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META-ANALYSIS

The diagnostic and prognostic role of neutrophil-to-lymphocyte ratio in COVID-19: a systematic review and meta-analysis

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ABSTRACT

Background: The world urgently requires surrogate markers to diagnose COVID-19 and predict its progression. The severity is not easily predicted via currently used biomarkers. Critical COVID-19 patients need to be screened for hyperinflammation to improve mortality but expensive cytokine measurement is not routinely conducted in most laboratories. The neutrophil-to-lymphocyte ratio (NLR) is a novel biomarker in patients with various diseases. We evaluated the diagnostic and prognostic accuracy of the NLR in COVID-19 patients.

Methods: We searched for relevant articles in seven databases. The quantitative analysis was conducted if at least two studies were evaluating the NLR role in COVID-19.

Results: We included 8,120 individuals, including 7,482 COVID-19 patients, from 32 articles. Patients with COVID-19 had significantly higher levels of NLR compared to negative individuals. Advanced COVID-19 stages had significantly higher levels of NLR than earlier stages.

Expert Opinion: We found significantly higher levels of NLR in advanced stages compared to earlier stages of COVID-19 with good accuracy to diagnose and predict the disease outcome, especially mortality prediction. A close evaluation of critical SARS-CoV-2 patients and efficient early management are essential measures to decrease mortality. NLR could help in assessing the resource allocation in severe COVID-19 patients even in restricted settings.

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1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, a.k.a. COVID-19) is now much more hazardous than previously thought when compared to other viral pandemics. The H1N1 pandemic outbreak of 2009 caused 12,429 deaths over a year while the SARS-CoV-2 outbreak resulted in >13,000 over 5 weeks in the USA alone[1]. SARS-CoV-2 may present as a mild disease with interstitial and alveolar pneumonia; however, it can affect other organs, such as the kidneys, heart, digestive tract, and nervous system [2–5]. There are no specific antiviral therapies or vaccines for COVID-19 patients. Consequently, researchers started to use clinically accessible interventions utilized previously during SARS-CoV and the Middle East respiratory syndrome-coronavirus (MERS-CoV) outbreaks due to their genetic and clinical similarities [6].

Because of the rapid spread of the pandemic, the world urgently requires surrogate markers to diagnose COVID-19 infection. Perhaps as importantly, markers that help predict disease progression and severity are needed to help identify high-risk individuals in efforts to ensure optimal resource allocation in a time of significant resource demand. Effective predictors could also help screening, clinical management, and prevention of fatal sequelae. Indeed, critical COVID-19 status is not easily predicted via routinely used laboratory parameters including levels of platelets, eosinophil, hemoglobin, D-dimer, IL-6, lactate dehydrogenase, prothrombin time, activated partial thromboplastin time and transaminases [7–12]. Further, patients with severe COVID-19 infection need to

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Supplemental data for this article can be accessed here.

be screened for hyper-inflammatory status using laboratory biomarkers in efforts to improve morbidity and mortality since numerous studies suggest that a subgroup of critical COVID-19 infected patients could have immune dysregulation potentially contributing to the development of a virally induced hyper-inflammatory state [13]. Expensive cytokine profile measurement is not routinely performed in most laboratories and is needed to identify patients who would potentially benefit from anti-IL6 immunotherapies with tocilizumab [7]. In contrast, routine full blood count and white cell differentials are readily available and performed across the vast majority of healthcare settings caring for COVID-19 infected patients. Therefore, reliable markers of infection such as neutrophil-to-lymphocyte ratio (NLR), associated with IL-6, could be considered valuable in efforts to help diagnosis and prognosis.

The NLR, an inflammatory index reflecting systemic inflammatory cascades, is a novel biomarker in patients with pneumonia, various cardiovascular diseases, sepsis, multiple organ damage, cancer, and pregnancy complications [14–21]. Accumulated evidence has shed light on the pivotal diagnostic and prognostic role of NLR in infections. Han and coworkers demonstrated that NLR had better accuracy compared to the total leukocyte count, neutrophil or lymphocyte count and is used as an efficient diagnostic measure to screen individuals infected with influenza virus [22] because it is less influenced by physiological interference such as that seen with dehydration or physical activity. In addition, NLR has been measured and used to forecast recurrence in those with hepatitis B [23]. A comprehensive analysis of all published studies has not been conducted yet to investigate the estimated accuracy of NLR in the context of COVID-19 infections although several studies revealed its findings from routine blood tests in severe and non-severe COVID-19 patients. With this in mind, this systematic review and meta-analysis aimed to investigate the diagnostic and prognostic accuracy of the NLR in COVID-19 patients.

2. Methods

2.1. Search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental File 1) [24]. The protocol was registered on the International Prospective Register of Systematic Reviews PROSPERO (CRD42020201117). In July 2020, we conducted an electronic search to acquire pertinent studies on the following databases; PubMed, Embase, Institute of Science Index, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL). Prespecified search terms were utilized and adapted to each database to yield the most accurate results (Supplementary File 2). Moreover, the references from relevant studies and previous reviews were manually searched. Furthermore, Chinese databases such as Wanfang as well as China National Knowledge Infrastructure databases were searched. Three reviewers independently screened titles and abstracts according to our inclusion and exclusion criteria and any disagreements were resolved through discussion.

2.2. Selection criteria

The inclusion criteria were studies investigating the diagnostic and/or prognostic role of NLR in COVID-19 patients against the reference standard (polymerase chain reaction (PCR) test). Any original studies including clinical trials and observational studies with no restrictions regarding language, race, sex, country, year, and age were included. Our exclusion criteria were overlapped data sets and duplicated studies. Articles such as animal studies, case reports, previous reviews, conference, books, or thesis or author responses which do not have enough information to be extracted were excluded. Included studies were required to have a two-by-two table for the analysis constructed from the reported information, raw data, or sensitivity, and specificity of the NLR. We contacted the authors if these values were not reported. All full texts were reviewed carefully by three independent reviewers and where there was any disagreement it was resolved through discussion to reach a final decision.

2.3. Outcomes and extracted data

A standardized data extraction sheet was produced in Microsoft Excel. The data were extracted by three independent authors. The discussion was held if there were any disagreements. Conclusions were drawn with the consensus of the three authors or, if needed, discussed with a fourth author. Papers published by the same research group and/or studying the same outcomes were examined for potential duplicate information based on the month and year of patients' recruitment and hospital where the patients were recruited and confirmation from authors of the study. The extracted information included the authors' names, study design, year, number of patients, hospital, and country. Moreover, patients' demographics (such as age and gender), the cutoff value of NLR and the definition of the different groups such as severe COVID-19 patients were extracted.

Our primary outcome was to determine the diagnostic and/or prognostic accuracy of NLR in COVID-19 patients whereas our secondary outcome was to compare the values of NLR in different groups (control individuals versus mild, moderate, severe, and lethal COVID-19 infections).

2.4. Quality assessment

We used the quality assessment of diagnostic accuracy studies (QUADAS-2) method. The QUADAS-2 evaluates four items for bias and applicability of the research question including patients' selection, index test, reference standard, and flow and timing [25]. The quality of the included studies was evaluated by three authors independently and if any disagreement occurred, it was resolved through discussion.

2.5. Statistical analysis

The quantitative analysis was conducted if at least two studies were evaluating the role of NLR in COVID-19 diagnosis and prognosis. The accuracy measures included the sensitivity, specificity, likelihood ratios, and diagnostic odds ratio (DOR) with their 95% confidence intervals (CIs). A higher DOR indicates a higher diagnostic accuracy. AUC values of ≥0.5, 0.75, 0.93, or 0.97 were considered to represent fair, good, very good, or excellent accuracy, respectively [26,27]. Moreover, we also constructed a hierarchical summary receiver operator curve (SROC).

We used mean difference (MD) to compare values of NLR across different groups. A fixed-effect method [28] was applied when there was no evidence of heterogeneity between studies, otherwise, a random-effects method was chosen [29,30]. The heterogeneity between studies was evaluated using Q statistic and I^2 test [29,31,32]; where P-value = 0.1 and/or I^2 > 50% indicating a significant heterogeneity [33,34]. The heterogeneity was explored using meta-regression, and sensitivity as well as subgroup analysis according to the potential covariates such as study design, risk of bias, percentage of the event (such as severe or lethal cases of COVID-19 infection), males' per cent, the cutoff value of the NLR. The meta-regression has been used to explore between-study heterogeneity in meta-analysis studies aiming to incorporate the effect of the aforementioned covariates on summary measures of performance. Since the publication bias analysis is a concern for meta-analysis, it was conducted using the funnel plot and the Egger test [35]. We used the *Midas* command in Stata software version 12 [36] and Comprehensive Meta-analysis (CMA) software version 3 (Biostat, NJ, USA) for the analysis. A P-value <0.05 was considered significant.

3. Results

3.1. Search Results

Our search retrieved 291 articles, among which 74 duplicates were removed. The rest underwent abstract screening to yield 92 articles for full-text screening. Ultimately, a total of 32 articles with 8,120 individuals, including 7,482 COVID-19 patients, were included. Three articles were investigating the role of NLR in COVID-19 diagnosis, 2 in diagnosis and severity, 17 in severity, 4 in severity and mortality, 6 in mortality prediction only (Figure 1).

3.2. Studies and Patients' Characteristics

There were 28 retrospective articles with a male percentage ranging from 37.3 to 69% with only one study including only females, and mean age ranging from 28.4 to 65 years (Table 1). All studies used PCR as an inclusion criterion except for Pascual Gómez *et al*. who had 74.2% of the patients as positive SARS-CoV-2 cases by PCR [37].

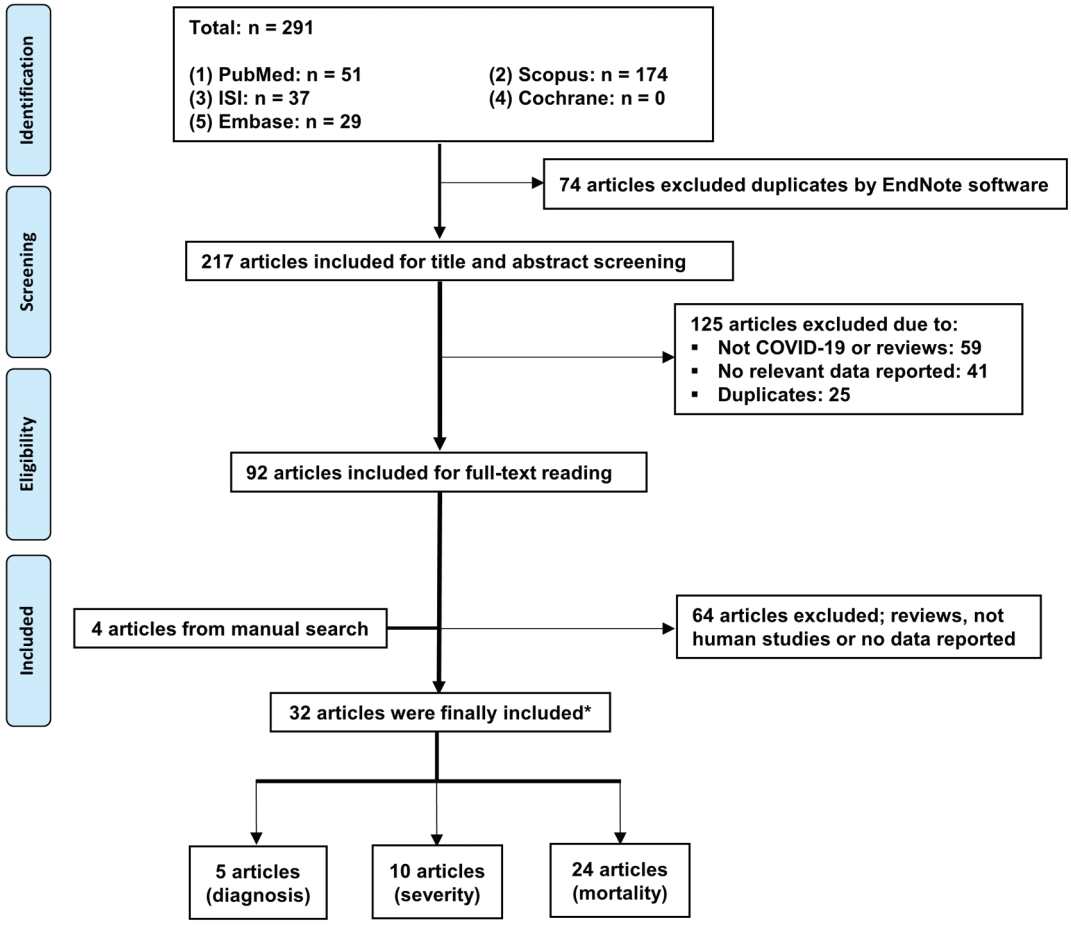

Figure 1. The PRISMA chart showing the flow of publications via the review process. *Out of 291 articles, a total of 32 articles with 8,120 individuals, including 7,482 COVID-19 patients, were included.*

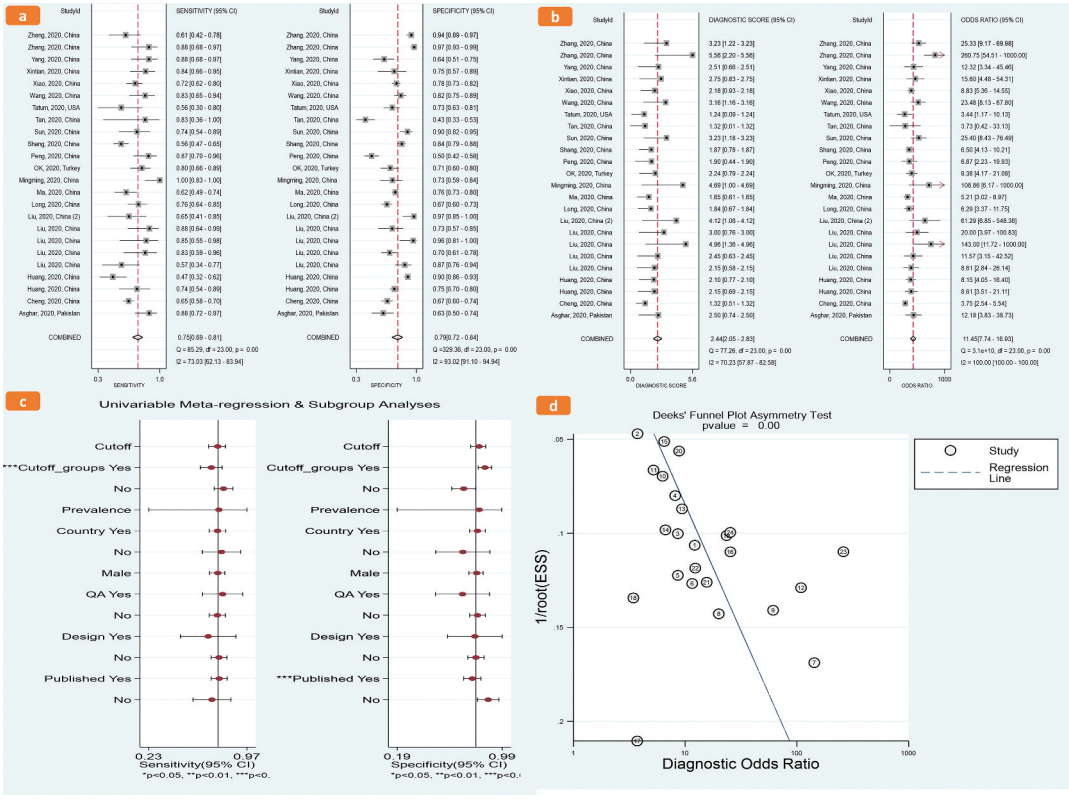

Figure 2. **The prognostic accuracy of NLR for prediction of severity of COVID-19**. *(a) forest plot showing the sensitivity and specificity with its 95% confidence intervals, (b) forest plot showing the positive and negative LR with its 95% confidence intervals, (c) uni-variable meta-regression to explore heterogeneity between studies assessing the prognostic accuracy of NLR, (d) Deeks' funnel plot asymmetry test for detecting the publication bias. Each circle indicates an individual study in the meta-analysis. The figures show that the accuracy measures for predicting severity were a sensitivity of 75% [69, 81%], a specificity of 79% [72, 84%] and DOR of 11.45 [7.74, 16.93]) and the P-values for heterogeneity and publication bias were <0.001.*

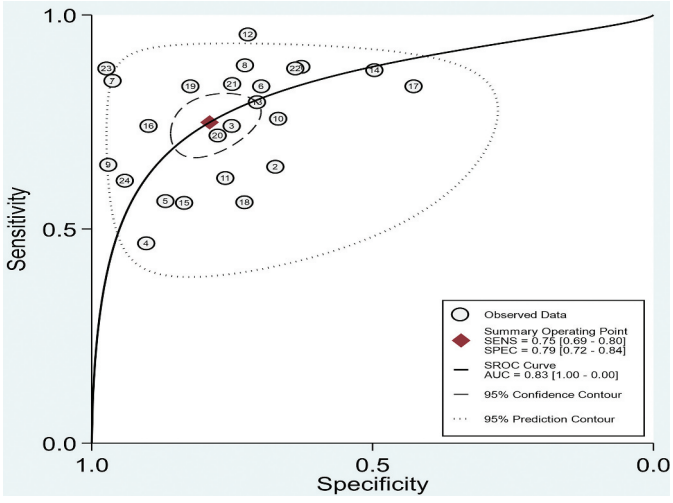

Figure 3. **The SROC and the AUC with each circle indicates an individual study in the meta-analysis**. *The curve is the regression that summarizes the overall test accuracy. The AUC = 0.83.*

3.3. Quality Assessment

Of the included articles, 27 were at low risk of bias, while only 5 were at high risk of bias (Table S2).

3.4. Quantitative Synthesis

3.4.1. Diagnosis

Patients with COVID-19 infection had significantly higher levels of NLR in comparison to negative individuals (MD [95% CI] = −1.48 [−1.74, −1.22], P-value<0.001), with an estimated sensitivity and specificity of 62% [52, 72%] and 80% [62, 91%], respectively and DOR of 6.69 [3.66, 12.25]). The positive and negative likelihood ratios [95% CI] were 3.14 [1.74, 5.67] and 0.47 [0.4, 0.55], respectively, and the AUC was 0.73 [0.69, 0.76]. With no publication bias (P-value = 0.48).

3.5. Severity

Moderate and severe COVID-19 infected patients had significantly higher levels of NLR than mild and non-severely infected patients, (MD [95% CI] = −1.09 [−1.58, −0.59] and −7.14 [−8.67, −5.6], respectively), yet, there was a significant publication bias (P-value <0.009). The accuracy measures for predicting severity were sensitivity of 75% [69, 81%], specificity of 79% [72, 84%], DOR of 11.45 [7.74, 16.93]) and AUC of 0.82 [0.78, 0.85] (Figures 2–4). The positive and negative likelihood ratios [95% CI] were 3.59 [2.74, 4.71] and 0.31 [0.25, 0.39], respectively, with a significant publication bias (P-value <0.001).

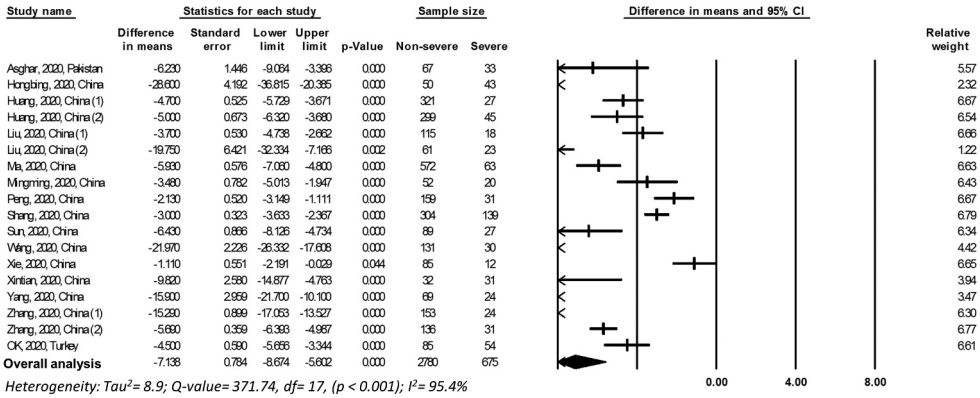

Figure 4. **A meta-analysis of the association between the NLR and COVID-19 severity**. *Forest plot showing the pooled MD with its 95% CI using a random-effects model. The black diamond represents the pooled effect size. The figure shows that moderate and severe COVID-19 infected patients had significantly higher levels of NLR than mild and non-severely infected patients.*

3.6. Mortality

Lethal cases of COVID-19 infection had significantly higher levels of NLR compared to non-lethal cases (MD [95% CI] of −16.1 [−27.24, −4.96], P-value = 0.005), with a sensitivity of 83% [75, 89%], specificity of 80% [71, 86%] and DOR of 18.69 [11.72, 29.81]) (Table 2). The AUC [95% CI] was 0.88 [0.85, 0.91] and the positive and negative likelihood ratios [95% CI] were 4.05 [2.9, 5.64] and 0.22 [0.15, 0.31], respectively, with no publication bias (P-value = 0.78).

3.7. Sensitivity and subgroup analysis and meta-regression

Our sensitivity analysis, through removing one study each time, did not alter the results (Table 3). Of note, we used subgroup analysis and meta-regression to see the effect of covariates and heterogeneity on the accuracy of the NLR in diagnosis and prediction. It is worth mentioning that heterogeneity was found. However, setting the cutoff value of NLR to ≥3.63 to predict COVID-19 severity was associated with lower sensitivity (70% [62–78%]) and higher specificity (86% [81–-91%]) while high risk of bias studies had lower accuracy in mortality prediction (sensitivity = 77% [66–89%] and specificity = 76% [64–89%]) (Table S3).

4. Discussion

In this study, we found significantly higher levels of NLR in advanced stages compared to earlier stages of COVID-19 with good accuracy to diagnose and predict the disease, especially to predict mortality from COVID-19.

COVID-19 diagnosis relies primarily on SARS-CoV-2 detection via PCR. Yet, there are still numerous drawbacks including false-negative findings due to a low viral load and the relative shortage of detection kits [65]. A test with the ability to discern quickly and early COVID-19 is needed as a biomarker to help predict and prevent associated morbidity and mortality. It was also suggested that routine blood tests were more acceptable for screening individuals with asymptomatic or mild COVID-19 and may be used for screening in outbreak areas [66]. NLR is readily calculated and cost-effective such that clinicians can screen high-risk individuals earlier. This is especially desirable in settings experiencing healthcare resource scarcity. It was stated that the NLR was the most helpful independent prognostic biomarker in determining the COVID-19 prognosis and the treatment efficacy [13,22,67–70]. Besides, NLR had a higher diagnostic accuracy than other assessment tools such as the CURB-65 and MuLBSTA scores [67]. It was demonstrated that procalcitonin does not enable clinicians to immediately decide if the infection is viral or bacterial and consequently if antibiotics are better to be administered or withheld [71]. Yet, the NLR is better compared to inflammatory markers including c-reactive protein or interleukin [13].

Acute respiratory distress syndrome (ARDS), featured by a rapid onset of generalized pulmonary inflammation, is the leading cause of death in SARS-CoV-2 patients. With this, elevated NLR reflecting an enhanced inflammation may suggest a poorer prognosis compared to those with lower NLR. Additionally, individuals with serious viral infection could have a bacterial co-infection due to their low immune response, resulting in an increased NLR [72]. The NLR elevation could occur due to dysregulation of inflammatory cytokine expression, an aberrant increase of pathological low-density neutrophils and up-regulation of genes involved in lymphocytic apoptosis [73–75]. Lymphocytes also are depleted as the virus is engulfed. Recent studies reported that the COVID-19 may primarily affect T-cells (particularly CD4+ and CD8 + T-cells) [76] but not absolute B-cell and natural killer (NK) cells [77]. The virus' ability to infect T-cells through ACE-2 receptors and cluster of differentiation (CD)147-spike proteins is another mechanism [78]. The inflammatory response may trigger hyper-secretion of inflammatory cytokines including TNF-α and IL-6, leading to permanently high neutrophils. In contrast, catecholamines, cortisol, and the increased pro-inflammatory mediators will bind to lymphocytic surface receptors and subsequently initiate lymphocytic apoptosis, leading to lymphopenia [79], and clinical deterioration in COVID-19. The rise of pro-inflammatory cytokines with lymphopenia predisposes severe COVID-19 patients to cytokine storm, thus leading to more lymphocytic apoptosis and multi-organ failure [13,67,80,81].

The severity of pathologic injury during SARS or MERS correlates with the extensive infiltration of neutrophils in the lung and increased neutrophils in the peripheral blood [82]. The extent of

Table 1. Summary of characteristics of the included studies*.

Author, year, country	Study design	Sample size	COVID-19 Cases/Severe/Died	Age, years*	Male, %	Risk of bias#
Anggraini, 2020, Indonesia[66]	Cross-sectional***[38]***	9	9/NR/0	28.44	0	Low
Asghar, 2020, Pakistan[39]	Retrospective	100	100/33/22	52.58	69	High
Chen, 2020, China[40]	Retrospective	681	681/681/104	65	53.2	Low
Cheng, 2020, China[41]	Retrospective	456	456/251/46	54.97	46.27	Low
Hongbing, 2020, China[42]	Retrospective	93	93/43/31	62.07	59.1	Low
Huang, 2020, China[43]	Retrospective	415	415/29/NR	44	52.3	Low
Huang, 2020, China[44]	Retrospective	344	344/45/15	52.9	54.7	Low
Hui, 2020, China[45]	Retrospective	84	84/NR/42	66.5	66.7	Low
Liu, 2020, China[67]	Prospective	115	115/37/0	42.5**	55.7	Low
Liu, 2020, China[77]	Retrospective	40	40/13/3	48.7	37.5	Low
Liu, 2020, China[46]	Retrospective	84	84/43/3	53	56	Low
Liu, 2020, China[47]	Retrospective	134	134/19/0	51.5	47	High
Long, 2020, China[70]	Prospective	301	301/66/17	51	49.8	Low
Shi, 2020, China[48]	Retrospective	723	696/63/NR	45.27	52.1	Low
Mingming, 2020, China[49]	Retrospective	72	72/20/NR	58.01	44.4	Low
Nalbant, 2020, Turkey[50]	Retrospective	80	54/NR/NR	55.3	51	Low
Ok, 2020, Turkey[51]	Retrospective	139	139/54/13	55.5	44.6	Low
Pascual Gómez, 2020, Spain[37]	Retrospective	163	163/NR/33	64.75	49.7	High
Peng, 2020, China[52]	Retrospective	485	190/31/NR	46.64	48.7	Low
Rocio, 2020, Spain[53]	Prospective	501	501/42/36	52	63.3	High
Shang, 2020, China[54]	Retrospective	443	443/139/NR	56	49.7	Low
Sun, 2020, China[55]	Retrospective	116	116/27/NR	54.5**	51.7	Low
Tan, 2020, China[56]	Retrospective	102	27/6/two	39.2**	37.3	Low
Tatum, 2020, USA[57]	Retrospective	125	125/16/23	58.7	45.6	High
Wang, 2020, China[58]	Retrospective	45	45/10/NR	39	51.1	Low
Xiao, 2020, China[59]	Retrospective	442	442/103/19	NR	50.2	Low
Xie, 2020, China[60]	Retrospective	324	109/12/1	50.25**	54.2	Low
Xintian, 2020, China[69]	Retrospective	63	63/31/NR	62.25	52.4	Low
Yan, 2020, China[61]	Retrospective	1,004	1004/66/40	65**	49.1	Low
Yang, 2020, China[62]	Retrospective	93	93/24/NR	46.4	60.2	Low
Zhang, 2020, China[63]	Retrospective	177	177/24/NR	44.13	55.9	Low
Zhang, 2020, China[64]	Retrospective	167	167/31/0	46	60	Low

*Abbreviations; NR. *Mean or median as reported by the included study. **This is the mean of two reported values for two groups as reported by the included study. #According to the QUADAS-2 tool recommendations, if a study is judged as 'low' on all domains relating to bias or applicability, then it is appropriate to have an overall judgment of 'low risk of bias' or 'low concern regarding applicability' for that study while If a study is judged 'high' or 'unclear' in one or more domains, then it may be judged 'at risk of bias' or as having 'concerns regarding applicability'*[25].

the increased neutrophils could therefore suggest the intensity of inflammatory responses in COVID-19. Bearing both of these issues in mind, the NLR may serve as a useful factor to reflect the intensity of imbalance of inflammation and immune responses in COVID-19, particularly seeing as how it drops upon improvement of the clinical condition [66,83].

Growing evidence has revealed that neutrophils exhibit both pathological and protective functions [84]. Neutrophil survival may be prolonged for several days after viral infection [85]. The prolonged activation of neutrophils leads to the production of pro-inflammatory mediators and toxins, which are harmful to cells [86,87]. Neutrophils constitute the non-specific immunity that initiates the body's responses to inflammation, whereas lymphocytes constitute the protective element against inflammation, indicate the extent of immune system impairment and are important for dampening over-active innate immune responses during viral infection [88]. Thus, lymphopenia may result in aggravated inflammatory processes while restoration of T-lymphocytes may alleviate them. Some studies have suggested that lymphopenia indicates that SARS-CoV-2 consumes many immune cells, inhibits the cellular immune function, and results in a reduced but hyper-activated peripheral T – lymphocytes; actions that partially account for the severe immune injury in COVID-19[62].

Of note, we included missing data given by included article's authors, conducted risk of bias evaluation, and provided sensitivity analysis by removing articles with a high risk of bias. Our results are robust because our findings were the same in nearly all sensitivity and subgroup analyses where exclusion of studies with a poor QUADAS-2 assessment or a study with negative PCR for some of the included patients did not alter the conclusions [37]. Our analysis is however not without some limitations. The effect of heterogeneity may be low because most of the studies were in China. Additionally, it was unclear when in the disease course the NLR values were measured; depending on the severity of COVID-19 infection, NLR values may change during the disease course. Although the NLR had high accuracy, no unified cutoff is present, and its accuracy can be influenced by clinician experience. With this in mind, due diligence should be made while interpreting NLR findings in this context.

5. Expert Opinion

Laboratory biomarkers to forecast the severity of COVID-19 are essential in a pandemic because resource allocation must be carefully planned. NLR could help in assessing the allocation of respiratory equipment in ICU patients and early evaluation for those in need of ECMO. The close evaluation of COVID-19 severity and effective early interventions are key measures to reduce mortality. Indeed, it is strongly recommended that physicians should use a combination of readily available biomarkers to better diagnose and/or predict COVID-19 than depending on a single test. A prospective data collection

Table 2. The summary estimates of the diagnostic and prognostic role of NLR in COVID-19.

Prediction	Studies/individuals number	Sensitivity, 95% CI	Specificity, 95% CI	DOR, 95% CI	LR, 95% CI		AUC, 95% CI	P-value of heterogeneity	P-value of *publication bias*
					Positive	Negative			
Diagnosis	5/885	62 [52, 72]	80 [62, 91]	6.69 [3.66, 12.25]	3.14 [1.74, 5.67]	0.47 [0.4, 0.55]	0.73 [0.69, 0.76]	<0.001	0.48
Severity	24/4,845	75 [69, 81]	79 [72, 84]	11.45 [7.74, 16.93]	3.59 [2.74, 4.71]	0.31 [0.25, 0.39]	0.82 [0.78, 0.85]	<0.001	<0.001
Mortality	10/3,333	83 [75, 89]	80 [71, 86]	18.69 [11.72, 29.81]	4.05 [2.9, 5.64]	0.22 [0.15, 0.31]	0.88 [0.85, 0.91]	<0.001	0.78

Abbreviations; CI = confidence interval, DOR = diagnostic odds ratio, LR = likelihood ratio.

Table 3. The summary estimates of comparisons between negative control and different COVID-19 groups.

Comparison	Studies	Number of individuals	MD (95% CI)	P-value	Heterogeneity		Egger's 2-tailed bias p-value	Largest p-value after removing any single study
					P-value	I^2, %		
Negative versus positive SARS-CoV-2 groups	4	392/394	**−1.48 [−1.74, −1.22]**	**<0.001**	0.817	0	-	<0.001
Mild versus Moderate	2	103/605	**−1.09 [−1.58, −0.59]**	**<0.001**	0.319	0	-	<0.001
Non-severe versus Severe	18	2,780/675	**−7.14 [−8.67, −5.6]**	**<0.001**	<0.001	95.4	0.009	<0.001
Survived versus Died	7	2,380/290	**−15.04 [−23.92, −6.16]**	**0.001**	<0.001	99.1	-	0.034

Abbreviations; CI = confidence interval, MD = mean difference, LR = likelihood ratio. Significant differences are in bold.

with a multi-variable prediction model is required to derive a robust score for COVID-19 diagnosis and prediction.

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Prospero Registration ID: CRD42020201117.

- **Question**: What is the diagnostic and prognostic accuracy of neutrophil-to-lymphocyte ratio (NLR) in COVID-19?
- **Finding**: We found significantly higher levels of NLR in advanced stages compared to earlier stages of COVID-19 with good accuracy to diagnose and predict the disease, especially to predict the mortality from COVID-19.
- **Meaning**: NLR could help in assessing the resource allocation in severe COVID-19 patients even in restricted settings.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Availability of data and material

The dataset supporting the conclusions of this article is included within the article (and its additional files).

Authors' contributions

AAAMMA: this author helped in developing the idea, designing the study, writing the protocol, searching the databases, screening, data extraction, writing, and reviewing the manuscript and approving the final version.

MGK: this author helped in developing the idea, designing the study, writing the protocol, searching the databases, screening, data extraction, writing, and reviewing the manuscript and approving the final version.

MKH: this author helped in writing the protocol, screening, data extraction, writing, and reviewing the manuscript and approving the final version.

EMF: this author helped in writing the protocol, screening, data extraction, writing, and reviewing the manuscript and approving the final version.

HMY: this author helped in writing the protocol, screening, data extraction, writing, and reviewing the manuscript and approving the final version.

ME: this author helped in writing the protocol, screening, data extraction, writing, and reviewing the manuscript and approving the final version.

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Supplementary material

Supplemental data for this article can be accessed here.

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