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# Systemic inflammation indices predict mortality in patients with COVID-19

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## ABSTRACT

**Aim:** In recent years, inflammation-based indices obtained from hematologic parameters have been shown to have prognostic value in various inflammatory diseases and cancer types. In this study, we aimed to investigate whether inflammation indices could be used to predict mortality in patients with COVID-19.

**Material and Method:** A total of 295 patients with a proven diagnosis of COVID-19 who were followed up in the intensive care unit were included in this retrospective, cross-sectional study. The patients were divided into two groups, survivors and non-survivors.

**Results:** D-dimer (HR:1.001, 95% CI:1-1.001) and troponin (HR: 1.001 95% CI: 1-1.001) levels of non-survivors were significantly higher in univariate analyses ($p<0.05$). Procalcitonin levels of whom were found to be high in univariate (HR: 1.018 95% CI: 1.003 – 1.034) and multivariate (HR:1.02 95% CI: 1.004-1.037) analyses ($p<0.05$). There was no significant difference between the groups in terms of median values of PLR, SIRI, and AISI indices ($p>0.05$). The median NLR value of the survivors was 7.45, while it was 11.39 in the non-survivors, and this difference was statistically significant ($p<0.001$). The median value of the SII index of the non-survivors was found as 2421.02, which was significantly higher than the survivors ($p<0.001$). The value of NLR and SII indices in predicting mortality in COVID-19 was evaluated using ROC analysis (NLR: AUC=0.644, 95%CI: 0.581-0.708, $p<0.001$; SII: AUC=0.584, 95%CI: 0.517-0.651, $p=0.017$). When the cut-off value for NLR was accepted as 9.574, the sensitivity was 59.3% and the specificity was 67% in predicting mortality. When the cut-off value for SII was accepted as 2285,846, it was found that it could predict mortality with a sensitivity of 52.38% and specificity of 66.04%.

**Conclusion:** SII and NLR indices can predict mortality in patients with COVID-19 followed up in the intensive care unit.

**Keywords:** COVID-19, inflammatory index, SII, NLR

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic that emerged in the Wuhan province of China in December 2019 and still threatens humanity. It infected more than 386 million people and killed approximately 6 million people worldwide (1). The virus can cause a wide variety of symptoms with the involvement of multiple organs, especially the respiratory tract. It is well known that COVID-19–related organ dysfunction and mortality are associated with an increased inflammatory response (2). Studies conducted in this context have shown that inflammatory parameters can be used as a biomarker to predict prognosis in patients with COVID-19 (3-5).

The complete blood count is an easy and inexpensive test used in clinical practice. It can provide the physician with extensive information about the cell types involved in the immune response and their number and morphology. In addition, it is also possible to obtain ratios such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic inflammation index (SII), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI), which are defined as inflammation indices, from these parameters. NLR and PLR reflect systemic inflammation with neutrophil and platelet activation. It has been associated with increased mortality in cardiovascular diseases and with poor prognosis in various cancers (6). It has been proven that SII and SIRI reflect the inflammatory response and can predict prognosis in many inflammatory diseases and cancer types (7-9). It has been shown that these indices can also have diagnostic value in COVID-19

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and can be used to determine the severity of the disease (10,11). Based on these findings, we aimed to investigate whether these indices could be used to predict mortality in patients with COVID-19 followed up in the intensive care unit (ICU).

## MATERIAL AND METHOD

The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 14.01.2022, Decision No: 2022/022). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who were admitted to Konya Numune Hospital between March 2020 and January 2021 and were followed up in the ICU were included in this study. It was designed as a single-center, retrospective, cross-sectional study.

Clinical, demographic, and laboratory data of the patients were extracted from electronic medical records (Karmed) using a standardized data collection form. The records of a total of 312 patients aged over 18 years were analyzed for the study. Among these patients, a total of 295 patients were included in the analysis after the diagnosis of COVID-19 was eliminated during their follow-up. Those with a history of head trauma, malignancy, or cerebrovascular disease, and those who were pregnant were excluded.

The diagnosis of COVID-19 was made through respiratory tract swab samples (throat swabs) using real-time qualitative polymerase chain reaction (RT-qPCR). Data on the main comorbidities included diabetes mellitus (DM), hypertension (HT), pulmonary disease, and history of cardiac disease. The results of complete blood count and serum biochemical tests (D-dimer, myocardial enzymes [troponin], urea, creatinine, procalcitonin, albumin, lactate dehydrogenase [LDH], and ferritin levels) were recorded.

Systemic inflammation indices were determined from the first complete blood count using the following formulae:NLR: neutrophil count/lymphocyte count; PLR: platelet count/lymphocyte count; SII: neutrophil count x platelet/lymphocyte count; SIRI: neutrophil x monocytes/lymphocyte; AISI: neutrophil x platelet x monocytes/lymphocytes.

### Statistical analysis

The data were analyzed using the IBM SPSS V 23 software package. Conformity to normal distribution was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare indices according to mortality status. Cut-off values of indices for mortality were analyzed using receiver operating characteristics (ROC) analysis. Cox regression analysis was used to examine the risk factors affecting the survival time in the ICU. Analysis results are presented as mean±standard deviation and median (Q1 – Q3) for quantitative data, and frequency (percent) for categorical variables. The significance level was accepted as $p<0.05$.

## RESULTS

A total of 295 patients who were diagnosed as having COVID-19 were included in the study and followed up during their stay in the ICU. All patients were divided into survivors and non-survivors. Of the patients,45.8% were female and no significant difference was observed between the groups in terms of sex distribution ($p>0.05$). Risk factors affecting survival time in the ICU were analyzed using univariate and multivariate models. As a result of the univariate analysis, it was determined that age was an independent risk factor that affected the mortality status (hazard ratio [HR]: 1.017, 95% confidence intervals [CI]: 1.004-1.03). The mean age of the patients who died (72.51±12.58) was significantly older than the patients who survived (67.58±13.37) ($p=0.009$). (**Table 1**)

No significant difference was observed in terms of white blood cell count (normal range: 4.49-12.68 $10^9$/L), neutrophil count (normal range: 2.1-8.89 $10^9$/L), lymphocyte count (normal range: 1.26-3.35 $10^9$/L), platelet count (normal range: 173-390 $10^9$/L), monocyte count (normal range: 0.25-0.84 $10^9$/L), ferritin level (normal range 23.9-336.2 ng/mL), albumin level (normal range: 35-52 g/L), C-reactive protein (CRP) (normal range: 0-8 mg/L), and alanine aminotransferase(ALT) and aspartate transaminase(AST) values (normal range: 3-50 IU/L)between the groups (**Table 1**).

D-dimer (normal range: 0-0.5 µg/mL) (HR:1.001, 95% CI:1-1.001) and troponin (normal range: 0-19.8 ng/L)(HR: 1.001, 95% CI: 1-1.001)levels of non-survivors were significantly higher in univariate analyses($p<0.05$). Procalcitonin level (normal range: 0-0.55 µg/L) (HR:1.02, 95% CI: 1.004-1.037) was found to be high in multivariate analyses.

When the patients (n=256) who did not receive Tocilizumab treatment were taken as a reference, the mortality risk of patients who received treatment (n=39) was found 0.458 times less ($p=0.004$). When patients who were not treated with plasmapheresis were taken as reference, the mortality of patients who underwent plasmapheresis was found to be significantly lower ($p=0.005$). (**Table 2**).

**Table 1.**

| | Mortality | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| | Survivors | Non-survivors | HR (95% CI) | p | HR (95% CI) | p |
| Sex[a] | | | | | | |
| Female | 45 (42.5) | 90 (47.6) | 0.921 (0.691 – 1.228) | 0.575 | 0.964 (0.703 – 1.321) | 0.819 |
| Male | 61 (57.5) | 99 (52.4) | Reference | | | |
| Age[b] | 67.58±13.37 | 72.51±12.58 | 1.017 (1.004 – 1.03) | 0.009 | 1.011 (0.995 – 1.027) | 0.197 |
| Neutrophil count[b] | 7.64±3.51 | 9.30±4.00 | 1.016 (0.98 – 1.054) | 0.391 | 1.03 (0.971 – 1.093) | 0.322 |
| Lymphocyte count[b] | 1.02±0.42 | 0.95±0.70 | 1.09 (0.83 – 1.432) | 0.534 | 1.136 (0.835 – 1.545) | 0.417 |
| Platelet count[b] | 263.88±115.66 | 234.28±93.86 | 0.999 (0.998 – 1.001) | 0.267 | 0.999 (0.998 – 1.001) | 0.356 |
| Ferritin[b] | 417.99±429.95 | 656.66±808.85 | 1 (1 - 1) | 0.166 | 1 (1 - 1) | 0.485 |
| D-Dimer[b] | 244.09±918.36 | 834.87±3639.95 | 1.001 (1 – 1.001) | 0.004 | 1 (1 - 1) | 0.201 |
| Troponin[b] | 167.59±928.58 | 556.38±2692.98 | 1.001 (1 – 1.001) | <0.001 | 1 (1 - 1) | 0.081 |
| Lactate dehydrogenase[b] | 381.25±165.38 | 607.60±801.69 | 1.002 (1 – 1.003) | 0.033 | 1 (1 - 1) | 0.188 |
| Urea[b] | 50.55±26.83 | 80.46±58.98 | 1.004 (1.002 – 1.006) | 0.001 | 1.001 (0.997 – 1.004) | 0.715 |
| Creatine[b] | 1.03±0.84 | 1.50±1.29 | 1.198 (1.084 – 1.323) | <0.001 | 1.184 (1.009 – 1.39) | 0.039 |
| Procalcitonin[b] | 1.74±9.55 | 3.31±8.80 | 1.018 (1.003 – 1.034) | 0.018 | 1.02 (1.004 – 1.037) | 0.016 |
| Albumin[b] | 2.94±0.56 | 2.57±0.58 | 1.113 (0.869 – 1.425) | 0.396 | 1.124 (0.807 –1.564) | 0.489 |
| Monocyte count[b] | 0.63±0.34 | 0.56±0.42 | 0.715 (0.487 – 1.049) | 0.086 | 0.627 (0.393 – 0.999) | 0.049 |
| White blood cell count[b] | 9.71±4.84 | 11.43±5.78 | 1.011 (0.986 – 1.037) | 0.381 | 1.003 (0.962 – 1.047) | 0.881 |
| C-reactive protein[b] | 101.91±81.21 | 146.20±100.80 | 1.001 (1 – 1.003) | 0.040 | 1.001 (0.999 – 1.002) | 0.378 |
| Aspartate aminotransferase[b] | 54.20±65.39 | 84.69±157.69 | 1 (1 – 1.001) | 0.271 | 1 (0.998 – 1.003) | 0.724 |
| Alanine aminotransferase[b] | 48.61±81.27 | 61.43±122.19 | 1 (0.999 – 1.001) | 0.547 | 0.999 (0.996 – 1.002) | 0.668 |
| Duration of mechanical ventilation[b] | 1.63±7.04 | 9.60±12.23 | 0.95 (0.935 – 0.964) | <0.001 | 0.929 (0.911 – 0.949) | <0.001 |
| Length of stay at intensive care unit[b] | 10.33±8.42 | 13.64±13.61 | | --- | | --- |

[a]n (%); [b]Mean±StandardDeviation

**Table 2.** Comparison of treatments according to mortality status

| | Mortality | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| | Survivors | Non-survivors | HR (95% CI) | p | HR (95% CI) | p |
| Tocilizumab[a] | | | | | | |
| No | 91 (85.8) | 165 (87.3) | Reference | | | |
| Yes | 15 (14.2) | 24 (12.7) | 0.564 (0.366 – 0.868) | 0.009 | 0.458 (0.27 – 0.776) | 0.004 |
| Favipiravir[a] | | | | | | |
| No | 5 (4.7) | 11 (5.8) | Reference | | | |
| Yes | 101 (95.3) | 178 (94.2) | 0.609 (0.33 – 1.124) | 0.113 | 1.314 (0.553 – 3.123) | 0.536 |
| Plasmapheresis[a] | | | | | | |
| No | 44 (41.5) | 85 (45) | Reference | | | |
| Yes | 62 (58.5) | 104 (55) | 0.551 (0.411 – 0.738) | <0.001 | 0.583 (0.4 – 0.849) | 0.005 |
| Steroid[a] | | | | | | |
| No | 19 (17.9) | 45 (23.8) | Reference | | | |
| Yes | 87 (82.1) | 144 (76.2) | 0.414 (0.293 – 0.584) | <0.001 | 0.596 (0.371 – 0.956) | 0.032 |

[a]n (%)

When the inflammation indices were examined to evaluate the mortality risk, there was no significant difference between the groups in terms of median values of PLR, SIRI, and AISI indices (p>0.05). The median NLR value of the survivors was 7.45, whereas the median NLR value of the non-survivors was 11.39, which was statistically significantly different (p<0.001). When the cut-off value of NLR was accepted as 9.574, it was found that it could predict mortality with 59.3% sensitivity and 67% specificity. (**Figure 1**).

The median value of the SII index of non-survivors was found as 2421.02, which was significantly higher than in survivors (p<0.001) (**Table 3**). The cut-off value of the SII was found as 2285,846. The area under the ROC curve (AUC) cut-off value was 0.584,which was statistically significant (p=0.017). It was observed that the sensitivity was 52.38% and the specificity was 66.04%. (**Figure 2**).

The mean length of stay in the ICU was 10.33±8.42 days in survivors and 13.64±13.61 days in non-survivors. The duration of invasive mechanical ventilation was 1,63±7,04 days in survivors and 9.60±12.23 days in non-survivors, which was higher than in survivors (p<0.001).

**Table 3.** Comparison of index values according to mortality status

| | Survivors, n=106 | Non-survivors, n=189 | Total, n=295 | Test statistics | pb |
|---|---|---|---|---|---|
| NLR[a] | 7.45 (4.75 – 11.64) | 11.39 (6.01 – 17.9) | 9.55 (5.32 – 15.78) | 7129.00 | <0.001 |
| AISI[a] | 902.22 (423.69 – 1831.61) | 1137.67 (454.24 – 2062.23) | 1081.93 (434.47 – 1942.72) | 9500.00 | 0.462 |
| SII[a] | 1703.73 (1036.19 – 3126.15) | 2421.02 (1166.47 – 4071.58) | 2072.27 (1081.65 – 3733.53) | 8332.00 | <0.001 |
| SIRI[a] | 3.79 (1.99 – 7.2) | 4.96 (2.61 – 8.84) | 4.52 (2.2 – 8.42) | 8846.00 | 0.096 |
| PLR[a] | 237.08 (176.58 – 363.64) | 286.27 (182.65 – 409.09) | 260.8 (180.56 – 392.77) | 9217.00 | 0.255 |

[a]Median (Q1 – Q3); [b]Mann-Whitney U test

**Table 4.** Examining the cut-off values of the indices for mortality status using ROC analysis

| | Cut-off value | AUC (%95CI) | p | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|---|
| NLR | ≥9.574 | 0.644 (0.581 - 0.708) | <0.001 | 59.3% | 67.0% | 76.2% | 48.0% | 62.0% |
| AISI | --- | 0.526 (0.458 – 0.594) | 0.462 | --- | --- | --- | --- | --- |
| SII | ≥2285.846 | 0.584 (0.517 – 0.651) | 0.017 | 52.38% | 66.04% | 73.33% | 43.75% | 57.3% |
| SIRI | --- | 0.558 (0.491 – 0.626) | 0.096 | --- | --- | --- | --- | --- |
| PLR | --- | 0.540 (0.472 – 0.608) | 0.255 | --- | --- | --- | --- | --- |

---:Cut-off values were not calculated because the AUC value was not significant.

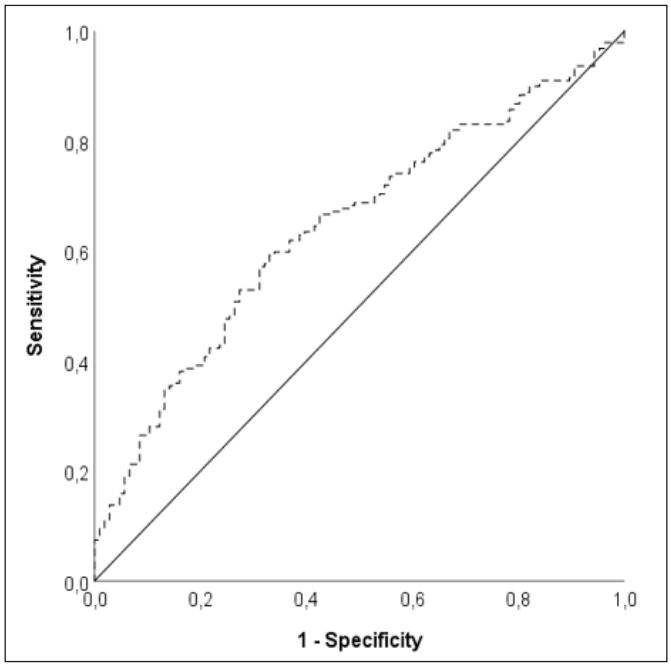


**Figure 1.** ROC curve of NLR according to the groups

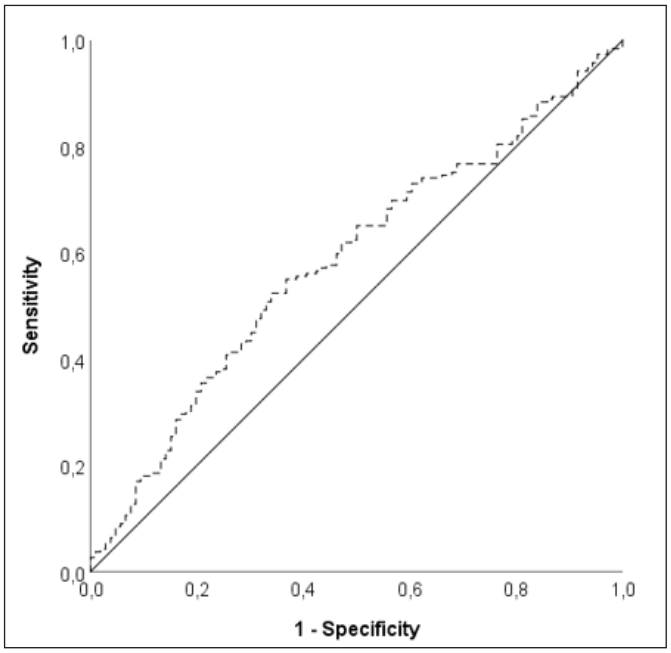


**Figure 2.** ROC curve of SII

## DISCUSSION

The COVID-19 pandemic has caused many deaths and severe economic consequences around the world. These results have led the scientific community to search for inexpensive and easily obtainable biomarkers that can be used to predict mortality. Thus, it will be possible to reduce mortality with an early and appropriate therapeutic approach. In this study, we investigated whether the inflammation indices obtained from the complete blood count could be used to predict mortality in patients with COVID-19.

Age-related defects in T-cell and B-cell function and overproduction of type 2 cytokines may lead to a defect in the control of viral replication and longer-lasting proinflammatory responses, resulting in poor outcomes (13). In various studies conducted on patients with COVID-19, age alone has emerged as a significant risk factor for mortality (14-16). Our study supports the literature by revealing a significant relationship between increasing age and mortality.

It has been shown that high D-dimer levels are one of the most common laboratory findings observed in hospitalized patients with COVID-19. Zhang et al. (17) found that in-hospital mortality was higher in patients with COVID-19 with D-dimer levels higher than 2.0 µg/mL at the time of admission. This situation has been associated with an increased pro-inflammatory response due to virus infection and excessive thrombin production due to endothelial damage triggered by the insufficient anti-inflammatory response, increased blood viscosity secondary to hypoxia, and prolonged bed rest (17). High D-dimer levels were found to be associated with mortality in two studies examining patients with stroke who were

COVID-19 positive, which might be explained by an increased susceptibility to thrombosis (18, 19). In our study, it was determined that the risk of mortality increased as the D-dimer value increased (HR: 1,001 %95 CI: 1 – 1,001).

It is known that COVID-19-related organ dysfunction and mortality are associated with the inflammatory response (20). In addition to high inflammatory cytokine levels in patients with COVID-19 (3), serologic inflammation parameters such as CRP, LDH, and procalcitonin also increased (5). Our study revealed that these serologic inflammatory parameters could also predict mortality in patients with COVID-19.

The NLR can be defined as the ratio of the neutrophil count to the lymphocyte count. Previous studies revealed that NLR was elevated in chronic conditions with low-grade inflammatory nature, such as obesity, HT, DM, metabolic syndrome, atherosclerotic events of the heart and brain, and various cancers (21-23). After the pandemic started, studies focused on patients with COVID-19 and it was reported that increased NLR predicted poor prognosis, mortality, the possibility of intubation, risk of serious disease in intubated patients, and longer admission to the ICU in these patients (24-29). In our study, when compared according to mortality status, the median NLR value of the survivors was 7.45, whereas the median value of the non-survivors was 11.39, and this difference was found to be statistically significant.

In studies related to COVID-19, SII was found to be a reliable biomarker. When Xue et al. (30) examined the relationship between various markers and disease severity, they found that SII could significantly predict disease severity in univariate analyses. In a study of 397 patients, Doğancı et al. (31) showed that SII was significantly lower in surviving patients. Another study showed that SII was the only significant marker superior to NLR in predicting mortality in multivariate analyses (32). In our study, the median value of SII was 2421.02 (1166.47-4071.58) in the non-survivors, which was significantly higher than the survivors.

The most important limitation of our study is that it is a retrospective study. The relatively small number of patients and the inability to specify the severity of illness during hospitalization are other limitations of our study.

## CONCLUSION

Our study showed that NLR and SII could predict mortality in patients with COVID-19, albeit with low specificity and sensitivity. The most important advantage of these indices is that they are obtained from very cheap and easily accessible hematologic parameters, regardless of the level of development of countries and ICUs. Our study is a guide for more comprehensive and detailed studies.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 14.01.2022, Decision No: 2022/022).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The author have no conflicts of interest to declare.

**Financial Disclosure:** The author declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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