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The Impact of Neutrophil-Lymphocyte Count Ratio in COVID-19: A Systematic Review and Meta-Analysis

Soumya Sarkar, MD, Puneet Khanna, MD, and Akhil Kant Singh, MD

Abstract

Background: The neutrophil–lymphocyte count ratio (NLR) has emerged as a potential prognostic tool for different diseases. In the current coronavirus disease (COVID-19) pandemic, the NLR may be a useful tool for risk scarification and the optimal utilization of limited healthcare resources. However, there is no consensus regarding the optimal value of NLR, and the association with disease severity and mortality. Thus, this study aims to systematically analyze the current evidence of the utility of baseline NLR as a predictive tool for mortality, disease severity in COVID-19 patients. **Methods:** A compendious screening of electronic databases up to June 15, 2021, was done after enlisting the protocol in PROSPERO (CRD42020202659). Studies evaluating the utility of baseline NLR in COVID-19 are included for this review as per the PRISMA statement. **Results:** We retrieved a total of 13112 and 12986 COVID-19 patients for survivability and severity over 90 studies. The expired and critically sick patients had elevated baseline NLR on admission, in comparison to survivors and noncritical patients. (SMD = 3.82; 95% CI: 2.79-4.85; I^2 = 100% and SMD = 1.42; 95% CI: 1.22-1.63; I^2 = 95%, respectively). The summary receiver operating curve analysis for mortality (AUC = 0.87; 95% CI: 0.86-0.87; I^2 = 94.7%), and severity (AUC = 0.82; 95% CI: 0.80-0.84; I^2 = 79.7%) were also suggestive of its significant predictive value. **Conclusions:** The elevated NLR on admission in COVID-19 patients is associated with poor outcomes.

Keywords

COVID-19, SARS-CoV-2, Neutrophil to Lymphocyte ratio

Introduction

The global healthcare system is going through an extraordinary crisis due to the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Identification of rapid and reliable clinical biomarkers for risk stratification and optimal utilization of the limited resources is the burning need of the moment.

Of late the neutrophil–lymphocyte count ratio (NLR), a systemic inflammatory indicator has generated a lot of interest regarding the potential prognostic role in several clinical conditions including acute respiratory distress syndrome, liver diseases, cardiovascular disease, and malignancies.[1–6]

Usually, the neutrophil count increases, and the lymphocyte count decreases with the advancement of any inflammatory condition. The NLR, which seems to be more sensitive than the isolated value of absolute neutrophil, or lymphocyte count in bacterial as well as viral pneumonia, is a marker of the systemic inflammatory response.[7,8]

Multiple recent studies have found the increase in NLR is consistent with critical illness and mortality, particularly in inflammatory diseases.[9] A recent meta-analysis also found NLR as a potential prognostic biomarker in sepsis patients and an elevated NLR in deceased than in survivors (SMD = 1.18, 95% CI: 0.42-1.94)[9]

Thus, the NLR on admission may be beneficial for early risk stratification and the necessary prioritization of resources. However, there is no consensus regarding the association between NLR and clinical prognosis.

Thus, we aim to comprehensively analyze the current evidence of the utility of baseline NLR in COVID-19 management as per the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA-P) guidelines.[10,11]

Methods

Protocol and Registration

We prospectively enlisted the protocol for this review in PROSPERO (ID: CRD42020202659) and did not deviate from the published protocol.

AIIMS, New Delhi, India

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Corresponding Author:
Puneet Khanna, Department of Anaesthesia, Pain Medicine & Critical Care, AIIMS, New Delhi, Ansari Nagar, New Delhi 110029, India.
Email: k.punit@yahoo.com

Search Strategy

SS and PK carried out the comprehensive search individually in "PubMed," "Medline," and "Embase" databases, Google Scholar (https://scholar.google.com), and preprint platforms MedRxiv (https://www.medrxiv.org) from January first, 2020 to June 15, 2021, with the following terminologies: ("COVID-19") OR ("SARS-CoV-2") AND ("NLR" OR "neutrophil-lymphocyte count ratio" OR "neutrophil to lymphocyte ratio").

Inclusion and Exclusion Criteria

Prospective as well as retrospective articles presenting clinical data for the utility of baseline NLR in COVID-19 patients were included for full-text review. Full articles in other than English languages were also retrieved using Google Translate (https://translate.google.com).

Cohort studies, cross-sectional studies, case series, and randomized controlled trials were incorporated. The reference section of selected articles for inclusion was also searched to identify any additional studies for potential inclusion. The primary objective under evaluation was mortality and severity.

The editorials, letters, articles without retrievable full text, and necessary data, were excluded (PRISMA flow diagram).[10,11]

Study Selection

PK and SS scrutinized every title and abstracts separately to determine whether they met the incorporating criteria, followed by evaluating the full-text of studies, fulfilled the said criteria. The difference in point of view was sorted out by consulting with the other researcher (AKS).

Data Extraction

SS and PK extracted the following data: study design (retrospective vs prospective), country/region of study, sample size, baseline NLR, disease extremity, and fatality in COVID-19 patients from the incorporated studies using a spreadsheet and substantiate the accuracy independently. The number of events & the overall number of patients per group, and the mean ± SD were extracted for dichotomous and continuous data, respectively. In the absence of a consensus definition and grading of COVID-19 severity across the studies, we considered any patient either with mechanical ventilation or a ratio of the partial pressure of arterial blood oxygen (PaO_2)/oxygen concentration (FiO_2) ≤300 mmHg as severe/critically ill and the rest all as nonsevere patients.

Risk of Bias Assessment

PK and SS assessed each included study for potential bias independently. The opinion of the third researcher (AKS) was sorted to resolve any different point of view. We applied the "Risk of Bias in Non-randomized Studies—of Interventions" (ROBINS-I)[12] tool to assess the risk of bias in nonrandomized studies. It comprises 7 domains: "bias due to confounding," "selection of participants, classification of interventions," "deviations from intended interventions," "missing data," "measurement of outcomes," and "selection of the reported result." Each domain is graded as "Low," "Moderate," "Serious," and "Critical."

Quality of the Evidence

PK and AKS examined the quality of evidence independently and classified each outcome as "High," "Moderate," "Low," or "Very low" depending upon the 5 downgrading factors ("study limitations, consistency of effect, imprecision, indirectness, and publication bias") and 3 upgrading factors ("large magnitude of the effect, dose-response relation, and plausible confounders or biases") as per the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) tool.[13–20]

Data Synthesis

SS and PK used Review Manager version 5.4 and Medcalc software 16.2 for conducting this frequentist meta-analysis. The standardized mean difference, and area under the receiver operating curve along with respective 95% confidence intervals (CIs) were calculated as per the "Cochrane Handbook for Systematic Reviews of Interventions."[21] Statistical heterogeneity was evaluated with the I^2 statistic, >50% indicating substantial heterogeneity. Begg's test, Egger's test along the funnel plot were used to evaluate the potential publication bias.

Results

Basic Characteristics

A total of 90 studies[22–111] (82 retrospectives, 5 prospective, 3 cross-sectional) out of 7352 identified publications were included after satisfying the inclusion criteria (Figure 1). While 44 articles[41,42,44,46,47,49,50–71,73–76,78–80,101,103–106,108–111] assessed baseline NLR as a predictor for determining only severity, 32 articles[24,25,29–34,38–40,43,45,48,77,82–93,96–98,100,102] assessed only mortality, 14 studies[22,23,26–28,35–37,72,81,94,95,99,107] addressed both survivability and severity. Out of the 46 articles, assessed survivability 36 were with only dichotomous data, 10 with only receiver operating curve, and 11 with both types of data. Among the 58 studies assessing severity 13 studies also assessed receiver operating curve.

A total of 68.8% ($n = 62$) of the included studies were from China, 6.6% ($n = 6$) were from European countries, 5.5% ($n = 5$) from the United States and 18.8% ($n = 17$) were from other Asian countries (Turkey, Pakistan, Iran, India, and Bangladesh) (Table 1).

Out of the 90 studies, 77 were peer-reviewed, and 13 were preprints and 25 studies had a moderate degree of bias (Figure 2).

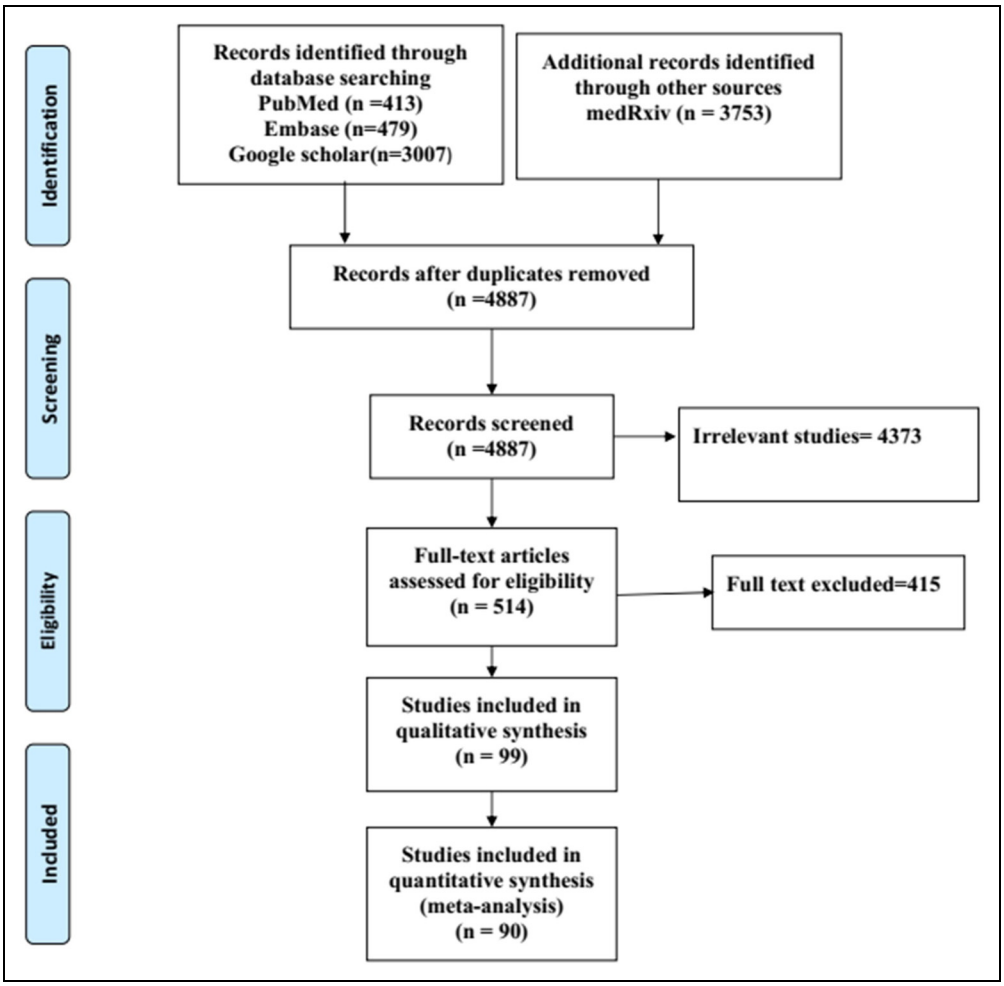

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-2009 flow diagram.

Meta-Analyses

Mortality. Mortality was evaluated in 36 articles with a total of 13 112 patients. A significantly exacerbated risk of mortality is found in patients with increased NLR on admission in comparison to the control group. (SMD = 3.82; 95% CI: 2.79-4.85; I^2 = 100%) (Figure 3a).

Summary Receiver Operating Curve Analysis. Twenty-one studies with a total of 8431 patients assessed ROC with optimum NLR cut-off on admission (ranging 3.19-11.75) for mortality. Raised NLR on admission suggestive of significant predictive value (AUC = 0.87; 95% CI: 0.84-0.91; I^2 = 83.2%) (Figure 3b).

Severity. Fifty-eight studies with a total of 12 986 patients were included for assessing the severity of COVID-19. Severely ill patients are associated with elevated baseline NLR. (SMD = 1.42; 95% CI: 1.22-1.63; I^2 = 95%), (Figure 4a).

Summary Receiver Operating Curve Analysis. Thirteen studies with a total of 2160 patients assessed ROC with optimum NLR cut-off on admission (ranging 2.3-10.1) for severity. Raised NLR on admission suggestive of significant predictive value (AUC = 0.82; 95% CI: 0.80-0.84; I^2 = 79.7%) (Figure 4b).

The heterogeneity across studies assessing the severity and mortality was remarkable.

Quality of Evidence

The quality of evidence on the utility of raised NLR on COVID-19 outcome was low. Significant indirectness in terms of the difference in population, and outcome measures were noted (Table 2).

Publication Bias

While qualitatively a publication bias is likely as per the Funnel plot for the studies on COVID-19 mortality due to smaller studies with large effect (Supplemental Figure 1), the Begg's

Table 1. Characteristics of Included Studies for Quantitative Synthesis.

SN	Author, Year	Type of study, center	Country	Total no. of patients	Outcome
1.	Asghar et al,[22] 2020	Retrospective, SC	Pakistan	100	NLR increasing with disease severity, NLR (AUC: 0.806, PPV: 95.8%) for mortality
2.	Chen et al,[23] 2020	Retrospective, SC	China	132	The mortality rate of COVID-19 patients is associated with the lower lymphocytes and higher NLR
3.	Chen et al,[24] 2020	Retrospective, SC	China	363	High NLR value was associated with disease severity, progression and an overall poor prognosis
4.	Chen et al,[25] 2020	Retrospective, MC	China	1859	High NLR associated with risk of in-hospital death in persons with COVID-19
5.	Chen et al,[26] 2020	Retrospective, MC	China	548	Nonsurvivors kept a high level or showed an upward trend for neutrophils
6.	Cheng et al,[27] 2020	Retrospective, SC	China	456	Higher levels of NLR at admission were associated with a poor prognosis of individuals with moderate COVID-19
7.	Huang et al,[28] 2020	Retrospective, SC	China	299 + 45	Serum albumin level was inversely correlated to NLR, hypoalbuminemia is associated with the outcome of COVID-19
8.	Li et al,[29] 2020	Retrospective, SC	China	93	The mortality rate of COVID-19 monotonously increased with chest CT scores, which positively correlated with the neutrophil-to-lymphocyte ratio, neutrophil percentage,
9.	Luo et al,[30] 2020	Retrospective, SC	China	298	Patients with severe or critical illness tended to exhibit elevated NLR
10.	Pakos et al,[31] 2020	Retrospective, SC	USA	242	NLR was positively associated with death (OR = 1.038; 95% CI: 1.003-1.074, $P = .031$
11.	Ye et al,[32] 2020	Retrospective, SC	China	349	The rising trend in D-dimer and NLR, or the test results higher than the critical values may indicate a risk of death for participants with COVID-19
12.	Yan et al,[33] 2020	Retrospective, SC	China	1004	NLR appears to be a significant prognostic biomarker of outcomes in critically ill patients with COVID-19.
13.	Yang et al,[34] 2020	Retrospective, SC	China	226	Higher NLR was also found to increase COVID-19 patients' mortality risk.
14.	Zhang et al,[35] 2020	Retrospective, SC	China	315	NLR >8.0 (HR 4.56, 95% CI: 2·25-9·23; $P < .0001$)was associated with 28-day mortality
15.	Zhang et al,[36] 2020	Retrospective, SC	China	60	Higher CRP and NLRs with diffuse lung involvement were more likely to die of COVID-19
16.	Zhang et al,[37] 2020	Retrospective, MC	China	516	Older age, high lactate dehydrogenase, NLR, and direct bilirubin level were independent predictors of 28-day mortality in adult hospitalized patients with confirmed COVID-19.
17.	Tatum et al,[38] 2020	Prospective, SC	USA	125	NLR is a prognostic factor for endotracheal intubation upon hospital admission and an independent predictor for risk of mortality in SARS-CoV-2 patients
18.	Chen et al,[39] 2020	Retrospective, SC	China	681	Patients with a high NLR (>6.66) combined with myocardial injury are highly predictive of mortality.
19.	Ok et al,[40] 2020	Retrospective, SC	Turkey	139	NLR may be associated with disease severity, and routine use of these parameters may be beneficial in the evaluation of the disease.
20.	Song et al,[41] 2020	Retrospective, SC	China	84	NLR >6.1 has a sensitivity of 76.2% and specificity of 88.1% for predicting mortality in COVID-19 patients
21.	Huang et al,[42] 2020	Retrospective, SC	China	415	The NLR of patients in the severe group had 1.729-fold higher than that of the no-severe group (OR 1.729; 95% CI: 1.050-2.847, $P = .031$)
22.	Sun et al,[43] 2020	Retrospective, SC	China	116	Patients with COVID-19 have lower counts of lymphocytes, eosinophils, platelets, and higher neutrophil-lymphocyte ratio (NLR) in comparison to controls ($P < .001$).
23.	Fu et al,[44] 2020	Retrospective, SC	China	75	The dynamic change of NLR and D-dimer levels can distinguish severe COVID-19 cases from mild/moderate.
24.	Yang et al,[45] 2020	Retrospective, SC	China	93	Elevated age and NLR can be considered independent biomarkers for indicating poor clinical outcomes.
25.	Wang et al,[46] 2020	Retrospective, SC	China	45	The combined NLR and RDW-SD may help clinicians to predict the severity of COVID-19 patients

(continued)

Table 1. (continued)

SN	Author, Year	Type of study, center	Country	Total no. of patients	Outcome
26.	Peng et al,[47] 2020	Retrospective, SC	China	220	Compared with nonsevere patients, the severe ones had significantly higher levels of neutrophil percentage (74.9% vs 62.1%; $P < .001$), NLR (4.1 vs 2.1; $P < .001$)
27.	Zhang et al,[48] 2020	Retrospective, SC	China	652	NLR + SaO_2 is an appropriate and promising method for predicting severe illness
28.	Zhang et al,[49] 2020	Retrospective, SC	China	80	Compared with nonsevere patients, the severe ones had significantly higher levels of neutrophil percentage
29.	Chen et al, 2020[50]	Retrospective, SC	China	139	↑NLR in severely ill COVID-19 patients
30.	Chen et al,[51] 2020	Retrospective, SC	China	296	The NLR was higher in the severe group
31.	Chen et al,[52] 2020	Retrospective, MC	China	291	↑NLR in severely ill COVID-19 patients
32.	Ding et al,[53] 2020	Retrospective, SC	China	72	NLR from day 5 after admission was found to be positively correlated with the duration of hospitalization
33.	Gong et al,[54] 2020	Retrospective, MC	China	189	Early identification of patients who will progress to severe COVID-19,
34.	Hou et al,[55] 2020	Retrospective, SC	China	49	The NLR was higher in the severe group
35.	Kong et al,[56] 2020	Retrospective, SC	China	40	Compared with mild/moderate COVID-19 cases, severe cases had a higher NLR
36.	Kong et al,[57] 2020	Retrospective, SC	China	210	NLR was identified as an early risk factor for severe COVID-19 illness.
37.	Liao et al,[58] 2020	Retrospective, MC	China	380	The NLR, platelet count, D-dimer, and prothrombin time might provide a reliable and convenient method for classifying and predicting the severity and outcomes of patients with COVID-19.
38.	Liu et al,[59] 2020	Retrospective, SC	China	134	The NLR was higher in the severe group
39.	Liu et al,[60] 2020	Prospective, SC	China	122	Age $\geq$ 50 and NLR $\geq$ 3.13 are predicted to develop a critical illness.
40.	Liu et al,[61] 2020	Retrospective, SC	China	61	The NLR was significantly associated with mortality in patients with COVID-19
41.	Ma et al,[62] 2020	Retrospective, SC	China	37	The NLR was higher in the severe group
42.	Ma et al,[63] 2020	Retrospective, SC	China	149	NLR $\geq$ 2.22 could be utilized as a predicting indicator for the early recognition COVID-19 and facilitate detection timely.
43.	Peng et al,[64] 2020	cross-sectional study, MC	China	190	NLR may be a reliable marker to evaluate the disease severity of COVID-19.
44.	Peng et al,[65] 2020	Retrospective, SC	China	112	Critical patients are characterized by lower lymphocyte counts.
45.	Qin et al,[66] 2020	Retrospective, SC	China	452	Surveillance of NLR is helpful in the early screening of critical illness, diagnosis, and treatment of COVID-19
46.	Shang et al,[67] 2020	Retrospective, SC	China	443	NLR, CRP, and platelets can effectively assess the severity of COVID-19, among which NLR is the best predictor of severe COVID-19,
47.	Song et al,[68] 2020	Retrospective, SC	China	73	The NLR was significantly higher in the COVID-19 patients.
48.	Wang et al, 2020[69]	Retrospective, SC	China	138	The NLR was higher in the severe group.
49.	Wang et al,[70] 2020	Retrospective, SC	China	323	The potential risk factors of males, older age, with comorbidities, low T lymphocyte level and high level of NLR, CRP, IL-6.
50.	Wang et al,[71] 2020	Retrospective, SC	China	30	The NLR was higher in the severe group.
51.	Wang et al,[72] 2020	Retrospective, SC	China	131	The NLR was significantly associated with mortality in patients with COVID-19
52.	Wei et al,[73] 2020	Retrospective, SC	China	167	Decline in T lymphocytes and significant increases in the levels of inflammatory factors, including CRP and IL-6, can be associated with severe infection
53.	Wu et al,[74] 2020	Retrospective, SC	China	270	↑NLR in severely ill COVID-19 patients
54.	Xie et al,[75] 2020	Retrospective, SC	China	97	Eosinophil counts had a good value for COVID-19 prediction, even higher when combined with NLR.
55.	Xie et al,[76] 2020	Retrospective, MC	China	373	The NLR was higher in the severe group.
56.	Xu et al, 2020[77]	Retrospective, MC	China	338	NLR qualifies as an independent predictor of disease progression in COVID-19 patients.
57.	Zhang et al,[78] 2020	Retrospective, SC	China	148	NLR may act as a predictive tool to discriminate between severe and nonsevere COVID-19 patients

(continued)

Table 1. (continued)

SN	Author, Year	Type of study, center	Country	Total no. of patients	Outcome
58.	Zhang et al,[79] 2020	Retrospective, SC	China	115	↑NLR in severely ill COVID-19 patients
59.	Zhou et al,[80] 2020	Retrospective, SC	China	304	NLR, PLR, troponin-I, creatinine, and BUN are important indicators for severity grading in COVID-19.
60.	Zhu et al,[81] 2020	Retrospective, SC	China	127	NLR, fibrinogen, C-reaction protein (CRP), IL-6, interleukin-10 (IL-10), and interferon-γ (IFN-γ) in the severe group were significantly higher.
61.	Archana et al, 2021[82]	Cross-sectional, SC	India	302	NLR had a sensitivity of 85% and specificity of 51% in predicting mortality of COVID-19 patients.
62.	Asgar et al,[83] 2020	Retrospective, SC	Pakistan	191	Elevated NLR is positively correlated with morbidity and mortality of COVID-19 patients (AUC: 0.860, PPV: 91.1%)
63.	Baqi et al,[84] 2021	Retrospective, SC	Pakistan	299	NLR, C-reactive protein (CRP), and lactate dehydrogenase (LDH) were higher among the deceased COVID-19 patients
64.	Bisso et al,[85] 2020	Retrospective, SC	Argentina	168	NLR was higher among nonsurvivors.
65.	Cervantes et al,[86] 2021	Cross sectional,SC	Israel	337	NLR $\geq$ 8.5 increased the probability of death in severe COVID-19 (odds ratio 11.68).
66.	Lopez-Escobar et al,[87] 2021	Retrospective, MC	Spain	1955	NLR is useful in predicting in-hospital mortality risk due to COVID-19 (0.873 [95% CI: 0.849-0.898])
67.	Güneysu et al,[88] 2020	Retrospective, SC	Turkey	169	NLR $\geq$ 3.9 can be used as an early predictor of mortality in COVID-19 patients
68.	Prasetya et al,[89] 2021	Retrospective, MC	Indonesia	391	NLR $\geq$ 6 at hospital admission can be a good predictor for poor outcomes in COVID-19 patients.
69.	Kalabin et al,[90] 2021	Retrospective, SC	USA	184	NLR and PLR have no statistically significant predictive role in suspecting COVID-19 mortality.
70.	Kaufmann et al,[91] 2021	Retrospective, SC	Austria	423	COVID-19 patients with elevated NLR values had a higher frequency of in-hospital mortality
71.	Nasir et al,[92] 2021	Retrospective, SC	Bangladesh	99	Nonsurvivors had a high level of NLR (9.76) in comparison to survivors (5.9) at admission.
72.	Nicholson et al,[93] 2021	Retrospective, MC	USA	1042	NLR was significantly high among the deceased COVID-19 patients.
73.	Pujani et al,[94] 2021	Prospective, SC	India	506	NLR has an excellent prognostic role in predicting severity and mortality.
74.	Rasyid et al,[95] 2021	Retrospective, SC	Indonesia	295	NLR can be considered as an early predictive factor of COVID-19 disease progression.
75.	Rokni et al,[96] 2020	Retrospective, SC	Iran	233	Nonsurvivors had a high level of NLR (11.08) in comparison to survivors (4.69) at admission.
76.	Ruiz et al,[97] 2020	Retrospective, SC	Spain	119	COVID-19 patients with initial elevated NLR at admission had a poor outcome.
77.	Allahverdiyev et al,[98] 2020	Retrospective, SC	Turkey	455	The mortality rate of COVID-19 positively correlated with higher NLR (OR = 1.261, 95% CI: 1.054-1.509, $P = .011$)
78.	Yufei et al,[99] 2020	Retrospective, SC	China	191	Elevated NLR was found to be an independent risk factor for COVID-19.
79.	Ghazanfari et al,[100] 2021	Retrospective, MC	Iran	79	NLR showed a significant association with the mortality of COVID-19 patients
80.	Jian-bo Xu et al,[101] 2020	Retrospective, MC	China	76	NLR has not been proven as an independent predictor of survival in patients with COVID-19.
81.	Zhi-Yong Zeng et al,[102] 2021	Prospective, SC	China	352	NLR at admission can be used as a predictor for disease severity and mortality in COVID-19 patients.
82.	Wang P et al., 2020[103]	Retrospective, MC	China	441	NLR and D dimer ($\geq$1 μg/mL) helps to predict the severity of COVID-19 patients.
83.	Xia et al,[104] 2020	Retrospective, SC	China	63	NLR can be used as an early warning signal for severe COVID-19
84.	Mousavi-Nasab et al,[105] 2020	Retrospective, SC	Iran	70	NLR and CRP are potential early markers for assessing the prognosis and severity of COVID-19 patients
85.	Sepulchre et al,[106] 2020	Retrospective, SC	Belgium	198	Elevated NLR in COVID-19 Patients had a higher rate of in-hospital mortality
86.	Tahtasakal et al,[107] 2021	Retrospective, SC	Turkey	534	An elevated baseline NLR, CRP, troponin I, LDH are associated with increased severity.
87.	Asan et al,[108] 2021	Retrospective, SC	Turkey	695	Initial NLR was associated with the severity of COVID-19 disease

(continued)

Table 1. (continued)

SN	Author, Year	Type of study, center	Country	Total no. of patients	Outcome
88.	Imran et al,[109] 2021	Prospective, SC	Pakistan	63	NLR can be used as an early warning signal for deteriorating severe COVID-19
89.	Bastung et al,[110] 2020	Retrospective, SC	Turkey	191	Elevated D-dimer, NLR, and CRP were significant laboratory predictors of severe prognosis in COVID-19 patients.
90.	Mingming Fe et al,[111] 2020	Retrospective, SC	China	72	NLR can be used to stratify the severity of COVID-19 patient

Abbreviations: SC, single center; Mc, multicenter; NLR, neutrophil-to-lymphocyte ratio.

test ($P = .01$) and Egger's test (0.23) indicate a mild risk of publication bias quantitatively.

Discussion

We discovered low-quality evidence with variability for the baseline elevated NLR on admission as a potential predictor of poor outcomes in COVID-19 patients.

Similarly, the severe COVID-19 patients have been reported to have increased, neutrophilia, lymphopenia, and thrombocytopenia than those with milder disease.[112] Most of these patients were reported to develop ARDS and thereby required intensive care unit (ICU) admission.[113,114] Thus, the raised NLR could be a potential cost-effective biomarker for predicting the disease severity as it indicates a combination of relative neutrophilia and lymphopenia in near real-time without any specific assay requirement unlike other biomarkers: D-dimer, IL6, C-reactive protein, and so on.

A recent meta-analysis also reported severe COVID-19 patients had a higher NLR value (SMD: 2.80, 95% CI: 2.12-3.48) in comparison to patients with nonsevere disease. They have also found raised NLR values in the expired in comparison to the survivors (SMD: 3.72, 95% CI: 0.53-6.90).[115]

Similarly, Feng et al[116] have found that that elevated NLR is associated with disease severity in COVID-19 patients. (OR = 2.50, 95% CI: 2.04-3.06, $P < .001$).

The current study not only found that baseline elevated NLR was associated with mortality and disease severity but also quantified the predictive value through Summary Receiver operating curve analysis.

While Zhang et al[117] have reported NLR ≥ 8 is associated with increased 28-day mortality (HR 9.74, 95% CI: 5.96-15.94) in the Univariable Cox regression model of 516 COVID-19 patients, Li et al[118] have reported the cut-off NLR ≥ 4.5 and 6.5 for severity (AUC 0.86, 95% CI: 0.83-0.89) and mortality (AUC 0.92, 95% CI: 0.89-0.94).

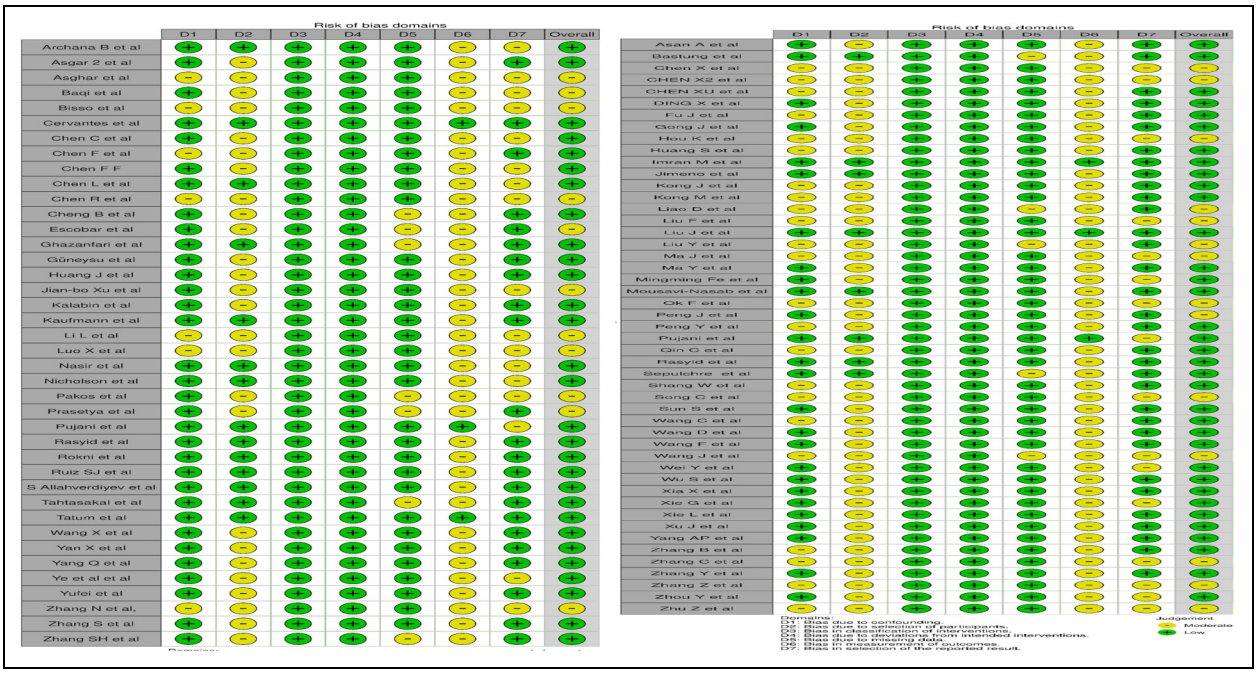

Figure 2. Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) assessment for the included non-randomized cohort studies.

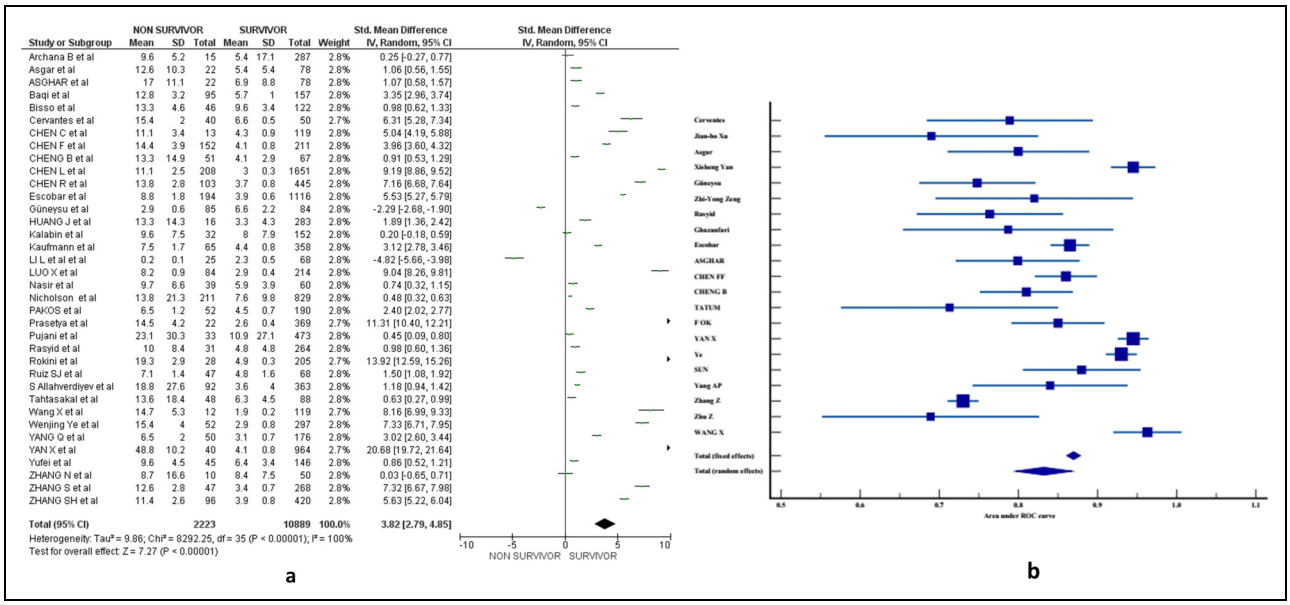

Figure 3. (a) The impact of the NLR on mortality in COVID-19 patients and (b) summary receiver operating curve analysis of the NLR on mortality in COVID-19 patients.
Abbreviations: NLR, neutrophil–lymphocyte count ratio; COVID-19, coronavirus disease 2019.

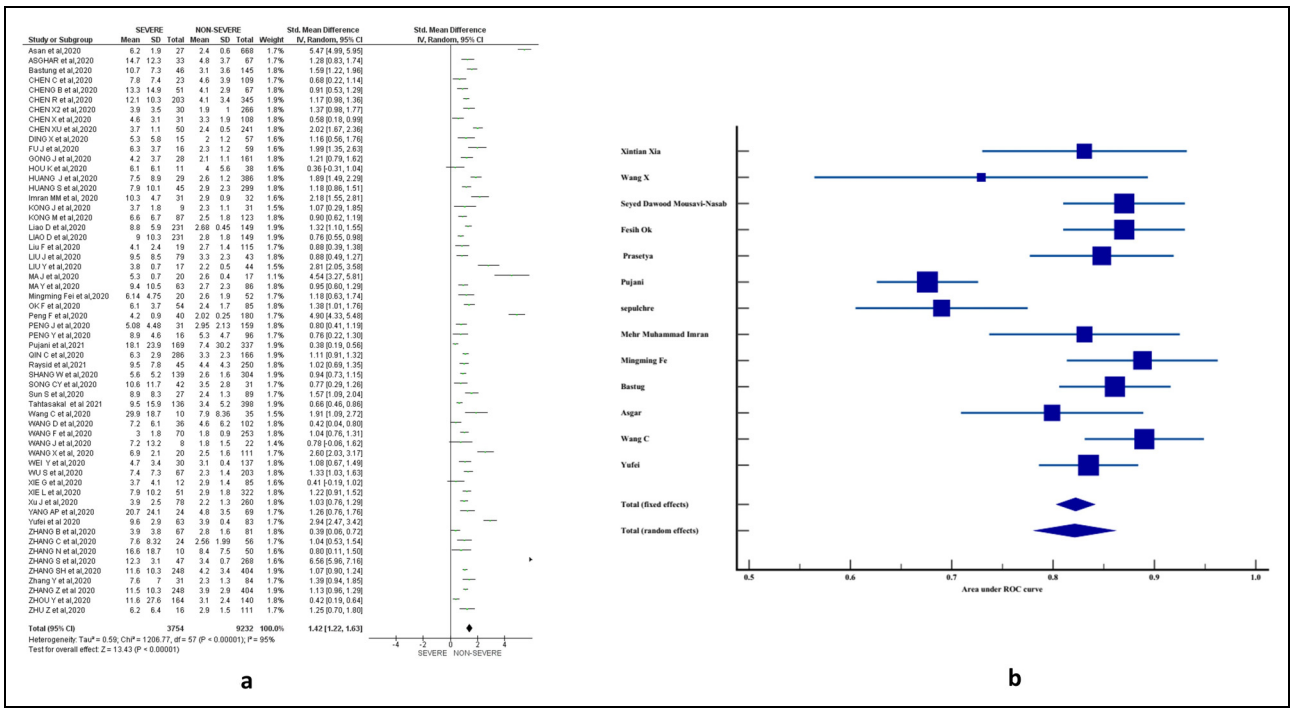

Figure 4. (a) The impact of NLR on disease severity in COVID-19 patients and (b) summary receiver operating curve analysis of the NLR on disease severity in COVID-19 patients.
Abbreviations: NLR, neutrophil–lymphocyte count ratio; COVID-19, coronavirus disease 2019.

There is no NLR consensus regarding the optimal cut-off value for determining the elevated level, particularly for COVID-19 patients. The wide variation implies that optimal cut-off values may vary in different populations as previously NLR has been found to vary with ethnicity, age, and sex.[119–121]

Table 2. GRADE Evidence Profile of COVID-19 Studies.

Out come	No. of participants			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence (Grade)	Relative effect
	Total no.	Raised NLR	Control							
Mortality	13 112	2223	10 889	No	No	Yes	No	None	Low ⊕⊕⊖⊖	SMD = 3.82 (95% CI: 2.79-4.85)
Severity	12 433	3538	8895	No	No	Yes	No	None	Low ⊕⊕⊖⊖	SMD = 1.40 (95% CI: 1.19-1.60)

Strengths and Limitations

This study is one of the substantial and compendious reviews of the effectiveness of baseline NLR at admission in COVID-19 patients for predicting the mortality and severity and can be contemplated for decision making at present.

However, the majority of the included studies are retrospective ($n = 82$) in nature, originated from China ($n = 62$), and associated with significant heterogeneity probably due to the use of different cut-off values of NLR. The outcome of the disease could be impacted by other confounding factors: comorbid conditions, frailty, gender, etc also, which we could not assess due to the unavailability of appropriate data. We also acknowledged that few included studies are preprint and not peer-reviewed ($n = 13$), and the optimum value of NLR is yet to be standardized and information in this context is still evolving.

Conclusion

NLR is a promising tool for risk stratification and prompt decision making about intensifying the management, further studies for assessing the suitable cut-off points of NLR to utilize the already constrained healthcare resources during the ongoing pandemic are the need of the hour.

Author Contributions

SS: Conceptualization, Search strategy, Study selection, Data extraction, Data synthesis, Risk of bias assessment, and Drafted the manuscript. PK: Conceptualization, Search strategy, Study selection, Risk of bias assessment, Quality of the evidence assessment, and Editing. AKS: Study selection, Data extraction, Risk of bias assessment, Quality of the evidence assessment, and Editing.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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ORCID iD

Puneet Khanna https://orcid.org/0000-0002-9243-9963

Supplemental Material

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