Prognostic value of Neutrophil-to-lymphocyte ratio in COVID-19 patients: A systematic review and meta-analysis

ABSTRACT

Background: Neutrophil-to-lymphocyte ratio (NLR) is an accessible and widely used biomarker. NLR may be used as an early marker of poor prognosis in patients with COVID-19.

Methods: We conducted a systematic review and meta-analysis. Observational studies that reported the association between baseline NLR values (i.e. at hospital admission) and severity or all-cause mortality in COVID-19 patients were included. The quality of the studies was assessed using the Newcastle-Ottawa scale (NOS). Random effects models and inverse variance method were used for meta-analyses. The effects were expressed as odds ratios (OR) and their 95% confidence intervals (CI). Small study effects were assessed with the Egger's test.

Results: Twenty studies, 19 cohorts and one case-control were included. An increase of one unit of NLR was associated with a higher odds of COVID-19 severity (OR 6.6, 95% CI: 4.71 - 7.19; p<0.001) and higher odds of all-cause mortality (OR 12.7, 95% CI: 1.32, 123.36; p=0.025). No differences were found in subgroup analyses by study design. The subgroup analysis of the studies, by country of origin, showed that the strength of the association between NLR and mortality was greater in Chinese studies (OR 31.1; 95%CI 19.57 to 49.3; p<0.0001) with moderate heterogeneity (I^2 =43%). In our sensitivity analysis, we found that 7 studies with low risk of bias maintained strong association between both outcomes and the NLR values (severity: OR 4.7; 95% CI 3.5 to 6.34; p < 0.001 vs mortality: OR 31.1; 95% CI 19.57 to 49.3; p <0.0001), with low (I^2 = 37%) and moderate (I^2 = 43%) heterogeneity for

severity and mortality outcomes, respectively. No publication bias was found for studies that evaluated effects for the severity of disease.

Conclusions: Higher values of NLR were associated with severity and all-cause mortality in hospitalized COVID-19 patients.

Keywords: COVID-19, NLR, Prognosis, Severity, Mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection caused by SARS-CoV-2 [1–3]. On January 30, 2020, the WHO declared the epidemic as a public health emergency of international interest[4]. After more than 20 000 cases and 1 000 deaths in the European Region, the WHO classified the disease as a pandemic [5]. To date (October 14, 2020), more than 48 million cases and 1.10 M deaths have already been reported across the world [6] According to recent studies, the basic reproduction number (R0) is 3.38, suggesting high transmissibility[7]. Besides the significant human losses, the quarantine and social distancing have had a great impact on the global economy [8]. However, despite the implementation of these strategies, the incidence of cases has been increasing in some countries, and nowadays, some nations are experiencing a second wave.

Sociodemographic and clinical factors, such as older age, male sex, hypertension and diabetes mellitus increase the mortality rate of COVID-19 [9,10]. However, these factors have different distributions between countries [11]. In June 2020, a meta-analysis reported that the global mortality rate was 2.72% (95%CI 2.19-4.76)[12]. Additionally, a current meta-analysis reported a 46% (95% CI 18.48−73.6) prevalence of asymptomatic patients, which has made it difficult to control the pandemic [12]. On the other hand, in symptomatic patients, the most common manifestations are fever, cough, dyspnea, muscle fatigue or muscular pain, and chest distress. Moreover, 29.3% of those infected require admission to the intensive care unit [12]. Regarding the patients admitted to the intensive care unit, reports do not suggest high mortality in them[13].

The Neutrophil-to-Lymphocyte Ratio (NLR) is an accessible, reproducible, and widely used biomarker for evaluating the prognosis of many health-related problems such as cardiovascular diseases, various types of cancer, ocular diseases, infectious diseases, among

others [14–20]. The biological basis of this biomarker is related to the response of the innate immune system against systemic inflammation, injury, and stress. This is characterized by lymphocytopenia and neutrophilia[21]. Although there is no consensus on normal cut-off values, two studies reported a cut-off value of 1.65 and 1.70 [22,23]. Recently, a study showed that NLR is elevated in patients with severe COVID-19 and the authors suggest that its performance in the prognosis of severe disease should be further evaluated [24]. A brief meta-analysis, with several limitations, reported that the NLR was a good tool to assess the prognosis of severity in patients with COVID-19 [25]. NLR evaluation can help physicians in initiating treatment and monitoring patient, thereby improving the prognosis and outcomes.

Several studies have evaluated the performance of the NLR in the prognosis of patients with COVID-19, so it is necessary to synthesize these results to give a more reliable tool for physicians. The objective of this study was to evaluate the prognostic value of the NLR in patients diagnosed with COVID-19.

METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [26] statement to report our systematic review. A short version of our protocol has been registered in the International Prospective Register of Systematic Review (PROSPERO) [CRD42020190508]

Data sources and searches

We conducted a bibliographic search of studies assessing the association between NLR and clinical outcomes in patients diagnosed with COVID-19 in the following databases: OVID Medline, OVID Embase, PubMed, Web of Science, Scielo, Scopus, LILACS, Cochrane Library, WHO COVID-19 Global Research Database. Additionally, a manual search was performed in ScienceDirect, Springer Link, CNKI databases, and pre-prints platforms, such as medRxiv and Scielo Preprints (see Supplemental Appendix 1). The search strategy was done using the Peer Review of Electronic Search Strategies (PRESS) Checklist [27]. Our team co-built the search strategy in PubMed, and it was adapted to the other bibliographic databases. We did not apply language restrictions.

Study selection and data extraction

We included studies that complied the following criteria: (1) prospective or retrospective observational studies (cross-sectional, case-control and cohort studies), (2) adult patients (aged > 18 years old) who were diagnosed with COVID-19, (3) NLR values reported at hospital admission, (4) studies that assessed the association between NLR values and disease severity or other clinical outcomes in COVID-19 patients, and (5) studies published until June 14, 2020. Moreover, we excluded studies that met the following criteria:1) studies conducted in animals, 2) duplicate studies, 3) conference abstracts, 4) case reports, 5) systematic reviews and 6) scoping reviews. Our primary outcome was disease severity, which

was defined as meeting at least one of the following criteria: ICU admission, shortness of breath, respiration rate (RR) ≥30 times per minute, blood oxygen saturation at rest ≤ 93%, $PaO_2/FiO_2 \leq 300$ mmHg. However, definitions of severity vary among studies. Mortality was also considered as a secondary outcome.

The articles that were found by the search strategy were grouped, eliminating duplicate studies. Four reviewers (IST, JRU, EAB-B and AAC) independently analyzed the titles and abstracts of the selected articles to choose potentially relevant articles. Once the potential literature to be included in our study was found, four authors (IST, JRU, EAB-B and AAC) independently read the full text of each article selected. If an article did not meet with one or more selection criteria, it was excluded from our study. Discrepancies were resolved by consensus among the team of researchers in each stage. We used Rayyan QCRI software to conduct the process of screening and selection of studies [28]. Finally, two authors (IS and JRU) extracted the data from studies through a standardized data extraction sheet made in Microsoft Excel. We extracted the following information: title of the study, first author, year of publication, study design, country and name of the hospital where the study was performed, number of participants, sex, age, comorbidities, stratified sample data, mean or median NLR of the whole sample and according to sample stratification, crude and adjusted association measures, type of outcome and its definition.

Evaluation of study quality and publication bias

The quality of the studies was assessed with the Newcastle-Ottawa Scale (NOS)[29] by two authors. This tool evaluates the quality of published non-randomized studies and is based on three items: selection, comparability, and outcome/exposure. Each item has subitems, on which a star-based score was assigned. Studies with scores≥6 were considered as having a low risk of bias (high quality), scores of 4–5 as having a moderate risk of bias, and scores<4

as having a high risk of bias. Furthermore, funnel plots and Egger's test was carried out to assess publication bias, p-values >0.1 were considered as indicative of no publication bias.

Data synthesis and analysis

The statistical analyses were performed using Review Manager 5.3 (RevMan 5.3) (The Cochrane Collaboration, Copenhagen, Denmark). Measures of association such as Hazard Ratio (HR) and Relative Risk (RR) were converted into Odds Ratio (OR) which was the only association measure used [30,31]. In order to analyze continuous NLR values, we used the Chinn´s method [32]. This method allowed us to transform standardized mean differences to their equivalent OR per study. Then we calculated the natural logarithm of the OR (*logOR*) and its standard error (*SE[logOR]*) for each one of the studies. The variables reported as medians and interquartile ranges (IQR) were converted into means and standard deviations (SD), respectively. The mean was estimated by the formula $x = (a + 2m + b)/4$ using the values of the median (m), P25 and P75 (a and b, respectively). Likewise, the SD was estimated using the following formula: SD= IQR/1.35 [33,34].

The heterogeneity of the studies in the measure of the effects was evaluated using the I^2 statistic. Values greater than 60% were considered as severe heterogeneity, 40-60% as moderate heterogeneity and less than 40% as mild heterogeneity. The Cochran Q test was also reported. A p-value of <0.05 was considered statistically significant. We conducted a random effects meta-analyses as we anticipated that there was heterogeneity of among studies. We performed subgroup analyses by location of the study (Chinese vs Non-Chinese studies) and study design (cohorts, case-control studies), and reported the interaction test p-value per subgroup analysis. Finally, sensitivity analyses were performed only using the low risk of bias studies.

RESULTS

Study selection

The flow diagram summarizing the process of study retrieval is shown in Figure 1. In the initial electronic search, a total of 221 records were found. After excluding duplicate studies, 77 studies were preserved. Subsequently, during the evaluation of titles and abstracts, 38 more records were excluded. Finally, during the full-text assessment, 19 articles were removed due to group imbalance, wrong analysis, wrong exposure, or the patients were not older than 18 years. Finally, 20 studies were selected for the qualitative synthesis and 20 studies for quantitative synthesis.

Study characteristics

The characteristics of the studies are presented in Table 1 [35–50] and supplemental Table S1 [51–54] For this systematic review, 19 cohort studies and only one case-control study were included, most of them conducted in China, having only one study conducted in the USA. On the other hand, our primary outcome severity was present in 16 studies [35-50], the secondary outcome, mortality, was present in 2 studies [51,52], and two studies analyzed both outcomes [53,54].

There was a total of 3963 patients within the studies, 51.32% were males, and age ranged from 39 to 58.7 years, only two studies did not present information about age. In five studies, the days elapsed for the development of severity, from the day of admission, were reported, giving an average of 8.62 days that range from 6 to 13 days.

The Newcastle-Ottawa Scale was used for the quality assessment of the studies (see supplemental Table S2). It was identified that 1 study had a high risk of bias, 12 studies had a moderate risk of bias, and only 7 had a low risk of bias.

Association of NLR with disease severity in hospitalized COVID-19 patients

This association was evaluated in 18 studies (n=3745). As shown in Figure 2A, we found that higher NLR levels were associated with higher odds of severity in patients with hospitalized COVID-19 diagnosis (OR 6.58; 95% CI 4.71 to 7.19; p<0.001). Because of severe heterogeneity (I^2 =75%, Chi-square p<0.10), subgroup analysis by study design (Figure 2B) did not change the main effects (cohorts: OR 6.94; 95% CI 4.93 to 9.76; p<0.001 vs. case-control studies: OR 2.46; 95% CI 41 to 3.06; p 0.05; interaction test p-value = 0.03) . In sensitivity analysis including only studies at low risk of bias, the association between NLR values and severity was still present (OR 4.72; 95% CI 3.5 to 6.34; p<0.001) with low heterogeneity (I^2 =37%, Chi-square p=0.13) (Figure 2C).

Association of NLR with all-cause mortality in hospitalized COVID-19 patients

This association was evaluated in 4 studies (n=1064). As presented in Figure 3A, we found that higher values of NLR were associated with higher odds of all-cause mortality in hospitalized COVID-19 patients (OR 12.74; 95%CI 1.32 to 123.36; p=0.025) with high heterogeneity of effects. The subgroup analysis by country of origin showed that the strength of the association between NLR and mortality was even higher in Chinese studies (OR 31.06; 95%CI 19.57 to 49.3; p<0.0001) with low heterogeneity (I^2 =43%); the association in the non-Chinese studies was very different to the main mortality analysis (OR 1.15 95%CI 1.02 to 1.29; p=0.0196), and there was differences between effects by country of origin (p-value of interaction test <0.00001). In the sensitivity analysis of low risk of bias studies, the heterogeneity (I^2 =43%, Chi-square p=0.17) and the association between NLR values and mortality was similar to the subgroup of Chinese studies (OR 31.06; 95%CI 19.57 to 49.3; p<0.0001) (Figure 3C).

Publication bias

There was no indication that there were small study effects for the severity of disease (Egger test p=0.205) (see Supplemental Figures S4.A and S4.B).

DISCUSSION

In the current context of the COVID-19 pandemic, an efficient, fast, and cheap method is required to determine the prognosis of patients with COVID-19. Given the growing number of studies that established NLR as a possible prognostic biomarker of severity and mortality in patients diagnosed with COVID-19, we decided to carry out a systematic review and a meta-analysis to consolidate the information regarding this topic. The present meta-analysis incorporated a total of 20 studies and found that high NLR values on admission day were associated with progression towards severity and mortality.

The prognostic value of NLR has been studied and correlated to multiple chronic, inflammatory and infectious diseases [14-20], like community-acquired pneumonia (CAP), where, NLR had a more significant prognostic performance towards severity than other markers such as white blood cell count, CRP, and neutrophil count [55]. Likewise, NLR has also been proven to predict 30-day mortality in CAP with a positive predictive value of 100% and a negative predictive value of 78% [56].

The hemogram is usually altered in COVID-19 patients, being higher in patients with severe illness compared to mild illness[57]. This could be reflected in the cohort study conducted by Wang S. et al. in COVID-19 patients where was found that an increase on NLR values was associated with severity (OR 8.56, 95% CI, 1.39 - 52.61, p = 0.021) as we found in our study [58]. The biological mechanism by which these variations arise in the neutrophil and lymphocyte counts has not been elucidated so far; however, several possible explanations have been proposed. The first one is based on the physiological relationship that exists between systemic inflammation and stress with the appearance of neutrophilia and lymphocytopenia. The second possible explanation is based on the depletion of the number of lymphocytes, especially CD4 + and CD8 + T cells. These two agents have as one of their

functions, the regulation of the immune system response against viral infections. A low circulating number of these two lymphocytes could cause a generalized dysregulation of the immune system, especially of neutrophils. On the other hand, lymphocytopenia has been linked to lymphocyte exhaustion and to the ability of SARS-CoV-2 to infect lymphocytes. Lymphocyte exhaustion occurs in chronic inflammatory processes where there is a continuous and excessive stimulation of T lymphocytes that causes their exhaustion and therefore impairing their functions [59–62].

Two meta-analyses have previously been published where the prognostic value of NLR was analyzed in patients diagnosed with COVID-19; the first one by Lagunas-Rangel[63] and the second one by Xudong Feng et al. [25] . Despite the existence of these studies, it was necessary to carry out a systematic review exclusively about the neutrophil-lymphocyte ratio because the previous studies presented an exceedingly small number of studies incorporated in the meta-analysis (only 5 and 6 studies respectively). Moreover, they used few databases for the literature search, and they did not perform the sensitivity analysis, which allows identifying possible sources of heterogeneity. Specifically, in the article done by Lagunas-Rangel, a heterogeneity of 96,45% was reported, and despite this, it was concluded that there was an association between the NLR and the progression to severity. This is an error since high variability suggest that studies should not be combined in a meta-analysis.

Our metanalysis contribution was to perform a conversion from the mean difference to a more reliable measure of effect, such as Odds Ratio through Chinn's method [32]. This conversion allowed us to include those studies that have not continuous values for NLR. In our sensibility analysis, the moderate/high risk of bias studies was possibly the primary source of heterogeneity. It is important to emphasize this last point because the desire to produce scientific knowledge that helps guide therapeutic decisions during the pandemic has

caused studies to be carried out in an expeditious manner, often by personnel with little methodological knowledge and without adequate advice[64]. This has resulted in a low-quality scientific production that has been reflected in the present work since 13 of the 20 studies analyzed have a moderate to high risk of bias.

Limitations

Our study has several limitations. Firstly, our metanalysis reported high OR values and broad CI for both outcomes. This could be due to some small sample sizes and clinical diversity. When we did the conversion, the values of the standardized mean differences, which we use for the OR conversion, were very high, so that also influences the high OR values. The broad CI could be explained by some small sample sizes, so the effect is detected but has low precision. Secondly, all the incorporated studies in this systemic review, except for one, were developed in China, which does not allow a fair ethnic comparison in COVID-19 patients.

Third, we found high heterogeneity between the included studies, which was traced back to the bad quality found in some publications. Finally, there was no consensus among the articles analyzed regarding the cut-off to define elevated NLR and the severity definition differed between some studies which could lead to bias.

CONCLUSIONS

In the presented systematic review and meta-analysis, the elevated NLR values were clearly associated with the development of severity and mortality in patients diagnosed with COVID-19. Therefore, an elevated NLR could be used as an early and easy prognostic parameter for severity and mortality in COVID-19 patients.

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Table 1: Characteristics of studies evaluating the association of NLR and severity

Author	*Year*	*Participants (Male)*	*Median/ mean Age (IQR/SD)*	*Exposure*	*Outcome*	*Severe*	*No Severe*	*Std Mean Difference*	*OR (Categorical)*	*HR (Categorical)*
Chuan Qin et al.	2020	452(235)	57.5 (14.81)	Quantitative	Severity	6.1 (4.96)	3.27(2.3)	0.67[0.48 , 0.87]	NR	NR
Xiurong Ding et al.	2020	72(33)	49 .75(20)	Quantitative	Severity	4.8(5.33)	2(1.18)	1.06[0.47 , 1.66)	NR	NR
Yafei Zhang al.	2020	115(49)	49.52 (17.06)	Quantitative	Severity	758(7.04)	2.28(1.29)	1.39[0.94 , 1.74)	NR	NR
Fengjun Liu et al.	2020	134(63)	51.25(20.74)	Quantitative	Severity	3.85(2.22)	2.72(1.41)	0.73[0.23 , 1.22]	NR	NR
Xiaomin Luo et al.	2020	298(150)	55.75(21.48)	Quantitative	Severity Mortality	6.28(4.17)	2.68(1.32)	1.47[1.02 , 1.93]	NR	NR
Ruchong Chen et al.	2020	548(313)	56(14.5)	Quantitative	Severity Mortality	9.89(9.2)	3.86(3.4)	1.03 [0.83, 1.23]	NR	NR
Hou Keke et al.	2020	56(29)	48 (13.5)	Quantitative	Severity	6.13(6.08)	4.01(5.62)	0.36 [-0.31, 1.04]	NR	NR
Changzheng Wang et al.	2020	45(23)	39(34.07)	Quantitative	Severity	29.9(18.7)	7.93(8.36)	1.90 [1.09, 2.72]	NR	NR
Jianhong Fu et al.	2020	75(45)	46.6 (14)	Quantitative	Severity	6.29(3.72)	2.3(1.22)	1.97 [1.33, 2.61]	NR	NR
Shaoping Huang et.al	2020	415(217)	44.75(22.9)	NLR < 3.5 NLR≥3.5	Severity	6.53(8.5)	2.63(1.22)	1.55 [1.16, 1.94]	NR	NR

Ai-ping Yang et al.	2020	93(56)	46.4 (17.6)	NLR <3 NLR ≥3	Severity	20.7(24.1)	4.8(3.5)	1.26 [0.76, 1.76]	NR	NR
Weifeng Shang et al.	2020	443(220)	55.475 (17.4)	NLR≥ 4.283 NLR <4.283	Severity	5.36(5.11)	2.51(1.59)	0.9[0.69 , 1.11]	NR	NR
Chen Xi et al.	2020	139(76)	45.5 (13.3)	NLR<4.5 NLR≥4.5	Severity	4.47(2.99)	3.31(1.92)	0.52[0.12 , 0.93]	NR	NR
Xintian Xia et al.	2020	63(33)	NR	NLR<4.795 NLR >4.795	Severity	12.1(14.32)	5.77(10.2)	0.50 [0.00, 1.01]	NR	NR
Li Long et al.	2020	301(150)	50.25 (20)	NLR < 2.973 NLR ≥ 2.973	Severity	NR	NR	NR	NR	2.641 (1.421–4.908) p=0.002 †
Yue-Ping Liu et al.	2020	84(47)	54.25 (52.59)	NLR <4.87 NLR ≥4.87	Severity	19.75(48.96)	4.3(7.88)	0.58 [0.10, 1.07]	NR	NR
Suyu Sun et al.	2020	116(60)	49.5(11.85)	NLR<4.5 NLR≥4.5	Severity	8.9(7.9)	2.5(1.28)	1.61 [1.14, 2.09]	NR	NR
Chen Xing et al.	2020	296(137)	NR	NR	Severity	3.86(3.28)	1.88(1.03)	1.39 [1.00, 1.78]	NR	NR

†: OR ADJUSTED , ‡ NR : NOT REPORTED.