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# Evaluation of the efficacy of systemic inflammatory indices in determining mortality in very low birth weight infants

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## SUMMARY

**OBJECTIVE:** In our study, we aimed to investigate whether systemic inflammatory indices could be an indicator of mortality in very low birth weight (<1,500 g) preterm infants.

**METHODS:** Very low birth weight preterm infants were included in our study, and patient data were recorded retrospectively. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, systemic immune-inflammation index, pan-immune-inflammation value, and systemic inflammation response index were calculated and recorded. The survivors and infants who died were compared for systemic inflammatory indices.

**RESULTS:** A total of 1,243 very low birth weight infants were included in the study. Of the patients, 1,034 survived and 209 died. Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, pan-immune-inflammation value, systemic immune-inflammation index, and systemic inflammation response index were found to be statistically significantly lower in the mortality group than those in the survivor group (p=0.039, p=0.001, p<0.001, p<0.001, p<0.001, and p=0.002, respectively). According to the receiver operating curve analysis, systemic immune-inflammation index with the highest area under the curve (0.844) was found to be the most effective systemic inflammatory indices in predicting mortality with a cutoff level of ≤28.87 (p=0.0001). Multiple regression analysis showed that a lower level of systemic immune-inflammation index (≤28.87) was independently associated with mortality (OR: 1.677, 95%CI 1.061–2.685, p=0.001).

**CONCLUSION:** We have shown that low systemic immune-inflammation index value in very low birth weight preterm infants may be a novel systemic inflammatory index that can be used to predict mortality.

**KEYWORDS:** Mortality. Infant. Inflammation. Very low birth weight.

## INTRODUCTION

The most important factors affecting neonatal mortality are gestational week (GW) and birth weight (BW)[1]. Preterm infants may require a variety of diagnostic and therapeutic interventions depending on their GW, BW, and medical conditions[2]. Determining the risk factors that affect mortality and taking precautions for these risk factors help to reduce mortality[3]. Moreover, it is clear that, besides reducing mortality, effective/reliable parameters to predict mortality can provide valuable information about the prognosis of preterm infants to pediatricians, neonatal specialists, and families. Therefore, the search for new markers that can predict the prognosis of the preterm infant still continues[2-4].

Systemic inflammatory indices are calculated by numeric ratios of cells derived from complete blood count parameters. It has been reported that some systemic inflammatory indices can be an important determinant of mortality and a predictor of the prognosis in adult patients[5-7]. There is very less information available about systemic inflammatory indices in newborns[8,9]. Especially in preterm infants, it is still unknown whether systemic inflammatory indices can be used as indicators of mortality. In this study, which we designed based on these possible advantages, we aimed to evaluate whether systemic inflammatory indices could be an indicator of mortality in very low BW (VLBW) preterm infants.

## METHODS

### Study design

All VLBW (<1,500 g) infants who were admitted to the neonatal intensive care unit between January 2019 and April 2022 were retrospectively analyzed. Preterm infants with major congenital anomalies and BW ≥1,500 g were excluded from the study. Ethical approval was obtained from the local ethics committee (dated April 11, 2019; decision no. 47/2019), and the study followed the tenets of the Declaration of Helsinki.

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## Demographical features and clinical outcomes

The data related to GW, BW, antenatal steroid, male gender, cesarean section, Apgar scores at 5th minute, early onset sepsis (EOS), late onset sepsis (LOS), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), and mortality were recorded.

## Complete blood count analysis

Blood samples were taken from all VLBW premature babies within the first hour after birth and placed in ethylenediaminetetraacetic acid tubes for complete blood count. Complete blood count was performed using Cell-Dyn 3700 automatic hemocytometer (Abbott, Abbott Park, IL, USA). Leukocyte count ($10^3$ μ/L), platelet (P) count ($10^3$ μ/L), neutrophil (N) count ($10^3$ μ/L), monocyte (M) count ($10^3$ μ/L), and lymphocyte (L) count ($10^3$ μ/L) values were recorded.

## Calculation of systemic inflammatory indices

N, M, L, and P counts were used to calculate systemic inflammatory indices. Neutrophil-to-lymphocyte ratio (NLR)=N/L, platelet-to-lymphocyte ratio (PLR)=P/L, monocyte-to-lymphocyte ratio (MLR)=M/L, pan-immune-inflammation value (PIV)=P×N×M/L, systemic immune-inflammation index (SII)=P×N/L, and systemic inflammation response index (SIRI)=N×M/L values were calculated using the mentioned formulations[10].

Patients with and without mortality were compared in terms of demographic features and clinical outcomes, preterm morbidities, complete blood count, and systemic inflammatory indices.

## Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago, IL, USA) analysis program. Histogram and Kolmogorov-Smirnov test were used to analyze the distribution of the data. Fisher's exact test or Pearson chi-square test was used for the analysis of categorical variables, and t-test or Mann-Whitney U test was used in the analysis of continuous variables. Normally distributed continuous variables were presented as mean±standard deviation, and non-normally distributed variables were presented as median and interquartile range (IQR). The results of categorical variables were presented as frequency. The receiver operating characteristics (ROC) analysis was carried out to evaluate the significance level of the variables. The area under the curve (AUC) and cutoff values were calculated using the ROC analysis. COX regression analysis was performed for investigating the association between the survival time of patients and one or more predictor variables. Odds ratios (ORs) and 95% confidence intervals (CI) were defined. A p-value of <0.05 was considered significant.

# RESULTS

During the study period, 1,243 preterm infants were included in the study. Of these patients, 1,034 survived and 209 died. The mortality rate in VLBW infants was 16.8%. The GW (28.2±1.2 weeks) and BW (1,091±222 g) of preterm infants in the survivor group was significantly higher than the GW (27.5±1.1 weeks) and BW (911±227 g) of the infants in the mortality group (p<0.001 and p<0.001, respectively). The frequency of antenatal steroid administration and Apgar scores at the 5th minute were found to be significantly lower in the mortality group than those in the survivor group (p=0.006 and p<0.001, respectively). The frequency of RDS and IVH was significantly higher in the mortality group than that in the survivor group (p<0.001 and p<0.001, respectively). Gender, cesarean section, and the frequency of EOS, LOS, PDA, NEC, ROP, and BPD were found to be similar in both groups (p>0.05) (Table 1).

**Table 1.** Demographic characteristics and clinical outcomes in relation to mortality in very low birth weight infants.

| Characteristics | Survivors (n=1034) | Mortality (n=209) | p-value |
|---|---|---|---|
| Gestational age, weeks[a] | 28.2±1.2 | 27.5±1.1 | <0.001* |
| Birth weight, g[a] | 1091±211 | 911±227 | <0.001* |
| Antenatal steroid[b] | 715 (69.1) | 128 (61.2) | 0.006* |
| Male gender[b] | 511 (49.4) | 113 (54.1) | 0.221 |
| Apgar 5th minute[c] | 8 (1) | 7 (3) | <0.001* |
| EOS[b] | 111 (10.7) | 29 (13.8) | 0.102 |
| LOS[b] | 227 (21.9) | 53 (25.3) | 0.445 |
| RDS[b] | 604 (58.4) | 173 (82.7) | <0.001* |
| IVH[b] | 67 (6.5) | 44 (21.1) | <0.001* |
| PDA[b] | 383 (37.0) | 84 (40.2) | 0.397 |
| NEC[b] | 23 (2.2) | 3 (1.4) | 0.427 |
| ROP[b] | 102 (9.8) | 16 (7.65) | 0.124 |
| BPD[b] | 204 (19.7) | 31 (14.8) | 0.215 |

[a]Mean±standard deviation. [b]n (%). [c]Median (interquartile range). *p<0.05 was considered statistically significant. BPD: bronchopulmonary dysplasia; EOS: early onset sepsis; IVH: intraventricular hemorrhage; LOS: late-onset sepsis; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity.

Platelet and neutrophil counts were significantly lower in the mortality group than those in the survivor group (p<0.001 and p=0.031, respectively). There was no difference between the groups in terms of leukocyte, monocyte, and lymphocyte counts (p=0.294, p=0.153, and p=0.551, respectively). NLR, MLR, PLR, PIV, SII, and SIRI were significantly lower in the mortality group than those in the survivor group (p=0.039, p=0.001, p<0.001, p<0.001, p<0.001, and p=0.002, respectively) (Table 2 and Figure 1).

ROC analysis was performed for systemic inflammatory indices that were statistically significant in terms of mortality. The AUC value of NLR was 0.568, and the cutoff

**Table 2.** Systemic inflammatory indices in very low birth weight infants.

| Laboratory parameters | Survivors (n=1034) | Mortality (n=209) | p-value |
|---|---|---|---|
| Leukocyte count ($10^3$ μ/L)[a] | 10.90 (8.32) | 12.30 (11.00) | 0.294 |
| Platelet count ($10^3$ μ/L)[a] | 232.00 (101.25) | 198.00 (87.50) | <0.001* |
| Neutrophil count ($10^3$ μ/L)[a] | 2.25 (2.62) | 2.21 (2.01) | 0.031* |
| Monocyte count ($10^3$ μ/L)[a] | 0.66 (0.58) | 0.66 (0.80) | 0.153 |
| Lymphocyte count ($10^3$ μ/L)[a] | 7.05 (5.75) | 8.56 (7.29) | 0.551 |
| NLR[a] | 0.33 (0.37) | 0.27 (0.32) | 0.039* |
| MLR[a] | 0.09 (0.06) | 0.08 (0.07) | 0.001* |
| PLR[a] | 35.34 (31.55) | 21.65 (17.76) | <0.001* |
| PIV[a] | 48.91 (100.64) | 35.39 (65.29) | <0.001* |
| SII[a] | 82.81 (94.65) | 17.48 (41.52) | <0.001* |
| SIRI[a] | 0.20 (0.32) | 0.18 (0.33) | 0.002* |

[a]Median (interquartile range). *p<0.05 was considered statistically significant. MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PIV: pan-immune-inflammation value; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index.

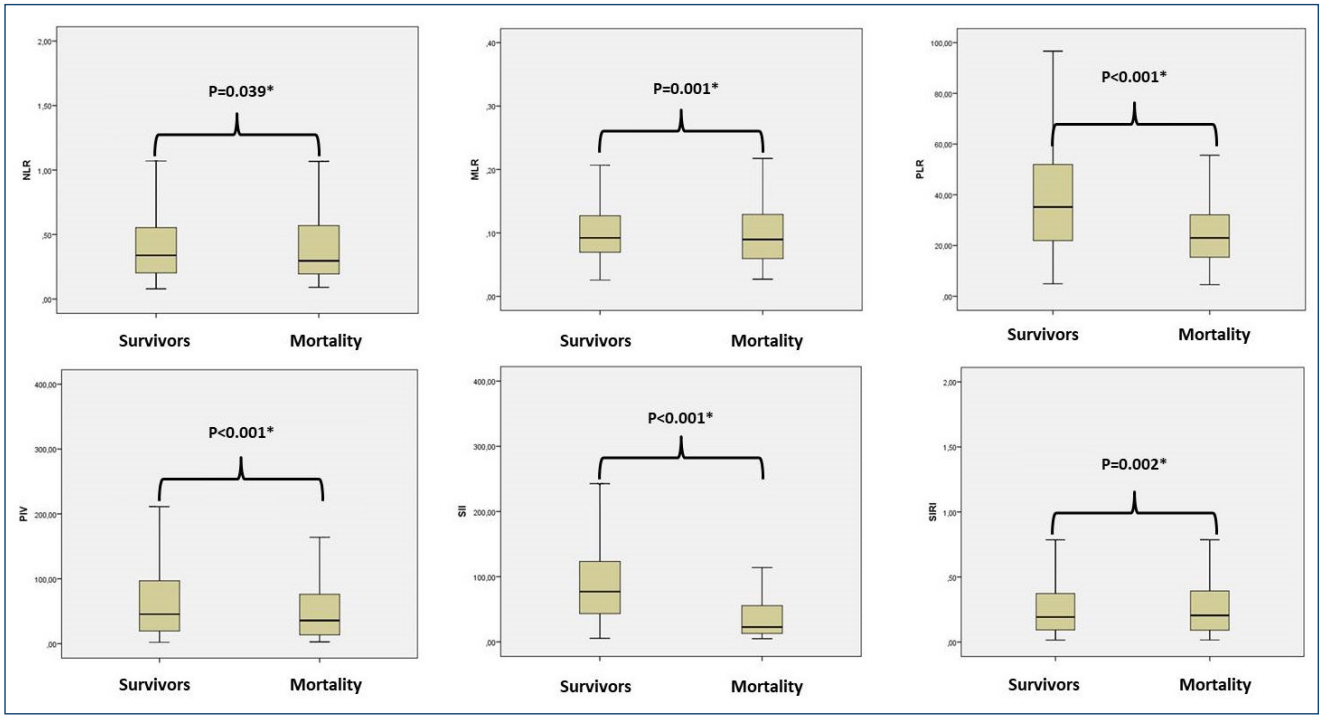


**Figure 1.** Box plot of systemic inflammatory indices for mortality in preterm infants. *p<0.05 was considered statistically significant. MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PIV: pan-immune-inflammation value; PLR: platelet-to-lymphocyte ratio; RDS: respiratory distress syndrome; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index.

level was ≤0.33 for the estimation of mortality. The AUC value of MLR for the predictivity of mortality was 0.546, and the cutoff level was ≤0.06. The AUC value of PLR for the predictivity of mortality was 0.702 and the cutoff level was ≤27.46. PIV had an AUC of 0.577 and a cutoff level of ≤66.65 for the predictive of mortality. The AUC of SII for predictivity of mortality was 0.844, and the cutoff level was ≤28.87. The AUC value of SIRI for the predictivity of mortality was 0.541, and the cutoff level was ≤0.10 (p=0.0013, p=0.0330, p=0.0001, p=0.0002, p=0.0001, and p=0.0430, respectively). The ROC graph for SII is presented in Figure 2.

COX regression analysis was performed for investigating the association between the survival time of patients and one or more predictor variables. The potential confounder risk factors, including GW, BW, and antenatal steroid administration, were subsequently entered into the multivariable COX regression model. It was found that the risk of mortality was independently associated with antenatal steroid administration of completed doses (OR: 1.323, 95%CI: 1.112–1.575, P=0.001), GW (OR: 1.878, 95%CI: 1.777–1.991, P=0.001), and BW (OR: 1.997, 95%CI: 1.897–2.219, P=0.001). Multiple Cox analysis showed that a lower level of SII (≤28.87) was independently associated with mortality (OR: 1.677, 95%CI 1.061–2.685, P=0.001).

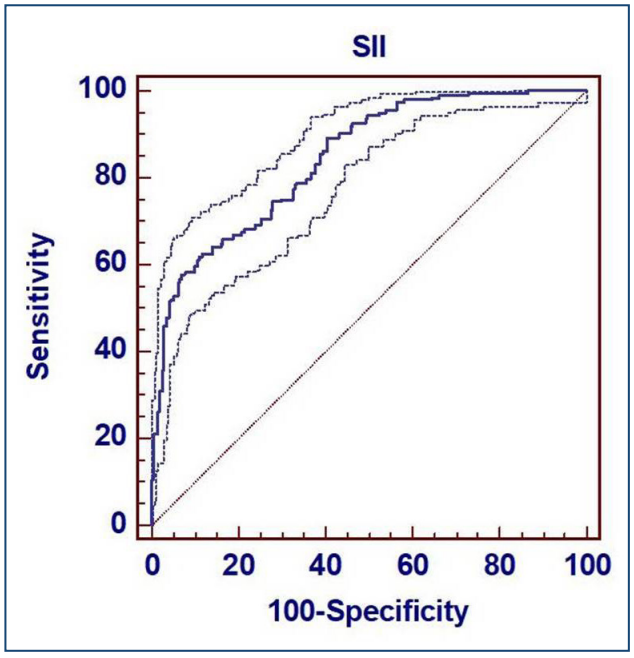


**Figure 2.** Receiver operating characteristic curves for mortality in very low birth weight infants.

## DISCUSSION

In this study, we evaluated the relationship between mortality and systemic inflammatory indices in VLBW infants, including NLR, MLR, PLR, PIV, SII, and SIRI. We determined that all mentioned systemic inflammatory indices were lower in patients who died. When the predictivity significance level of mortality of the six systemic inflammatory indices was evaluated, SII was the most effective systemic inflammatory index among others. SII values of ≤28.87 were related to the predictivity of mortality. Moreover, GW and BW were lower in VLBW infants who died, while RDS and IVH were found to be more frequent[2].

The most important factors determining morbidity and mortality in premature infants are their GW and BW. As GW and BW decrease, morbidities and mortality increase inversely. If antenatal steroid administration decreases, the mortality rate may increase even more, as in our results. The use of Apgar scores to evaluate mortality and clinical outcomes in preterm infants is limited. The use of laboratory parameters in addition to clinical scores may be more useful in predicting mortality, especially in VLBW infants[2-4]. For this purpose, systemic inflammatory indices were evaluated in our study in order to assist in the early and effective estimation of mortality, especially in VLBW infants who were at higher risk for mortality.

Low platelet count in newborn infants may be associated with increased mortality. The main relationship between increased mortality and decreased platelet count is due to increased inflammation, which decreases platelet production and circulating megakaryocyte progenitors. In our results, although the platelet count decreased in the mortality group, a decrease in neutrophil count seems to be evidence of higher inflammation. However, low platelet count alone may not always be an indicator of mortality. Therefore, it may be more beneficial to use markers that can be recognized as indicators of inflammation as a predictor of mortality. In this respect, in our study, we showed, for the first time, that among the six systemic inflammatory indices, the marker with the highest predictive value for mortality was the SII value[11].

It has been shown that higher NLR, MLR, PLR, PIV, SII, and SIRI are positively associated with the severity of the disease and the mortality of the patients in oncology, patients and those with sepsis[5,12]. Particularly, SII has been reported to be closely associated with the prognosis of cancer, multiple sclerosis, coronary artery bypass surgery, and pulmonary embolism compared to other systemic inflammatory indices[6,7,13]. As can be seen from this information, according to the results of these studies in adults, the effectiveness and significance level of systemic inflammatory indices may vary depending on the type of disease.

Based on the results of studies conducted on adults, the relationship between systemic inflammatory indices and neonatal

disease has recently been investigated. When maternal systemic inflammatory indices were examined, it was reported that the NLR value of the systemic inflammatory indices was the most effective indicator of preterm delivery in mothers who gave preterm delivery[14]. It has been reported that higher NLR, MLR, and PLR may be an indicator in the diagnosis of preterm morbidities[8,9]. Six systemic inflammatory indices have been evaluated for the diagnosis of HIE in preterm infants. Higher NLR, PIV, SII, and SIRI and lower MLR and PLR have been reported to be useful markers for the diagnosis of HIE. Among these systemic inflammatory indices, NLR and SII, which have the highest AUC values for the diagnosis of HIE, are reported to be the most effective diagnostic markers. The cutoff value of SII for the diagnosis of HIE is found to be >410, and the AUC value is 0.763[10]. In our results, the AUC value of SII for the predictivity of mortality in VLBW infants was 0.844, and the cutoff value was ≤28.87. It has been reported that an SII level ≥78.2 after birth may be a risk factor for the development of RDS in preterms ≤32 weeks of gestation[15]. It was found that the high SIRI value could predict moderate to severe BPD in preterm infants[16]. According to these results, when using systemic inflammatory indices in the evaluation of neonatal diseases, it seems to be a more accurate approach to evaluate each index specific to the diseases. To the best of our knowledge, in this study, for the first time, SII was found to be the most effective parameter in the predictivity of mortality in VLBW infants among the six systemic inflammatory indices.

One question is why the most effective parameter among these indices for mortality indicator was found to be SII. The neutrophil, lymphocyte, and platelet values used in the SII formulation may help us understand the relationship between mortality and systemic inflammatory indices. Neutrophils and platelets used in the SII formulation decreased significantly in VLBW infants who died. There was no significant difference between our groups in terms of lymphocyte count. However, when lymphocyte counts were used together with neutrophils and platelets in the formulation of SII, it could be interpreted that the significance level of SII increases as an indicator of mortality. Additionally, each disease occurs with its own different pathophysiological mechanisms. The immune response to any disease may vary according to the patient's postnatal age and GW[17]. According to our results of the study group consisting of preterm infants, it seems that adequate neutrophil and platelet cell response did not occur in patients who died. Moreover, outcomes seemed to be reflected as mortality in the clinical follow-up of these patients and as a lower SII value in the laboratory follow-up.

Both scoring systems and laboratory parameters were evaluated for the indicator of mortality in newborn infants. However, the immaturity of preterm infants limits the use of these tools for mortality. Therefore, the search for additional indicators continues. The ideal tool for demonstrating mortality should be a powerful parameter that is quickly available and does not create additional costs for the clinician to predict mortality. With the parameters that meet these features, the clinician will have more reliable information about the patient's prognosis. In addition, it will provide more reliable information about the prognosis of the preterm infant to both parents and other doctors who treat the patient. Thus, the SII value can be a new and active parameter. As the SII value was effective, rapid, and readily available obtained from blood counts in VLBW infants, it may also provide an advantage as it can show mortality without additional costs[2-4].

The main strengths of our study are as follows: a large case series was studied with 1,243 VLBW infants. In addition, there are currently no strong enough parameters to indicate mortality in these highly frail infants. According to our results, it was shown, for the first time, that the SII value among the parameters evaluated based on inflammation could be a safe indicator for predicting mortality in VLBW infants. Finally, the SII value could be an easy-to-use parameter as it did not require additional costs and extra time to predict mortality.

Although the large number of patients was the strength of our study, there were also some limitations. Our main limitation was that the study was conducted retrospectively in a single center. The inability to monitor the systemic inflammatory indices serially on postnatal days and not being able to compare them with the values in term babies could be counted among our other limitations.

## CONCLUSION

The research for an effective parameter that can be used for the predictivity of mortality in preterm infants is still ongoing. Our results determined, for the first time, that six systemic inflammatory indices were decreased in preterm infants resulting in mortality compared to survivors. In addition, among these six indices, SII was found to be the most effective systemic inflammatory indices for predicting mortality. Another important advantage of SII was that it was cheap, simple, fast, and easily accessible. Further prospective studies conducted with larger case series should be warranted.

## AUTHORS' CONTRIBUTIONS

**UC:** Conceptualization, Methodology, Writing – original draft.
**AUT:** Data curation, Formal Analysis, Investigation, Validation.
**CT:** Supervision, Writing – review & editing.

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