

Defining the role of neutrophil-to-lymphocyte ratio in COPD: a systematic literature review

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Abstract: COPD is characterized by a pulmonary and systemic inflammatory process. Several authors have reported the elevation of multiple inflammatory markers in patients with COPD; however, their use in routine clinical practice has limitations. The neutrophil-to-lymphocyte ratio (NLR) is a useful and cost-effective inflammatory marker derived from routine complete blood count. We performed a systematic literature review using the PRISMA statement. Twenty-two articles were included, recruiting 7,601 COPD patients and 784 healthy controls. Compared with controls, COPD patients had significantly higher NLR values. We found a significant correlation between the NLR and clinical/functional parameters (FEV₁, mMRC, and BODE index) in COPD patients. Elevation of the NLR is associated with the diagnosis of acute exacerbation of COPD (pooled data propose a cut-off value of 3.34 with a median sensitivity, specificity, and area under the curve of 80%, 86%, and 0.86, respectively). Additionally, increased NLR is also associated with the diagnosis of a bacterial infection in exacerbated patients, with a cut-off value of 7.30, although with a low sensitivity and specificity. The NLR is an independent predictor of in-hospital and late mortality after exacerbation. In conclusion, the NLR could be a useful marker in COPD patients; however, further studies are needed to better identify the clinical value of the NLR.

Keywords: acute exacerbations of COPD, bacterial infection, mortality in COPD, inflammatory biomarkers, eosinophilia, GOLD stage

Introduction

COPD is a major public health problem worldwide and is characterized by poorly reversible airflow limitation and/or alveolar abnormalities. It is usually associated by persistent respiratory symptoms, disease progression, and, in some patients, multiple acute exacerbations.¹ COPD accounted for 6% of all deaths globally in 2012 and is currently ranked as the fourth leading cause of death worldwide with a projection to increase in the coming decade.^{2,3} Chronic inflammation of the airways and the lung parenchyma is the classic paradigm for the pathogenesis of COPD and is associated with goblet cell proliferation, gland hyperplasia, fibrosis, collapse of small airways, and parenchymal destruction.⁴ However, there is increasing evidence that COPD also results in systemic inflammation and extra-pulmonary manifestations.⁵

Acute exacerbation of COPD (AECOPD) is related to more severe airway and systemic inflammation than in stable disease patients, and is associated with worse clinical symptoms, reduced lung function, increase hospitalization and intensive care unit admission rates, and more intensive treatments.^{6,7} The main causes of exacerbations in COPD are viral or bacterial infections, while 15%–20% are caused by other microorganisms or unspecified causes.⁸

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There are limited data regarding inflammatory biomarkers in stable and exacerbated patients in standard clinical practice. However, recent studies have shown that the neutrophil-to-lymphocyte ratio (NLR) is a reliable marker of systemic inflammation and a routinely performed test (complete blood counts), because of its rapidity and easy detection, availability, and cost-effectiveness.^{9,10} Based on the physiological response of circulating leukocytes to precipitating stress factors, with increased numbers of neutrophils and fewer lymphocytes, the ratio between these two subgroups has been evaluated in periods of inflammation in different diseases, such as lung cancer, colorectal cancer, end-stage renal disease, and acute coronary syndrome, among others.^{11–14}

The aim of the present systematic review was to investigate 1) the role of the NLR in the severity of COPD according to clinical and functional outcomes (airflow obstruction [FEV₁], dyspnea [mMRC], and exercise capacity [BODE index]); 2) the relation between NLR and other inflammatory biomarkers; and 3) the ability of the NLR to detect or predict the diagnosis of exacerbation, bacterial infection, and mortality.

Materials and methods

Design

This systematic review was performed in accordance with the PRISMA statement.¹⁵

Search strategy

The search was carried out using the databases PubMed/Medline, Google Scholar, Scielo, and Scopus, using a combination of the key words: “neutrophil-to-lymphocyte ratio”, “NLR”, “chronic obstructive pulmonary disease”, “COPD”, “lung disease”, “exacerbation”, “prognosis”, and “lung function”. The search included articles published up to January 2018 and was limited to English language studies. The automatic search was complemented by a manual search to identify relevant articles. The search results were exported to the reference manager EndNote (Thompson Reuters), with a total of 482 records identified after duplicates were removed.

Inclusion criteria and study eligibility

The articles were screened by abstracts and full text. Disagreements were resolved by a senior author. Articles that contained the following information were included: 1) diagnosis of COPD according to the GOLD or the American Thoracic Society or the European Respiratory Society, or clearly defined similar criteria; 2) analysis of the associations

between NLR and clinical features or outcomes of COPD patients; and 3) NLR cut-off value. The exclusion criteria were 1) review articles, editorial comments, letters, conference abstracts; 2) preclinical studies; or 3) full text unavailable and non-English article.

Data extraction

A standardized extraction form was used to collect data. The data extracted were: 1) authors, year of publication, study design, and sample size; 2) participant characteristics (age, gender); 3) NLR cut-off value and accuracy characteristics; 4) total NLR value in patient subgroups (healthy controls, stable COPD, exacerbated COPD); 5) total NLR value in different severity subgroups according to GOLD; 6) correlation coefficient between NLR and FEV₁; 7) correlation coefficient between NLR and clinical parameters of COPD (6-minute walking distance, body mass index, airflow obstruction, and mMRC dyspnea scale); and 8) correlation coefficient between NLR and other inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and white blood cells).

Quality assessment

The quality of the included studies was analyzed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort, case-control, and cross-sectional studies. This scale is based on three characteristics: selection, comparability, and outcome or exposure (in case-control studies).¹⁶ In this “star system”, a maximum of nine stars can be given for cohort and case-control studies, while cross-sectional studies can be given a maximum of ten stars. The thresholds for converting the NOS to Agency for Healthcare Research and Quality standards (good, fair, and poor) were: good quality – 3 or 4 stars in selection domain, 1 or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain; fair quality – 2 stars in selection domain, 1 or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain; and poor quality – 0 or 1 star in selection domain, or 0 stars in comparability domain, or 0 or 1 stars in outcome/exposure domain.¹⁷

Statistical analysis

The continuous variables were expressed as mean \pm SD. In articles in which the continuous variables were expressed as median and interquartile range, mean and SD were calculated according to Hozo et al.¹⁸ Accuracy data and the correlation between the NLR and clinical parameters or other inflammatory markers were expressed as Pearson’s

correlation coefficient or Spearman's Rho. The differences in NLR between groups were estimated using one-way ANOVA with Bonferroni as post hoc test or an unpaired *t*-test. Statistical analysis was performed using SPSS v22 (IBM SPSS Inc., Armonk, NY, USA). Statistical significance was considered with a value of $P < 0.05$.

Results

Selected studies

Figure 1 shows the flow diagram of the studies. A total of 803 references were found through the literature search (795 automatic searches and eight manual searches). Initially, 321 were duplicates, and the remaining 483 were screened by title and abstract; of these, 459 were excluded and 25 were selected for full-text screening, of which 22 were eligible for inclusion, recruiting a total of 8,385 patients (7,601 COPD patients and 784 healthy controls) with a mean age of 65.65 ± 6.20 years, 5,812 (70%) males, and 2,573 (30%) females. Table 1 summarizes the characteristics of the articles and the population included. Articles in which the same group of COPD patients was evaluated in both periods of the

disease (stable and exacerbated) were considered as providing independent data for statistical analysis.^{10,19–21}

Quality assessment

The present systematic review included five cohort studies, six cross-sectional studies, and eleven case-control studies. Using the NOS form, 20 articles were identified as high quality (five cohort studies, five cross sectional studies, and ten case-control studies), and only two articles were identified as poor quality (one cross-sectional study and one case-control study) (Table 2).

Neutrophil-to-lymphocyte ratio and COPD exacerbation

The mean NLR values of healthy controls and stable and exacerbated COPD patients were extracted from 8,^{10,21,23–28} 18,^{9,10,19–21,23–25} and 17 articles,^{9,10,19–26,28,32,34–38} respectively. The pooled data showed that the mean NLR values of healthy controls, and stable and exacerbated COPD patients were 1.71 ± 0.22 , 2.97 ± 1.10 , and 7.76 ± 3.79 , respectively (Table 3). The NLR in COPD patients with exacerbation was significantly

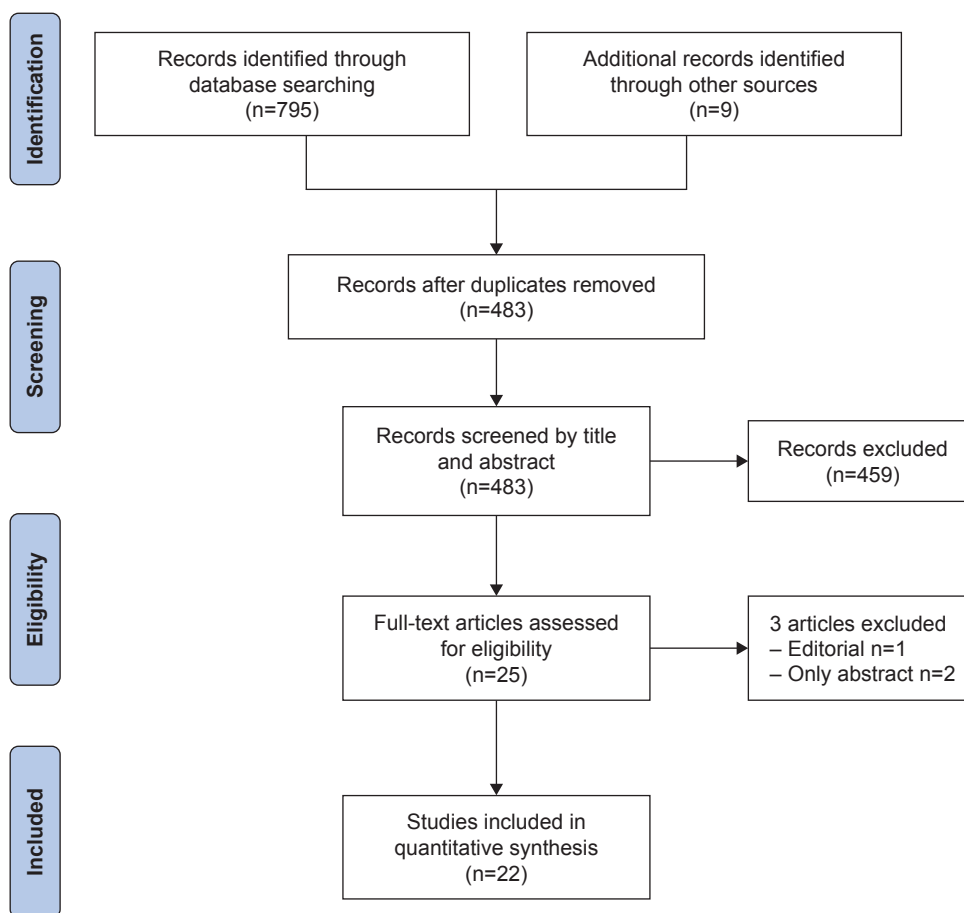


Figure 1 Flowchart of the systematic review.

Table 1 Characteristics of included articles and population

Author, year	Study design	Age, years (SD)	Gender		Number of patients				Total patients
			Male	Female	Control	COPD			
						Stable	Exacerbated	Total COPD	
Günay et al, 2014 ²²	Retrospective	65.76 (7.62)	216	103	50	178	91	269	319
Tanrıverdi et al, 2015 ³⁶	Prospective	71.70 (9.50)	56	21	–	–	77	77	77
Sørensen et al, 2015 ²⁹	Prospective	70.13 (3.16)	191	195	–	386	–	386	386
Taylan et al, 2015 ¹⁰	Retrospective	63.97 (11.60)	117	63	80	100	100	100	180
Saltürk et al, 2015 ¹⁹	Retrospective	67.75 (6.05)	523	124	–	647	647	647	647
Duman et al, 2015 ²⁰	Retrospective	70.50 (4.90)	1,116	588	–	1,704	1,704	1,704	1,704
Kurtipek et al, 2015 ⁹	Prospective	64.66 (9.79)	94	0	–	48	46	94	94
Bilir et al, 2016 ²³	Retrospective	54.90 (13.97)	519	98	215	216	186	402	617
Furutate et al, 2016 ³⁰	Prospective	71.20 (7.46)	137	4	–	141	49	141	141
In et al, 2016 ²⁴	Retrospective	65.67 (9.17)	112	31	40	56	47	103	143
Duyar, 2016 ³¹	Retrospective	67 (NS)	39	0	–	39	–	39	39
van de Geijn et al, 2016 ³²	Retrospective	67.55 (2.45)	22	18	–	17	23	40	40
Lee et al, 2016 ³³	Prospective	70.85 (7.70)	809	76	–	885	233	885	885
Lee et al, 2016 ²⁵	Prospective	70.4 (6.13)	139	9	28	61	59	120	148
Yousef and Alkhiary, 2017 ²⁶	Prospective	48.9 (8.29)	188	0	60	60	68	128	188
Xiong et al, 2017 ²⁷	Prospective	69.65 (7.15)	252	412	296	368	–	368	664
Rahimirad et al, 2017 ³⁷	Retrospective	69.89 (10.87)	174	141	–	–	315	315	315
Kumar et al, 2017 ²¹	Retrospective	71 (10)	93	88	–	181	181	181	181
Mohamed-Hussein et al, 2017 ³⁴	Retrospective	58.1 (16.95)	107	41	–	74	74	148	148
Yao et al, 2017 ³⁸	Retrospective	61 (10)	200	103	–	–	303	303	303
Farah et al, 2017 ²⁸	Prospective	58.1 (10.70)	72	28	15	13	72	85	100
Acartürk et al, 2017 ³⁵	Retrospective	66 (13)	636	430	–	993	73	1,066	1,066

Note: Values are given as geometric mean \pm SD.

Abbreviation: NS, not specified.

higher than that in stable patients and healthy controls ($P < 0.0005$) (Figure 2). There were no significant differences between stable COPD patients and healthy controls when one-way ANOVA with Bonferroni post hoc test was used, but differences were found using an unpaired t -test ($P < 0.0001$).

Two observational prospective studies have assessed the NLR as an independent predictor of COPD exacerbation during the first year follow-up, although only one found statistically significant differences (OR 2.083, 95% CI: 0.918–4.723, $P = 0.079$ ²⁵ and OR 2.05, 95% CI: 1.03–4.06, $P = 0.041$ ³³).

The accuracy of NLR data for detecting COPD exacerbation was described in seven articles (Table 4).^{9,10,23,24,26,34,35} The median cut-off value for a high NLR was 3.34 (range 1.5–3.35) with a sensitivity, specificity, and under the curve (AUC) being in the range 69%–93%, 59%–90%, and 0.58–0.89, respectively. Three articles described the accuracy of NLR data for distinguishing between bacterial and non-bacterial exacerbation in patients admitted to the emergency room with a diagnosis of acute exacerbation of COPD.^{28,32,36} The median cut-off value for detecting bacterial infection in exacerbated patients was 7.30 (range 4.52–11.5) with a sensitivity, specificity, and AUC in the range 61%–91%, 46%–73.1%, and 0.58–0.79, respectively (Table 4).

Correlation between NLR and clinical outcomes in COPD patients

Six authors evaluated the correlation between NLR and FEV₁.^{24–26,30,33,34} In four articles, the data were analyzed using Pearson's correlation coefficient^{24–26,33} and in two using Spearman's rank correlation (Spearman's Rho) (Table 5). Five articles showed a significant negative correlation between the two parameters. Pooled data showed a median Pearson's correlation of -0.22 (range -0.17 to -0.28) and a median Spearman's correlation of -0.43 (range -0.38 to -0.49).

Three articles evaluated the relationship between the NLR values and GOLD stages,^{22,23,31} and a pooled analysis showed no significant differences in NLR values between GOLD stages (GOLD 1/2: 2.40 ± 0.36 and GOLD 3/4: 2.22 ± 0.36 ; $P = 0.63$). However, one study showed positive linear relationship between NLR and COPD severity in the stable group, whereas the results in patients exacerbated in stages 1 and 4 were similar (Table 6).²³

The correlation between NLR and other clinical parameters was evaluated by two authors.^{25,30} However, the heterogeneity in the statistical analysis precludes pooling the results. Furutate et al³⁰ showed a significant positive correlation between NLR and mMRC or BODE index

Table 2 Study quality assessment using the Newcastle-Ottawa scale

Studies	Selection	Comparability	Outcome	Total stars
Cohort studies				
Sørensen et al, 2015 ²⁹	★★★★	★★	★★★	9
Saltürk et al, 2015 ¹⁹	★★★★	★	★★★	8
Duman et al, 2015 ²⁰	★★★★	★★	★★★	9
Lee et al, 2016 ³³	★★★★	★★	★★	8
Kumar et al, 2017 ²¹	★★★★	★	★★★	8
Studies	Selection	Comparability	Exposure	Total stars
Cross-sectional studies				
Tanrıverdi et al, 2015 ³⁶	★★★	★	★★★	7
Kurtipek et al, 2015 ⁹	★★★★	★★	★★★	9
Bilir et al, 2016 ²³	★★★★★	★★	★★★	10
Furutate et al, 2016 ³⁰	★★★★	★★	★★★	9
Duyar, 2016 ³¹	★★	–	★★★	5
Acartürk et al, 2017 ³⁵	★★★★	★	★★★	8
Studies	Selection	Comparability	Exposure	Total stars
Case-control studies				
Günay et al, 2014 ²²	★★★★	★	★★★	8
Taylan et al, 2015 ¹⁰	★★★★	★★	★★	8
In et al, 2016 ²⁴	★★★★	★	★★★	8
van de Geijn et al, 2016 ³²	★★★	★	★★★	7
Lee et al, 2016 ²⁵	★★★★	★★	★★★	9
Yousef and Alkhiary, 2017 ²⁶	★★★★	★★	★★★	9
Xiong et al, 2017 ²⁷	★★★★	★★	★★★	9
Rahimirad et al, 2017 ³⁷	★★★	★★	★★★	8
Mohamed-Hussein et al, 2017 ³⁴	★★★	–	★★★	6
Yao et al, 2017 ³⁸	★★★	★	★★★	7
Farah et al, 2017 ²⁸	★★★	★	★★★	7

Table 3 NLR value of healthy controls, and stable and exacerbated COPD patients

Author, year	NLR, mean (SD)			
	Control	Stable COPD	Exacerbated COPD	P-value
Günay et al, 2014 ²²	1.71 (0.41)	2.59 (1.05)	4.28 (2.38)	<0.001
Tanrıverdi et al, 2015 ³⁶	–	–	18.5 (16.60)	–
Sørensen et al, 2015 ²⁹	–	3.08 (0.76)	–	–
Taylan et al, 2015 ¹⁰	1.7 (0.90)	3.1 (2.50)	7.1 (5.40)	<0.001
Saltürk et al, 2015 ¹⁹	–	5.86 (1.80)	9.45 (2.80)	–
Duman et al, 2015 ²⁰	–	5.18 (1.39)	6.12 (1.73)	–
Kurtipek et al, 2015 ⁹	–	2.75 (1.11)	7.99 (5.72)	0.001
Bilir et al, 2016 ²³	1.9 (0.66)	2.41 (2.90)	4.22 (2.51)	<0.001
Furutate et al, 2016 ³⁰	–	2.56 (0.23)	–	<0.001
In et al, 2016 ²⁴	1.68 (0.41)	2.67 (1.13)	5.78 (3.14)	<0.05
Duyar, 2016 ³¹	–	2.14 (0.40)	–	–
van de Geijn et al, 2016 ³²	–	3.08 (1.51)	5.89 (4.92)	<0.001
Lee et al, 2016 ³³	–	2.4 (0.27)	–	–
Lee et al, 2016 ²⁵	1.4 (0.50)	2.4 (0.70)	12.4 (10.60)	<0.001
Yousef and Alkhiary, 2017 ²⁶	1.45 (0.21)	2.36 (0.55)	4.44 (1.61)	<0.001
Xiong et al, 2017 ²⁷	2.02 (1.92)	2.98 (1.89)	–	–
Rahimirad et al, 2017 ³⁷	–	–	10.22 (11.19)	–
Kumar et al, 2017 ²¹	–	–	10 (9)	–
Mohamed-Hussein et al, 2017 ³⁴	–	1.2 (0.70)	3.7 (0.30)	<0.05
Yao et al, 2017 ³⁸	–	–	7.92 (8.79)	–
Farah et al, 2017 ²⁸	1.9 (0.60)	3.8 (2.20)	6.3 (5.40)	<0.001

Note: Values are given as geometric mean \pm SD.

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

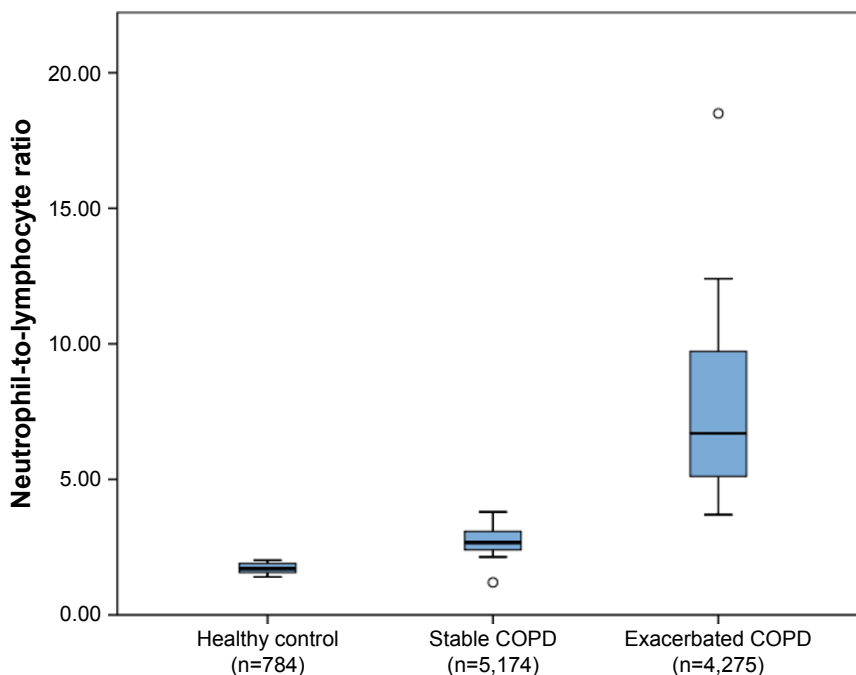


Figure 2 Neutrophil-to-lymphocyte ratio in healthy controls, and stable and exacerbated COPD patients.
Note: Box plots represent median, interquartile range, and range with outliers plotted separately.

($Rho=0.403$; $P<0.001$ and $Rho=0.46$; $P<0.001$, respectively). Likewise, Lee et al²⁵ showed a significant positive correlation between these parameters ($r=0.39$; $P=0.01$ and $r=0.45$; $P=0.003$, respectively).

NLR and other inflammatory biomarkers in COPD patients

Data on the correlation between NLR and other inflammatory parameters were extracted from ten articles (Table 7).^{9,10,22–24,26,28,30,34,38} CRP was the most frequently evaluated parameter.^{9,10,22–24,26,28,30,38} The pooled data show that the median correlation between NLR and CRP values was $Rho=0.43$ (range 0.20–0.48) in stable COPD patients.

In exacerbated COPD patients, four articles analyzed the data using Pearson's correlation coefficient^{9,10,26,38} and two using Spearman's rank correlation (Spearman's Rho),^{22,23} showing a median of 0.46 (range 0.28–0.60) and 0.59 (range 0.53–0.66), respectively. In all articles, the correlation was statistically significant. Analyzing the comparative individual studies, a similar trend was observed in both CRP and NLR markers during the stable and exacerbation phases of COPD (CRP 7.39 ± 8.15 mg/dL stable vs 26.49 ± 24.32 mg/dL exacerbated; $P<0.001$). The median cut-off value of CRP for detecting AECOPD was 2.56 mg/dL (range 1.17–3.35) with a sensitivity, specificity, and AUC in the range 68%–91%, 52%–62%, and 0.75–0.82, respectively.

Table 4 Accuracy data of NLR for detecting COPD global and bacterial infection exacerbation

Author, year	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Kurtipek et al, 2015 ^{9,a}	3.30	87	82	0.88 (NS)
Tanriverdi et al, 2015 ^{36,b}	11.50	61	52	0.58 (0.45–0.71)
Taylan et al, 2015 ^{10,a}	3.29	80.80	77.70	0.89 (0.84–0.94)
Bilir et al, 2016 ^{23,a}	3.35	69	59	0.68 (0.63–0.73)
In et al, 2016 ^{24,a}	3.34	78.70	73.20	0.86 (0.79–0.93)
van de Geijn et al, 2016 ^{32,b}	4.52	91	46	0.75 (0.60–0.91)
Yousef and Alkhiary, 2017 ^{26,a}	3.12	86.70	76.70	0.88 (0.90–1.00)
Mohamed-Hussein et al, 2017 ^{34,a}	1.50	93	90	0.68 (0.54–0.81)
Farah et al, 2017 ^{28,b}	7.30	76.80	73.10	0.79 (NS)
Acartürk et al, 2017 ^{35,a}	3.54	78	69	–

Notes: ^aNLR for detecting COPD global exacerbation; ^bNLR for detecting COPD bacterial infection exacerbation.

Abbreviations: AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; NS, not specified.

Table 5 Correlation data between NLR and FEV₁

Author, year	Correlation coefficient	P-value
Furutate et al, 2016 ³⁰	Rho=-0.387	<0.001
In et al, 2016 ²⁴	r=-0.288	0.003
Lee et al, 2016 ³³	r=-0.176	<0.001
Lee et al, 2016 ²⁵	r=-0.285	0.071
Yousef and Alkhiary, 2017 ²⁶	r=-0.176	<0.001
Mohamed-Hussein et al, 2017 ³⁴	Rho=-0.498	<0.01

Abbreviations: r, Pearson's correlation coefficient; Rho, Spearman's rank correlation coefficient; NLR, neutrophil-to-lymphocyte ratio.

The second most studied parameter was ESR. The pooled data show that the median correlation between NLR and ESR values was $r=0.42$ (range 0.27–0.71)^{10,26} and $Rho=0.49$ (range 0.29–0.55)³⁴ in exacerbated patients, and only one article showed a significant correlation between parameters in total COPD patients ($Rho=0.26$; $P<0.001$).²⁴ Likewise, three articles showed a significant positive correlation between NLR and leukocytes.^{10,26,34} The pooled data show a median Pearson's correlation of $r=0.49$ (range 0.30–0.69). Only one article reported Spearman's Rho ($Rho=0.33$; $P<0.05$),³⁴ and the correlation between NLR and leukocytes was evaluated only in exacerbated COPD patients.

Analyzing individual studies for which data were available,^{9,10,19,20,22–24,26,28,32} although all markers showed significant differences in mean values between the stable and exacerbation phases, the difference was quantitatively greater in the NLR (3.57 ± 1.54 stable vs 6.72 ± 4.77 exacerbated) than in the absolute values of neutrophils ($5.76\pm 1.08\times 10^3/\mu\text{L}$ stable vs $7.36\pm 1.55\times 10^3/\mu\text{L}$ exacerbated) or lymphocytes ($1.54\pm 0.59\times 10^3/\mu\text{L}$ stable vs $1.19\pm 0.54\times 10^3/\mu\text{L}$ exacerbated) assessed separately, with differences between their absolute values being 3.15, 1.6, and -0.35, respectively.

Two studies^{19,20} analyzed the relationship between eosinophilia and the NLR in acute and stable phase patients. In both studies, the NLR was higher in patients with a lower percentage of eosinophils (<2%) both in stable COPD (overall mean value, 6.99 ± 1.25 vs 3.99 ± 0.71 , $P=0.001$) and in AECOPD (11.33 ± 2.11 vs 4.25 ± 0.65 , $P=0.001$).

Table 6 NLR during stable and exacerbation periods according to GOLD stage

Author, year	Group	GOLD 1	GOLD 2	GOLD 3	GOLD 4	P-value
Günay et al, 2014 ²²	Stable	2.44 (1.19)	2.90 (2.00)	2.46 (1.41)	3.16 (4.87)	0.254
	Exacerbation	2.29 (4.39)	4.28 (3.51)	4.35 (4.26)	6.15 (5.38)	0.178
Bilir et al, 2016 ²³	Stable	1.64 (1.60)	2.33 (2.09)	2.60 (3.58)	2.66 (3.86)	<0.001
	Exacerbation	6.19 (2.94)	4.18 (4.48)	3.47 (3.53)	6.29 (6.38)	0.028
Duyar, 2016 ³¹	Stable	1.81 (0.33)		2.57 (0.34)		0.091

Note: Values are given as geometric mean \pm SD.

Prognostic significance of NLR in COPD patients

Five articles found that the NLR represents an independent predictor of mortality in COPD patients (Table 8).^{19–21,27,37} Saltürk et al¹⁹ and Rahimirad et al³⁷ conducted a multivariate analysis and found that high NLR values represent an independent predictor of in-hospital mortality during exacerbation, showing 2–3.5-fold more probability (OR 1.96, 95% CI: 1.13–3.39; $P=0.016$ and OR 3.586, 95% CI: 1.69–7.60; $P=0.001$, respectively) with a median NLR cut-off value of 10 (range 4–16). On the other hand, Duman et al,²⁰ Xiong et al,²⁷ and Kumar et al²¹ found that the NLR is an independent predictor of early (first 90 days) and late (within 6 and 24 months) mortality during the follow-up after exacerbation. According to Duman et al,²⁰ there was an almost twofold (OR 1.79, 95% CI: 1.37–2.34; $P=0.001$) higher probability of mortality within 6 months after exacerbation with an NLR cut-off value of 7, while Xiong et al²⁷ showed that there was an almost fourfold (OR 3.95, 95% CI: 2.54–6.38; $P<0.001$) higher probability of mortality within 24 months after exacerbation with an NLR cut-off value of 3.3.

Discussion

COPD is characterized by an increase in pulmonary and systemic inflammatory responses³⁹ that are maintained after smoking cessation and could progressively increase over time.⁴⁰ Different studies have shown that lung inflammation induced by COPD is mediated by innate and adaptive immune system deprivation.^{41,42}

Changes in the innate immune system in COPD patients are related to injury of the alveolar epithelium, a decrease in phagocytosis mediated by macrophages, a reduction in dendritic cells in airways, and an increase in neutrophil migration into the airways that is not accompanied by correct bacterial clearance. This neutrophil migration stimulates cytokine production and subsequent destruction of lung tissue,^{40,43–45} which leads to changes in the microbiome of patients with COPD that seem to be related to the perpetuation of the inflammatory response in the airway despite the cessation of smoking.⁴⁶

Table 7 Correlation between NLR and other inflammatory parameters in COPD patients

Correlation	Author/year	COPD		
		Stable	Exacerbated	Total
NLR/CRP	Günay et al, 2014 ²²	Rho=0.485, P<0.001	Rho=0.665, P<0.001	–
	Taylan et al, 2015 ¹⁰	–	r=0.415, P<0.001	–
	Kurtipek et al, 2015 ⁹	–	r=0.512, P<0.001	–
	Bilir et al, 2016 ²³	Rho=0.436, P<0.001	Rho=0.534, P<0.001	–
	Furutate et al, 2016 ³⁰	Rho=0.209, P=0.015	–	–
	In et al, 2016 ²⁴	–	–	r=0.641, P<0.001
	Yousef and Alkhiary, 2017 ²⁶	–	r=0.609, P<0.000	–
	Yao et al, 2017 ³⁸	–	r=0.281, P<0.001	–
	Farah et al, 2017 ²⁸	–	–	r=0.556, P<0.000
NLR/ESR	Taylan et al, 2015 ¹⁰	–	r=0.275, P=0.035	–
	In et al, 2016 ²⁴	–	–	r=0.276, P=0.005
	Yousef and Alkhiary, 2017 ²⁶	–	r=0.714, P<0.000	–
	Mohamed-Hussein et al, 2017 ³⁴	–	Rho=0.558, P<0.01	–
NLR/WBC	Taylan et al, 2015 ¹⁰	–	r=0.304, P=0.002	–
	Yousef and Alkhiary, 2017 ²⁶	–	r=0.694, P<0.000	–
	Mohamed-Hussein et al, 2017 ³⁴	–	Rho=0.330, P<0.01	–

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio; Rho, Spearman's rank correlation coefficient; r, Pearson's correlation coefficient; WBC, white blood cell.

Changes in the adaptive immune system are due to an increase in CD8⁺ T lymphocytes within the airway,⁴² which has been related to the production of larger amounts of cytotoxic perforins, granzyme B, and macrophage elastase (MMP-12), leading to tissue damage.⁴⁷ On the other hand, some studies have found that CD4⁺ T lymphocytes participate in the amplification of the adaptive immune response.⁴⁸ In addition, they seem to play a role in the development of autoimmunity;⁴⁹ however, the clinical role of these data remains to be elucidated.

Several studies have suggested that patients with COPD present elevated serum inflammatory markers. It has been estimated that ~70% of patients with COPD have at least one elevated serum inflammatory parameter.⁴⁹ Some data have shown that the persistent elevation of inflammatory markers is related to the progression of the disease,⁵⁰ clinical and functional parameters,⁵¹ and the development of comorbidities.⁴⁰ The most studied serum inflammatory markers are CRP, IL-6, and TNF- α .⁵⁰ However, their use in routine clinical practice has limitations, while NLR is a rapid, easy,

and cost-effective method derived from routine complete blood count tests. The NLR has been reported to be a useful indicator of clinical outcome and severity in malignant and inflammatory diseases.^{51–54}

In the present study, the NLR showed a positive and significant correlation with other traditional inflammatory markers such as CRP, leukocytes, and ESR. Analyzing the comparative individual studies, a similar trend was observed in both CRP and NLR markers during the stable and exacerbation phases of COPD. Therefore, the data seem to indicate that both are equally effective in the detection of AECOPD. However, NLR is easy to calculate from a routine complete blood count and is cheaper than serum CRP-level measurement. On the other hand, the difference is quantitatively greater in the NLR compared to absolute values of neutrophils and lymphocytes, which is expected, since the NLR includes both biomarkers. This analysis shows the potential usefulness of NLR as an inflammatory marker in patients with COPD and indicates the possibility of using the NLR as a useful marker in routine clinical

Table 8 Predictive value of NLR in COPD patients' mortality based on multivariate analysis

Author, year	Cut-off	Odds ratio	95% CI	P-value	Event
Saltürk et al, 2015 ¹⁹	NLR \geq 16	1.96	1.13–3.39	0.016	In-hospital mortality (respiratory failure)
Duman et al, 2015 ²⁰	NLR \geq 7	1.79	1.37–2.34	0.001	Late mortality (within 6 months)
Xiong et al, 2017 ²⁷	NLR \geq 3.3	3.95	2.54–6.38	<0.001	Late mortality (within 24 months)
Rahimirad et al, 2017 ³⁷	NLR \geq 4	3.586	1.69–7.60	0.001	In-hospital mortality
Kumar et al, 2017 ²¹	–	0.95	0.84–1.08	0.46	Early mortality (at 90 days after hospital admission)

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

practice, although more validation studies are required in this regard.

The pooling of data in this systematic review demonstrated that the NLR value was significantly elevated in stable COPD patients compared with healthy subjects, which suggests that systemic inflammation is persistent in this population. This observation is consistent with other published data that showed elevation of inflammatory markers such as IL-6 and CRP in patients with stable COPD compared with healthy controls.^{55–57}

It was also shown that exacerbated COPD patients had significantly higher NLR values compared with stable COPD patients. In addition, it was observed that the NLR decreased in patients with exacerbated COPD after recovery of the exacerbation.^{10,19,21} These findings are consistent with other studies in which the same behavior of other inflammatory markers was observed, along with a greater inflammatory response during exacerbation of COPD.^{58,59} Taken together, these data suggest that the NLR is a marker that could be used to evaluate the inflammatory status of patients with COPD and predict the remission of the inflammatory process during exacerbations.

In the present systematic review, only one out of two single studies found that elevation of the NLR is an independent predictor of acute exacerbation in patients with COPD, with a twofold increase in the likelihood of exacerbation in patients with a high NLR in the stable phase. A previous prospective study demonstrated that the single best predictor of future exacerbations, across all GOLD stages, was a treated exacerbation in the year before study entry (OR 4.30, 95% CI: 3.58–5.17; $P < 0.001$).⁶⁰ Other studies have also shown a predictive value of other inflammatory markers for acute exacerbation in COPD patients.^{58,61} Hence, the discordant findings of the NLR in the present review do not support the value of this marker as a predictor of future exacerbations. However, the NLR seems to be a good marker for detecting an acute exacerbation in COPD patients. The pooled data indicate that a cut-off value of 3.34 would allow the diagnosis of acute exacerbation with a median AUC of 0.86, sensitivity of 80%, and specificity of 86%. Similarly, the pooled data suggest a median cut-off value of 7.30 for detecting infectious exacerbation of COPD patients with a median AUC of 0.75, but with a wide range of cut-off values and rather low sensitivity (76.8%) and specificity (52%). The possibility that the NLR could predict bacterial exacerbation appears more interesting, in view of its clinical implications. Although the results shown here do not support this hypothesis, future studies are required to validate this information.

In our review, the NLR was higher in patients with a lower percentage of eosinophils (<2%) both in stable COPD and in AECOPD, and it should be noted that these patients presented greater therapeutic failure after corticosteroid treatment for the exacerbation. These findings agree with other studies that show a negative correlation between the eosinophil count and bacterial isolates in the sputum of patients with stable COPD.⁶² The percentage of blood eosinophils is also inversely correlated to the presence of bacterial infection in AECOPD.⁶² Hence, the combination of both markers (NLR and eosinophilia) could identify a therapeutic phenotype (the one that requires antibiotic and/or the one that requires systemic corticosteroids). Therefore, NLR could be used to monitor the exacerbation and to support therapeutic decision making.

On the other hand, no statistically significant differences were found in the NLR when patients were stratified using the GOLD airflow obstruction classification. However, one study showed a positive linear relationship between NLR and COPD severity in the stable group.²³ The data regarding the association of inflammatory markers with GOLD classification are contradictory. In this regard, De Moraes et al⁵⁵ found no direct association between IL-6 and IL-8 and the severity of COPD in ex-smokers. Nevertheless, Mathanraj et al⁶³ and Torres-Ramos et al⁵⁶ reported a significant increase in TNF- α and CRP, respectively, according to GOLD stage. The findings in the different studies show the heterogeneity of the cohorts studied and the potential impact of comorbidities associated with COPD on systemic inflammatory markers. In addition, a high percentage of patients in GOLD stage II (about 22% according to the ECLIPSE study)⁶⁰ also have frequent exacerbations, which are related to an increased and persistent inflammatory status in the stable stage.

The relationship between inflammatory markers and clinical/functional parameters in COPD patients was described in some articles. A positive correlation between IL-6 and a rapid decline in FEV₁ has been demonstrated previously.^{51,59} Other authors reported a significant correlation between IL-6, CRP, and BODE index.^{64,65} These data suggest that the inflammatory status of COPD patients is associated with disease progression, and worsening dyspnea and exercise tolerance.⁵⁵ In the present review, some authors found a moderate correlation between NLR and FEV₁, mMRC, and BODE index. These findings suggest that NLR could be used as a clinical performance marker in COPD patients.^{25,30}

The prognostic value of different inflammatory markers in COPD patients has previously been reported by other authors.

In a cross-sectional prospective study, Shafiek et al⁶⁶ found that high levels of IL-6 predict in-hospital mortality. Similarly, a recent meta-analysis found that a high baseline level of CRP is significantly associated with higher late mortality in COPD patients.⁶⁷ Other inflammatory markers such as IL-1 β and fibronectin have also been described to be associated with mortality of COPD.⁶⁸ In the present study, we found that the NLR is an independent predictor of in-hospital mortality, with 2–3.5-fold higher probability of mortality with a median NLR cut-off value of 10. In addition, the NLR seems to be an independent predictor of late mortality, with a high NLR value being associated with two- to four fold higher probability of death after exacerbation. All-cause mortality analysis is the method most usually performed in the studies, and the influence of other systemic diseases (such as lung cancer) on the NLR may introduce a certain bias. However, in favor of the NLR as an AECOPD biomarker, Rahimirad et al³⁷ showed a statistically significant relationship between the ratio and the in-hospital mortality due to respiratory causes.

Regarding the potential effect of the patient's treatment on the NLR, most studies in this review excluded patients with a history of antibiotic treatment and the use of systemic steroids in at least the two preceding months. Hence, treatment with steroids was started at the time of AECOPD diagnosis; it was thus able to influence the subsequent neutrophil and lymphocyte counts, but not the baseline measurement. Dividing patients into two groups according to systemic glucocorticoid use at baseline, Sørensen et al²⁹ concluded that treatment with systemic glucocorticoids has a significant impact on the ability of inflammatory biomarkers to predict all-cause mortality, with higher mortality in the group not undergoing this treatment. The use of inhaled corticosteroids to treat COPD patients is not recorded in the studies, and so the potential effect of this therapy on the NLR is unknown.

Limitations

There are several limitations in this systematic review. First, most studies included were retrospective, with the possibility of selection bias. Second, most studies included had a small number of patients. Furthermore, the heterogeneity in the methodology and the primary outcomes between studies limited the gathering of some clinical parameters evaluated. No meta-analysis was possible due to the heterogeneity and the impossibility of extracting the necessary data.

Conclusion

In conclusion, this is the most comprehensive systematic review to date to show that the NLR is higher in stable COPD

patients than healthy controls, and that the NLR is also higher in exacerbated compared with stable COPD patients. The NLR is a good marker for detecting acute exacerbation in COPD patients. This systematic review proposes a cut-off value of 3.34, which achieves an acceptable degree of accuracy. There was no evidence of a relationship between NLR and GOLD airflow obstruction classification. However, we found that there was a significant correlation between the NLR and clinical/functional parameters (FEV₁, mMRC, and BODE index) in COPD patients, which suggests that a high NLR could be associated with a worsening of dyspnea, clinical performance, and degree of bronchial obstruction. Besides, we found that the NLR may provide an added value to predict the risk of in-hospital and late mortality in COPD patients. Further prospective studies to address confounders with larger sample sizes and including different disease stages are needed to better identify the clinical value of the NLR.

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Author contributions

All authors contributed toward data acquisition, analysis and interpretation of results, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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