Immunologic Research (2024) 72:147–154
https://doi.org/10.1007/s12026-023-09424-x

ORIGINAL ARTICLE

Elevated neutrophil-lymphocyte ratio is associated with high rates of ICU mortality, length of stay, and invasive mechanical ventilation in critically ill patients with COVID-19

NRL and severe COVID-19

Heitor O. Santos[1] · Felipe M. Delpino[2] · Octavio M. Veloso[3] · Juliana M. R. Freire[4] · Erlaine S. N. Gomes[4] · Cristina G. M. Pereira[3,4]

Received: 1 December 2022 / Accepted: 12 September 2023 / Published online: 28 September 2023

Abstract
Neutrophil and lymphocyte ratio (NLR) has emerged as a complementary marker in intensive care. This study aimed to associate high NLR values with mortality as the primary outcome, and length of stay and need for invasive mechanical ventilation as secondary outcomes, in critically ill patients with COVID-19. A cross-sectional study encompassing 189 critically ill patients with COVID-19 was performed. The receiver operating characteristic curve was used to identify the best NLR cutoff value for ICU mortality (≥ 10.6). An NLR ≥ 10.6, compared with an NLR < 10.6, was associated with higher odds of ICU mortality (odds ratio [OR], 2.77; 95% confidence interval [CI], 1.24–6.18), ICU length of stay ≥ 14 days (OR, 3.56; 95% CI, 1.01–12.5), and need for invasive mechanical ventilation (OR, 5.39; 95% CI, 1.96–14.81) in the fully adjusted model (age, sex, kidney dysfunction, diabetes, obesity, hypertension, deep vein thrombosis, antibiotics, anticoagulants, antivirals, corticoids, neuromuscular blockers, and vasoactive drugs). In conclusion, elevated NLR is associated with high rates of mortality, length of stay, and need for invasive mechanical ventilation in critically ill patients with COVID-19.

Keywords COVID-19 · Intensive care unit · Lymphocytes, neutrophils · NLR

Introduction

Neutrophils and lymphocytes are immune system cells that are part of the pathophysiological process of many diseases, whose blood concentrations can be used to monitor hospitalized patients [1–4]. Since neutrophils produce several pro-inflammatory cytokines, high blood concentrations of neutrophils are indicative of increased oxidative stress mainly in more vulnerable patients [5–8], including critically ill patients with Coronavirus Disease 2019 (COVID-19), in which excessive levels of reactive oxygen species are responsible for lung tissue damage, thrombosis, and red blood cell dysfunction, thus resulting in the COVID-19 disease severity [9]. Regarding lymphocytes, the lower the concentration, the greater the oxidative stress, given that several anti-inflammatory cytokines (e.g., interleukin (IL)-4, IL-10, IL-13, and interferon-gamma) are derived from lymphocytes [10, 11]. More importantly, lymphopenia is

✉ Heitor O. Santos
heitoroliveirasantos@gmail.com

Cristina G. M. Pereira
crisgama@bol.com.br

1 School of Medicine, Federal University of Uberlandia (UFU), Para Street, 1720, Umuarama. Block 2H, Uberlandia 38400-902, MG, Brazil

2 Postgraduate in Nursing, Federal University of Pelotas (UFPel), Pelotas, Rio Grande do Sul, Brazil

3 Department of Medicine, Federal University of Sergipe (UFS), Sergipe. Augusto Franco Avenue, 3500. Unit 134. Aracaju – Sergipe, Aracaju, Sergipe, Brazil

4 São Lucas Hospital – Rede D'OR (HSL), Aracaju, Sergipe, Brazil

widely recognized as a marker of poor survival outcomes and was used in the COVID-19 pandemic [12].

The neutrophil and lymphocyte ratio (NLR) has emerged through massive research as a complementary marker of critical care-related disorders [12–15]. However, NLR merits further investigation as a marker in severe COVID-19 due to the lack of cutoff values and therefore we performed a cross-sectional study in this regard. The primary aim of this research was to ascertain the association (or lack thereof) between elevated NLR values and intensive care unit (ICU) mortality in critically ill patients with COVID-19. In addition, associations between high NLR values with length of stay and need for mechanical ventilation were considered as secondary outcomes.

Methods

Study design and patients

A cross-sectional study was conducted in an ICU specialized in the treatment of COVID-19 at Hospital São Lucas (HSL), Rede D'OR – São Luiz, Aracaju/Sergipe, Brazil. This research is affiliated with the Federal University of Sergipe and was approved by the local Research Ethics Committee (nº 35128820.0.0000.5546.). Volunteers or their legal guardians who agreed to be evaluated signed a consent form.

Inclusion criteria were ≥ 18 years, patients of both sexes, COVID-19 diagnosis, and available neutrophil and lymphocyte count. One hundred ninety volunteers were enrolled, of which only one patient was excluded due to the lack of neutrophil and lymphocyte count. The low number of exclusions occurred mainly because neutrophil and lymphocyte counts are routine markers ordered by critical care physicians. Clinical and demographic variables were acquired directly by physicians or medical students under supervision using medical records.

Biochemical analyses

The diagnosis of COVID-19 was detected by reverse-transcription PCR (RT-PCR), which was collected non-randomly, without the patient contact, from electronic medical records. Peripheral blood collection with anticoagulants was performed by a phlebotomy specialist and then aspirated and injected into the analyzer.

More specifically, an automated hemocytometer (Sysmex XN-1500™) working on the flow cytometry principle was used to count and categorize the types of white blood cells by arranging these cells in a single file line, passing in front of a laser beam, scattered light and fluorescent light. Ultimately, NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count.

Statistical analyses

We estimated the best NLR cutoff point for ICU death by calculating the sensitivity, specificity, and area under the Receiver Operating Characteristic (ROC) curve. The significance level was set at 5%. The cutoff value was chosen based on the area under the curve (AUC) and the balance between specificity and sensitivity values. NLR ≥ 10.6 was the cutoff value chosen employing an AUC equivalent to 0.6551 ± 0.05 (95% CI, 0.57–0.73) (Fig. 1).

Sex was categorized as male or female, while comorbidities (obesity, diabetes, kidney failure, deep vein thrombosis, hypertension, respiratory failure, sepsis, etc.) and diarrhea were categorized as "no" or "yes". Categorical variables were described through absolute frequency (N) and percentage (%), whereas continuous or discrete variables were defined with median and standard deviation (SD).

Differences between groups were tested with Pearson's chi-squared test for categorical variables and Student's t-test for continuous variables. We performed the analyses for crude and adjusted models. Model 1 included adjustments for age, sex, kidney dysfunction, diabetes, obesity, hypertension, and deep vein thrombosis. Model 2 included adjustments for model 1 variables plus drugs (antibiotics, anticoagulants, antivirals, corticoids, neuromuscular blockers, and vasoactive drugs).

Logistic regression was performed with a confidence interval of 95%, and the results were presented as Odds Ratio (OR). P-values < 0.05 were considered significant. We performed the analyses using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Demographic and clinical characteristics

Table 1 depicts demographic and clinical characteristics divided by NLR cutoff values.

Regarding clinical data, participants with NLR ≥ 10.6 were older than those with NLR < 10.6 and had a high prevalence of kidney dysfunction. Moreover, a high need for vasoactive drugs and invasive mechanical ventilation, as well as a high mortality rate, was observed for an NLR ≥ 10.6.

As far the biochemistry parameters, an NLR ≥ 10.6 was associated with low lymphocyte levels, along with high C-reactive protein, leucocyte, neutrophil, NLR, and red blood cell distribution width levels.

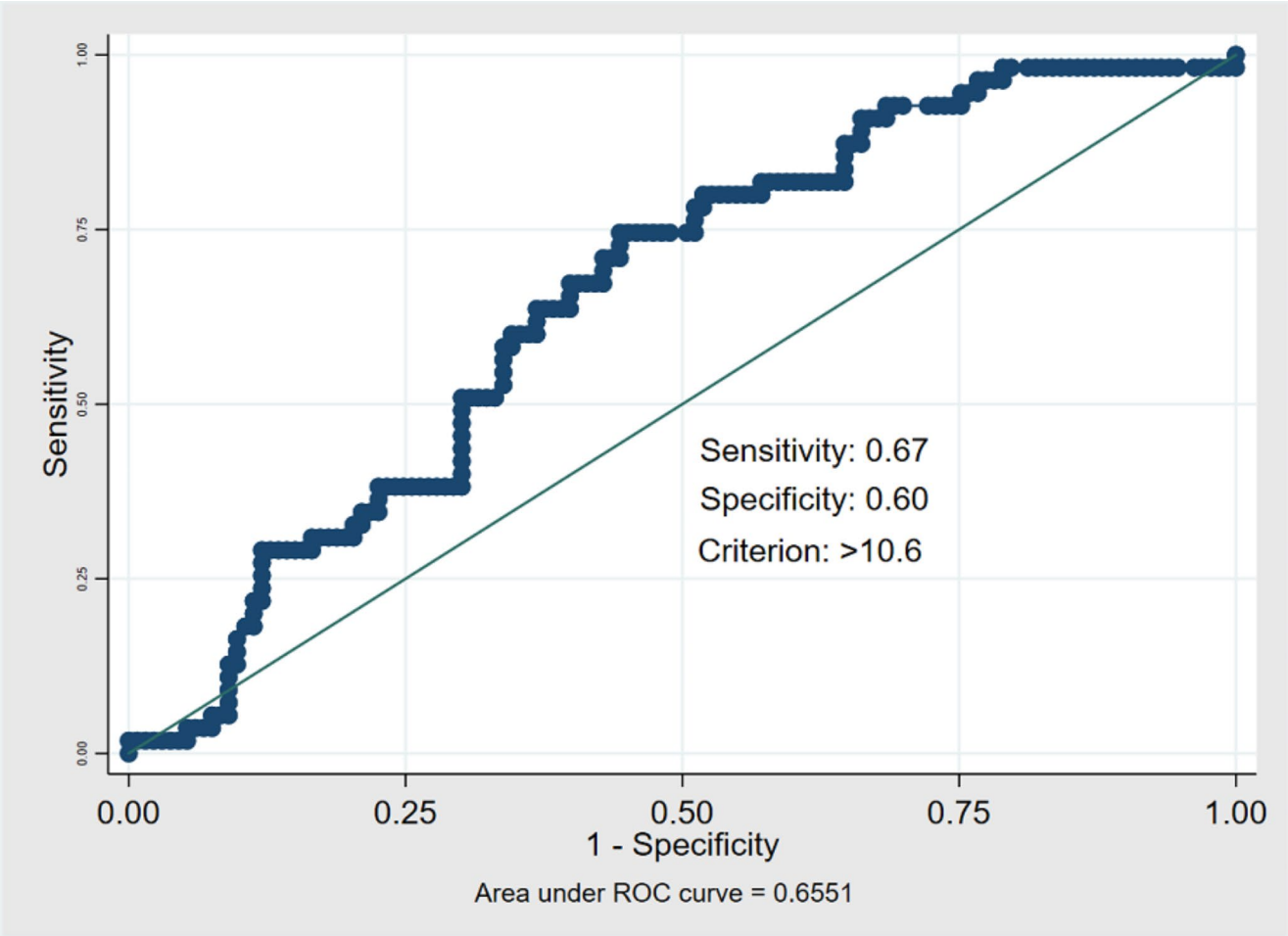

Fig. 1 Receive Operating Characteristic (ROC) curve analysis for neutrophil-lymphocyte rate (NLR) cutoff to discriminate ICU mortality risk in COVID-19 patients

Main outcomes

Table 2 shows the association between NLR and mortality as the primary outcome. Table 3, in turn, shows the association between NLR and secondary outcomes (i.e., length of stay and invasive mechanical ventilation).

Collectively, an NLR ≥ 10.6 was associated with higher odds of ICU mortality, length of stay, and invasive mechanical ventilation in both crude and fully adjusted models compared with an NLR < 10.6.

More specifically, patients with higher NLR had 2.77 (95% CI, 1.24–6.18), 3.56 (95% CI, 1.01–12.5), and 5.39 (95% CI, 1.96–14.81) more likely to have ICU mortality, length of stay ≥ 14 days, and need for invasive mechanical ventilation, respectively.

Discussion

In this study, higher NLR (≥ 10.6) was considered a marker associated with a high likelihood of ICU mortality, length of stay, and invasive mechanical ventilation in critically ill patients with COVID-19, compared to those with lower NLR (< 10.6). The higher mean NLR (20.6 ± 12.3 for NLR ≥ 10.6) found here seemingly is related to an exceedingly high inflammatory response to COVID-19-related critical illness triggered by a cytokine storm [16–18]. However, it is noteworthy to mention that even the lower NLR mean (5.9 ± 2.6 for NLR < 10.6) in our study is an alarming rate if extrapolated to other populations, such as inpatients, given the close link of this NLR level with chronic low-grade systemic inflammation (e.g., diabetes, obesity, and cardiovascular and renal diseases) [19–22].

Low lymphocyte count is a recognized predictor marker of mortality in intensive care [23–25]. That said, a higher NLR is expected in COVID-19 mortality due to low lymphocyte counts, and we confirmed this clinical link by

Table 1 Demographic and clinical characteristics of the patients according to the neutrophils-lymphocytes ratio

Variables	NLR < 10.6 (n = 99)	NLR ≥ 10.6 (n = 90)	p-value
Demographic data			
Age (years)	60.4 ± 17.6	68.7 ± 13.6	**< 0.001**
Sex n (%)			
Male	54 (55)	60 (67)	0.069
Female	45 (45)	30 (33)	
Body weight (kg)	78.3 ± 16.2	80.9 ± 28.2	0.241
Body mass index (kg/m^2)	28.7 ± 7.1	27.7 ± 5.3	0.706
Comorbidities			
Hypertension (n, %)	56 (57)	60 (67)	0.215
Obesity (n, %)	33 (33)	28 (31)	0.670
Diabetes (n, %)	41 (41)	30 (33)	0.208
Deep vein thrombosis (n, %)	7 (7)	13 (14)	0.094
Kidney dysfunction (n, %)	20 (20)	30 (33)	**0.045**
Clinical parameters			
Diarrhea (n, %)	17 (17)	14 (16)	0.764
Heart rate (per minute)	90.3 ± 18.7	92.5 ± 19.7	0.219
Lung tissue damage (total volume, %)			0.864
< 25%	22 (29)	23 (31)	
25–50%	31 (40)	27 (36)	
> 50%	24 (31)	25 (33)	
SAPS3 (score)	12.6 ± 11.9	13.7 ± 12.8	0.277
Criteria for ICU admission			0.095
Respiratory failure (n, %)	75 (76)	78 (87)	
Sepsis (n, %)	8 (8)	3 (3)	
Other reasons † (n, %)	15 (15)	7 (8)	
Biochemical parameters (venous blood samples)			
Albumin (g/L)	2.9 ± 5.7	2.7 ± 3.9	**0.998**
B-type natriuretic peptide (pg/mL)	2605.6 ± 5213.2	3719.1 ± 9503.6	0.195
C-reactive protein (mg/dL)	10.6 ± 13.9	14.8 ± 11.4	**0.014**
D-dimer (ng/mL)	1825.4 ± 1491.4	2135.1 ± 1724.2	0.109
Hemoglobin (g/L)	12.2 ± 2.3	11.8 ± 2.0	0.868
Hematocrit (%)	38.4 ± 5.2	38.3 ± 5.4	0.556
Leucocytes (mm^3)	9747.6 ± 5615.5	12319.6 ± 5788.2	**0.001**
Lymphocytes (mm^3)	1490.5 ± 1825.4	640.2 ± 346.4	**< 0.001**
Neutrophils (mm^3)	7124.1 ± 4005.7	11267.4 ± 5197.3	**< 0.001**
NLR	5.9 ± 2.6	20.6 ± 12.3	**< 0.001**
Platelets (cells/mcL)	237986.3 ± 120053.1	222277.2 ± 102486.9	0.8310
Red blood cells (cells/mcL)	4370510.2 ± 734339.3	4294157.3 ± 938855.5	0.733
Red blood cell distribution width	13.7 ± 1.2	14.1 ± 1.9	**0.024**
Arterial blood gas analysis			
Bicarbonate (mEq/L)	24.3 ± 5.4	23.4 ± 5.5	0.819
Lactate (mmol/L)	1.5 ± 0.98	1.7 ± 0.94	0.274
PaO_2 (mm Hg)	89.2 ± 40.4	92.8 ± 47.5	0.312
pH	8.2 ± 8.3	7.2 ± 0.4	0.844
SpO_2 (%)	89.2 ± 40.4	92.8 ± 47.5	0.312
Drugs			
Antibiotics (n, %)	95 (96)	86 (96)	0.905
Anticoagulants (n, %)	88 (89)	80 (89)	0.983
Antivirals (n, %)	48 (48)	33 (37)	0.101
Corticoids (n, %)	69 (70)	72 (80)	0.096
Neuromuscular blockers (n, %)	18 (18)	19 (21)	0.634
Vasoactive drugs (n, %)	30 (30)	41 (46)	**0.026**

Table 1 (continued)

Variables	NLR < 10.6 (n = 99)	NLR ≥ 10.6 (n = 90)	p-value
Demographic data			
Outcomes			
Death (n, %)	18 (18)	37 (41)	**< 0.001**
Length of stay (days)	36.2 ± 7.2	31.9 ± 2.7	0.7413
Invasive mechanical ventilation (n, %)	47 (47)	66 (73)	**< 0.001**

Significant differences between NLR categories are in bold

Pearson's chi-squared test was used to test differences between categorical variables and the Student's t-test for continuous variables

† Other reasons for ICU admission: acute abdomen (n = 1), arrhythmia (n = 5), bronchopneumonia (n = 1), convulsive crisis (n = 1), chest pain (n = 2), encephalopathy (n = 1), femur fracture (n = 1), heart failure (n = 2), hypotension (n = 1), massive pulmonary embolism (n = 1), multiple organ dysfunction syndrome (n = 1), myocarditis (n = 1), puerperal sepsis (n = 2), pulmonary edema (n = 1), decompensated diabetes (n = 1)

Table 2 Association between NLR cutoffs with ICU mortality (n = 55)

Statistical Models	NLR < 10.6, Reference Category	NLR ≥ 10.6, OR (95% CI)	p-value
Crude	1	3.20 1.65–6.21	**0.001**
Model 1	1	2.50 1.22–5.14	**0.013**
Model 2	1	2.77 1.24–6.18	**0.013**

Significant differences between NLR cutoffs are in bold

OR (Odds Ratio)

Model 1: Adjusted for age, sex, kidney dysfunction, diabetes, obesity, hypertension, and deep vein thrombosis

Model 2: adjusted for model 1 variables + drugs (antibiotics, anticoagulants, antivirals, corticoids, neuromuscular blockers, and vasoactive drugs)

Table 3 Association between NLR cutoffs with ICU length of stay ≥ 14 days (86 patients) and need for mechanical ventilation (113 patients)

Statistical Models	NLR < 10.6, Reference Category	NLR ≥ 10.6, OR (95% CI)	p-value
Need for invasive mechanical ventilation (n = 113)			
Crude	1	3.83 1.82–8.03	**< 0.001**
Model 1	1	4.82 2.05–11.30	**< 0.001**
Model 2	1	5.39 1.96–14.81	**0.001**
ICU length of stay ≥ 14 days for all patients (n = 86)			
Crude	1	1.95 0.75–5.11	0.173
Model 1	1	2.74 0.93–8.10	0.068
Model 2	1	3.56 1.01–12.5	**0.048**

Significant differences between NLR cutoffs are in bold

OR (Odds Ratio)

Model 1: Adjusted for age, sex, kidney dysfunction, diabetes, obesity, hypertension, and deep vein thrombosis

Model 2: adjusted for model 1 variables + drugs (antibiotics, anticoagulants, antivirals, corticoids, neuromuscular blockers, and vasoactive drugs)

comparing patients with NLR ≥ 10.6 vs. <10.6. Similarly, Ullah et al. considered NLR > 11 as a predictor of COVID-19 mortality compared to < 10, but did not perform specific analyses to find an ideal cutoff value [26]. Noteworthy, the higher NLR mean (20.9 ± 12.5 for patients with NLR ≥ 10.6) of our study was similar to the mean (20.7 ± 24.1) observed by Yang et al. in critically ill patients with COVID-19, [27] which presented a smaller sample size (n = 24) compared to our data. In contrast, some studies show low mean or median NLR values (3.7 (2.0, 6.7) n = 28 [28]; 4.24 (3.00-10.87) n = 16 [29]; 6.29 ± 3.72, n = 16 [30]) for patients with severe COVID-19 compared to our findings, but their sample size is insufficient to draw a reliable cutoff value.

A recent meta-analysis of COVID-19 patients showed that elevated NLR levels on admission were associated with a 174% higher risk of mortality [31]. The authors emphasized the importance of establishing an optimal cutoff value for NLR, and our study helped to expand this background into clinical practice [31]. We considered the NLR cutoff ≥ 10.6 to maintain a balanced sensitivity (67%) and specificity (60%), avoiding very high or moderate levels that are ubiquitously associated with many diseases, primarily cardiovascular diseases and related metabolic problems.

Little is known about the association between NLR and COVID-19-associated diseases and mortality in South America, and thus our study provides an important finding consisting of a representative sample from a continental country such as Brazil. Most research evaluating this association has been conducted in China [27–30, 32–36], with a couple of studies in the US [26, 37] and Europe (e.g., Turkey and Italy) [38–41], in which high NLR was deemed a marker of COVID-19-related mortality and overall severity.

Our secondary outcomes (i.e., ICU length of stay and invasive mechanical ventilation) must be discussed in more detail. In different regions of England, the ICU length of

stay was estimated at 12–19 days [42]. Compelling European and American data show a mean ICU length of stay between 7 and 21 days [43–46]. Interestingly, there are reports of longer ICU length of stay, as found in a French study, in which the mean time required for intensive care was one month (27 days for those who survived and 45 days for those who died) [47]. Here, we observed an ICU length of stay close to one month (36.2 ± 7.2 and 31.9 ± 2.7 days for NLR < 10.6 versus ≥ 10.6). Thus, we selected an ICU length of stay equal to or greater than two weeks to afford a relevant outcome.

Although invasive mechanical ventilation is used to allow adequate gas exchange, we consider it a critical outcome due to its relationship with high morbidity and mortality in patients with COVID-19 [48, 49]. On average, 59% of our population required invasive mechanical ventilation [50]. Nevertheless, higher rates can also be observed, as reported by a Brazilian study whereby ~ 84% of patients needed invasive mechanical ventilation at ICU admission [50].

The present work has limitations. The cross-sectional design does not infer a cause-effect relationship between the NLR and medical outcomes in COVID-19. Thus, due to the methodology employed, we did not perform survival analysis since it is more suitable for studies designed to analyze time-to-event data (longitudinal studies) [51]. In light of this, we used ORs as the measure of association rather than Hazard ratios, the latter of which analyzes the impact of an intervention on survival or time-to-event outcomes [52]. Moreover, although we evaluated 189 patients, this sample is from a single-center study and hence reproducibility ought to be interpreted with caution, even for critically ill patients with COVID-19.

Finally, the pros and cons of using NLR as a surrogate inflammatory marker in the clinical setting must be highlighted. Considering the benefits, NLR is a cheap parameter as it is obtained by two components of the blood cell count (neutrophils and lymphocytes), which is perhaps the most ordered laboratory test worldwide to monitor basic and advanced clinical conditions (e.g., anemias and cancers). Pathophysiologically, however, attention to NLR per se as a marker of inflammation lacks meticulousness, given the plethora of pro-inflammatory cytokines that are part of the COVID-19 disease. Taking into account that cytokines are not often analyzed in the real-life scenario due to the lack of laboratory tools (reagents, kits, and devices) and cutoff values for the general population, NLR deserves consideration to guide practitioners.

Conclusion

Elevated NLR values are associated with high rates of ICU mortality, length of stay, and need for invasive mechanical ventilation in critically ill patients with COVID-19. Therefore, further attention to NLR is crucial in clinical practice as an inexpensive and valuable complementary tool to monitor patients with COVID-19 in intensive care.

Acknowledgements We are thankful for the São Lucas Hospital. This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. HOS has been supported by *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*—Brazil (CAPES).

Authors' contributions HOS – Conceptualization, writing of original draft, review of manuscript. FMD – Statistical analyses. OMV – data collection. JMRF – data collection. ESNG – data collection. CGMP – project administration, data collection, and supervision. All authors critically revised the article and finally approved the version to be published.

Funding None.

Data availability The data that support the findings of this study are available in the article. If additional data were required, it may be requested to the corresponding author.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This research was ratified by the Federal University of Sergipe and was approved by the local Research Ethics Committee (nº 35128820.0.0000.5546.). Data were collected from the medical record system. There was no intervention.

References

1. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017;10:1–4. https://doi.org/10.1186/S13104-016-2335-5.
2. Karabinos I, Koulouris S, Kranidis A, Pastromas S, Exadaktylos N, Kalofoutis A. Neutrophil count on admission predicts major in-hospital events in patients with a non-ST-segment elevation acute coronary syndrome. Clin Cardiol. 2009;32:561–8. https://doi.org/10.1002/CLC.20624.
3. Honda T, Uehara T, Matsumoto G, Arai S, Sugano M. Neutrophil left shift and white blood cell count as markers of bacterial infection. Clin Chim Acta. 2016;457:46–53. https://doi.org/10.1016/J.CCA.2016.03.017.
4. Pereira CGM, Santana ERS, Ramos JER, da Silva HMBS, Nunes MAP, Forbes SC, et al. Low serum zinc levels and Associated Risk factors in hospitalized patients receiving oral or Enteral Nutrition: a case-control study. Clin Ther. 2021;43:e39–55. https://doi.org/10.1016/J.CLINTHERA.2020.12.006.
5. Vitte J, Michel BF, Bongrand P, Gastaut JL. Oxidative stress level in circulating neutrophils is linked to neurodegenerative diseases.

J Clin Immunol. 2004;24:683–92. https://doi.org/10.1007/S10875-004-6243-4.
6. Maor I, Rainis T, Lanir A, Lavy A. Oxidative stress, inflammation and neutrophil superoxide release in patients with Crohn's disease: distinction between active and non-active disease. Dig Dis Sci. 2008;53:2208–14. https://doi.org/10.1007/S10620-007-0141-6.
7. Johnson J, Jaggers RM, Gopalkrishna S, Dahdah A, Murphy AJ, Hanssen NMJ, et al. Oxidative stress in neutrophils: implications for Diabetic Cardiovascular Complications. Antioxid Redox Signal. 2022;36:652–66. https://doi.org/10.1089/ARS.2021.0116.
8. Santos HO, Fernando L, Izidoro M. Neutrophil-lymphocyte ratio in Cardiovascular Disease Risk Assessment. Int J Cardiovasc Sci. 2018;31:532–7. https://doi.org/10.5935/2359-4802.20180038.
9. Laforge M, Elbim C, Frère C, Hémadi M, Massaad C, Nuss P, et al. Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nat Reviews Immunol 2020. 2020;20:9. https://doi.org/10.1038/s41577-020-0407-1.
10. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9:7204. https://doi.org/10.18632/ONCOTARGET.23208.
11. Foster M, Samman S. Zinc and regulation of inflammatory cytokines: implications for cardiometabolic disease. Nutrients. 2012;4:676–94. https://doi.org/10.3390/NU4070676.
12. Montiel-Cervantes LA, Medina G, Cruz-Domínguez MP, Perez-Tapia SM, Jiménez-Martínez MC, Arrieta-Oliva HI, et al. Poor survival in COVID-19 Associated with Lymphopenia and higher neutrophile-lymphocyte ratio. Isr Med Assoc J. 2021;23:153–9.
13. Salciccioli JD, Marshall DC, Pimentel MAF, Santos MD, Pollard T, Celi AA, et al. The association between the neutrophil-to-lymphocyte ratio and mortality in critical illness: an observational cohort study. Crit Care. 2015;19. https://doi.org/10.1186/S13054-014-0731-6.
14. Akilli NB, Yortanli M, Mutlu H, Günaydin YK, Koylu R, Akca HS, et al. Prognostic importance of neutrophil-lymphocyte ratio in critically ill patients: short- and long-term outcomes. Am J Emerg Med. 2014;32:1476–80. https://doi.org/10.1016/J.AJEM.2014.09.001.
15. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18:1–12. https://doi.org/10.1186/S12967-020-02374-0/FIGURES/7.
16. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39:2085–94. https://doi.org/10.1007/S10067-020-05190-5.
17. Santos HO. Therapeutic supplementation with zinc in the management of COVID-19-related diarrhea and ageusia/dysgeusia: mechanisms and clues for a personalized dosage regimen. Nutr Rev. 2022;80:1086–93. https://doi.org/10.1093/NUTRIT/NUAB054.
18. Santos HO, Tinsley GM, da Silva GAR, Bueno AA. Pharmaconutrition in the Clinical Management of COVID-19: a lack of evidence-based Research but Clues to personalized prescription. J Pers Med. 2020;10:1–18. https://doi.org/10.3390/JPM10040145.
19. Sari I, Sunbul M, Mammadov C, Durmus E, Bozbay M, Kivrak T, et al. Relation of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio with coronary artery disease severity in patients undergoing coronary angiography. Kardiol Pol. 2015;73:1310–6. https://doi.org/10.5603/KP.A2015.0098.
20. Guo X, Zhang S, Zhang Q, Liu L, Wu H, Du H, et al. Neutrophil:lymphocyte ratio is positively related to type 2 diabetes in a large-scale adult population: a Tianjin Chronic Low-Grade systemic inflammation and health cohort study. Eur J Endocrinol. 2015;173:217–25. https://doi.org/10.1530/EJE-15-0176.
21. Turkmen K, Guney I, Humeyra F, Halil Y, Tonbul Z, Yerlikaya FH, et al. The relationship between neutrophil-to-lymphocyte ratio and inflammation in end-stage renal disease patients. Ren Fail. 2012;34:155–9. https://doi.org/10.3109/0886022X.2011.641514.
22. Bozkuş F, Dikmen N, Samur A, Bilal N, Atilla N, Arpağ H. Does the neutrophil-to-lymphocyte ratio have any importance between subjects with obstructive sleep apnea syndrome with obesity and without obesity? Tuberk Toraks. 2018;66:8–15. https://doi.org/10.5578/TT.66535.
23. Izaks GJ, Remarque EJ, Becker SV, Westendorp RGJ. Lymphocyte count and mortality risk in older persons. The Leiden 85-Plus study. J Am Geriatr Soc. 2003;51:1461–5. https://doi.org/10.1046/J.1532-5415.2003.51467.X.
24. Kuwae N, Kopple JD, Kalantar-Zadeh K. A low lymphocyte percentage is a predictor of mortality and hospitalization in hemodialysis patients. Clin Nephrol. 2005;63:22–34. https://doi.org/10.5414/CNP63022.
25. Vulliamy PE, Perkins ZB, Brohi K, Manson J. Persistent lymphopenia is an independent predictor of mortality in critically ill emergency general surgical patients. Eur J Trauma Emerg Surg. 2016;42:755–60. https://doi.org/10.1007/S00068-015-0585-X.
26. Ullah W, Basyal B, Tariq S, Almas T, Saeed R, Roomi S, et al. Lymphocyte-to-C-Reactive protein ratio: a novel predictor of adverse outcomes in COVID-19. J Clin Med Res. 2020;12:415–22. https://doi.org/10.14740/JOCMR4227.
27. Yang AP, Liu J, ping, Tao W, qiang, Li H. ming. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020;84:106504. https://doi.org/10.1016/J.INTIMP.2020.106504.
28. Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. A Tool to early predict severe Corona Virus Disease 2019 (COVID-19): a Multicenter Study using the risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis. 2020;71:833–40. https://doi.org/10.1093/CID/CIAA443.
29. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:332–9. https://doi.org/10.1016/J.IJID.2020.04.041.
30. Fu J, Kong J, Wang W, Wu M, Yao L, Wang Z, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. Thromb Res. 2020;192:3. https://doi.org/10.1016/J.THROMRES.2020.05.006.
31. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: a meta-analysis. Am J Emerg Med. 2021;42:60. https://doi.org/10.1016/J.AJEM.2021.01.006.
32. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. J Med Virol. 2020;92:2573–81. https://doi.org/10.1002/JMV.26061.
33. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol. 2020;146:89–100. https://doi.org/10.1016/J.JACI.2020.05.003.
34. Ding X, Yu Y, Lu B, Huo J, Chen M, Kang Y, et al. Dynamic profile and clinical implications of hematological parameters in hospitalized patients with coronavirus disease 2019. Clin Chem Lab Med. 2020;58:1365–71. https://doi.org/10.1515/CCLM-2020-0411/PDF.
35. Liu F, Zhang Q, Huang C, Shi C, Wang L, Shi N, et al. CT quantification of pneumonia lesions in early days predicts progression to severe illness in a cohort of COVID-19 patients. Theranostics. 2020;10:5613. https://doi.org/10.7150/THNO.45985.

36. Sun S, Cai X, Wang H, He G, Lin Y, Lu B, et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta. 2020;507:174–80. https://doi.org/10.1016/J.CCA.2020.04.024.
37. Tatum D, Taghavi S, Houghton A, Stover J, Toraih E, Duchesne J. Neutrophil-to-lymphocyte ratio and outcomes in Louisiana COVID-19 patients. Shock. 2020;54:652–8. https://doi.org/10.1097/SHK.0000000000001585.
38. Ciccullo A, Borghetti A, Zileri Dal Verme L, Tosoni A, Lombardi F, Garcovich M, et al. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the italian front line. Int J Antimicrob Agents. 2020;56:106017. https://doi.org/10.1016/J.IJANTIMICAG.2020.106017.
39. Gelzo M, Cacciapuoti S, Pinchera B, De Rosa A, Cernera G, Scialò F, et al. Prognostic role of neutrophil to lymphocyte ratio in COVID-19 patients: still valid in patients that had started therapy? Front Public Health. 2021;9. https://doi.org/10.3389/FPUBH.2021.664108.
40. Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive values of blood urea nitrogen/creatinine ratio and other routine blood parameters on disease severity and survival of COVID-19 patients. J Med Virol. 2021;93:786. https://doi.org/10.1002/JMV.26300.
41. Güner R, Hasanoğlu İ, Kayaaslan B, Aypak A, Kaya Kalem A, Eser F, et al. COVID-19 experience of the major pandemic response center in the capital: results of the pandemic's first month in Turkey. Turk J Med Sci. 2020;50:1801–9. https://doi.org/10.3906/SAG-2006-164.
42. Vekaria B, Overton C, Wiśniowski A, Ahmad S, Aparicio-Castro A, Curran-Sebastian J, et al. Hospital length of stay for COVID-19 patients: Data-driven methods for forward planning. BMC Infect Dis. 2021;21:1–15. https://doi.org/10.1186/S12879-021-06371-6/TABLES/2.
43. Larsson E, Brattström O, Agvald-Öhman C, Grip J, Campoccia Jalde F, Strålin K, et al. Characteristics and outcomes of patients with COVID-19 admitted to ICU in a tertiary hospital in Stockholm, Sweden. Acta Anaesthesiol Scand. 2021;65:76–81. https://doi.org/10.1111/AAS.13694.
44. Alimohamadi Y, Yekta EM, Sepandi M, Sharafoddin M, Arshadi M, Hesari E. Hospital length of stay for COVID-19 patients: a systematic review and meta-analysis. Multidiscip Respir Med. 2022;17. https://doi.org/10.4081/MRM.2022.856.
45. Chiam T, Subedi K, Chen D, Best E, Bianco FB, Dobler G, et al. Hospital length of stay among COVID-19-positive patients. J Clin Transl Res. 2021;7:377. https://doi.org/10.18053/jctres.07.202103.010.
46. Dongelmans DA, Termorshuizen F, Brinkman S, Bakhshi-Raiez F, Arbous MS, de Lange DW, et al. Characteristics and outcome of COVID-19 patients admitted to the ICU: a nationwide cohort study on the comparison between the first and the consecutive upsurges of the second wave of the COVID-19 pandemic in the Netherlands. Ann Intensive Care. 2022;12:1–10. https://doi.org/10.1186/S13613-021-00978-3/FIGURES/3.
47. Boëlle PY, Delory T, Maynadier X, Janssen C, Piarroux R, Pichenot M, et al. Trajectories of hospitalization in COVID-19 patients: an observational study in France. J Clin Med 2020. 2020;9:9:3148. https://doi.org/10.3390/JCM9103148. Page 3148.
48. Elsayed HH, Hassaballa AS, Ahmed TA, Gumaa M, Sharkawy HY, Moharram AA. Variation in outcome of invasive mechanical ventilation between different countries for patients with severe COVID-19: a systematic review and meta-analysis. PLoS ONE. 2021;16. https://doi.org/10.1371/JOURNAL.PONE.0252760.
49. Brioni M, Meli A, Grasselli G. Mechanical ventilation for COVID-19 patients. Semin Respir Crit Care Med. 2022;43:405–16. https://doi.org/10.1055/S-0042-1744305.
50. de Macedo BR, Garcia MVF, Garcia ML, Volpe M, de Araújo Sousa ML, Amaral TF, et al. Implantação de telemedicina de terapia intensiva durante a pandemia de COVID-19. Jornal Brasileiro de Pneumologia. 2021;47:e20200545–5. https://doi.org/10.36416/1806-3756/E20200545.
51. Van Es B, Klaassen CAJ, Oudshoorn K. Survival analysis under cross-sectional sampling: length bias and multiplicative censoring. J Stat Plan Inference. 2000;91:295–312. https://doi.org/10.1016/S0378-3758(00)00183-X.
52. Abd Elhafeez S, D'Arrigo G, Leonardis D, Fusaro M, Tripepi G, Roumeliotis S. Methods to Analyze Time-to-Event Data: the Cox Regression Analysis. Oxid Med Cell Longev 2021;2021. https://doi.org/10.1155/2021/1302811.