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SEX- AND GENDER-SPECIFIC DIFFERENCES IN THE INFLAMMATORY RESPONSE TO COVID-19: THE ROLE OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO

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ABSTRACT

INTRODUCTION: The neutrophil-to-lymphocyte ratio (NLR) is a simple blood test marker used to predict the severity of COVID-19. The study aimed to describe the correlation between neutrophil-to-lymphocyte ratio sex- and gender-specific differences in the inflammatory response to COVID-19.

MATERIAL AND METHODS: This retrospective observational study was conducted with patients diagnosed with COVID-19 in the emergency department of a tertiary hospital between January 1, 2022, and May 31, 2022. The receiver operating characteristic (ROC) area under the curve (AUC) analysis was conducted to verify NLR predictive capacity.

RESULTS: The study population consisted of 47% women and 53% men with a mean age of 72.42 years. Women were significantly older than men on average. At admission, 73% of patients were classified as nonsevere, while 27% were severe. Overall, 63% of patients survived the infection.

CONCLUSIONS: There were slight but not statistically significant differences in neutrophil counts between men and women. However, there were significant differences in lymphocyte counts and the NLR, with women having higher lymphocyte counts and men having higher NLR. The study found very weak correlations between age and neutrophil counts, lymphocyte counts, and NLR, suggesting no strong relationship between age and these variables. Patients with severe disease had higher neutrophil counts and NLR but lower lymphocyte counts compared to nonsevere patients. Survivors had lower neutrophil counts and NLR but higher lymphocyte counts compared to those who did not survive. NLR was a significant predictor of both admission status and survivor status, with ROC AUC values indicating its predictive capacity. These findings highlight the potential importance of NLR as a biomarker in predicting disease severity and survival in patients.

KEYWORDS: biomarkers; inflammation; immune system; COVID-19; sex- and gender-specific differences

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INTRODUCTION

The neutrophil-to-lymphocyte ratio (NLR) is a biomarker obtained by dividing the count of neutrophils by the count of lymphocytes, both of which are types of white blood cells measured through a routine complete blood count (CBC) test [1, 2]. This ratio, just like the platelet-to-lymphocyte ratio and the lymphocyte-to-monocyte ratio, has gained attention as a potential prognostic and diagnostic tool in various medical conditions, including infections, inflammatory diseases, and cancer [3–6]. It reflects the balance between the innate (neutrophils) and adaptive (lymphocytes) immune responses [7].

In the context of COVID-19, caused by the SARS-CoV-2 virus, the NLR has been studied for its predictive value concerning disease severity and outcomes [8, 9]. During the COVID-19 pandemic, healthcare systems worldwide have been overwhelmed [10], and there has been an urgent need for simple, rapid, and cost-effective methods to stratify patients based on their risk of developing severe disease or complications [11, 12].

The neutrophil-to-lymphocyte ratio fits well into this need due to its ease of calculation from a CBC, a test that is widely available and frequently performed on patients presenting with infections. Elevated NLR values have been associated with a hyperinflammatory state, which is a hallmark of severe COVID-19 [13]. This state can lead to a cascade of complications, including acute respiratory distress syndrome (ARDS), multiorgan failure, and death [14].

Numerous studies have indicated that patients with higher NLR values upon admission or during hospitalization tend to have worse outcomes than those with lower values. The link between these two things is thought to be caused by the neutrophilic inflammatory response and lymphopenia, which is a drop in lymphocytes that happens a lot during viral infections and is especially noticeable in severe COVID-19 cases. By using NLR as a predictor, doctors may be able to find patients who are more likely to get worse quickly. This can help them decide whether to admit them to the hospital or intensive care unit (ICU) and start aggressive therapy [15]. Furthermore, monitoring NLR values over time may provide insights into a patient's response to treatment and disease progression.

Nevertheless, while NLR is promising, it is not without limitations. Stress, smoking, corticosteroid use, and other comorbidities that may affect neutrophil or lymphocyte counts can all have an impact on the ratio. Moreover, the threshold values for "high" NLR that correlate with adverse COVID-19 outcomes can vary across populations and individual patient factors, making standardization challenging. It is also essential to consider NLR within the broader context of a patient's clinical presentation and in conjunction with other laboratory markers and imaging findings. Neutrophil-to-lymphocyte ratio should be one component of a multifaceted assessment rather than a standalone indicator. Given the dynamic nature of COVID-19 and the immune response it elicits, ongoing research is crucial to further delineate the role of NLR in COVID-19 [16, 17]. This includes investigating whether interventions that modulate the immune response can impact NLR and, by extension, patient outcomes.

As of March 2023, the world has witnessed several waves of COVID-19, with different variants of the virus causing varying degrees of illness [18, 19]. Vaccination efforts have been successful in reducing the incidence of severe disease, but breakthrough infections and cases in unvaccinated individuals continue to occur. In this evolving scenario, the potential role of NLR as a prognostic tool remains relevant, particularly in regions with limited healthcare resources.

The NLR has emerged as a potential biomarker for predicting the severity of COVID-19. Its predictive value lies in its ability to reflect the inflammatory state of a patient and to be easily derived from a common blood test. While promising, NLR should be used judiciously, in conjunction with other clinical indicators, to inform patient management decisions. Continuous research and validation in diverse populations are necessary to solidify the role of NLR in the management of COVID-19 and possibly other infectious diseases in the future. In this article, the utility of NLR was examined as a predictor of COVID-19 severity in a sample of patients with COVID-19. The study aimed to describe the correlation between neutrophil–to–lymphocyte ratio sex- and gender-specific differences in the inflammatory response to COVID-19.

MATERIAL AND METHODS

The present retrospective observational study was conducted in the Emergency Department of the Kartal Dr. Lütfi Kırdar City Hospital (Istanbul, Türkiye). The institutional review board approved the

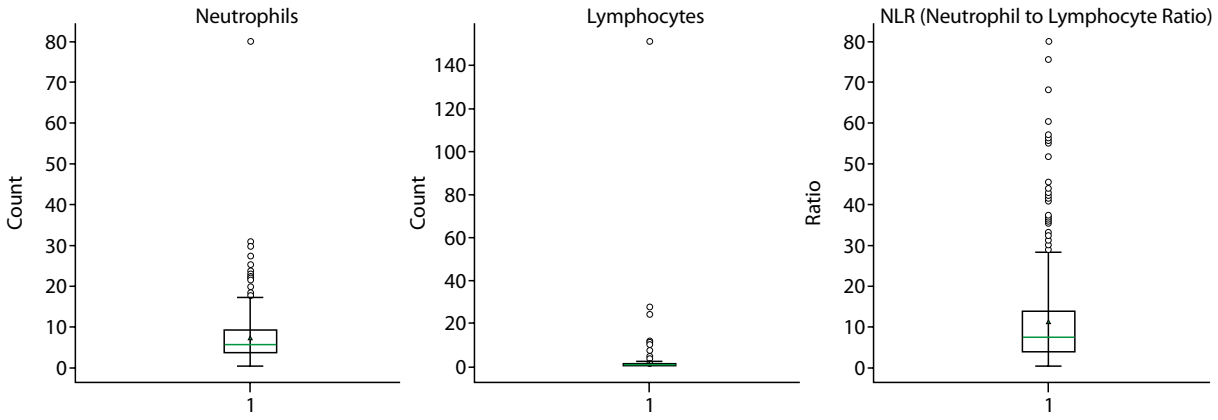

FIGURE 1. Neutrophil, lymphocyte, and neutrophil-to-lymphocyte ratio values in the study population

analysis and granted a waiver of consent (ethical committee ruling number: 2022/514/228/25, date: 30.06.2022). This research included all individuals aged 18 years and older who were diagnosed with COVID-19 and sought medical attention at the emergency department between January 1, 2022, and May 31, 2022. The determination of the COVID-19 diagnostic was made in accordance with the recommendations provided by the World Health Organization (WHO). Data was collected using the digital records of the Hospital Information Management System. When the research participants went to the emergency room, their vital signs, chronic illnesses, and the results of lab tests, such as the levels of neutrophils and lymphocytes, were recorded in a standard way. This information included their age and gender. The study excluded patients who had a negative reverse transcription-polymerase chain reaction test result, patients whose mortality status was unclear, patients who were referred from another institution, and patients for whom neutrophil and lymphocyte levels were unavailable.

Before proceeding with statistical analysis, data were visually inspected for capturing potential outliers. Continuous variables were computed as means and standard deviations, while categorical parameters were calculated as percentages. Student's t-test or its non-parametric version (the Mann-Whitney U test) was used to shed light on eventual differences in terms of sex/gender, age, admission, and survivor status. Receiver operating characteristic (ROC) analysis for verifying NLR's predictive capacity in predicting admission and survivor status.

RESULTS

Out of 513 subjects, 239 (47%) and 274 (53%) were women and men, respectively. Mean age was 72.42 ± 13.46 years [median 74 years (IQR 14)] (Supplementary Fig. 1). Women were slightly older [73.77 ± 14.78 years, median 76 (IQR 16)] than men [71.21 ± 12.16 years (IQR 13)]. This difference was statistically significant (p=0.00065).

At the admission, 376 patients (73%) were non-severe, while 137 (27%) were severe; 63% survived the infection, whereas 37% died. Neutrophils, lymphocytes, and NLR were 7.23 ± 5.83 x $10^3/\mu$L, 1.57 ± ± 6.97 x $10^3/\mu$L, and 9.86 ± 10.60, respectively (Fig. 1). If in terms of sex/gender, only a borderline difference for neutrophils could be computed (p = 0.087), with values slightly higher in men (7.29 × × $10^3/\mu$L vs 7.20 × $10^3/\mu$L), sex-specific differences were significant for lymphocytes (p = 0.00000138), with values higher in women (1.96 × $10^3/\mu$L vs 1.20 × × $10^3/\mu$L), and NLR (p = 0.0000171), with values higher in men (11.24 vs 8.42) (Fig. 2).

The Spearman's rho correlation coefficients between age and neutrophils, lymphocytes, and NLR were −0.018765, 0.034798, and −0.035239. These values suggest that there is very little to no monotonic relationship between age and each of the other three variables under study. The correlation coefficients are very close to zero, indicating that as age increases, there is no consistent increase or decrease in the values of neutrophils, lymphocytes, or the NLR that would suggest a strong relationship (Fig. 3).

Stratifying according to admission status, neutrophil levels were higher in severe patients (9.94 vs 6.24, p = = 1.65 x 10^{-12}), while lymphocyte concentrations

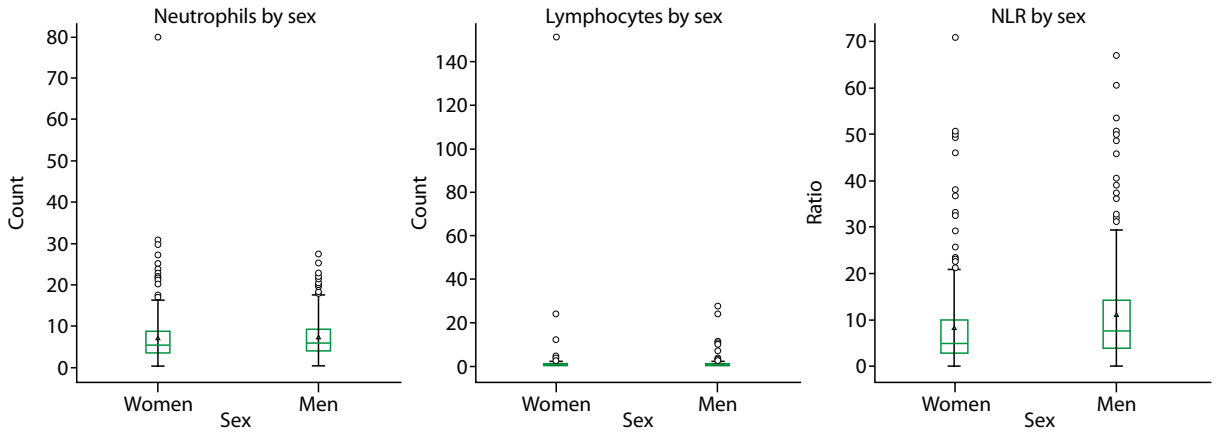

FIGURE 2. Neutrophil, lymphocyte and neutrophil-to-lymphocyte ratio values in the study population stratified by sex/gender

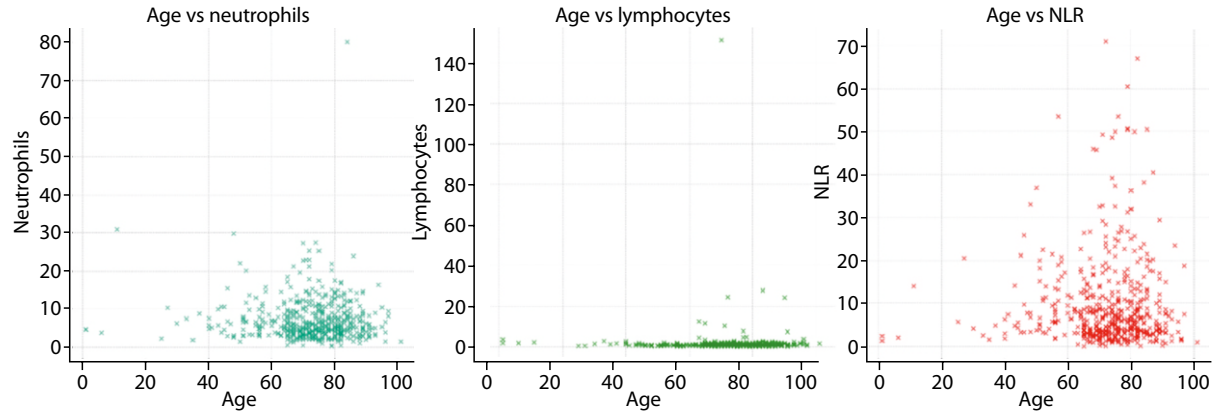

FIGURE 3. Scatterplots showing the lack of correlation between age and neutrophil, lymphocyte levels, and neutrophil-to-lymphocyte ratio (NLR) values in the study population

were lower (1.35 vs 2.18, p = 0.0139). Neutrophil-to-lymphocyte ratio was elevated in severe individuals (14.81 vs 8.06, $p = 3.94 \times 10^{-9}$), as shown in Figure 4.

Similar trends could be obtained when stratifying based on survivor status. Mean neutrophil levels were lower in survivors (6.31 vs 8.78, 1.82×10^{-10}), while mean lymphocyte concentrations were higher (1.98 vs 1.33, p = 0.0088). Mean NLR was significantly elevated in survivors (12.64 vs 8.21, $p = 8.47 \times 10^{-9}$), as shown in Figure 5.

In conclusion, NLR was a significant predictor of admission (with a ROC AUC of 0.76 [95% CI 0.61–0.72]) and survivor status (with a ROC AUC of 0.65 [95% CI 0.60–0.70]), as pictorially reported in Figures 6 and 7.

Stratifying by sex/gender (Fig. 8), the mean ROC AUC value for NLR in predicting admission status was 0.70 in males and 0.64 in females, whilst the ROC AUC value for NLR in predicting survivor status was 0.64 in male subjects and 0.65 in female subjects. While ROC AUC values were higher in men for admission status, they were comparable for survivor status.

Stratifying according to median age (Fig. 9), no impact of age could be detected. Receiver operating characteristic AUC values for NLW in predicting admission (0.67 and 0.66 for older and younger subjects, respectively) and survivor status (0.65 and 0.67) were comparable, without any statistically significant difference.

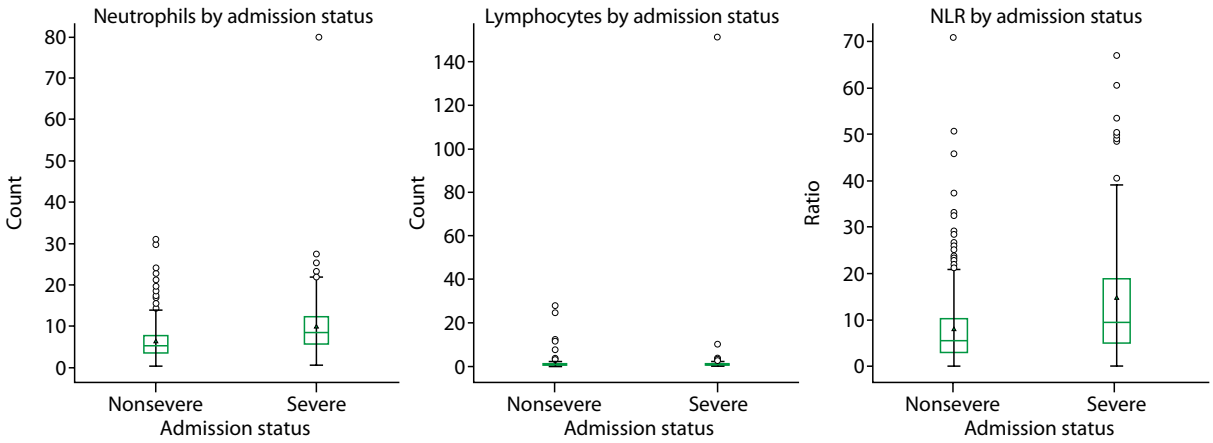

FIGURE 4. Neutrophil, lymphocyte and neutrophil-to-lymphocyte ratio values in the study population stratified by admission status

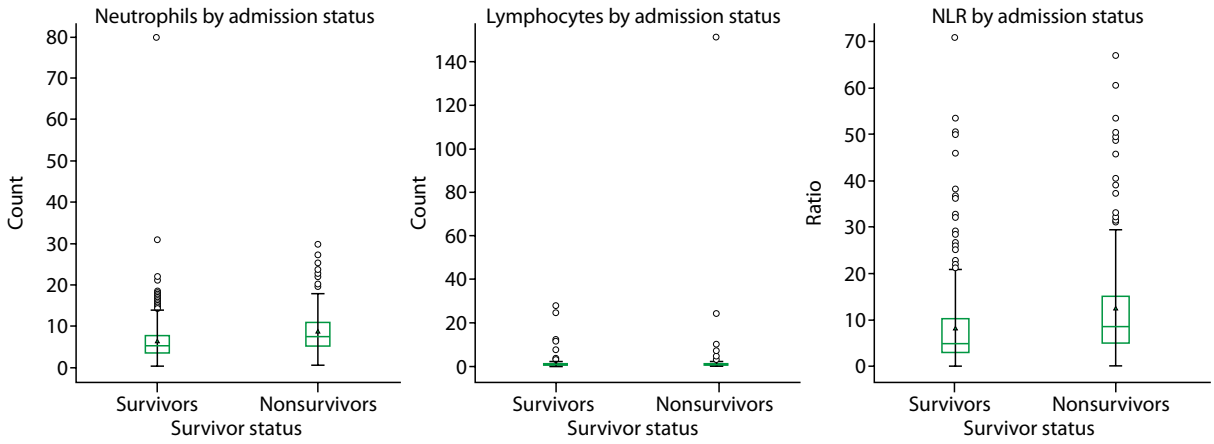

FIGURE 5. Neutrophil, lymphocyte and neutrophil-to-lymphocyte ratio values in the study population stratified by survivor status

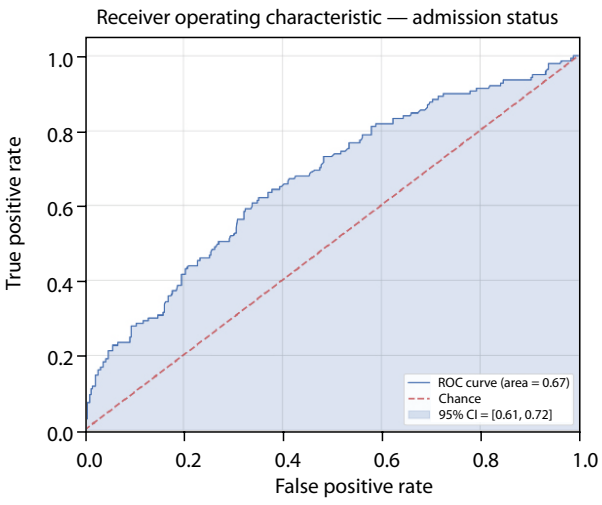

FIGURE 6. Receiver operating characteristic (ROC) analysis for neutrophil-to-lymphocyte ratio (NLR) in predicting admission status

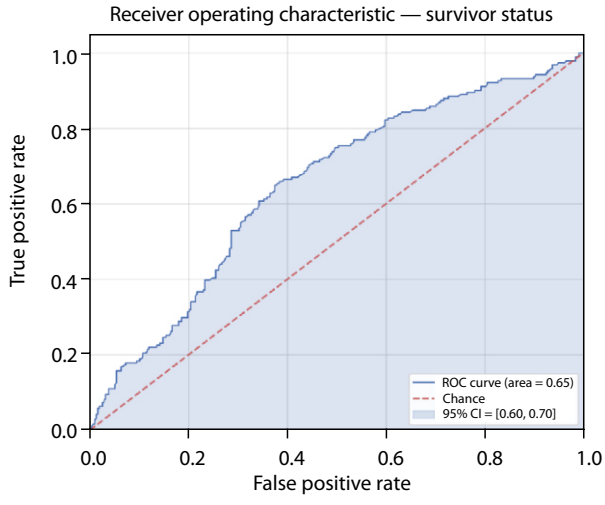

FIGURE 7. Receiver operating characteristic (ROC) analysis for neutrophil-to-lymphocyte ratio (NLR) in predicting survivor status

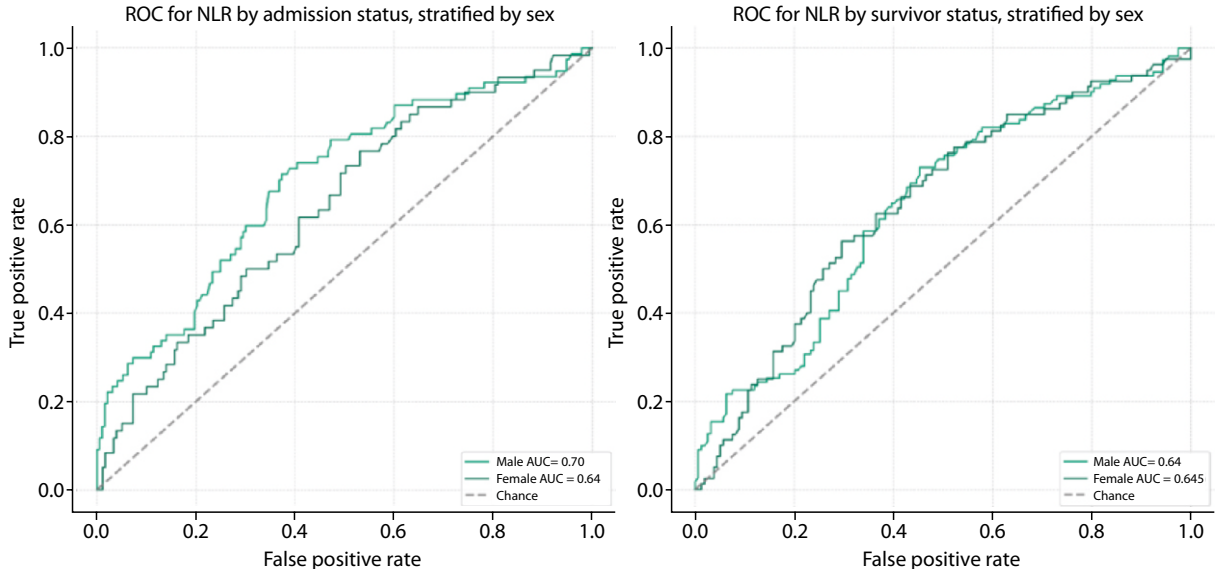

FIGURE 8. Receiver operating characteristic (ROC) analysis for Neutrophil-to-Lymphocyte ratio (NLR) in predicting admission and survivor status stratified by sex/gender; AUC — area under the curve

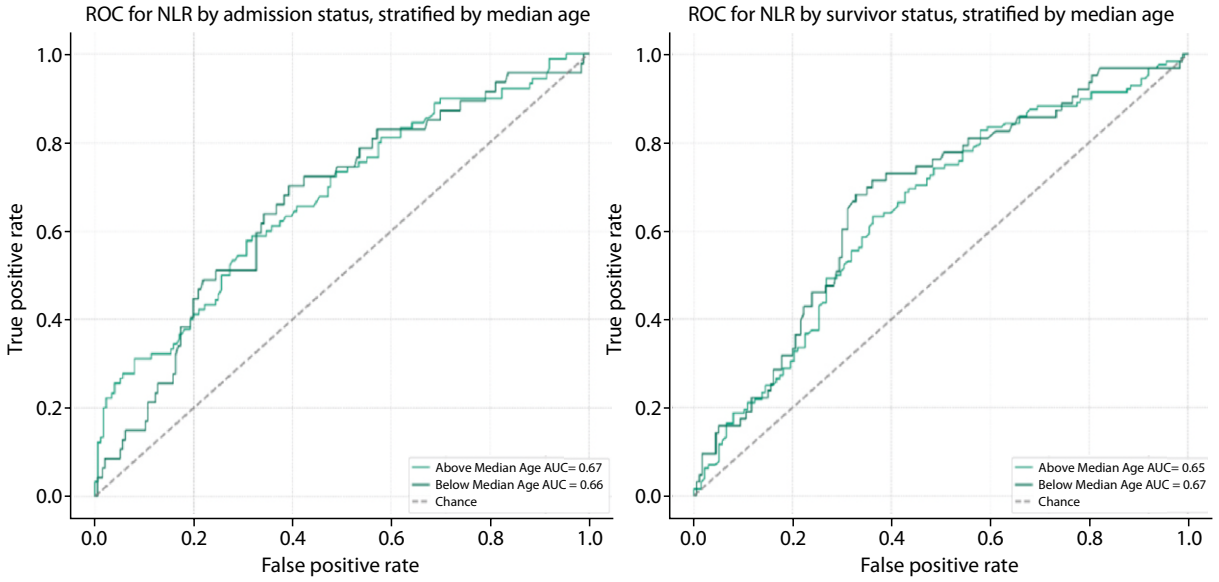

FIGURE 9. Receiver operating characteristic (ROC) analysis for Neutrophil-to-Lymphocyte ratio (NLR) in predicting admission and survivor status stratified by median age; AUC — area under the curve

DISCUSSION

During the COVID-19 outbreak, NLR has emerged as a significant, simple, and cost-effective blood test marker for predicting the severity of COVID-19, reflecting the body's inflammatory response to infection. Higher NLR values indicate an increased risk of severe outcomes. Its utility is especially pronounced in settings with limited resources, but caution is advised when interpreting NLR due to variability across different populations and other influencing factors. It should be integrated with additional clinical data to inform patient management decisions effectively. The statistical analysis of NLR, using the ROC AUC, validates its predictive ability. In the present study population, with an almost equal representation of women and men and a mean age of over 72 years, findings indicated that women were generally older than men. At the time of hospital admission, the

majority of patients were in a nonsevere condition, and about two-thirds survived their COVID-19 infection. Although there was a slight, non-significant difference in neutrophil counts between sexes, significant differences were observed in lymphocyte counts and NLR — women had higher lymphocyte counts and men had higher NLR. Age showed a very weak correlation with neutrophils, lymphocytes, and NLR, suggesting that age might not be a strong determinant of these measures. When stratifying patients by severity at admission and survivorship, clear patterns emerged: severe patients and non-survivors had higher neutrophils and NLR but lower lymphocytes compared to their counterparts. These trends underscore the value of NLR as a biomarker for assessing disease severity and survival prospects in patients with COVID-19.

The Neutrophil-to-Lymphocyte Ratio is a measure derived from a standard CBC test [1, 20]. It compares the levels of neutrophils, which increase in response to infection and stress, to lymphocytes, which can decrease in the context of a systemic inflammatory response. A higher NLR thus suggests a body under significant stress from an infection like COVID-19, indicating a possible shift towards a more severe disease state [21]. The predictive power of NLR for COVID-19 severity is particularly valuable because it is a readily available test that can be done quickly and at a low cost, making it accessible even in resource-limited settings [22].

Of note, gender differences were found in the inflammatory response to COVID-19. The present study's findings on the slight differences in neutrophil counts between genders, although not statistically significant, may indicate subtle variances in how men's and women's immune systems react to COVID-19. Significantly higher lymphocyte counts in women and higher NLR in men could point to a more robust inflammatory response in men, which has been observed in other studies. This could be related to hormonal differences or other genetic and immunological factors that influence how each gender responds to infections.

In terms of the correlation between age and inflammatory markers, the very weak correlations between age and the inflammatory markers (neutrophils, lymphocytes, and NLR) suggest that, unlike many other diseases where age is a strong risk factor, age alone does not significantly influence these particular immune response markers in COVID-19 patients [20, 23]. This could mean that the body's inflammatory response to COVID-19 is similar across different ages or that other factors, such as comorbidities or previous health status, are more important in determining these levels than age itself.

In terms of associations between clinical outcomes and NLR, in patients with severe disease, higher neutrophil counts and NLR and lower lymphocyte counts were observed. This aligns with the understanding that a severe infection can lead to an elevated neutrophil response and lymphocyte depletion, which is reflected in an increased NLR [24]. Conversely, survivors tended to have lower neutrophil counts and NLR but higher lymphocyte counts [22]. This suggests that a balanced immune response with less inflammation (as indicated by a lower NLR) is associated with better outcomes.

As such, NLR can play a key role in clinical decision-making. The present study further reinforces the role of NLR as an integral part of clinical decision-making. Since NLR is associated with disease severity and survival, it could potentially guide interventions, risk stratification, and monitoring. The ROC AUC values for NLR in predicting admission status and survival status show that it has good discriminative ability, although it's not perfect. In clinical practice, NLR should be one of several factors considered when assessing a patient's condition, used in conjunction with other clinical signs, symptoms, and tests.

In terms of implications for healthcare systems, especially those facing resource constraints, NLR offers a practical metric for quickly identifying patients at higher risk of severe disease [25, 26]. This can be crucial for triaging patients, optimizing the allocation of limited resources, and initiating timely treatments that could potentially reduce the risk of adverse outcomes. In conclusion, the results illuminate the utility of NLR in managing COVID-19 by providing a simple and cost-effective tool for assessing disease severity. They also underscore the need for careful interpretation of NLR values, considering the influence of gender, age, and clinical context. As the understanding of COVID-19 evolves, so too will the strategies for utilizing such biomarkers in patient care.

CONCLUSIONS

There were slight but not statistically significant differences in neutrophil counts between men and women. However, there were significant differences in lymphocyte counts and the NLR, with women

having higher lymphocyte counts and men having higher NLR. The study found very weak correlations between age and neutrophil counts, lymphocyte counts, and NLR, suggesting no strong relationship between age and these variables. Patients with severe disease had higher neutrophil counts and NLR but lower lymphocyte counts compared to nonsevere patients. Survivors had lower neutrophil counts and NLR but higher lymphocyte counts compared to those who did not survive. NLR was a significant predictor of both admission status and survivor status, with ROC AUC values indicating its predictive capacity. These findings highlight the potential importance of NLR as a biomarker in predicting disease severity and survival in patients.

Article information and declarations

Author contributions

Conceptualization, K.D.; methodology, K.D., M.K., R.A.; software, K.D., N.L.B. and L.S.; validation, M.Y., K.D. and L.S.; formal analysis, K.D., N.L.B.; investigation, M.K. and R.K.; resources, K.D., M.K., R.A..; data curation, K.D., N.L.B and L.S; writing — original draft preparation, K.D. and M.L.B.; writing — review and editing, all authors; visualization, K.D., N.L.B., L.S.; supervision, F.C., N.L.B., K.D., and L.S.; project administration, K.D. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

The institutional review board of the Kartal Dr Lütfi Kırdar City Hospital (Istanbul, Türkiye) approved the analysis (ethical committee ruling number: 2022/514/228/25, date: 30.06.2022).

Informed consent statement

Not applicable.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author (K.D.).

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Conflicts of interest

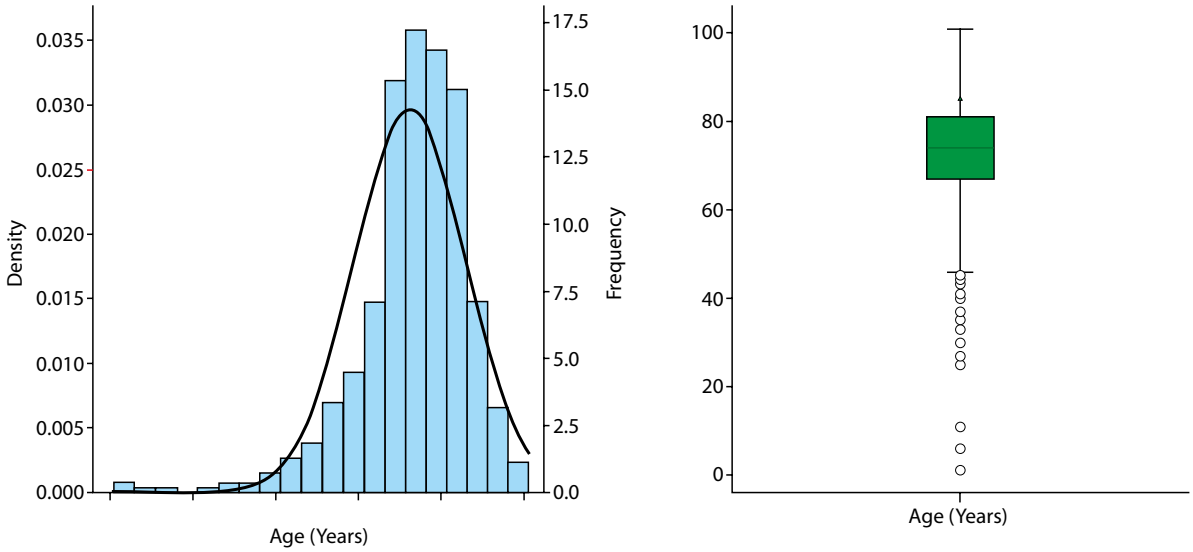
The authors declare no conflict of interest.

REFERENCES

1. Buonacera A, Stancanelli B, Colaci M, et al. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. Int J Mol Sci. 2022; 23(7), doi: 10.3390/ijms23073636, indexed in Pubmed: 35408994.
2. Kilic M, Hokenek UD. Association between D-dimer and mortality in COVID-19 patients: a single center study from a Turkish hospital. Disaster Emerg Med J. 2022; 7(4): 225–230, doi: 10.5603/demj.a2022.0039.
3. Gong P, Liu Y, Gong Y, et al. The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke. J Neuroinflammation. 2021; 18(1): 51, doi: 10.1186/s12974-021-02090-6, indexed in Pubmed: 33610168.
4. Matuszewski M, Szarpak L, Pruc M, et al. Platelet-to-lymphocyte ratio as a prognostic biomarker for COVID-19 severity: a single center retrospective data analysis and systematic review with meta-analysis of 187 studies. Disaster Emereg Med J. ; 2023, doi: 10.5603/demj.96811.
5. Li W, Hou M, Ding Z, et al. Prognostic value of neutrophil-to-lymphocyte ratio in stroke: a systematic review and meta-analysis. Front Neurol. 2021; 12: 686983, doi: 10.3389/fneur.2021.686983, indexed in Pubmed: 34630275.
6. Cupp MA, Cariolou M, Tzoulaki I, et al. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med. 2020; 18(1): 360, doi: 10.1186/s12916-020-01817-1, indexed in Pubmed: 33213430.
7. Platini H, Ferdinand E, Kohar K, et al. Neutrophil-to-Lymphocyte ratio and platelet-to-lymphocyte ratio as prognostic markers for advanced non-small-cell lung cancer treated with immunotherapy: a systematic review and meta-analysis. Medicina (Kaunas). 2022; 58(8): 1069, doi: 10.3390/medicina58081069, indexed in Pubmed: 36013536.
8. Parthasarathi A, Padukudru S, Arunachal S, et al. The role of neutrophil-to-lymphocyte ratio in risk stratification and prognostication of COVID-19: a systematic review and meta-analysis. Vaccines (Basel). 2022; 10(8), doi: 10.3390/vaccines10081233, indexed in Pubmed: 36016121.
9. Sarkar S, Khanna P, Singh AK. The impact of neutrophil-lymphocyte count ratio in COVID-19: a systematic review and meta-analysis. J Intensive Care Med. 2022; 37(7): 857–869, doi: 10.1177/08850666211045626, indexed in Pubmed: 34672824.
10. Smereka J, Szarpak L. COVID 19 a challenge for emergency medicine and every health care professional. Am J Emerg Med. 2020; 38(10): 2232–2233, doi: 10.1016/j.ajem.2020.03.038, indexed in Pubmed: 32241630.
11. Ruetzler K, Szarpak L, Filipiak K, et al. The COVID-19 pandemic — a view of the current state of the problem. Disaster Emerg Med J. 2020; 5(2): 106–107, doi: 10.5603/demj.a2020.0015.

12. Szarpak Ł, Nowak B, Kosior D, et al. Cytokines as predictors of COVID-19 severity: evidence from a meta-analysis. Pol Arch Intern Med. 2021; 131(1): 98–99, doi: 10.20452/pamw.15685, indexed in Pubmed: 33219785.
13. Fernandez-Botran R, Furmanek S, Ambadapoodi RS, et al. Association and predictive value of biomarkers with severe outcomes in hospitalized patients with SARS-CoV-2 infection. Cytokine. 2022; 149: 155755, doi: 10.1016/j.cyto.2021.155755, indexed in Pubmed: 34773859.
14. Sayah W, Berkane I, Guermache I, et al. Interleukin-6, procalcitonin and neutrophil-to-lymphocyte ratio: potential immune-inflammatory parameters to identify severe and fatal forms of COVID-19. Cytokine. 2021; 141: 155428, doi: 10.1016/j.cyto.2021.155428, indexed in Pubmed: 33550165.
15. Zahorec R, Hulin I, Zahorec P. Rationale use of neutrophil-to-lymphocyte ratio for early diagnosis and stratification of COVID-19. Bratisl Lek Listy. 2020; 121(7): 466–470, doi: 10.4149/BLL_2020_077, indexed in Pubmed: 32989997.
16. Jimeno S, Ventura PS, Castellano JM, et al. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. Eur J Clin Invest. 2021; 51(1): e13404, doi: 10.1111/eci.13404, indexed in Pubmed: 32918295.
17. Faria SS, Fernandes PC, Silva MJ, et al. The neutrophil-to-lymphocyte ratio: a narrative review. Ecancermedicalscience. 2016; 10: 702, doi: 10.3332/ecancer.2016.702, indexed in Pubmed: 28105073.
18. Miyashita K, Hozumi H, Furuhashi K, et al. Changes in the characteristics and outcomes of COVID-19 patients from the early pandemic to the delta variant epidemic: a nationwide population-based study. Emerg Microbes Infect. 2023; 12(1): 2155250, doi: 10.1080/22221751.2022.2155250, indexed in Pubmed: 36469641.
19. Chen YH, Cheuh YN, Chen CM, et al. Epidemiological characteristics of the three waves of COVID-19 epidemic in Taiwan during April 2022 to March 2023. J Formos Med Assoc. 2023; 122(11): 1174–1182, doi: 10.1016/j.jfma.2023.05.027, indexed in Pubmed: 37301691.
20. Yang AP, Liu JP, Tao WQ, et al. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020; 84: 106504, doi: 10.1016/j.intimp.2020.106504, indexed in Pubmed: 32304994.
21. Palladino M. Complete blood count alterations in COVID-19 patients: a narrative review. Biochem Med (Zagreb). 2021; 31(3): 030501, doi: 10.11613/BM.2021.030501, indexed in Pubmed: 34658642.
22. Ponti G, Maccaferri M, Ruini C, et al. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020; 57(6): 389–399, doi: 10.1080/10408363.2020.1770685, indexed in Pubmed: 32503382.
23. Battaglini D, Lopes-Pacheco M, Castro-Faria-Neto HC, et al. Laboratory biomarkers for diagnosis and prognosis in COVID-19. Front Immunol. 2022; 13: 857573, doi: 10.3389/fimmu.2022.857573, indexed in Pubmed: 35572561.
24. Borges L, Pithon-Curi TC, Curi R, et al. COVID-19 and neutrophils: the relationship between hyperinflammation and neutrophil extracellular traps. Mediators Inflamm. 2020; 2020: 8829674, doi: 10.1155/2020/8829674, indexed in Pubmed: 33343232.
25. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. Am J Pathol. 2021; 191(1): 4–17, doi: 10.1016/j.ajpath.2020.08.009, indexed in Pubmed: 32919977.
26. Cesta MC, Zippoli M, Marsiglia C, et al. Neutrophil activation and neutrophil extracellular traps (NETs) in COVID-19 ARDS and immunothrombosis. Eur J Immunol. 2023; 53(1): e2250010, doi: 10.1002/eji.202250010, indexed in Pubmed: 36239164.

SUPPLEMENTARY MATERIAL



SUPPLEMENTARY FIGURE 1. Age of the study population: histogram showing the frequency and density of the various age groups (left), and boxplot showing the distribution of the age groups (right)