

Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19

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Abstract

Background: As the pandemic of coronavirus disease 2019 (COVID-19) continues, prognostic markers are now being identified. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are easily accessible values that have been known to correlate with inflammation and prognosis in several conditions. We used the available data to identify the association of NLR and PLR with the severity of COVID-19.

Methods: A literature search using EMBASE, MEDLINE, and Google Scholar for studies reporting the use of NLR and PLR in COVID-19 published until April 28, 2020, was performed. Random effects meta-analysis was done to estimate standard mean difference (SMD) of NLR and PLR values with 95% confidence interval (CI) between severe and non-severe COVID-19 cases.

Results: A total of 20 studies with 3,508 patients were included. Nineteen studies reported NLR values, while five studies reported PLR values between severe and non-severe COVID-19 patients. Higher levels of NLR (SMD: 2.80, 95% CI: 2.12 - 3.48, $P < 0.00001$) and PLR (SMD: 1.82, 95% CI: 1.03 - 2.61, $P < 0.00001$) were seen in patients with severe disease compared to non-severe disease.

Conclusions: NLR and PLR can be used as independent prognostic markers of disease severity in COVID-19.

Keywords: COVID-19; NLR; PLR; Prognostic markers

Introduction

The world is currently going through an unprecedented pandemic of the coronavirus disease 2019 (COVID-19) that has

now affected millions of people [1]. Compared to seasonal influenza, COVID-19 is more contagious, has a longer incubation period, and is associated with higher hospitalization and mortality rates [2-4]. The clinical presentation varies from no symptoms to acute respiratory failure, shock, and multi-organ system dysfunction [2]. Those with older ages, male gender, obesity, and chronic comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer were more likely to have worse outcomes [2, 5, 6]. Patients with COVID-19 present with multiple hematological abnormalities, of which lymphopenia and thrombocytopenia were prominent. Acute phase reactants like C-reactive protein, lactate dehydrogenase, ferritin, and D-dimer have also been well correlated with disease severity and progression [7].

Inflammation plays a major role in the pathophysiology of COVID-19. Both the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) indirectly reflect a patient's inflammatory state. The NLR is calculated as the absolute neutrophil count divided by the absolute lymphocyte count, while the PLR is calculated by platelet count divided by absolute lymphocyte count. In the recent years, NLR and PLR have been validated as prognostic markers in various disorders such as cardiac conditions, solid tumors, sepsis, pneumonia, and acute respiratory distress syndrome (ARDS) [8-13]. Few studies have evaluated the role of NLR and PLR in patients with severe and non-severe COVID-19. We performed this meta-analysis to identify the association of NLR and PLR in relation to the severity of COVID-19.

Materials and Methods

We performed a literature search using EMBASE, MEDLINE, and Google Scholar for studies reporting the use of NLR and PLR in COVID-19 published until April 28, 2020. We used the medical subject headings (MESH) terms: "neutrophil-to-lymphocyte ratio," "platelet-to-lymphocyte ratio," "NLR", "PLR," "COVID-19," "novel coronavirus", and "SARS-CoV-2." Inclusion criteria were: 1) Descriptive studies comparing between severe versus non-severe, or survivor versus deaths in COVID-19 patients; 2) Non-pregnant adult patients; 3) Studies reporting NLR or PLR values. Eligible studies were reviewed, and data including study design, sample size, baseline characteristics, NLR, and PLR values were obtained. Definitions of COVID-19 disease severity were based on individual studies.

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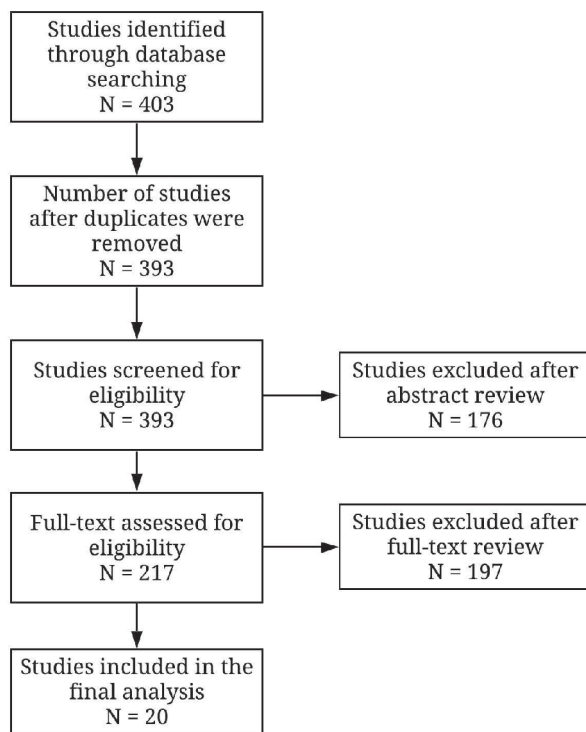


Figure 1. PRISMA diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. We used the Cochrane Review Manager version 5.3 for our analysis. Mean and standard deviation were extrapolated from median and interquartile range (IQR) using the method outlined by Hozo et al [14]. For each outcome, standard mean difference and 95% confidence interval (CI) were calculated using the random effects model utilizing the inverse variance method. A P value of 0.05 or less was assigned as the measure of statistical significance. Study heterogeneity was assessed by calculating I^2 statistics; heterogeneity was considered significant if $I^2 > 50\%$.

Results

The initial search yielded a total of 403 studies, of which 20 studies were included in the final analysis (Fig. 1) [15-34]. All studies were conducted in China. A total of 3,508 patients, with 946 in severe COVID-19 group and 2,561 in non-severe, were included. Clinical demographics are outlined in Table 1 [15-34]. The criteria for severe and non-severe disease varied between each study, but most studies considered respiratory distress and care in intensive units as severe disease. Study specific definitions are listed here (Supplementary Material 1, www.jocmr.org).

A total of 19 studies with 3,478 patients reported NLR values [15-19, 21-34]. Fifteen studies reported NLR between severe and non-severe disease, while four studies reported NLR

based on survival. PLR was identified in five studies [17, 20, 23, 25, 29]. Patients with severe COVID-19 disease had higher NLR values (standard mean difference (SMD): 2.80, 95% CI: 2.12 - 3.48, $P < 0.00001$) when compared to patients with non-severe disease (Fig. 2). In the subgroup analysis, NLR values were higher in non-survivors when compared to survivors (SMD: 3.72, 95% CI: 0.53 - 6.90, $P = 0.02$) (Supplementary Material 2, www.jocmr.org). Similarly, PLR was elevated in patients with severe disease compared to non-severe disease (SMD: 1.82, 95% CI: 1.03 - 2.61, $P < 0.00001$) (Fig. 3). Significant heterogeneity was noted in the study results ($I^2 = 97\%$ for NLR and $I^2 = 89\%$ for PLR).

Discussion

Patients with severe COVID-19 disease had higher NLR and PLR values compared to non-severe disease. The present study shows that levels of NLR and PLR correlate with COVID-19 disease severity.

Patients with severe COVID-19 disease present with increased leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia than those with non-severe disease [7]. These patients were more likely to develop ARDS and require intensive care unit (ICU) level of care [35-37]. NLR and PLR are easily obtained from a serum complete blood count with a differential profile. They serve as a function of relative neutrophilia, thrombocytosis, and lymphopenia. The different mechanisms of lymphopenia in COVID-19 patients have been linked to the virus's ability to infect T cells through the angiotensin-converting enzyme 2 (ACE2) receptors and cluster of differentiation (CD)147-spike proteins [38, 39]. The final results were decreased levels of CD3⁺, CD4⁺, CD8⁺ T lymphocytes, and increased regulatory T cells. The rise of pro-inflammatory cytokines with T cell lymphopenia predisposes severe COVID-19 patients to cytokine storm, thus resulting in more lymphocytic apoptosis and multi-organ failure. Overall, the decreased levels of CD4⁺ and CD8⁺ T lymphocytes correlated with disease severity, which can lead to increase NLR or PLR [2, 4, 15, 16].

In cases of other viral and bacterial pneumonia, NLR was more sensitive than individual levels of neutrophils and lymphocytes [40]. Similarly, PLR correlated well with mortality and disease severity in bacterial pneumonia [12, 41]. In the study by Liu et al, NLR was found to be the most prognostic among multiple variables in determining the severity of illness. Furthermore, when compared to other risk assessment tools such as CURB-65 and multilobar infiltration, hypolymphocytosis, bacterial coinfection, smoking history, hypertension, and age (MuLBSTA), NLR had a higher sensitivity and specificity [16]. While many inflammatory markers like C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, ferritin, and procalcitonin are frequently measured in COVID-19 patients, NLR and PLR can be easily calculated using the differential count and are cost-effective especially for many third world countries. A previous meta-analysis composed of 828 patients and six studies concluded that a high NLR and low lymphocyte-to-C-reactive protein ratio indicated

Table 1. Clinical Characteristics of Included Studies

Study	Baseline characteristics	Num-ber of patients	Study design	Age, mean/median	Female, n (%)	Comorbidities									
						COPD	Hypertension	Cardio-vascular	Cerebro-vascular	Chronic liver disease	Diabetes mellitus	Cancer	Chronic kidney disease		
Qin et al, 2020 [15]	Non-severe	166	Retrospective review	53	86 (51.8)	3 (1.8)	30 (18.1)	3 (1.8)	3 (1.8)	3 (1.8)	22 (13.3)	4 (2.4)	4 (2.4)		
	Severe	286		53	131 (45.8)	9 (3.1)	105 (36.7)	24 (8.4)	8 (2.8)	3 (1.0)	53 (18.5)	10 (3.5)	6 (2.1)		
Liu et al, 2020 [16]	Non-severe	44	Prospective review	41	23 (52.3)	2 (4.5)	6 (13.6)	0 (0)	-	-	2 (4.5)	-	-		
	Severe	17		56	7 (41.2)	3 (17.6)	6 (35.3)	1 (5.9)	-	-	3 (17.6)	-	-		
Yang et al, 2020 [17]	Non-severe	69	Retrospective review	42.1	31 (44.9)	-	7 (10.1)	4 (5.8)	-	9 (13.0)	8 (11.6)	2 (2.9)	-		
	Severe	24		57.9	6 (25)	-	16 (66.8)	9 (37.5)	-	4 (16.7)	13 (54.2)	8 (33.3)	-		
Xia et al, 2020 [18]	Non-severe	7	Case series	54	2 (28.6)	-	1 (14)	-	-	1 (14)	-	-	-		
	Severe	3		61.6	2 (66.7)	-	-	-	-	-	-	-	-		
Zhang et al, 2020 [19]	Non-severe	81	Retrospective review	59.3	42 (52.8)	-	-	-	-	-	-	-	-		
	Severe	67		60.8	29 (43.3)	-	-	-	-	-	-	-	-		
Qu et al, 2020 [20]	Non-severe	27	Case series	49.4	-	-	-	-	-	-	-	-	-		
	Severe	3		60	-	-	-	-	-	-	-	-	-		
Ye et al, 2020 [21]	Survivor	297	Retrospective review	60	160 (53.9)	-	73 (24.6)	-	-	-	41 (13.8)	-	-		
	Non-survivor	52		69	16 (30.8)	-	30 (57.7)	-	-	-	16 (30.8)	-	-		
Zhang et al, 2020 [22]	Non-severe	84	Retrospective review	44	55 (65.5)	-	-	-	-	-	-	-	-		
	Severe	31		64.6	11 (35.5)	-	-	-	-	-	-	-	-		
Sun et al, 2020 [23]	Non-severe	89	Retrospective review	47	47 (52.8)	-	-	-	-	-	-	-	-		
	Severe	27		62	9 (33.3)	-	-	-	-	-	-	-	-		
Song et al, 2020 [24]	Non-severe	31	Retrospective review	48	30 (71.4)	1 (3.2)	4 (12.9)	1 (3.2)	-	3 (9.7)	2 (6.5)	-	-		
	Severe	42		55.5	12 (28.6)	2 (4.8)	22 (52.4)	4 (9.5)	-	1 (2.4)	4 (9.5)	-	-		
Gong et al, 2020 [25]	Non-severe	161	Retrospective review	45	89 (55.3)	-	-	-	-	-	-	-	-		
	Severe	28		63.5	12 (42.9)	-	-	-	-	-	-	-	-		
Ma et al, 2020 [26]	Non-severe	17	Retrospective review	61	7 (41.1)	-	-	-	-	-	-	17 (100)	-		
	Severe	20		65.5	10 (50)	-	-	-	-	-	-	20 (100)	-		
Wei et al, 2020 [27]	Non-severe	137	Did not mention	40.83	62 (45.3)	2 (1.5)	-	17 (12.4)	2 (1.5)	-	4 (2.9)	-	-		
	Severe	30		49.03	10 (33.3)	2 (6.7)	-	7 (23.3)	0	-	7 (23.3)	-	-		
Zhang et al, 2020 [28]	Recovered	50	Retrospective review	62.6	14 (28)	4 (8)	18 (36)	11 (22)	4 (8)	-	5 (10)	-	-		
	Death	10		70.6	3 (30)	2 (20)	4 (40)	3 (30)	2 (20)	-	4 (40)	-	-		
Zhu et al, 2020 [29]	Non-severe	111	Retrospective review	50	38 (34.2)	4 (3.6)	23 (20.7)	4 (3.6)	-	5 (4.5)	10 (9)	4 (3.6)	-		
	Severe	16		57.5	7 (43.8)	2 (12.5)	8 (50)	2 (12.5)	-	2 (12.5)	0	1 (6.25)	-		
Zhang et al, 2020 [30]	Survivors	268	Case-control studies	56	131 (48.9)	3 (1.12)	64 (23.9)	30 (11.2)	7 (2.6)	7 (2.6)	34 (12.7)	8 (3)	2 (0.8)		
	Non-survivors	47		66	9 (19.1)	0	14 (29.8)	5 (10.6)	0	2 (4.3)	7 (14.9)	4 (8.5)	0		
Liu et al, 2020 [31]	Non-severe	43	Retrospective review	55	17 (39.5)	0	13 (30.2)	0	4 (9.3)	1 (2.3)	2 (4.7)	0	-		
	Severe	79		65	33 (41.8)	2 (2.5)	37 (46.8)	2 (2.5)	6 (7.6)	2 (2.5)	13 (16.5)	1 (1.3)	-		
Ma et al, 2020 [32]	Non-severe	572	Retrospective review	44	273 (47.7)	-	90 (15.7)	-	-	-	29 (5.1)	-	-		
	Severe	63		53.3	34 (54)	-	15 (24)	-	-	-	6 (10)	-	-		
Cheng et al, 2020 [33]	Survivors	67	Retrospective review	70.6	45 (67.2)	7 (10.4)	39 (58.2)	11 (16.4)	-	1 (1.5)	11 (16.4)	2 (3)	3 (4.5)		
	Non-survivors	51		73.1	20 (39.2)	6 (11.8)	25 (49)	12 (23.5)	-	0	16 (31.4)	0	3 (5.9)		
Chen et al, 2020 [34]	Non-severe	241	Retrospective review	42.1	123	5 (2.1)	20 (8.3)	7 (3)	5 (2.1)	13 (5.4)	15 (6.2)	2 (0.8)	1 (0.4)		
	Severe	50		60.5	23 (46)	5 (10)	19 (38)	5 (10)	3 (6)	2 (4)	7 (14)	0	1 (2)		

COPD: chronic obstructive pulmonary disease.

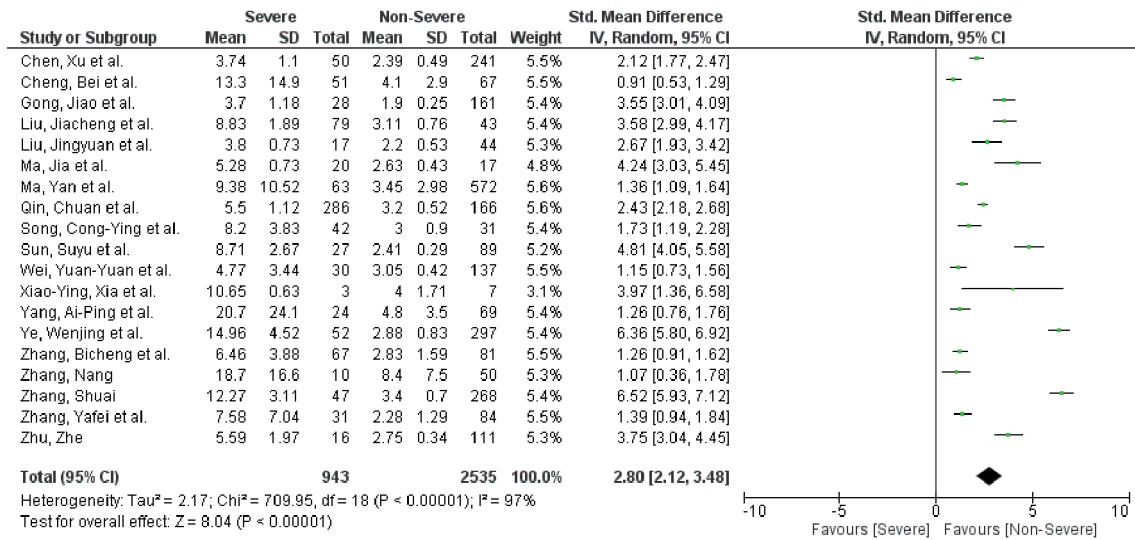


Figure 2. NLR in severe versus non-severe COVID-19 patients. NLR: neutrophil-to-lymphocyte ratio; COVID-19: coronavirus disease 2019; SD: standard deviation; CI: confidence interval.

poor prognosis [42]. The previous study used mean or median values of neutrophils and lymphocytes from individual studies to calculate NLR. For this meta-analysis, we have chosen to exclude studies that did not have the calculated NLR values. Nevertheless, the results of this study were consistent with the previous meta-analysis and individual studies. So far, this is the first meta-analysis to evaluate the prognostic significance of PLR in COVID-19.

There are some limitations to the study. First of all, most of the studies are retrospective reviews, and all included studies were conducted in China. Second, heterogeneity exists between the included patient populations, with some studies not elucidating on underlying comorbidities. Third, it was unclear when in the disease course, the NLR and PLR values were measured. Depending on the severity of COVID-19, disease values of NLR and PLR will likely change.

Conclusions

This study establishes NLR and PLR as independent prognostic markers to differentiate severe versus non-severe disease in COVID-19 patients. Early recognition of the severe cases allows for early triaging and timely initiation of management.

These markers are cost-effective and easily accessible in all laboratories. Future studies should compare the trends of NLR and PLR with disease progression.

Supplementary Material

Suppl 1. Study Specific Definitions of Non-Severe and Severe Disease Classifications

Suppl 2. Subgroup analysis showing NLR in severe versus non-severe disease and non-survivor versus survivor in COVID-19 patients.

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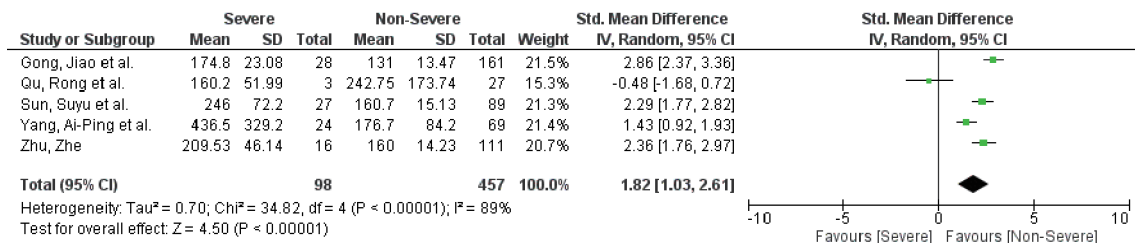


Figure 3. PLR in severe versus non-severe COVID-19 patients. PLR: platelet-to-lymphocyte ratio; COVID-19: coronavirus disease 2019; SD: standard deviation; CI: confidence interval.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

ASC and AR equally contributed to the paper in conceptualization, data collection and drafting of manuscript. AR performed the statistical analysis.

Data Availability

The studies supporting this meta-analysis are from previously reported studies and datasets, which have been cited in the references section. The processed data are available from the corresponding author upon request.

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