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ASSOCIATION OF MEAN PLATELET VOLUME AND PLATELET HISTOGRAM CHANGES WITH 28-DAY MORTALITY IN PATIENTS WITH SEVERE SEPSIS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT
Platelet activation and consumption are important components of the pathophysiology of severe sepsis. Mean platelet volume (MPV), a routinely available hematological parameter reflecting platelet size, may have potential value in assessing disease severity and prognosis. This prospective observational study evaluated the association of increased MPV and concurrent platelet histogram changes with 28-day mortality among 150 patients with severe sepsis admitted to the Intensive Medical Care Unit of tertiary care Hospital, over a period of 2 years. Venous blood samples were collected within 12 h of presentation and processed within 4-6 h of collection. Platelet count, MPV, and platelet histograms were analyzed using a three-part automated hematology analyzer (Sysmex XP-100). Clinical outcome was assessed as survival or mortality at 28 days. Of 150 patients, 80 survived and 70 died, corresponding to a 28-day mortality of 46.7%. Mean platelet count was significantly lower among non-survivors than survivors ($175.357 \pm 129.771 \times 10^3/\mu L$ vs $242.225 \pm 127.365 \times 10^3/\mu L$; $P < 0.001$), whereas mean MPV was significantly higher among non-survivors (10.997 ± 1.313 fL vs 10.065 ± 0.995 fL; $P < 0.001$). Platelet histogram changes were identified in 14 patients, including 10 non-survivors and four survivors, but were not significantly associated with mortality ($P = 0.09$). Higher MPV and lower platelet count were associated with 28-day mortality, whereas platelet histogram changes were not. MPV may have potential value as a complementary hematological parameter for mortality risk assessment in severe sepsis; however, its independent prognostic value requires further investigation.

KEYWORDS: Mean platelet volume; Mortality; Platelet count; Platelet histogram; Severe sepsis

INTRODUCTION

Sepsis is a life-threatening clinical syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection [1]. Despite advances in recognition and critical care management, sepsis and its more severe clinical manifestations remain associated with substantial morbidity and mortality worldwide [2]. The underlying pathophysiology involves complex interactions among inflammatory, immune, endothelial, coagulation, and cellular pathways, resulting in microcirculatory dysfunction and progressive organ injury [3,4].

Platelets have an important role in the pathogenesis of sepsis beyond their conventional function in hemostasis. During sepsis, inflammatory and endothelial activation promotes platelet activation, adhesion, aggregation, and consumption. Activated platelets also participate in inflammatory and immune responses, potentially contributing to microvascular thrombosis and organ dysfunction [5]. Increased platelet consumption and destruction may result in thrombocytopenia, which is frequently encountered in critically ill patients and has been associated with disease severity and adverse clinical outcomes [6].

Mean platelet volume (MPV) is an automated hematological parameter that reflects the average size of circulating platelets. Alterations in MPV may occur in response to changes in platelet activation, consumption, and production. Larger platelets are generally considered metabolically and functionally more active, and increased platelet turnover may be accompanied by the release of larger platelets into the circulation. In patients with severe sepsis and septic shock, increased MPV and changes in MPV during the clinical course have been investigated as potential markers of disease severity and mortality [7,8].

Other routinely available platelet parameters, including platelet count, platelet distribution width, and platelet-derived ratios, have also been evaluated for their potential prognostic relevance in sepsis [9]. Because these parameters are generated during routine automated hematological analysis, they may provide readily accessible and relatively inexpensive complementary information for risk assessment.

Automated hematology analyzers additionally generate platelet volume-distribution histograms. Alterations in platelet size distribution may produce abnormal histogram patterns associated with changes in platelet morphology and the presence of large or giant platelets, platelet aggregates, or other interfering particles. However, compared with quantitative platelet parameters such as platelet count and MPV, the prognostic relevance of platelet histogram alterations in patients with severe sepsis remains less clearly established.

The present study aimed to evaluate the association of increased MPV and concurrent platelet histogram changes with 28-day mortality in patients with severe sepsis. The relationship between platelet count and mortality was also assessed.

MATERIAL AND METHODS

Study design and setting

This prospective observational study was conducted in the Department of Clinical Pathology, Tertiary care hospial, over a period of 2 years. Patients hospitalized with severe sepsis in the Intensive Medical Care Unit were included. The final study population comprised 150 patients.

Eligibility criteria

Patients aged >16 years who were admitted to the Intensive Medical Care Unit with any two of the following four criteria were considered for inclusion: temperature >38°C or <36°C; heart rate >90/min; respiratory rate >20/min; and total leukocyte count >12,000 cells/mm³ or <4,000 cells/mm³, with associated organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension.

Patients aged <16 years and those with terminal illness due to malignancy, hematological disorders, acute coronary syndrome, or active gastrointestinal bleeding were excluded.

Study population

A total of 214 patients admitted with severe sepsis were initially assessed. Of these, 64 were excluded, leaving 150 patients for final analysis. Exclusions comprised hematological or platelet disorders (n = 18), malignancies (n = 14), active gastrointestinal bleeding or recent blood transfusion (n = 15), age <16 years (n = 6), and loss to follow-up or discharge against medical advice (n = 11).

Sample collection and laboratory analysis

Two milliliters of venous blood were collected into a vacutainer containing ethylenediaminetetraacetic acid. Samples were collected within 12 h of presentation and processed within 4-6 h of blood collection.

Platelet count, MPV, and platelet histograms were measured and analyzed using a three-part automated hematology analyzer (Sysmex XP-100). Platelet histogram changes were assessed as recorded during the study.

Outcome assessment

Clinical outcome was assessed at 28 days following presentation. Patients who died within 28 days of clinical presentation were classified as non-survivors, while the remaining patients were classified as survivors.

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as mean and standard deviation. Student's t-test was used to compare continuous variables, and the chi-square test was used to compare categorical variables between survivors and **non-**survivors. A P value <0.05 was considered statistically significant, with a significance level of 5%.

Statistical analysis was performed using SPSS version 22. Graphs and tables were generated using Microsoft Word and Microsoft Excel.

RESULTS

Study population and 28-day outcome

A total of 150 patients with severe sepsis were included in the final analysis. Of these, 80 were survivors and 70 were non-survivors at 28 days, corresponding to a 28-day mortality rate of 46.7%.

Demographic and clinical characteristics

The age of participants ranged from 19 to 76 years, with an overall mean age of 45.573 ± 16.624 years. Mean age was 45.150 ± 17.248 years among survivors and 46.057 ± 15.992 years among non-survivors, with no statistically significant difference (P = 0.74).

Of the 150 patients, 90 (60%) were male and 60 (40%) were female. Among survivors, 51 were male and 29 were female; among non-survivors, 39 were male and 31 were female. Gender was not significantly associated with 28-day outcome (P = 0.316). Comorbid conditions were present in 71 (47.3%) patients, comprising 32 survivors and 39 non-survivors. The association between the presence of comorbidity and outcome was P = 0.05. Type 2 diabetes mellitus was the most common comorbidity, followed by systemic hypertension and chronic kidney disease.

The genitourinary tract was the identified infection site in 31 (20.7%) patients, followed by the lung in 28 (18.7%) and gastrointestinal tract in 18 (12.0%); 73 (48.7%) patients had other sites of infection. Pulmonary infection was identified in eight survivors and 20 non-survivors (P < 0.001), whereas genitourinary tract infection was identified in 23 survivors and eight non-survivors (P = 0.01).

Table 1. Demographic and clinical characteristics according to 28-day outcome

Variable	Total (n = 150)	Survivors (n = 80)	Non-survivors (n = 70)	P value
Age, years, mean ± SD	45.573 ± 16.624	45.150 ± 17.248	46.057 ± 15.992	0.74
Male sex, n	90	51	39	0.316
Female sex, n	60	29	31	—

Comorbidity present, n	71	32	39	0.05
Lung infection, n (%)	28 (18.7)	8	20	<0.001
Genitourinary tract infection, n (%)	31 (20.7)	23	8	0.01
Gastrointestinal tract infection, n (%)	18 (12.0)	8	10	0.42
Other infection sites, n (%)	73 (48.7)	41	32	0.50

Platelet count and 28-day mortality

The overall mean platelet count was 211.020 ± 132.362 × 10^3/μL. Mean platelet count was significantly lower among non-survivors than survivors (175.357 ± 129.771 × 10^3/μL vs 242.225 ± 127.365 × 10^3/μL; P < 0.001).

Using the study-defined platelet-count threshold of 100 × 10^3/μL, 32 patients had platelet counts below this threshold. Of these, 24 (75.0%) were non-survivors and eight (25.0%) were survivors. Among 118 patients with platelet counts >100 × 10^3/μL, 46 (39.0%) were non-survivors and 72 (61.0%) were survivors. The difference was statistically significant (P < 0.001).

Table 2. Platelet count according to 28-day outcome

Platelet count parameter	Total (n = 150)	Survivors (n = 80)	Non-survivors (n = 70)	P value
Mean platelet count, ×10^3/μL	211.020 ± 132.362	242.225 ± 127.365	175.357 ± 129.771	<0.001
<100 ×10^3/μL, n	32	8	24	<0.001
>100 ×10^3/μL, n	118	72	46	—

Mean platelet volume and 28-day mortality

The overall mean MPV was 10.500 ± 1.242 fL. Mean MPV was significantly higher among non-survivors than survivors (10.997 ± 1.313 vs 10.065 ± 0.995 fL; P < 0.001).

Using the study-defined MPV threshold of 10.4 fL, 71 patients had MPV <10.4 fL; 22 (31.0%) were non-survivors and 49 (69.0%) were survivors. Among 79 patients with MPV >10.4 fL, 48 (60.8%) were non-survivors and 31 (39.2%) were survivors. The difference was statistically significant (P < 0.001).

Table 3. Mean platelet volume according to 28-day outcome

MPV parameter	Total (n = 150)	Survivors (n = 80)	Non-survivors (n = 70)	P value
Mean MPV, fL	10.500 ± 1.242	10.065 ± 0.995	10.997 ± 1.313	<0.001
MPV <10.4 fL, n	71	49	22	<0.001
MPV >10.4 fL, n	79	31	48	—

Platelet histogram changes and 28-day mortality

Platelet histogram changes were identified in 14 patients. Reported abnormalities included multiple peaks, failure of the histogram to reach baseline at the upper discriminator, increased platelet distribution width, and increased platelet-large cell ratio.

Of the 14 patients with histogram changes, 10 (71.42%) were non-survivors and four (28.57%) were survivors. Among 136 patients without histogram changes, 60 (44.11%) were non-survivors and 76 (55.88%) were survivors. Although histogram abnormalities were proportionally more frequent among non-survivors, their association with 28-day outcome was not statistically significant (P = 0.09).

Table 4. Platelet histogram changes according to 28-day outcome

Platelet histogram changes	Total	Survivors	Non-survivors	P value
Absent	136	76 (55.88%)	60 (44.11%)	0.09
Present	14	4 (28.57%)	10 (71.42%)	—
Total	150	80	70	—

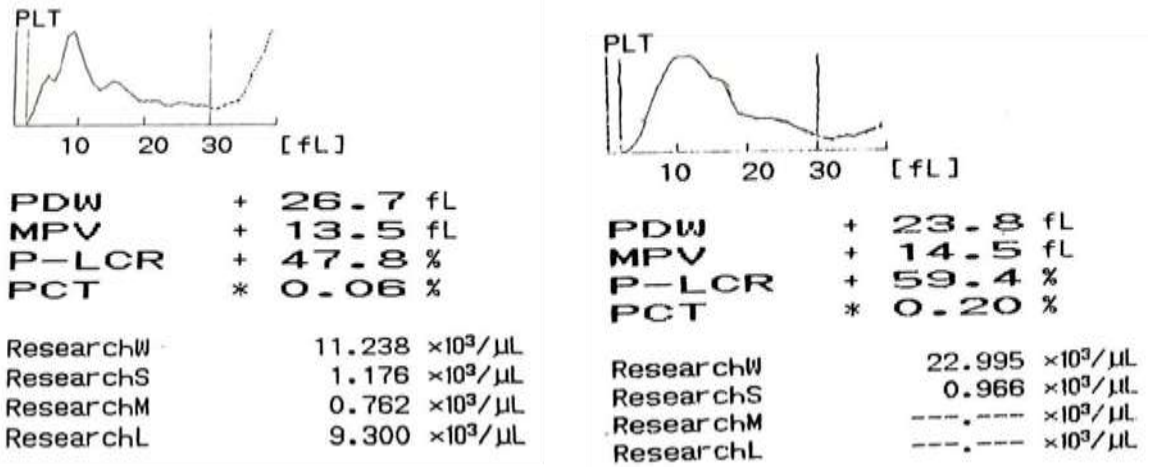

Figure 1. Representative platelet histograms in non-survivors with severe sepsis. Representative automated analyzer-generated platelet histograms from patients with severe sepsis who died during the 28-day follow-up period.

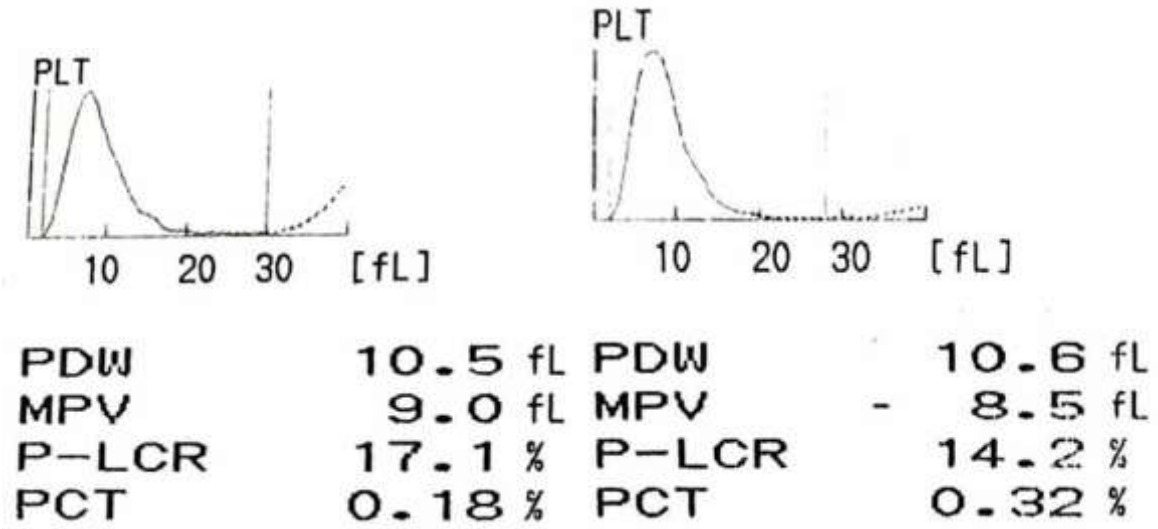

Figure 2. Representative platelet histograms in survivors with severe sepsis. Representative automated analyzer-generated platelet histograms from patients with severe sepsis who survived during the 28-day follow-up period.

DISCUSSION

The present prospective observational study evaluated the association of mean platelet volume (MPV), platelet count, and platelet histogram changes with 28-day mortality in 150 patients with severe sepsis. The principal findings were that non-survivors had a significantly higher mean MPV and a lower mean platelet count than survivors. In contrast, although platelet histogram abnormalities were proportionally more frequent among non-survivors, their association with 28-day mortality was not statistically significant. These findings suggest that routinely available quantitative platelet parameters, particularly MPV and platelet count, may provide complementary prognostic information in patients with severe sepsis.

Sepsis is associated with complex interactions among systemic inflammation, endothelial dysfunction, coagulation abnormalities, and platelet activation. Activated endothelium promotes platelet adhesion and aggregation, while ongoing platelet activation and consumption may contribute to microvascular thrombus formation and progressive organ dysfunction [3–5]. In severe systemic inflammation, platelet consumption may occur as part of the dysregulated coagulation response and, in some patients, disseminated intravascular coagulation [10]. Increased peripheral platelet consumption may also be accompanied by altered thrombopoiesis and the release of larger platelets into the circulation. These mechanisms provide a plausible biological context for the combination of reduced platelet count and increased MPV observed among non-survivors in the present study.

In the present study, 70 of 150 patients died within 28 days, corresponding to a mortality rate of 46.7%. Mortality in severe sepsis has varied considerably across populations and study periods. Harrison et al. described the epidemiology and outcomes of severe sepsis using a large critical-care database [11], while Stevenson et al., in a comparative meta-analysis, demonstrated changing mortality trends among patients with severe sepsis over time [12]. Differences in reported mortality rates may reflect variations in patient populations, disease severity, definitions of sepsis, comorbidities, infection sources, healthcare resources, and critical-care practices.

Age was not significantly associated with 28-day outcome in the present cohort. Similarly, although there was an overall male predominance, gender was not significantly associated with mortality. Previous studies examining the influence of gender on sepsis epidemiology and outcomes have yielded variable findings [13,14].

Comorbid conditions were present in 47.3% of patients, with a greater number of patients with comorbidities among non-survivors. Type 2 diabetes mellitus was the most frequently identified comorbidity, followed by systemic hypertension and chronic kidney disease. Given the relatively small numbers within individual comorbidity categories, these observations should be interpreted cautiously.

One of the major findings of the present study was the significantly lower mean platelet count among non-survivors. The mean platelet count was $175.357 \pm 129.771 \times 10^3/\mu L$ among non-survivors compared with $242.225 \pm 127.365 \times 10^3/\mu L$ among survivors. Furthermore, among patients with platelet counts $<100 \times 10^3/\mu L$, 75% were non-survivors.

The relationship between thrombocytopenia and adverse outcome in sepsis is biologically plausible. Platelet consumption may increase during systemic inflammation as a consequence of endothelial activation, platelet adhesion and aggregation, microvascular thrombus formation, and coagulation abnormalities. In more severe cases, disseminated intravascular coagulation may further contribute to platelet consumption [10]. Thrombocytopenia is frequently encountered in critically ill patients and has been investigated in relation to disease severity and clinical outcome [6].

Venkata et al. evaluated thrombocytopenia among adult patients with sepsis and examined its incidence, associated risk factors, and relationship with clinical outcome [15]. Zhang et al. similarly investigated platelet indices as indicators of illness severity and prognosis in critically ill patients [16]. An earlier study by van der Lelie and von dem Borne described increased MPV in septicemia [17]. Güçlü et al. evaluated the effects of severe sepsis on platelet count and platelet indices, illustrating that the prognostic relevance of individual platelet parameters has not been uniform across studies [18].

The present finding of lower platelet counts among non-survivors is consistent with evidence suggesting that disturbances in platelet number accompany severe systemic illness. However, differences among studies may reflect variations in

patient selection, severity of illness, timing of sample collection, underlying comorbidities, analytical methods, and whether single measurements or serial platelet trends were evaluated. Although lower platelet count was significantly associated with 28-day mortality in the present cohort, the absence of multivariable analysis precludes its interpretation as an independent predictor of mortality. The principal hematological finding of the present study was the significantly higher MPV observed among non-survivors. Mean MPV was 10.997 ± 1.313 fL among non-survivors compared with 10.065 ± 0.995 fL among survivors. Among patients with MPV >10.4 fL, 60.8% were non-survivors, compared with 31.0% among patients with MPV <10.4 fL. MPV reflects the average size of circulating platelets and may be influenced by alterations in platelet production, turnover, and activation. In severe sepsis, accelerated peripheral platelet activation and consumption may be accompanied by the release of larger platelets into the circulation. This provides a potential biological explanation for the combination of increased MPV and decreased platelet count observed among non-survivors. Kim et al. reported that an increase in MPV from baseline was associated with mortality among patients with severe sepsis or septic shock [7]. Oh et al. further evaluated the MPV-to-platelet-count ratio as a predictor of early mortality in severe sepsis, supporting continued investigation of routinely available platelet parameters for prognostic assessment [8]. Zampieri et al. reported that an increase in MPV after admission was associated with higher mortality among critically ill patients [19]. This observation suggests that dynamic changes in MPV may potentially provide prognostic information beyond a single baseline measurement.

Similarly, Rahul and Anita reported an association between MPV and outcome in severe sepsis [20]. However, not all studies have demonstrated a consistent relationship between MPV and mortality. Sadaka et al. reported that MPV was not a useful predictor of mortality in septic shock [21], while Güçlü et al. did not establish all platelet indices as independent predictors of mortality [18].

These differences indicate that the prognostic significance of MPV may be influenced by characteristics of the study population, severity of illness, timing of blood collection, pre-analytical variables, hematology analyzer methodology, and whether baseline MPV or serial changes are assessed. A systematic review and meta-analysis by Tajarernmuang et al. evaluated the role of MPV as a predictor of mortality in critically ill populations, highlighting broader interest in MPV as an accessible prognostic parameter while underscoring heterogeneity among available studies [22].

More recent evidence has continued to examine MPV and MPV-derived indices in sepsis. Vélez-Páez et al. evaluated MPV and the MPV-to-platelet-count ratio in relation to severity and mortality in patients with sepsis [23]. These findings support continued investigation of approaches integrating platelet size and platelet count rather than interpreting either parameter in isolation.

Importantly, the present study assessed an early single MPV measurement rather than serial changes. Therefore, the findings demonstrate an association between higher MPV and 28-day mortality but cannot establish whether MPV independently predicts mortality or whether serial changes in MPV provide greater prognostic information.

Platelet histogram abnormalities were identified in 14 patients, including 10 non-survivors and four survivors. Although 71.42% of patients with recorded histogram abnormalities were non-survivors, the association with 28-day outcome was not statistically significant ($P = 0.09$). The reported abnormalities included multiple peaks and failure of the platelet histogram to return to baseline at the upper discriminator, together with alterations in platelet distribution width and platelet-large cell ratio.

The small number of patients with histogram abnormalities may have limited the ability to detect a statistically significant difference. Furthermore, a standardized quantitative scoring system for platelet histogram morphology was not reported. Consequently, although histogram abnormalities occurred proportionally more often among non-survivors, this observation should not be interpreted as evidence of independent prognostic value. Further studies using standardized analyzer flags, prospectively defined histogram criteria, and correlation with peripheral blood smear findings may help determine whether platelet histogram morphology provides additional prognostic information beyond conventional platelet count and MPV.

MPV has practical characteristics that make it potentially attractive as a complementary laboratory parameter. It is routinely generated by automated hematology analyzers as part of the complete blood count and generally does not require an additional blood sample or specialized biomarker assay. In the present study, higher MPV and lower platelet count were significantly associated with 28-day mortality.

Nevertheless, the present findings do not support the use of MPV as a standalone prognostic test. Multivariable modeling was not performed to determine whether MPV remained associated with mortality after adjustment for disease severity and other potential confounders. Furthermore, diagnostic-performance measures such as sensitivity, specificity, predictive values, and area under the receiver operating characteristic curve were not established. The MPV threshold of 10.4 fL should therefore be regarded as a study-specific categorization rather than a universally validated prognostic cut-off.

The present study has several limitations. First, it was conducted at a single institution and included 150 patients, which may limit the generalizability of the findings. Second, MPV and other platelet parameters were assessed using a single early measurement. Serial monitoring might provide additional information regarding platelet dynamics during the course of severe sepsis, particularly given previous evidence associating changes in MPV over time with clinical outcome [7,19]. Third, potential factors influencing platelet function or MPV, including antiplatelet therapy, nonsteroidal anti-inflammatory drug use, and smoking, were not considered. Fourth, multivariable regression analysis was not performed; therefore, the independent prognostic value of MPV and platelet count cannot be determined. Fifth, the study-reported MPV threshold of 10.4 fL was not accompanied by receiver operating characteristic analysis or external validation. Finally, platelet histogram abnormalities were observed in only 14 patients, and standardized quantitative classification of histogram morphology was not reported.

Despite these limitations, the present study demonstrates that higher MPV and lower platelet count were significantly associated with 28-day mortality in this cohort of patients with severe sepsis. In contrast, platelet histogram changes were not significantly associated with mortality. These findings support further prospective evaluation of MPV, particularly serial MPV measurements and MPV-derived indices, as complementary and readily available hematological parameters for risk stratification in severe sepsis.

CONCLUSION

In this prospective observational study of patients with severe sepsis, non-survivors had significantly higher MPV and lower platelet counts than survivors. Platelet histogram abnormalities were proportionally more frequent among non-survivors but were not significantly associated with 28-day mortality.

These findings demonstrate an association between increased MPV, decreased platelet count, and 28-day mortality in the study population. As MPV is routinely generated by automated hematology analyzers and does not require an additional specialized assay, it may have potential value as a complementary hematological parameter for risk assessment in severe sepsis. However, the present findings do not establish MPV as an independent predictor of mortality.

Larger prospective multicenter studies incorporating serial MPV measurements, standardized assessment of platelet histogram abnormalities, and multivariable analysis are required to determine the independent prognostic value and potential clinical utility of MPV in severe sepsis.

ACKNOWLEDGMENTS

The authors have no acknowledgments to declare.

FUNDING

The authors received no specific funding for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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