NEUTROPHIL-TO-LYMPHOCYTE RATIO AND MEAN PLATELET VOLUME PREDICT 28-DAY MORTALITY IN SEPTIC SHOCK

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ABSTRACT

Background: Septic shock is associated with high mortality despite advances in critical care. The neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) are inexpensive inflammatory biomarkers, but the prognostic value of serial measurements remains uncertain.

Objective: To evaluate the prognostic value of Day 1 and Day 5 NLR and MPV measurements, and their temporal changes, for predicting 28-day mortality in patients with septic shock.

Methods: This prospective observational study included 40 adults with septic shock admitted to a tertiary intensive care unit. NLR and MPV were measured on Day 1 and Day 5 of admission. Changes in biomarker values were calculated as ΔNLR and ΔMPV. The primary outcome was 28-day mortality. Receiver operating characteristic (ROC) curve analysis was performed to assess prognostic performance.

Results: Twenty-seven of 40 patients (67.5%) died within 28 days. Significant differences between survivors and non-survivors were observed for Day 1 NLR (p=0.021), Day 5 NLR (p=0.005), Day 1 MPV (p=0.015), and Day 5 MPV (p=0.002). ΔNLR was not associated with mortality (p=0.686), while ΔMPV approached statistical significance (p=0.052). Day 5 MPV demonstrated the highest discriminatory performance (AUC, 0.805), with an optimal cut-off of 11.5 fL, sensitivity of 84.6%, and specificity of 66.7%.

Conclusions: Day 1 and Day 5 measurements of NLR and MPV were associated with 28-day mortality in patients with septic shock, with Day 5 MPV demonstrating the best discriminatory performance. Temporal changes in these biomarkers, particularly ΔNLR, did not provide additional prognostic value.

Keywords: Septic Shock, Neutrophil-To-Lymphocyte Ratio, Mean Platelet Volume, Mortality, Biomarkers, Intensive Care.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, whereas septic shock is characterized by profound circulatory and cellular abnormalities associated with a substantially increased risk of death [1]. Septic shock represents the most severe manifestation of sepsis and remains a leading cause of mortality among critically ill patients worldwide despite advances in critical care management [2].

Early identification of patients at increased risk of adverse outcomes is essential for optimizing treatment strategies and improving clinical outcomes [3].

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Although several biomarkers have been investigated for prognostic assessment in sepsis, many are expensive, require specialized assays, or are not universally available, particularly in resource-limited settings.

The neutrophil-to-lymphocyte ratio (NLR) is a readily available marker of systemic inflammation that reflects both neutrophilia and lymphocyte depletion [4]. Several studies have demonstrated an association between elevated NLR and increased disease severity and mortality in patients with sepsis [5,6].

Mean platelet volume (MPV), a marker of platelet size and activation, has also emerged as a potential prognostic biomarker in sepsis [7,8]. Platelet activation contributes to endothelial dysfunction, microvascular thrombosis, and multiple organ failure [9]. Elevated MPV has been associated with adverse outcomes and increased mortality in septic patients [10].

However, most previous studies have focused primarily on admission values of these biomarkers, and the prognostic significance of sequential measurements during the early course of septic shock remains uncertain [11,12]. Furthermore, few

studies have simultaneously evaluated serial changes in both NLR and MPV in patients with septic shock [13,14].

Therefore, the present study aimed to evaluate the prognostic value of repeated measurements of NLR and MPV during the first five days of septic shock and to determine their association with 28-day mortality.

MATERIALS AND METHODS

This single-center prospective observational study included 40 consecutive adult patients admitted with septic shock to the intensive care unit (ICU) of a tertiary care teaching hospital between January 2021 and June 2022. Septic shock was defined according to the Sepsis-3 criteria as sepsis requiring vasopressor therapy to maintain a mean arterial pressure of ≥65 mmHg and having a serum lactate concentration >2 mmol/L despite adequate fluid resuscitation [1].

Patients aged ≥18 years with a diagnosis of septic shock were included. Patients with hematological malignancies, immunosuppressive disorders, chronic liver disease, recent chemotherapy, or incomplete laboratory data were excluded.

The required sample size was estimated using the following formula:

\(n=\frac{(Z_{\alpha/2}+Z_{1-\beta})^2}{d^2} \)

where Zα/2=1.96Z_{\alpha/2}=1.96Zα/2=1.96 corresponds to a two-sided significance level of 5%, Z1−β=0.84Z_{1-\beta}=0.84Z1−β=0.84 corresponds to 80% study power, and d=0.45 (Cohen's effect size). The calculated sample size was 38.72, which was rounded up to 40 participants.

Ethical approval was obtained from the Institutional Ethics Committee, Kempegowda Institute of Medical Sciences, Bangalore (Ref No: KIMS/IEC/D003/M/2021; Date: 20-01-2021), and written informed consent was obtained from patients or their legally authorized representatives.

Venous blood samples were collected as part of routine clinical care under aseptic precautions in ethylenediaminetetraacetic acid (EDTA) vacutainers. Complete blood counts were analyzed using the Sysmex XN-1000 automated hematologyanalyzer (Sysmex Corporation, Kobe, Japan). Neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) were derived from complete blood counts performed on Day 1 and Day 5 of ICU admission. Changes in biomarker values were calculated as ΔNLR and ΔMPV (Day 5 value minus Day 1 value).

The primary outcome was all-cause mortality at 28 days following ICU admission.

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables as frequency and percentage. Between-group comparisons were performed using the Mann-Whitney U test for continuous variables and the Pearson chi-square test for categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic performance of NLR and MPV for predicting 28-day mortality. The area under the curve (AUC), 95% confidence intervals (CIs), optimal cut-off values determined using the Youden index, sensitivity, and specificity were calculated. A two-sided p value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

A total of 40 patients with septic shock were included. Twenty-seven patients (67.5%) died within 28 days of ICU admission, and 13 patients (32.5%) survived. The median age was comparable between survivors and non-survivors (55.00 [44.00-66.00] years vs. 56.00 [38.50-68.50] years; Mann-Whitney U = 171.0, p = 0.908). Sex distribution was also comparable between the groups (Pearson χ^2 = 0.189, p = 0.955). Baseline demographic characteristics are summarized in Table 1.

Variable	Survivors (n = 13)	Non-survivors (n = 27)	Test statistic	p value
Age, years, median [IQR]	55.00 [44.00–66.00]	56.00 [38.50–68.50]	U = 171.0	0.908
Sex, n (%)	**Male**10 (76.9)**Female**3 (23.1)	**Male**19 (70.4)**Female**8 (29.6)	χ^2 = 0.189	0.664

Table 1: Baseline demographic characteristics of the study population

Data are presented as median [interquartile range] or number (%). Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using the Pearson chi-square test.

NLR and MPV on Day 1 and Day 5

Significant differences in both NLR and MPV measurements were observed between survivors and non-survivors (Table 2 and Figures 1 and 2).

Day 1 NLR was significantly higher in survivors than in non-survivors (25.64 [IQR 20.07-28.86] vs. 14.88 [IQR 10.03-20.18], Mann-Whitney U = 256.0, p=0.021). Similarly, Day 5 NLR remained elevated

in survivors (16.93 [IQR 13.90-20.64] vs. 9.11 [IQR 8.19-14.28], Mann-Whitney U = 272.0, p=0.005). Day 1 MPV was higher in survivors (11.30 [IQR 11.10-11.80] fL vs. 10.90 [IQR 10.00-11.15] fL, Mann-Whitney U = 260.0, p=0.015). The difference was more pronounced on Day 5 (12.20 [IQR 11.50-12.40] fL vs. 11.10 [IQR 9.95-11.50] fL, Mann-Whitney U = 282.5, p=0.002).

Changes in biomarker values were not significantly associated with 28-day outcomes. ΔNLR did not differ between groups (Mann-Whitney U = 161.0, p=0.686), and ΔMPV did not reach statistical significance (Mann-Whitney U = 243.0, p=0.052).

Variable	Survivors (n=13)	Non-survivors (n=27)	Test statistic	*p* value
Day 1 NLR, median [IQR]	25.64 [20.07–28.86]	14.88 [10.03–20.18]	**U = 256.0**	0.021
Day 5 NLR, median [IQR]	16.93 [13.90–20.64]	9.11 [8.19–14.28]	**U = 272.0**	0.005
ΔNLR, median [IQR]	−11.74 [−11.93 to 0.57]	−2.97 [−11.67 to −0.83]	**U = 161.0**	0.686
Day 1 MPV (fL), median [IQR]	11.30 [11.10–11.80]	10.90 [10.00–11.15]	**U = 260.0**	0.015
Day 5 MPV (fL), median [IQR]	12.20 [11.50–12.40]	11.10 [9.95–11.50]	**U = 282.5**	0.002
ΔMPV (fL), median [IQR]	0.60 [−1.10 to 0.80]	0.20 [−0.10 to 0.30]	**U = 243.0**	0.052

Table 2: Comparison of neutrophil-to-lymphocyte ratio and mean platelet volume between survivors and non-survivors

Data are presented as median [interquartile range]. Comparisons between survivors and non-survivors were performed using the Mann-Whitney U test. NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume; IQR: interquartile range. ΔNLR and ΔMPV represent the difference between Day 5 and Day 1 values.

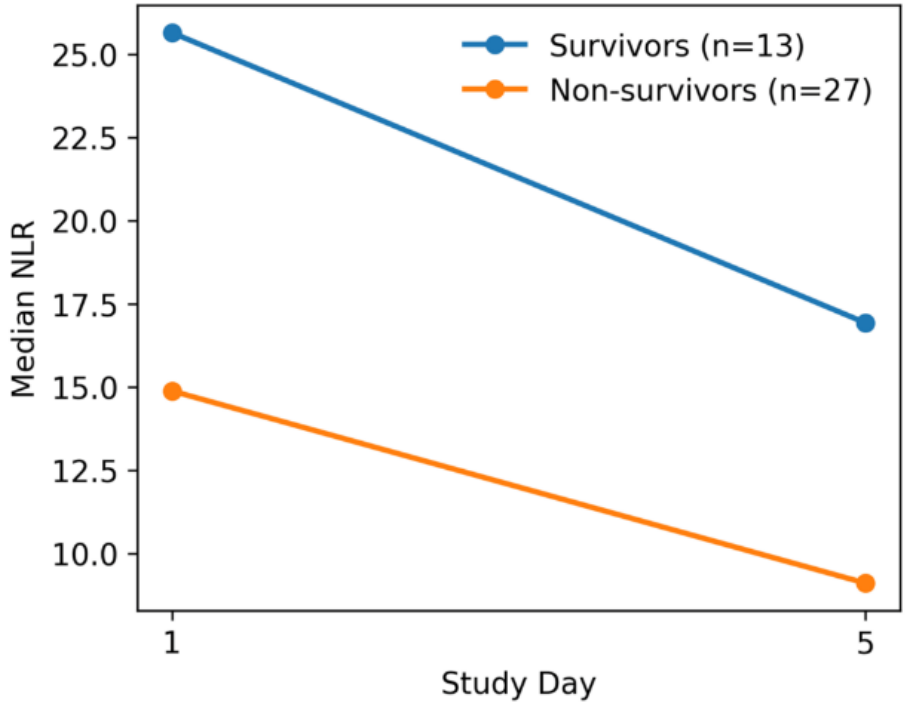

Figure 1: Serial Changes in Neutrophil-to-Lymphocyte Ratio among Survivors and Non-Survivors

Serial changes in neutrophil-to-lymphocyte ratio (NLR) among survivors and non-survivors during the first five days of intensive care unit admission. Data are presented as median values with interquartile ranges.

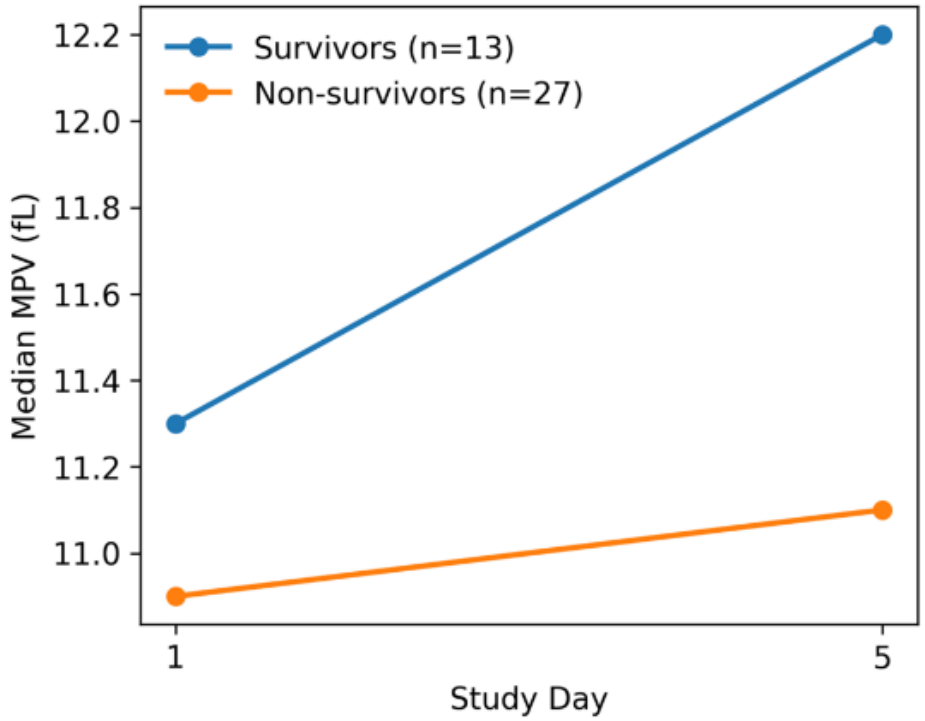

Figure 2: Serial Changes in Mean Platelet Volume Among Survivors and Non-Survivors

Serial changes in mean platelet volume (MPV) among survivors and non-survivors during the first five days of intensive care unit admission. Data are presented as median values with interquartile ranges.

Receiver Operating Characteristic Curve Analysis

ROC analysis was performed to evaluate the ability of NLR and MPV measurements to discriminate 28-day mortality (Table 3 and Figure 3).

Among the evaluated biomarkers, Day 5 MPV demonstrated the highest discriminatory ability (AUC 0.805, 95% CI [0.66-0.95]), followed by Day 5 NLR (AUC 0.775, 95% CI [0.62-0.93]), Day 1 MPV (AUC 0.741, 95% CI [0.58-0.90]), and Day 1 NLR (AUC 0.729, 95% CI [0.56-0.89]). ΔMPV demonstrated moderate discriminatory ability (AUC 0.692, 95% CI [0.53-0.86]), whereas ΔNLR showed poor discriminatory performance (AUC 0.541, 95% CI [0.37-0.71]).

Optimal cut-off values, sensitivities, and specificities are presented in Table 3. Day 5 MPV demonstrated the highest discriminatory performance (AUC 0.805). Although ΔMPV showed the highest specificity (100.0%), its overall discriminatory ability was only moderate.

Biomarker	AUC [95% CI]	Optimal cut-off	Sensitivity (%)	Specificity (%)
Day 1 NLR	0.729 [0.56-0.89]	≥20.07	76.9	70.4
Day 5 NLR	0.775 [0.62-0.93]	≥16.93	61.5	88.9
ΔNLR	0.541 [0.37-0.71]	≥0.57	38.5	85.2
Day 1 MPV	0.741 [0.58-0.90]	≥11.3 fL	61.5	85.2
Day 5 MPV	0.805 [0.66-0.95]	≥11.5 fL	84.6	66.7
ΔMPV	0.692 [0.53-0.86]	≥0.6 fL	69.2	100.0

Table 3: Receiver operating characteristic analysis of NLR and MPV measurements for prediction of 28-day mortality

AUC: area under the curve; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume. Optimal cut-off values were determined using the Youden index. ΔNLR and ΔMPV represent the difference between Day 5 and Day 1 values.

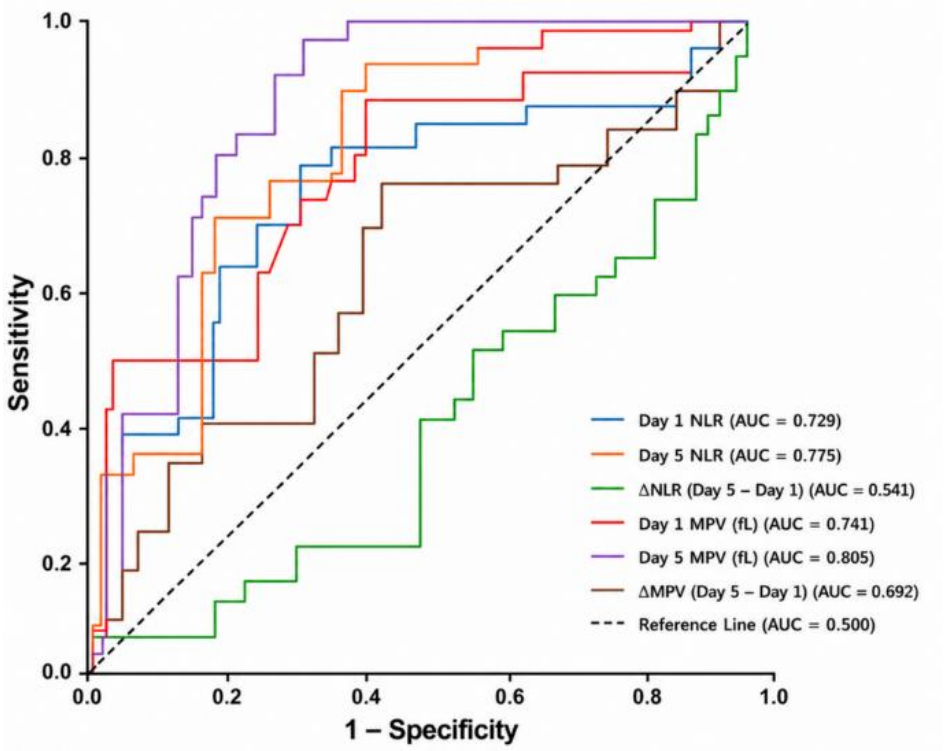

Figure 3: Receiver Operating Characteristic Curves of NLR and MPV Measurements for Prediction of 28-Day Mortality

Receiver operating characteristic (ROC) curves of Day 1 NLR, Day 5 NLR, ΔNLR, Day 1 MPV, Day 5 MPV, and ΔMPV for discrimination between survivors and non-survivors at 28 days.

DISCUSSION

In this prospective observational study of patients with septic shock, Day 1 and Day 5 measurements of neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) differed significantly between survivors and non-survivors. However, contrary to most previous studies, higher NLR and MPV values were observed among survivors rather than non-survivors. Changes in these biomarkers over the first five days of intensive care unit (ICU) admission (ΔNLR and ΔMPV) did not provide additional prognostic information. Among the evaluated biomarkers, Day 5 MPV demonstrated the highest discriminatory ability (AUC 0.805), suggesting that later measurements obtained after initial resuscitation may provide more clinically relevant prognostic information than admission values alone.

The prognostic utility of NLR in sepsis has been widely investigated. Previous studies have generally reported that elevated NLR is associated with increased disease severity and mortality in patients with sepsis [5,6,15]. Liu et al. demonstrated that higher admission NLR values were independently associated with poor outcomes in sepsis [6], while Hwang et al. reported that elevated NLR predicted mortality among critically ill septic patients [5]. Similarly, Riché et al. observed that persistent elevation of the neutrophil-to-lymphocyte ratio was associated with adverse outcomes in septic shock [11]. In contrast, our study found significantly higher Day 1 and Day 5 NLR values among survivors. This discrepancy may be explained by the small sample size, differences in patient characteristics, timing of biomarker measurement, and the complex immune dysregulation that occurs during septic shock. Severe sepsis is characterized by an initial hyperinflammatory response followed by immune exhaustion and immunosuppression [16,17]. Therefore, lower NLR values in non-survivors in our cohort may reflect profound immune dysfunction, lymphocyte apoptosis, and bone marrow suppression in patients with advanced, refractory disease.

MPV has also emerged as a potential prognostic biomarker in sepsis because platelet activation and consumption are important components of sepsis-associated coagulopathy and endothelial dysfunction [9]. Previous studies by Becchi et al. and Tajarernmuang et al. demonstrated that elevated MPV and increasing MPV trends were associated with increased mortality in sepsis and septic shock [7,10]. In the present study, however, higher MPV values were observed among survivors. The reasons for this finding are uncertain but may reflect differences in patient populations, underlying etiologies of sepsis, timing of blood sampling, and the relatively small sample size. It is also possible that preserved platelet reactivity and bone marrow

response among survivors contributed to higher MPV values.

Day 5 NLR also showed good predictive performance (AUC 0.775), whereas ΔNLR demonstrated poor discriminatory ability (AUC 0.541). Although ΔMPV demonstrated moderate discriminatory performance (AUC 0.692), the difference between survivors and non-survivors did not reach statistical significance. These findings suggest that absolute biomarker values may be more useful than temporal changes for risk stratification in septic shock. Similar observations regarding the prognostic value of serial MPV measurements have been reported previously [10].

The potential clinical utility of NLR and MPV lies in their widespread availability and low cost. Both parameters are routinely obtained as part of a complete blood count and therefore represent attractive biomarkers in resource-limited settings where access to more expensive biomarkers may be restricted. Although our findings require external validation, Day 5 MPV in particular may serve as a simple adjunctive tool for identifying patients at increased risk of adverse outcomes.

This study has several limitations. First, the study was conducted at a single center and included a relatively small sample size (n=40), which limits the generalizability of the findings and reduces statistical power. Second, biomarker measurements were obtained at only two time points, precluding assessment of more detailed temporal trends and potentially failing to capture the dynamic changes that occur during septic shock. Third, no multivariable analysis was performed to adjust for potential confounding factors such as illness severity scores (e.g., APACHE II [18] and SOFA [19]), comorbidities, or source of infection. Finally, the unexpected direction of association observed in our cohort should be interpreted cautiously and warrants confirmation in larger multicenter studies.

CONCLUSION

Day 1 and Day 5 measurements of neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) were significantly associated with 28-day mortality in patients with septic shock, with higher values observed among survivors and Day 5 MPV demonstrating the best discriminatory performance among the evaluated biomarkers. Changes in biomarker values over the first five days, particularly ΔNLR, did not provide additional prognostic value. Given their low cost and universal availability, NLR and MPV may serve as useful adjunctive biomarkers for risk stratification in septic shock; however, larger multicenter studies are required to validate these findings and clarify the unexpected associations observed in this cohort.

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