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# Platelet count patterns and patient outcomes in sepsis at a tertiary care center

## Beyond the APACHE score

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**Abstract**

Acute physiology and chronic health evaluation II (APACHE-II) scoring system is used to classify disease severity of patients in the intensive care unit. However, several limitations render the scoring system inadequate in identifying risk factors associated with outcomes. Little is known about the association of platelet count patterns, and the timing of platelet count and other hematologic parameters in predicting mortality in patients with sepsis.

This retrospective observational study included 205 septic shock patients, with an overall mortality of 47.8%, enrolled at a tertiary care hospital in Riyadh, Kingdom of Saudi Arabia between 2018 and 2020. Bivariate and multivariate regression analyses were used to identify hematologic risk factors associated with mortality. We used the bivariate Pearson Correlation test to determine correlations between the tested variables and APACHE-II score.

Two platelet count patterns emerged: patients with a decline in platelet count after admission (group A pattern, 93.7%) and those with their lowest platelet count at admission (group B pattern, 6.3%). The lowest mean platelet count was significantly lower in nonsurvivors ($105.62 \pm 10.67 \times 103/\mu L$) than in survivors ($185.52 \pm 10.81 \times 103/\mu L$), $P < .001$. Bivariate Pearson correlation revealed that the lowest platelet count and platelet count decline were significantly correlated with APACHE-II score ($r = -0.250$, $P < .01$), ($r = 0.326$, $P < .001$), respectively. In multiple logistic regression analysis, the independent mortality risk factors were degree of platelet count decline in group A (odds ratio, 1.028 [95% confidence interval: 1.012–1.045], $P = .001$) and platelet pattern in group B (odds ratio, 6.901 [95% confidence interval: 1.446–32.932], $P = .015$). The patterns, values, subsets, and ratios of white blood cell count were not significantly associated with mortality.

Nadir platelet count and timing, and degree of platelet count decline are useful markers to predict mortality in early septic shock. Therefore, platelet count patterns might enhance the performance of severity scoring systems in the intensive care unit.

**Abbreviations:** APACHE-II = acute physiology and chronic health evaluation II, ICU = intensive care unit, MLR = monocyte-lymphocyte ratio, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio.

**Keywords:** acute physiology and chronic health evaluation-II, platelet, sepsis, white blood cell

## 1. Introduction

Sepsis, defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection poses a considerable health burden and is a medical emergency with an alarmingly high mortality rate that ranges from 28% to 50%.[1,2] Each additional organ dysfunction increases the mortality rate by approximately 20%.[3] The pathophysiology of sepsis includes an immunologic systemic inflammatory response and non-immunologic mechanisms, including metabolic, neuroendocrine, and cardiovascular pathways.[4] Prognosis is linked to the duration and magnitude of the immune-inflammatory response, characterized by the activation of immune cells and the production of pro-inflammatory and anti-inflammatory cytokines and chemokines.[5] Furthermore, there were some mutated genes with certain diseases that could potentially lead to abnormal signaling mechanism that lead to exaggerated immune response in sepsis.[6] On other hand, platelets and small (2–4 μm) anucleated cytoplasmic fragments, load, and transport a variety of mediators involved in hemostasis, thrombosis, and immune responses.[7] Other than preventing bleeding, platelets are associated with homeostasis because of the crucial role they play in pathogen clearance, inflammation, tissue repair, and regeneration.[8,9] Platelet count changes frequently occur in intensive care unit (ICU) patients, with 20% to 30% of ICU patients suffering from thrombocytopenia, in which the platelet

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count is $<100{,}000/mm^3$ ($100 \times 10^9$/L).[10,11] Thrombocytopenia-associated mortality is higher with sepsis compared to other causes of thrombocytopenia in ICU.[12] However, the literature remains inconsistent on a direct link between the platelet count pattern and outcomes in septic ICU patients.

Acute physiology and chronic health evaluation (APACHE)-II, a simplified version of APACHE, is a cumulative scoring system used to assess the severity of diseases in an ICU setting.[13] APACHE-II is based upon 12 physiological measures, including vital signs (mean blood pressure, heart rate, respiratory rate, temperature, and Glasgow Coma Score), venous blood tests (hematocrit, white blood cell [WBC] count, potassium, sodium, and serum creatinine), and 2 arterial blood tests (serum pH and $Pa0_2$). Its score range is between 0 and 72, where higher scores indicate more severe disease and a higher risk of mortality.[14] However, several limitations render APACHE-II suboptimal as an indicator of the complicated course of ICU patients or as a predictor of patient outcomes.[15] APACHE-II is a heterogeneous system assessed within 24 hours of admission into the ICU, even though complications in critically ill patients may develop beyond this time-window that might affect a patient's overall outcome. Also, its wide score range of 0 to 72 is not of optimal utility in the realm of clinical practice where usual scores hover between 7 and 36, rarely exceeding 55.[15–17]

Thrombocytopenia is associated with septic shock through multiple mechanisms, such as hemodilution, endothelial-dysfunction, and altered thrombopoiesis.[18] Endothelial damage, platelet aggregation, and activation of the coagulation cascade leads to disseminated intravascular coagulation. Disseminated intravascular coagulation is a coagulopathy leading to vital organ dysfunction during sepsis and increased mortality.[19] Multiple factors are responsible for sepsis-induced thrombocytopenia, such as a decreased production of platelets in the bone marrow, which can be due to antibiotics, inhibitory effect of pathogenic toxins, and inflammatory mediators in hematopoiesis, or hemophagocytosis. In contrast, the sepsis induced immune response in the context of thrombocytopenia showed reduced signaling for leukocyte adhesion and increased complement signaling and both mechanisms are associated with disease severity.[20] However, activation of platelets is also associated with the severity of sepsis.[21,22] This is especially evident in early sepsis as proven by measuring the percentage of reticulated platelets in which higher values may reflect mortality.[23] In addition, Inflammatory responses and pathogens can mediate platelet activation, and these activated platelets further contribute to multi-organ failure in sepsis, worsening the inflammation.[24,25] Despite the paramount functions platelets play in sepsis, most studies report only the risk factors related to thrombocytopenia, and limited data are available on the association of the platelet count patterns and clinical outcomes in septic patients.[26–28]

Our primary objective of this study was to examine the association of platelet counts, platelet count patterns, and other hematological parameters with the prediction of mortality in patients during early septic shock. Our secondary objective was to test the correlation between these parameters and the APACHE-II scoring system.

## 2. Materials and methods

This study was approved by the ethical review committee of the King Saud University, College of Medicine, with Institutional Review Board Approval of Research Project No. E-20-4892

### 2.1. Study design, population, and setting

To evaluate the possible association of platelet count and outcomes in septic patients, we carried out a retrospective observational cohort study at a tertiary care ICU in Riyadh, Kingdom of Saudi Arabia between 2018 and 2020. Initially, all patients were screened using the data collected from the rapid response team (RRT) files by the quick sequential organ failure assessment score. Then, the second data was retrieved based on age and systemic inflammatory response syndrome criteria to increase the specificity of data for sepsis diagnosis.[1] Septic patients >18 years of age with a clearly proven source of infection either by clinical exam (e.g. skin and soft tissue infection), or radiologic (pneumonia) plus procalcitonin as supportive measurement with cutoff point of 0.5 ng/mL all confirmed after the RRT activation within 24 hours matching 2 or more criteria from systemic inflammatory response syndrome (heart rate >90/min, respiratory rate >20/min, temperature >38°C and <36°C, and WBC count $>12{,}000/mm^3$ or <4000) were included.[29,30] Inclusion criteria also comprised lactate levels >2 mmol/L whenever available, and those requiring vasopressors in the first 24 hours of admission. Exclusion criteria comprised of patients with an underlying bone morrow disease or chemotherapy in the last 30 days, active bleeding upon admission, or a blood transfusion in the first 24 hours to minimize any effect on platelet counts apart from sepsis.

### 2.2. Data collection

Data were collected on age, sex, APACHE II score, hematological variables, and a-28-day mortality. The 3 main categories of hematological variables were as follows:

(1) data on platelet count which included platelet count at admission, the lowest platelet count, and platelet count pattern (within 72 hours of admission),
(2) data on WBC count which included WBC count at admission, the highest WBC count, and WBC count pattern (within 72 hours of admission), and
(3) other hematological parameters, including absolute neutrophil count, monocyte and lymphocyte counts, and ratios such as platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and monocyte-lymphocyte ratio (MLR) and were all measured at the time of the RRT activation.

We chose a-28-day mortality to address the short-term outcome of sepsis. The outcome of discharge from the ICU or the hospital were deemed not suitable because many patients were either on chronic mechanical ventilation or from an in-hospital long-term facility.

### 2.3. Statistical analysis

Continuous variables were presented as means and standard deviations and categorically measured factors, such as sex and age, were presented as frequencies and percentages. Histograms and the Kolmogorov–Smirnov test were used to assess the statistical normality assumption of the continuous variables. The Levene test of equal variance was used to assess the homogeneity of variance assumption. A delta (difference) score was computed for platelet and WBC counts between 2 time points (admission time versus the lowest and highest values for the platelet and WBC counts). The delta score was then divided by the admission time value and multiplied by 100 to express the difference as a

percent (%) change from the baseline admission values during the first 72 hours from admission time. The Chi-squared ($\chi^2$) test of independence was used to assess the association between the categorically measured variables and the independent samples *t*-test was used to assess the statistical significance of mean differences on continuous variables across the levels of binary dichotomous variables. The nonparametric Mann–Whitney *U* test was used to compare the median length of stay (days) between the survivor and nonsurvivor patients. The Pearson (*r*) test was used to assess the correlations between metric variables. The multivariate logistic binary regression analysis was used to assess the combined and individual associations between the relevant set of predictor clinical and laboratory independent variables with mortality. The associations between the predictors and mortality was expressed as an odds ratio with a 95% confidence interval. The SPSS IBM V21 statistical analysis program was used for data analysis and the statistical significance level was considered $<.05$.

## 3. Results

### 3.1. Baseline characteristics

After an initial screening of medical records, 294 patients with septic shock were included in the study. Based on the inclusion and exclusion criteria, 89 patients were excluded (15 patients who received chemotherapy in the last month, 6 patients <18 years, 29 active bleeding patients, 36 patients who received a blood transfusion in the first 24 hours of ICU admission, 2 patients with myelodysplastic syndrome, and 1 patient with myelofibrosis). The sociodemographic characteristics and hematological values and patterns at admission and after 72 hours were retrospectively collected from the medical records of the final 205 patients are shown in Table 1. The mortality rate from sepsis was 47.8% (98 patients). The majority of patients (60%) were males and the mean age of the patients was $60.55 \pm 18.39$ years. However, 55.4% of the patients were >60 years. The mean APACHE II score was $19.28 \pm 8.54$, mean admission platelet count was $274.1 \pm 140.04 \times 10^3/\mu L$, lowest platelet count within 72 hours regardless of the timing was $149.79 \pm 114.93 \times 10^3/\mu L$, mean WBC count was $15.16 \pm 10.06 \times 10^3/\mu L$, and highest WBC count within 72 hours was $21.88 \pm 13.44 \times 10^3/\mu L$.

During the initial 72-hour ICU course, there were 2 distinct patterns of platelet counts identified:

(1) group A showed a nadir platelet count within 72 hours but not on admission, where 93.7% of patients had a mean drop of 46.6% (standard deviation = 28.99) in their platelet counts, and
(2) group B showed had the lowest platelet count on admission, which was only 6.3%.

In addition, we identified 2 patterns of WBC counts:

(1) group C showed a peak WBC count within 72 hours but not on admission, where 56.6% of patients had a mean rise in WBC count of 77.35% (standard deviation = 155.11), and
(2) group D showed the highest WBC count on admission, which was 43.4%.

Other hematologic parameters and ratios were also included in the analysis. The mean neutrophil count was $16.95 \pm 11.99 \times 10^3/\mu L$, mean lymphocyte count was $2.62 \pm 6.1 \times 10^3/\mu L$, mean monocyte count was $1.1 \pm 0.81 \times 10^3/\mu L$, mean NLR was 13.37 $\pm$ 13.7, mean PLR was $227.9 \pm 235.72$, and mean MLR was 0.70 $\pm$ 0.65. The median ICU length of stay was 8.5 days (interquartile range: 0.5–366) and 47.8% of patients died in the ICU or hospital.

**Table 1**

**Sociodemographic and admission clinical and hematologic findings of patients with septic shock (n = 205).**

| | n (%) | Mean (SD), Median (IQR) |
|---|---|---|
| Sex | | |
| Male | 123 (60) | |
| Female | 82 (40) | |
| Age (yr) | | 60.55 (18.39) |
| Age (yr) groups | | |
| Age <60 yr | 91 (44.4) | |
| Age >=60 yr | 114 (55.6) | |
| APACHE II score | | 19.28 (8.54) |
| Admission platelet count ($10^3/\mu L$) | | 274.1 (141.04) |
| Patients presented with lowest platelet on admission | | |
| No (group A pattern) | 192 (93.7) | |
| Yes (group B pattern) | 13 (6.3) | |
| Lowest platelet count within 72 h ($10^3/\mu L$) | | 149.79 (114.93) |
| Platelet decline percentage (%) (group A pattern) | | 46.60 (28.99) |
| Admission WBC count ($10^3/\mu L$) | | 15.16 (10.06) |
| Patients presented with the highest WBC on admission | | |
| No (group C pattern) | 116 (56.6) | |
| Yes (group D pattern) | 89 (43.4) | |
| Highest WBC count within 72 h ($10^3/\mu L$) | | 21.88 (13.44) |
| WBC rise percentage (%) (group C pattern) | | 77.35 (155.11) |
| Absolute neutrophil count ($10^3/\mu L$) | | 16.95 (11.99) |
| Absolute lymphocytes count ($10^3/\mu L$) | | 2.62 (6.10) |
| Absolute monocytes count ($10^3/\mu L$) | | 1.10 (0.81) |
| Neutrophil lymphocyte ratio (NLR) | | 13.37 (13.7) |
| Platelet lymphocyte ratio (PLR) | | 227.94 (235.72) |
| Monocyte lymphocyte ratio (MLR) | | 0.70 (0.65) |
| ICU length of stay | | 8.5 (0.5-366) |
| Final ICU outcome | | |
| Survival | 107 (52.2) | |
| Death | 98 (47.8) | |

APACHE-II = acute physiology and chronic health evaluation II, ICU = intensive care unit, IQR = interquartile range, SD = standard deviation, WBC = white blood cell.

### 3.2. Correlation of hematologic variables with APACHE II score

Table 2 displays the bivariate Pearson correlation coefficients between the APACHE-II score with the studied parameters. This correlation analysis matrix illustrates the convergences between the platelet and WBC values (at admission, within 72 hours of admission, and their 2 period-point deviation) and the APACHE-II score. The analysis showed that neither the admission platelet nor the WBC count was significantly correlated with the APACHE score. However, the lowest platelet count within 72 hours had a significant negative correlation with the APACHE-II score, denoting that the lower the value for the lowest platelet count, the greater their severity of illness on average, $r = -0.250$, $P < .01$. In addition, the platelet count decline percentage converged significantly and positively with the APACHE-II score, indicating that a further drop in a patient's mean platelet count during the first 72 hours is associated with greater severity of illness, $r = 0.326$, $P < .01$. In addition, the highest WBC count correlated significantly with the severity of illness, denoting that

**Table 2**

**Bivariate Pearson correlations between hematologic parameters and APACHE II score (n = 205).**

| | APACHE-II score | Admission platelet count ($10^3/\mu L$) | Admission WBC count ($10^3/\mu L$) | Lowest platelet count within 72 h ($10^3/\mu L$) | Platelet decline percentage (%) (group A pattern) | Highest WBC count within 72 h ($10^3/\mu L$) | WBC rise percentage (%) (group C pattern) |
|---|---|---|---|---|---|---|---|
| APACHE II score | 1 | | | | | | |
| Admission platelet count ($10^3/\mu L$) | 0.014 | 1 | | | | | |
| Admission WBC count ($10^3/\mu L$) | 0.015 | −0.010 | 1 | | | | |
| Lowest platelet count within 72 h ($10^3/\mu L$) | −0.250* | 0.659* | 0.013 | 1 | | | |
| Platelet decline percentage (%) (group A pattern) | 0.326* | −0.051 | −0.012 | −0.717* | 1 | | |
| Highest WBC count within 72 h ($10^3/\mu L$) | 0.230* | −0.049 | 0.539* | −0.282* | 0.371* | 1 | |
| WBC rise percentage (%) (group C pattern) | 0.202* | −0.084 | −0.322* | −0.318* | 0.392* | 0.527* | 1 |

APACHE-II = acute physiology and chronic health evaluation II, WBC = white blood cell.
* Correlation is significant at $P < .01$, 2-tailed).

the higher the peak WBC count, the greater the severity of illness, $r = 0.230$, $P < .01$. Similarly, the greater the deviation from the mean WBC count during the first 72-hours from admission to the peak, the greater the severity of illness, $r = 0.202$, $P < .01$. Remarkably, a decline in platelet count correlated significantly and positively with the rise of the WBC count during the first 72 hours, $r = 0.392$, $P < .010$.

### 3.3. Sepsis mortality risk factors

We compared the sociodemographic data and the measured parameters between patients who survived and those who died from sepsis to better understand the cause for mortality (Table 3). The findings showed no statistically significant associations between sex and mortality with sepsis ($P = .361$), however, patients who died from sepsis were significantly older than those who survived ($63.84 \pm 17.83$ vs $57.54 \pm 18.45$ years, $P = .014$). Also, comparing patient age groups and their mortality suggested that patients ≥60 years were predicted to die from sepsis at a statistically significant higher rate compared to those <60 years ($P = .035$). The overall mean APACHE II score for nonsurvivors was significantly higher ($23.57 \pm 7.57$) than that for survivors ($15.22 \pm 7.28$) ($P < .001$).

The admission platelet count did not differ significantly between survivors ($278.80 \pm 139.7 \times 10^3/\mu L$) and nonsurvivors ($268.86 \pm 143.03 \times 10^3/\mu L$) ($P = .616$). Furthermore, the platelet

**Table 3**

**Bivariate analysis of mortality in ICU patients with septic shock (n = 205).**

| | Final ICU outcome | | | |
|---|---|---|---|---|
| | Survived, n = 107 | Died, n = 98 | Test statistics | *P*-value |
| Sex | | | | |
| Male, n (%) | 61 (57) | 62 (63.3) | $\chi^2$ (1) = 0.83 | .361 |
| Female, n (%) | 46 (43) | 36 (36.7) | | |
| Age (yr), mean (SD) | 57.54 (18.45) | 63.84 (17.83) | $t$ (203) = 2.48 | .014 |
| Age (yr) groups | | | | |
| Age <60 yr, n (%) | 55 (51.4) | 36 (36.7) | $\chi^2$ (1) = 4.46 | .035 |
| Age ≥60 yr, n (%) | 52 (48.6) | 62 (63.3) | | |
| APACHE II score, mean (SD) | 15.22 (7.28) | 23.57 (7.57) | $t$ (203) = 8.18 | <.001 |
| Admission platelet count ($10^3/\mu L$), mean (SD) | 278.80 (139.70) | 268.86 (143.03) | $t$ (203) = 0.50 | .616 |
| Patients presented with low platelet on admission | | | | |
| No (group A pattern), n (%) | 99 (92.5) | 93 (94.9) | $\chi^2$ (1) = 0.48 | .486 |
| Yes (group B pattern), n (%) | 8 (7.5) | 5 (5.1) | | |
| Lowest platelet count within 72 h ($10^3/\mu L$), mean (SD) | 185.52 (10.81) | 105.62 (10.67) | $t$ (203) = 4.91 | <.001 |
| Platelet decline percentage (%) (group A pattern), mean (SD) | 35.69 (23.27) | 58.51 (30.02) | $t$ (182.54) = 6.10 | <.001 |
| Admission WBC count ($10^3/\mu L$), mean (SD) | 16.37 (11.77) | 13.85 (7.62) | $t$ (203) = 1.79 | .074 |
| Patients presented with high WBC on admission | | | | |
| No (group C pattern), n (%) | 46 (43) | 70 (71.4) | $\chi^2$ (1) = 16.84 | <.001 |
| Yes (group D pattern), n (%) | 61 (57) | 28 (28.6) | | |
| Highest WBC count within 72 h ($10^3/\mu L$), mean (SD) | 18.67 (11.76) | 25.40 (14.32) | $t$ (188.15) = 3.66 | <.001 |
| WBC rise percentage (%) (group C pattern), mean (SD) | 30.78 (100.11) | 128.20 (186.12) | $t$ (145.85) = 4.61 | <.001 |
| Absolute neutrophil count ($10^3/\mu L$), mean (SD) | 13.73 (10.13) | 20.48 (12.90) | $t$ (183.86) = 4.14 | <.001 |
| Absolute lymphocyte count ($10^3/\mu L$), mean (SD) | 1.83 (1.53) | 3.48 (8.60) | $t$ (102.61) = 1.88 | .063 |
| Absolute monocyte count ($10^3/\mu L$), mean (SD) | 0.99 (0.76) | 1.13 (0.86) | $t$ (203) = 1.28 | .202 |
| Neutrophil lymphocyte ratio (NLR), mean (SD) | 11.56 (10.50) | 15.33 (16.35) | $t$ (162.6) = 1.95 | .053 |
| Platelet lymphocyte ratio (PLR), mean (SD) | 225.31 (154.33) | 230.81 (301.35) | $t$ (141.7) = 0.16 | .871 |
| Monocyte lymphocyte ratio (MLR), mean (SD) | 0.703 (0.62) | 0.69 (0.68) | $t$ (196.72) = 0.12 | .905 |
| ICU length of stay (d), median | 7.75 | 18.5 | $U$ (110) = 1057 | .505* |

APACHE-II = acute physiology and chronic health evaluation II, ICU = intensive care unit, SD = standard deviation, WBC = white blood cell.
* Mann–Whitney-*U* nonparametric test.

**Table 4**

**Multivariate logistic binary regression analysis of mortality due to sepsis in the ICU (n = 205).**

| | | 95% CI for OR | | |
|---|---|---|---|---|
| | Multivariate adjusted OR | Lower | Upper | *P*-value |
| Sex = Female | 0.584 | 0.273 | 1.249 | .166 |
| Age ≥60 yr | 2.305 | 1.098 | 4.837 | .027 |
| APACHE II score | 1.139 | 1.086 | 1.195 | <.001 |
| Admission platelet count ($10^3/\mu L$) | 1.000 | 0.997 | 1.002 | .837 |
| Admission WBC count ($10^3/\mu L$) | 0.966 | 0.916 | 1.018 | .194 |
| Platelet decline percentage (group A pattern) | 1.028 | 1.012 | 1.045 | .001 |
| WBC rise percentage (group C pattern) | 1.002 | 0.998 | 1.006 | .235 |
| Patients presented with lowest platelet on admission = Yes (group B pattern) | 6.901 | 1.446 | 32.932 | .015 |
| Patients presented with highest WBC on admission = Yes (group D pattern) | 0.794 | 0.342 | 1.842 | .591 |
| Constant | 0.024 | | | <.001 |

Dependent Variable = Mortality in the ICU from sepsis (0 = No/1 = Yes). The overall model statistical significance was $\chi^2$ (9) = 92.11, $P < .001$, Hosmer–Lemeshow G.O.F test $\chi^2$ (8) = 4.24, $P = .835$, model area under the curve = 86%, $P < .001$.

APACHE-II = acute physiology and chronic health evaluation II, CI = confidence interval, OR = odds ratio, WBC = white blood cell.

patterns in groups A and B did not show a difference in mortality between the survivors and nonsurvivors ($P = .486$). However, the lowest platelet count in the first 72 hours was significantly lower in the nonsurvivors ($105.62 \pm 10.67 \times 10^3/\mu L$) than in the survivors ($185.52 \pm 10.81 \times 10^3/\mu L$) ($P < .001$). Also, the platelet count deviation percentage from admission to the lowest value was significantly higher in the nonsurvivors (58.51% ± 30.2%) compared to that in the survivors (35.69% ± 23.27%) ($P < .001$)

The WBC count at admission did not differ significantly between the survivors ($16.37 \pm 11.77 \times 10^3/\mu L$) and nonsurvivors ($13.85 \pm 7.62 \times 10^3/\mu L$) ($P = .074$). Furthermore, the WBC pattern identified as group C showed a higher mortality compared to the pattern associated with group D ($P < .001$). In addition, the highest WBC count was significantly higher in the nonsurvivors ($25.40 \pm 14.32 \times 10^3/\mu L$) compared to that in survivors ($18.67 \pm 11.76 \times 10^3/\mu L$) ($P < .001$). The mean percentage of the rise in the WBC count to the peak during the first 72 hours was significantly greater in the nonsurvivors (128.2% ± 186.12%) compared to that in survivors (30.78% ± 100.11%) ($P < .001$). The neutrophil count at admission was significantly greater for nonsurvivors ($20.48 \pm 12.90 \times 10^3/\mu L$) than for survivors ($13.73 \pm 10.13 \times 10^3/\mu L$) ($P < 0.001$), but there were no significant differences in the lymphocyte count, monocyte count, or in any of the ratios (e.g., NLR, PLR, MLR). The length of ICU stays in both survivors and nonsurvivors was also not statistically different ($P = .505$).

All significant and clinical variables of mortality in the bivariate analysis were tested in the multivariate logistic regression. Overall, the model was statistically significant with $\chi^2$ (9) = 92.11 ($P < .001$) (Table 4). The independent risk factors of sepsis mortality consisted of only 4 variables, age >60 years (2.305 [1.098–4.837], $P = .027$), APACHE-II score (1.139 [1.086–1.195], $P < .001$), percentage decline of platelet count (1.028 [1.012–1.045], $P = .001$), and group B platelet pattern, which is presenting with the lowest platelet count on admission (6.901 [1.446–32.932], $P = .015$) (Fig. 1). Receiver operating characteristic is depicted in Figure 2.

## 4. Discussion

Sepsis is a considerable health burden because of its high mortality rate despite extensive management with antimicrobials and fluid resuscitation in the ICU.[31,32] Such a complicated course of management needs new scoring parameters aside from APACHE-II for risk assessment for a better outcome.[33,34] To identify better parameters for risk assessment, we analyzed platelet counts, patterns and timing of platelet counts, and other hematological variables early in the course of septic shock. We also examined their association with APACHE-II scores and mortality. To the best of our knowledge, this is the first study to investigate the association of platelet count patterns, and not thrombocytopenia, with mortality early in the course of septic shock.

Boechat et al reported an association of APACHE-II scores with mortality in thrombocytopenic sepsis patients and non-thrombocytopenic sepsis patients. A 81.8% mortality rate was reported with APACHE II scores >22 in thrombocytopenic patients, whereas no deaths occurred among nonthrombocytopenic patients; a 74% mortality rate was reported with APACHE-II scores ≤22 in thrombocytopenic patients, whereas in nonthrombocytopenic patients the mortality rate was 42.8%.[35] In our study, APACHE-II score was significantly correlated with the platelet count pattern and not necessarily through thrombocytopenia, which may explain the importance of dysfunction rather than low values. Although APACHE-II is the most widely applied scoring system to assess the severity and outcomes in acute and critically ill patients, limitations in predicting the course of the disease and patient outcomes have been reported.[36] Sepsis-induced thrombocytopenia affects prognosis in critically ill patients; however, the literature remains paradoxical regarding the direct association of thrombocytopenia and outcomes in septic ICU patients. Observing the degree of the decline in the platelet count and platelet count patterns and not the absolute number, might give a better assessment for patient outcomes. In the current study, the severity of the decline and the lowest platelet count on admission were both significantly different between the survivors and nonsurvivors, affirming results from reported studies between the patterns of platelet count and a higher mortality rate.[17,37,38] The absolute platelet count is not as crucial as the change in platelet count over time.[39,40] Akca et al reported a biphasic state: reduction in platelet count followed by a recovery.[41] Likewise, a stark rise in the platelet count has also been linked to a poor outcome, which was supported by the results of this study with the group B platelet pattern, where the lowest platelet count was measured on admission. APACHE-II score is a widely used scoring system for

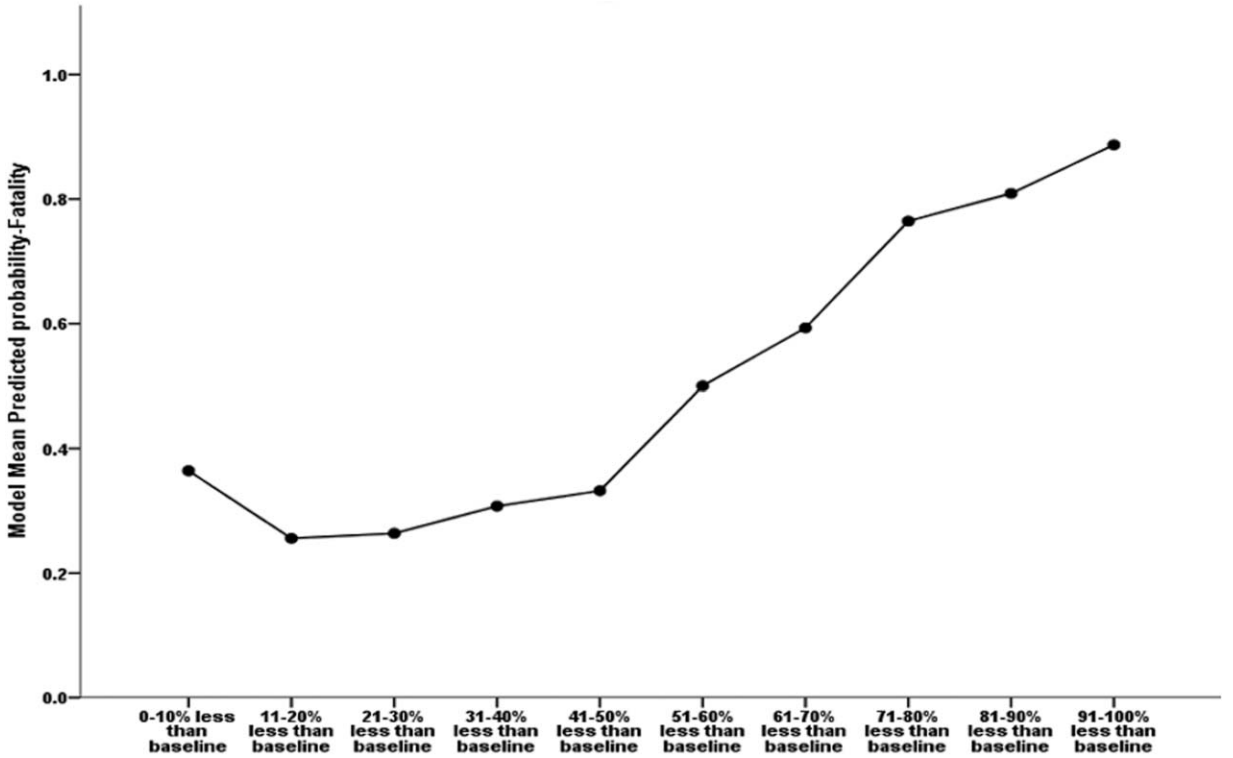


**Figure 1.** Association of the platelet count decline percentage and predicted mortality from early sepsis in ICU patients. ICU = intensive care unit.

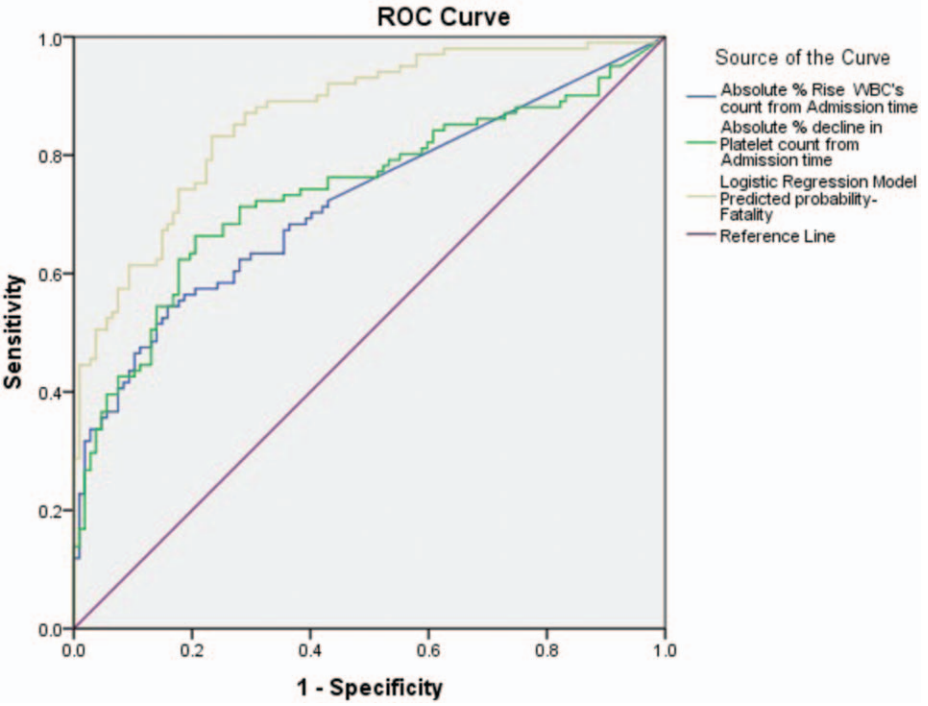


**Figure 2.** ROC curve. ROC = receiver operating characteristic.

mortality prediction, however, it is limited to the first day in the ICU and does not consider the course through repetitive assessment and the temporal association with the patients' outcomes.

WBC counts on admission is one of the elements of the APACHE II score, however, we were more interested in the pattern of the peak WBC count, which was not associated with mortality. Nevertheless, these parameters were not associated with mortality due to sepsis. NLR, PLR, and MLR are reported as biomarkers for the prediction of outcomes in critically ill patients. In the current study, we found no significant association because it was measured early in the course of sepsis. Higher NLR values, a marker of systemic inflammation,[31] have been found to be significantly associated with a poor outcome.[42] Rajnish et al reported a similar trend in the early and late phases of sepsis, suggestive of the role of NLR as a useful prognostic marker.[43] However, the initial NLR was not measured early in the course of sepsis, and our results showed no significant correlation with mortality.

### 4.1. Limitations

The limitations of our study need to be acknowledged in the interpretation of the findings. The majority of the nonsurvivors were older with expected more comorbidities, gathering data that include the comorbidities and the baseline functional status would add more explanation to the findings. Nonetheless, there were no difference in the initial values of hematologic variables in the early course of the disease which was necessary to look at the later patterns amongst survivors and nonsurvivors. Moreover, we did not ascertain the factors associated with patients' clinical course that led to the RRT activation and before the ICU admission, such as the duration of the hospital admission, the baseline hematologic variables, prior admission to ICU, and identifying the new medications given during the hospital course. Furthermore, there were many missing bacteriologic results for sepsis and the effect of such organisms based on gram stain, virulence, and the focus of infection on the hematologic patterns and specifically platelet count would add more to the validity of the study. Large-sample, high-quality studies are needed to avoid the selection bias associated with this study and to identify the decremental and incremental hematologic values associated with mortality.

## 5. Conclusions

Therefore, it is crucial to identify patients at a higher risk intended for a poor prognosis and outcome in the management of septic shock. We found that the degree of the platelet count decline and timing, and the lowest platelet count are independent risk factors for mortality early in the course of sepsis with a high correlation to the APACHE-II score. Determining the platelet count pattern, as opposed to its actual value, can potentially predict mortality during early septic shock in ICU patients.

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## References

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10.
[2] Torio CM, Moore BJ. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013: Statistical Brief# 204. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. 2006:2006–2016.
[3] Goyette RE, Key NS, Ely EW. Hematologic changes in sepsis and their therapeutic implications. Paper presented at: Seminars in respiratory and critical care medicine 2004; 2004;25:645–59.
[4] Dewitte A, Lepreux S, Villeneuve J, et al. Blood platelets and sepsis pathophysiology: a new therapeutic prospect in critical ill patients? Ann Intensive Care 2017;7:115.
[5] Hatherill M, Tibby SM, Turner C, et al. Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock. Crit Care Med 2000;28:2591–4.
[6] Dwivedi P, Muench DE, Wagner M, et al. Time resolved quantitative phospho-tyrosine analysis reveals Bruton's Tyrosine kinase mediated signaling downstream of the mutated granulocyte-colony stimulating factor receptors. Leukemia 2019;33:75–87.
[7] Machlus KR, Italiano JEJr. The incredible journey: from megakaryocyte development to platelet formation. J Cell Biol 2013;201:785–96.
[8] Coppinger JA, Cagney G, Toomey S, et al. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. Blood 2004;103:2096–104.
[9] Nurden AT, Nurden P, Sanchez M, et al. Platelets and wound healing. Front Biosci 2008;13:3532–48.
[10] Baughman RR, Lower EE, Flessa HC, et al. Thrombocytopenia in the intensive care unit. Chest 1993;104:1243–7.
[11] Strauss R, Wehler M, Mehler K, et al. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002;30:1765–71.
[12] Williamson DR, Lesur O, Tétrault J, et al. Thrombocytopenia in the critically ill: prevalence, incidence, risk factors, and clinical outcomes. Can J Anesth/J Can Anesth 2013;60:641–51.
[13] Khwannimit B, Geater A. A comparison of APACHE II and SAPS II scoring systems in predicting hospital mortality in Thai adult intensive care units. J Med Assoc Thai 2007;90:643–52.
[14] Wagner DP, Draper EA. Acute physiology and chronic health evaluation (APACHE II) and Medicare reimbursement. Health Care Financ Rev 1984;Suppl:91–105.
[15] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
[16] Beck DH, Taylor BL, Millar B, et al. Prediction of outcome from intensive care: a prospective cohort study comparing Acute Physiology and Chronic Health Evaluation II and III prognostic systems in a United Kingdom intensive care unit. Crit Care Med 1997;25:9–15.
[17] Zimmerman JE, Kramer AA. Outcome prediction in critical care: the Acute Physiology and Chronic Health Evaluation models. Curr Opin Crit Care 2008;14:491–7.
[18] Bedet A, Razazi K, Boissier F, et al. Mechanisms of thrombocytopenia during septic shock: a multiplex cluster analysis of endogenous sepsis mediators. Shock 2018;49:641–8.
[19] Iba T, Levy JH, Raj A, et al. Advance in the management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Clin Med 2019;8:728.
[20] Claushuis TA, van Vught LA, Scicluna BP, et al. Molecular diagnosis and risk stratification of sepsis consortium. Thrombocytopenia is associated with a dysregulated host response in critically ill sepsis patients. Blood 2016;127:3062–72.
[21] Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost 2015;114:449–58.

[22] Garraud O, Hamzeh-Cognasse H, Pozzetto B, et al. Bench-to-bedside review: platelets and active immune functions-new clues for immunopathology? Crit Care 2013;17:236.
[23] Wu Q, Ren J, Hu D, et al. An elevated percentage of reticulated platelet is associated with increased mortality in septic shock patients. Medicine (Baltimore) 2015;94:e814.
[24] Gawaz M, Dickfeld T, Bogner C, et al. Platelet function in septic multiple organ dysfunction syndrome. Intensive Care Med 1997;23:379–85.
[25] Katz JN, Kolappa KP, Becker RC. Beyond thrombosis: the versatile platelet in critical illness. Chest 2011;139:658–68.
[26] Zarychanski R, Houston DS. Assessing thrombocytopenia in the intensive care unit: the past, present, and future. Hematology Am Soc Hematol Educ Program 2017;2017:660–6.
[27] Wazny LD, Ariano RE. Evaluation and management of drug-induced thrombocytopenia in the acutely ill patient. Pharmacotherapy 2000; 20:292–307.
[28] Johansen ME, Jensen JU, Bestle MH, et al. The potential of antimicrobials to induce thrombocytopenia in critically ill patients: data from a randomized controlled trial. PloS One 2013;8:e81477.
[29] Sartelli M, Kluger Y, Ansaloni L, et al. Raising concerns about the Sepsis-3 definitions. World J Emerg Surg 2018;13:6.
[30] Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
[31] Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: the evolution in definition, pathophysiology, and management. SAGE Open Med 2019; 7:2050312119835043.
[32] Rudd KE, Kissoon N, Limmathurotsakul D, et al. The global burden of sepsis: barriers and potential solutions. Crit Care 2018;22:232.
[33] Fallenius M, Skrifvars MB, Reinikainen M, et al. Common intensive care scoring systems do not outperform age and Glasgow coma scale score in predicting mid-term mortality in patients with spontaneous intracerebral hemorrhage treated in the intensive care unit. Scand J Trauma Resusc Emerg Med 2017;25:102.
[34] Kellner P, Prondzinsky R, Pallmann L, et al. Predictive value of outcome scores in patients suffering from cardiogenic shock complicating AMI: APACHE II, APACHE III, Elebute-Stoner, SOFA, and SAPS II. Med Klin Intensivmed Notfmed 2013;108:666–74.
[35] de Oliveira Boechat T, da Silveira MFBB, Faviere W, et al. Thrombocitopenia in sepsis: an important prognosis factor. Rev Bras Ter Intensiva 2012;24:35–42.
[36] Civetta JM, Hudson-Civetta JA, Kirton O, et al. Further appraisal of APACHE II limitations and potential. Surg Gynecol Obstet 1992;175: 195–203.
[37] Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000;28:1871–6.
[38] Akca S, Haji-Michael P, de Mendonça A, et al. Time course of platelet counts in critically ill patients. Crit Care Med 2002;30: 753–6.
[39] Imtiaz F, Shafique K, Mirza SS, et al. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012;5:2.
[40] Vandijck DM, Decruyenaere JM, Blot SI. The value of sepsis definitions in daily ICU-practice. Acta Clin Belg 2006;61:220–6.
[41] Vandijck DM, Blot SI, De Waele JJ, et al. Thrombocytopenia as a marker of poor outcome in ICU patients with severe BSI. Crit Care Med 2006;34: A137.
[42] Liu X, Shen Y, Wang H, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in patients with sepsis: a prospective observational study. Mediators Inflamm 2016;2016:8191254.
[43] Kaushik R, Gupta M, Sharma M, et al. Diagnostic and prognostic role of neutrophil-to-lymphocyte ratio in early and late phase of sepsis. Indian J Crit Care Med 2018;22:660–3.