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Prognostic Value of Admission Neutrophil Count in Asthma Patients with COVID-19: A Comparative Analysis with Other Systemic Inflammation Indices for In-hospital Mortality Prediction

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ABSTRACT

Despite studies indicating that asthma patients do not exhibit a higher mortality rate or severity compared to the general population when infected with COVID-19, there have been few reports on predictive factors for mortality in this context. This study aimed to assess the predictive value of systemic inflammation indices, including neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR), platelet-to-lymphocyte (PLR), systemic inflammation response index (SIR-I), and systemic inflammation index (SII) in determining mortality rate among patients with COVID-19 and asthma.

In this prospective study, the laboratory parameters of 1792 COVID-19 patients were examined, comprising 112 patients with asthma and 1680 without asthma. Receiver operating characteristic (ROC) analysis was employed to assess the potential of inflammatory indices in indicating COVID-19 severity. Kaplan-Meier curves were utilized to analyze the survival probability with death as the outcome.

In deceased patients without asthma, leukocyte and differential cell counts and PLR, NLR, MLR, SII, and SIR-I values were higher than in survivors. In contrast, all the above values except PLR and MLR were significant in the asthma groups. The Kaplan-Meier survival curves were consistent with the ROC analysis. However, a multivariate Cox regression analysis revealed that neutrophil counts in patients without asthma and leukocyte and neutrophil counts in asthma patients were significant for survival.

In conclusion, while numerous inflammatory indices were associated with mortality in COVID-19 patients without asthma, neutrophil counts could independently predict mortality risk in asthma COVID-19 patients.

Keywords: Asthma; Coronavirus; COVID-19; Neutrophils

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INTRODUCTION

Several risk factors, including age, gender, platelet, neutrophil, and lymphocyte counts, and lipid profiles, have been correlated with the prediction of COVID-19 severity.[1-3] Although most studies have shown that patients with asthma are not at an increased risk of mortality or acquiring a more severe form of COVID-19 compared to the general population, few studies have tried to identify predictive indicators in this context.[4] Hematologic parameters such as leukocytosis, thrombocytopenia, eosinopenia, monocytopenia, lymphopenia, and neutrophilia have been associated with the severity and mortality from COVID-19.[5-7]

Calculated hematological parameters can also predict the progress, diagnosis, and risk stratification of inflammatory conditions. These parameters include monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation index (SII), and systemic inflammation response index (SIR-I).[8-10]

Most of these hematologic parameters have been investigated to diagnose the COVID-19 severity without taking into account the comorbidities. Asthma is one of the comorbidities associated with COVID-19. Some studies have reported asthma as a risk factor for severe COVID-19 outcomes, while other studies have not shown such a result.[4] Given the altered immune responses and inflammation in asthma, we hypothesized that inflammatory biomarkers may predict mortality in asthma patients with COVID-19. Therefore, this study aimed to determine the prognostic value of leukocyte, neutrophil, and lymphocyte counts and ratios of PLR, MLR, NLR, SII, and SIR for predicting mortality in asthma patients infected with COVID-19.

MATERIALS AND METHODS

This prospective study enrolled patients with and without asthma who had a positive PCR test for COVID-19. It was conducted at Imam Khomeini Hospital, Ardabil, Iran, between September and November 2020. Patients with negative or inconclusive PCR tests were excluded. The data were collected from the electronic medical record system and included the gender, age, laboratory results, duration of hospitalization, and disease outcome (recovered or deceased). Laboratory tests were evaluated within 24 hours of admission, and PLR, MLR, NLR, SII, and SIR-I were calculated for all patients. The following formula was used to calculate the SIR-I and SII.

SII = (neutrophil count × platelet count) / lymphocytes

SIR-I = (neutrophils × monocytes) / lymphocytes

Statistical Analysis

Data analysis was performed using SPSS version 21 and MedCalc version 19.4.1 software. Optimal cutoff values that maximized the sensitivity and specificity of the Youden index were determined via receiver operating characteristics (ROC) curves, and hospital admission time served as the starting point for survival analyses. Survival probability for the systemic inflammation index was calculated using Kaplan-Meier curves with death as the endpoint. The Cox regression model was applied to perform the univariate and multivariate analyses.[11] Values are expressed as hazard ratios (HR) and confidence intervals (CI).

RESULTS

This study included 1792 COVID-19 patients, of whom 112 had asthma, and 1680 did not. The mean age of the patients without asthma was 59.60±16.99, which did not significantly differ from patients with asthma (56.77±16.14). The percentage of female patients was significantly higher in the asthmatic COVID-19 group (59.8%) than in patients without asthma (43.9%, $p<0.001$). The mean hospital stay for patients with asthma (8.94±8.44) was longer than patients without asthma (8.06±7.13), although the difference was insignificant. On admission, most tests were normal in both groups, except for albumin, urea, blood glucose, aspartate transaminase, erythrocyte sedimentation rate, ferritin, alkaline phosphatase, and lactate dehydrogenase.

Of the 112 COVID-19 patients with asthma, 90 (80.4%) were discharged, and 22 (19.6%) died. In the group without asthma, 80.3% were discharged, and 19.7% died. In terms of severity of COVID-19 infection, 75% of patients with asthma were moderate, 5.4% were severe, and 19.6% were very severe. For patients without asthma, 73.2% were moderate, 9.3% were severe, and 17.6% were very severe.

Optimal cutoff values for evaluating survival were determined by ROC analysis and are summarized in

Table 1. In the group without asthma, AUC was significant for neutrophil, leukocyte, and lymphocyte counts, PLR, MLR, NLR, SII, and SIR-I (Table 1). Neutrophil counts had significantly higher AUC values compared with total leukocytes (z=5.232, p<0.001) and monocyte count (z=7.926, p<0.001) to distinguish deceased from survived patients. Likewise, lymphocytes had significantly higher AUC compared with total leukocytes (z=2.265, p<0.05) and monocytes (z=6.696, p<0.001) in distinguishing deceased from surviving patients. For systemic inflammation indices, NLR has a significantly higher AUC value than the PLR (z=5.815, p<0.001), SIR-I (z=4.699, p<0.001), MLR (z=6.100, p<0.001), and SII (z=4.574, p<0.001) for distinguishing deceased from surviving patients without asthma.

Asthma patients exhibited significant AUC values for leukocyte, neutrophil, and lymphocyte counts, NLR, SIR-I, and SII (Table 1). It is interesting to note that in deceased patients compared to recovered subjects, the neutrophils count had higher AUC values than lymphocytes (z=2.157, p<0.05), SIR-I (z=2.445, p<0.05), and SII (z=2.376, p<0.05). In addition, NLR had a higher AUC value compared to the lymphocytes count (z=2.634, p<0.01) in the deceased asthmatics compared to those who recovered.

Table 1. Receiver operating characteristics (ROC) curves and prognostic accuracy of blood cell count-derived inflammation indices in COVID-19 patients with and without asthma.

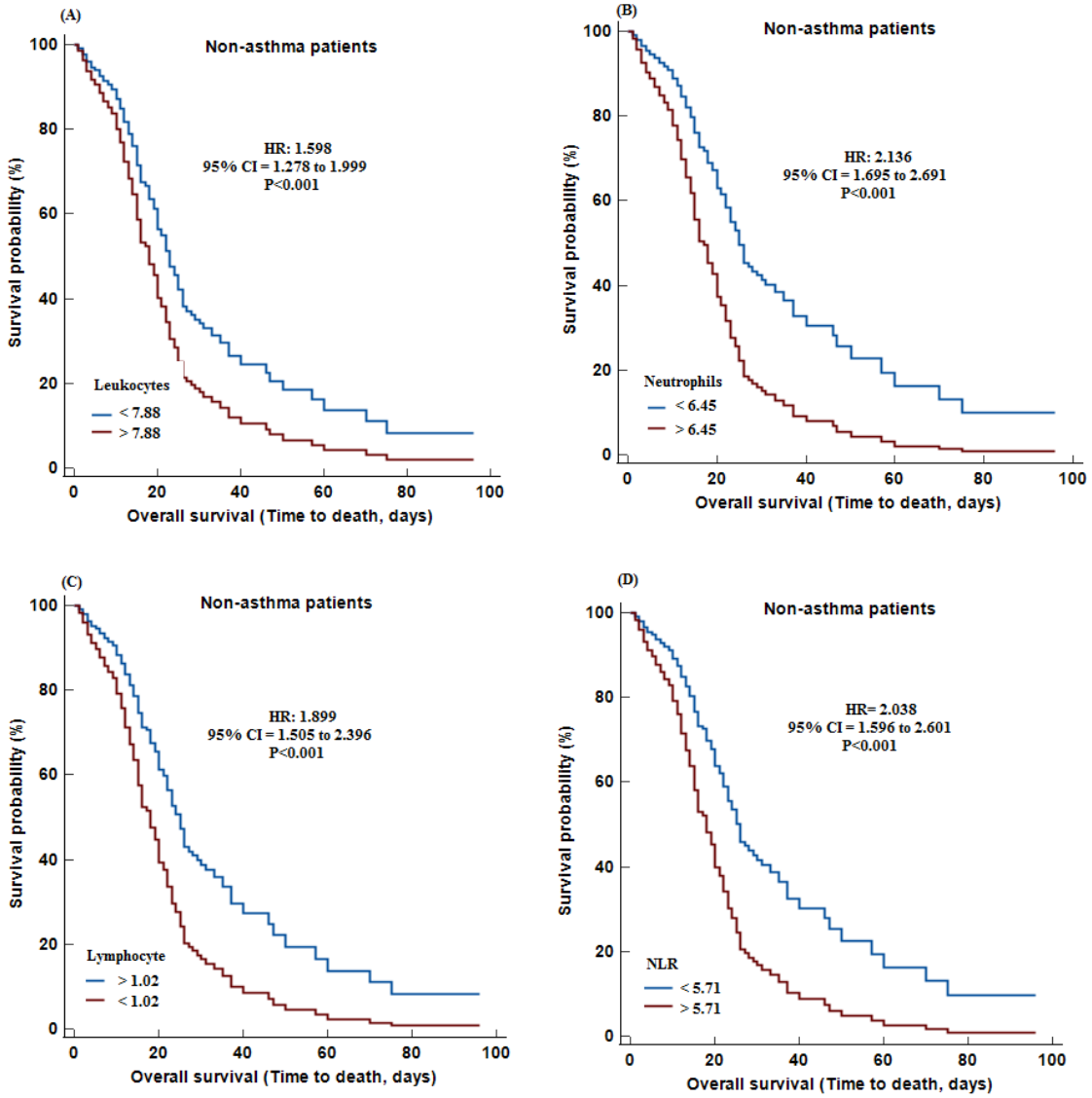
Variables	AUC	95% CI	*p*	Cutoff	Sensitivity	Specificity (%)
WBC						
Without asthma	0.635	0.611 to 0.658	0.000	> 7.88	59	62
With asthma	0.670	0.575 to 0.756	0.018	> 9.59	50	88.9
Neutrophil						
Without asthma	0.712	0.690 to 0.734	0.000	> 6.45	65	68
With asthma	0.797	0.711 to 0.867	0.000	> 7.01	95	61
Lymphocyte						
Without asthma	0.689	0.666 to 0.711	0.000	< 1.02	67	63
With asthma	0.713	0.620 to 0.795	0.000	< 1.33	73	67
NLR						
Without asthma	0.707	0.685 to 0.729	0.000	> 5.71	71	60
With asthma	0.738	0.647 to 0.817	0.000	> 4.44	81	59
MLR						
Without asthma	0.594	0.570 to 0.617	0.000	> 0.24	50	67
With asthma	0.592	0.496 to 0.684	0.181	> 0.20	59	64
PLR						
Without asthma	0.638	0.615 to 0.661	0.000	> 216	53	70
With asthma	0.621	0.524 to 0.711	0.081	> 117	77	51
SIR-I						
Without asthma	0.629	0.606 to 0.652	0.000	> 1.68	46	74
With asthma	0.647	0.551 to 0.735	0.030	> 1.15	72	58
SII						
Without asthma	0.663	0.640 to 0.686	0.000	> 1401	55	70
With asthma	0.655	0.559 to 0.743	0.015	> 811	77	50

MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic inflammation index; SIR-I: systemic inflammation response index; WBC: white blood cells.

We classified patients without asthma based on the Youden index cutoff from the ROC method and analyzed their survival using the Kaplan-Meier curves. We found significantly decreased survival in patients with high neutrophil and leukocyte counts, PLR, MLR, NLR, SII, and SIR-I, and low lymphocyte count (Figure

1). In contrast, the asthma patients' survival decreased significantly with increasing neutrophil count (HR, 15.180 [95% CI, 2.033–113.244]; $p<0.001$), leukocyte count (HR, 7.966 [95% CI, 2.923–21.711]; $p<0.001$), SIR-I (HR, 3.083 [95% CI, 1.090–8.722]; $p<0.05$), NLR (HR, 2.465 [95% CI, 1.007–11.923]; $p<0.05$), and decreasing the lymphocytes count (HR, 2.529 [95% CI=1.021 to 6.263]; $p<0.05$).

The Cox regression analyses found neutrophil count as the only significant predictor of survival in patients without asthma (HR, 1.46 [95% CI, 1.04-2.05]; $p<0.05$). However, both neutrophil count (HR, 11.71 [95% CI, 1.18-116.67]; $p<0.05$) and leukocyte count (HR, 4.58 [95% CI, 1.57-13.32]; $p<0.01$) were significant predictors in patients with asthma.



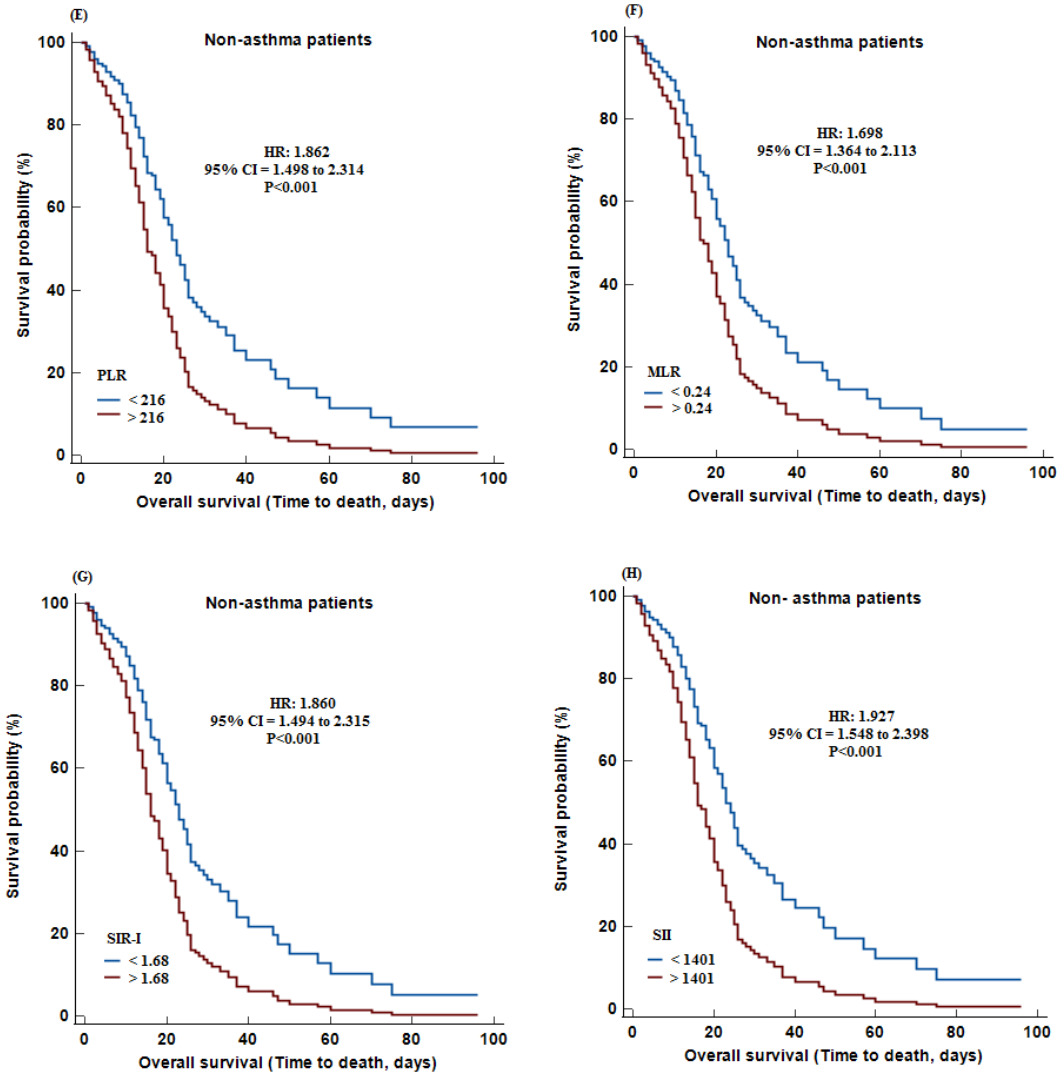


Figure 1. Kaplan-Meier survival curves during hospitalization of COVID-19 patients without asthma with different cutoff values for leukocytes and differential cells, as well as the systemic inflammation indices investigated. (A) leukocytes; (B) neutrophils; (C) lymphocytes; (D) NLP; (E) PLR; (F) MLR; (G) SIR-I; (H) SII. MLR: monocyte/lymphocyte ratio, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SII: systemic inflammation index, SIR-I: systemic inflammation response index, WBC: white blood cell.

DISCUSSION

Our analysis did not find significant differences between COVID-19 patients with and without asthma in terms of age, length of hospital stay, and disease severity. These results align with previous studies comparing COVID-19 outcomes in patients with or without asthma.[12-14] Moreover, the mortality rates were similar in both groups (19.6% vs. 19.7%). Various studies have shown a higher mortality rate in COVID-19 patients with comorbidities, such as pulmonary diseases, malignancies, diabetes, chronic kidney disease, and cardiovascular diseases.[15]

We observed that leukocyte and differential cell counts (neutrophil, monocyte, eosinophil, and lymphocyte) were significantly higher in COVID-19 patients with asthma compared to those without. However, PLR and NLR were significantly higher in patients without asthma. Moreover, leukocyte and differential cell counts were significantly higher in the

deceased patients than in survivors in both groups. Interestingly, WBC, lymphocyte, and neutrophil counts were higher in deceased patients with asthma than in deceased patients without asthma. In addition, NLR, SII, and SIR-I were higher in deceased patients in both groups.

Previous studies on COVID-19 patients have reported abnormal laboratory results, especially in critically ill and deceased patients.[11,16,17] Consistent with these findings, our study revealed that leukocytosis, lymphopenia, and an increase in the neutrophil count were more pronounced in deceased patients than in survivors, regardless of asthma status.[18-20] However, deceased patients with asthma had markedly greater leukocytosis and neutrophilia compared to deceased patients without asthma. Conversely, lymphopenia was more pronounced in deceased patients without asthma. Neutrophils play a key role in the immune system and act as the primary line of defense against bacterial and fungal infections.[21] However, their role in viral infections remains unclear. Human studies of COVID-19 have found numerous neutrophils infiltrating the pulmonary capillaries and alveolar spaces.[22]

NLR correlates with disease activity and systemic inflammation, major prognostic factors in cancer, cardiovascular, autoimmune, and other infectious diseases.[23-25] Previous studies have also found NLR to be a reliable indicator of COVID-19 severity and mortality.[11,26-28] Likewise, PLR can predict disease severity in autoimmune and cardiovascular diseases.[11,29,30] Moreover, PLR is important in diagnosing COVID-19, especially in the early stages of hospitalization.[30] Interestingly, SII and SIR-I reflect inflammation and immune responses of the diseases and are often used to predict the mortality of infectious diseases, autoimmune diseases, and cancers.[20,31,32]

While most studies have reported NLR as a superior indicator of severe COVID-19 compared to neutrophil and lymphocyte counts, we found that in patients without asthma, leukocytes and differential cells, as well as PLR, MLR, SIR-I, and SII, also had a significant increase in deceased patients. In contrast, leukocytes and differential cells, along with NLR, SIR-I, and SII, were associated with disease severity in patients with asthma.

Using cutoff values from the ROC curve, Kaplan-Meier survival curves showed that survival in patients without asthma correlated with leukocytes, lymphocytes, neutrophils, PLR, NLR, SIR-I, MLR, and SII. However, in patients with asthma, it was correlated with neutrophils, leukocytes, lymphocytes, SIR-I, and NLR. Interestingly, multivariate Cox regression analysis revealed that in patients without asthma, only the neutrophil count was significantly associated with survival. In contrast, in patients with asthma, both leukocyte and neutrophil counts were significantly associated with survival. These results indicate that NLR, PLR, and MLR do not reliably predict COVID-19 severity. Our findings suggest that neutrophil counts may effectively indicate mortality risk in asthma and patients without asthma with COVID-19, while leukocyte counts could help predict severity.

This investigation had several limitations, including 1) its retrospective design, 2) the inclusion of patients from a single hospital center, and 3) the variation in disease stages among COVID-19 patients with asthma despite examining pre-hospitalization tests.

To conclude, although systemic inflammation biomarkers are useful for assessing the severity of inflammatory diseases, they should be applied judiciously in COVID-19 patients. Neutrophil counts effectively indicated mortality risk in patients without asthma, while leukocyte and neutrophil counts predicted severity in patients with asthma. Therefore, asthma comorbidities can affect systemic inflammation biomarkers in COVID-19 patients, warranting further studies.

STATEMENT OF ETHICS

This research proceeded after the approval of the Ethics Committee of Ardabil University of Medical Sciences (IR.ARUMS.REC.1399.587).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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