patients with COPD show increased concentrations of serum inflammatory biomarkers. In particular, about 70% of subjects with COPD have been reported to have elevated serum concentrations of at least one inflammatory parameter [44]. Several lines of evidence suggest that clinical and functional parameters, disease progression and development of



**FIGURE 2** Odds ratios (ORs) obtained from forest plots, squares (proportional to weights) and associated confidence intervals (CIs) describing the association between the platelet-to-lymphocyte ratio and adverse outcomes. The vertical line represents the value of no effect. All ORs were from multivariate analysis. R: retrospective; NR: not reported.

comorbidities in COPD are strictly related to the persistent elevation of such inflammatory markers [45–47]. Serum CRP, interleukin-6 and tumour necrosis factor- $\alpha$  have been extensively studied as inflammation biomarkers both in COPD and in AECOPD [46]. However, apart from CRP, several limitations related to costs and turnaround time prevent the routine use of these biomarkers in clinical practice. In contrast, inflammatory indexes that are easily derived from routine haematological parameters, particularly the NLR and the PLR, are increasingly studied in inflammatory states, including COPD, in view of their simple and rapid determination and easy interpretation. The potential role of both the NLR and the PLR in clinical practice is supported by their capacity to predict adverse outcomes in a wide range of disease states [11–22]. In the context of COPD, it is well known that a state of chronic inflammation results not only in alterations of neutrophils and platelets but also in the increased production and release of specific inflammatory mediators by these cell types, which ultimately lead to irreversible airway damage. For example, neutrophil activation favours the release of several enzymes such as neutrophil elastase, cathepsin G, proteinase-3, matrix metalloproteinase (MMP)-8, MMP-9 and myeloperoxidase (MPO), which actively contribute to the pathophysiological mechanisms of emphysema and COPD [48]. It has been reported that MPO mediates the bactericidal effects of neutrophils [49]. However, at the same time, there is evidence that MPO can favour the initiation of oxidative tissue damage and alterations in cellular homeostasis and increase the response of lung epithelial cells to pro-inflammatory stimuli [50, 51]. Neutrophil elastase can stimulate the production and secretion of mucin, leading to excessive mucus secretion and airway obstruction [52]. Furthermore, MMP can degrade extracellular matrices, leading to structural damage and airway remodelling in COPD patients [52]. Platelets also play a key role in the modulation of inflammation and immune responses. Platelet p-selectin expression and the subsequent formation of platelet-leukocyte aggregates upregulate leukocyte pro-inflammatory functions. In addition, platelet  $\alpha$ -granules contain several types of cytokines with predominant pro-inflammatory effects [53, 54]. For these reasons, it has been suggested that indices that reflect an increase in the number of circulating neutrophils and platelets in relation to lymphocytes may be particularly useful as biomarkers of disease severity and outcome in AECOPD.

Our narrative review has shown that the current evidence supporting the presence of significant associations with several pre-defined adverse clinical outcomes in patients with AECOPD is stronger for the NLR than the PLR. Furthermore, among the 18 studies evaluating the NLR, 15 used multivariate logistic regression to assess the presence of independent associations with adverse outcomes [25, 27, 28, 30–35, 37–42], with significant relationships reported in 10 (OR 1.042–41.85) [27, 30–34, 37, 39, 41, 42]. It is important to emphasise that, in two studies [37, 42], the particularly high OR (10.783 and 41.85, respectively) likely reflects the use of relatively high NLR cut-offs (8.9 and 10.23, respectively), and consequently a greater magnitude of risk, between 10 and 40 times. Although NLR cut-off values were reported for various adverse outcomes, the number of studies investigating outcomes other than mortality was limited [30, 37–42].

In contrast to the NLR, the association between the PLR and adverse outcomes in AECOPD patients using multivariate logistic regression analysis was investigated in only five studies [25, 32–34, 38], with two reporting the presence of independent associations with mortality [25, 34]. Therefore, more research is warranted to investigate the predictive capacity of the PLR in AECOPD.

Limitations of our narrative review include the lack of a systematic assessment of publication bias as well as inherent limitations of the studies identified, particularly their predominantly retrospective nature, the relatively short follow-up (<90 days) and the lack of serial assessments of the NLR and the PLR and their association with clinical progress. Furthermore, information regarding the use of corticosteroids, antibiotics and bronchodilators was inconsistent. Therefore, well-designed prospective clinical studies with longer-term follow-ups are warranted to validate the use of these biomarkers in routine clinical practice. Such studies should ideally include AECOPD patients with a wide range of age, comorbidities, frailty and ethnic background, and assess several clinical end-points. The issue of whether the prognostic capacity of the NLR and/or the PLR is superior to that provided by established inflammatory biomarkers, *e.g.* CRP, is particularly important in order to justify their introduction in clinical practice. In this context, some of the identified studies reported the presence of significant positive associations between the NLR and CRP concentrations, raising the possibility that the NLR provides redundant clinical information [26, 29, 37]. However, in other studies, the prognostic capacity of the NLR was either independent [31, 33] or superior to that of the CRP [31, 37]. Furthermore, in one study, the combination of NLR, PLR and CRP concentrations further increased the predictive ability compared to the NLR alone [31]. Therefore, appropriate statistical analyses are also warranted in the proposed prospective studies to identify the best biomarker, or combination of biomarkers with or without other clinical characteristics, for prognosis in AECOPD.

#### Questions for future research

- Do the NLR and the PLR on admission significantly predict short- and long-term outcomes in patients admitted for AECOPD in appropriately designed prospective studies?
- Do the temporal changes in the NLR and the PLR during hospitalisation correlate with changes in clinical status and response to treatment?
- Can the NLR and PLR guide the selection of specific therapies and/or care pathways in patients with AECOPD?
- Does the combination of the NLR and/or the PLR with other inflammatory biomarkers and patient characteristics further improve the prognostic capacity in AECOPD?

#### Conclusions

This narrative review has shown that the NLR, a simple and inexpensive inflammatory index that has been increasingly investigated in a wide range of disease states, including COPD, appears to be a promising predictor of mortality in AECOPD patients. Cut-off values for mortality and other adverse outcomes have been identified, providing the basis for the adequate design of larger prospective studies that investigate several clinical end-points. By contrast, the current evidence regarding the prognostic value of the PLR is less clear and requires further studies. Pending the results of well-designed prospective studies, the routine use of these inflammatory markers may potentially influence the management of AECOPD.

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