IS THE THROMBOCYTOPENIA ONE OF USEFUL PREDICTIVE MARKERS OF MORTALITY IN PEDIATRIC SHOCK PATIENTS

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Platelet count is a routine laboratory measure associated with poor outcomes in adult patients with sepsis/septic shock. The aim of this study was to assess the usefulness of platelet count as a predictive marker of mortality in pediatric patients with septic shock. Over an 18-month period, 62 pediatric patients with septic shock had platelet count measured on the first day of PICU admission. The 28 day in-hospital mortality rate was 66% (41/62). Severe thrombocytopenia (≤ 50 x 109/L) was observed in 52.4% (33/62). In all patients, platelet count was independently associated with PICU mortality (OR 0.96, 95% CI 0.94, 0.99). The AUROC for thrombocytopenia to predict mortality was 0.93 (95% CI 0.87, 0.99). The AUROC of PRISM III score and pSOFA score were 0.81 (95% CI, 0.70 – 0.92) and 0.84 (95% CI, 0.74 – 0.94), respectively. Thrombocytopenia was associated with mortality in pediatric patients with septic shock and provides similar prognostic information as the more complex PRISM III and pSOFA scores.

Keywords: Mortality, Pediatrics, Septic Shock, Thrombocytopenia

I. INTRODUCTION

Thrombocytopenia is commonly seen in critically ill patients admitted to the intensive care unit. Its main cause in ICU setting is sepsis and septic shock. In severely ill adult patients, thrombocytopenia is common, and several studies have reported its association with poor prognosis.[1,2] Thrombocytopenia is also associated with adverse outcome and high mortality in adult patients with septic shock.[3-5] However, there were few studies in children regarding the association between thrombocytopenia and mortality in the pediatric intensive care unit (PICU).[6,7]

In one previous study on children with septic shock, Choi et al. found that the platelets were low in non-survivors and were associated with increased mortality.[8]

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Recently, many studies on adults have mentioned the crucial role of platelets in sepsis/ septic shock. Causes of thrombocytopenia in sepsis are often multifactorial, including consumption, immune-mediated destruction, bone marrow suppression and hemophagocytosis.[9]

In this study, we hypothesized that platelet decrease in children suffering from septic shock, which may be associated with increased mortality as being similarly noticed in adult septic patients.

The aim of this study was to show the association of thrombocytopenia and increased mortality, to determine its potential application as a useful biomarker in the pediatric population with septic shock.

II. SUBJECTS AND METHODS

1. Subjects

The study was a prospectively observational study. We enrolled 62 consecutive pediatric patients with septic shock, admitted to PICU of

Can Tho Children's Hospital between January 2018 and June 2019. Septic shock was defined according to the 2005 international pediatric sepsis consensus conference (IPSCC) criteria.[10]

All patients who presented with septic shock on admission were included. Patients with history of hematological diseases, immune thrombocytopenia and Dengue hemorrhagic fever were excluded from this study. The patients were followed until 28 days from the day of admission in PICU to determine dead or alive outcomes.

2. Data Collection

Platelet counts were measured at least once during the first 24 hours at the onset of shock by automated hematology analyzers. If several measurements were done within 24 hours, the lowest platelet count was retained.

Thrombocytopenia was defined as platelet count less than 100×109/L and severe thrombocytopenia when platelet count was less than 50 x 109/L

The demographic characteristics, sources of infection, and laboratory results were documented. The pediatric sequential organ failure assessment (pSOFA) scores and Pediatric risk of mortality III (PRISM III) scores were acquired via using the worst values during the first 24 hours. Following criteria were used to calculate pSOFA score11: PaO2/FiO2 or SpO2/FiO2, platelet count, bilirubin, mean blood pressure, Glasgow Coma Score (GSC) and creatinine. Following criteria were used to calculate PRISM III12 : Systolic blood pressure, body temperature, GSC, heart rate, pupillary reflexes, parameters of blood gas, plasma glucose, potassium, creatinine, blood urea nitrogen, white blood cell, platelet count, prothrombin time and activated partial thromboplastin time.

Disseminated Intravascular Coagulation (DIC) is defined by the International Society on Thrombosis and Hemostasis and Japanese Association in critically ill pediatric patients.[13]

Statistical analysis: Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM SPSS Inc., Chicago, IL). Continuous data were expressed as mean and standard deviation (SD) or median with interquartile, as appropriate. Qualitative data were expressed as absolute numbers and percentages. The comparisons were performed using a Student t test or Mann–Whitney test according to their distribution.

Bivariate analysis was first done to see the association between each independent variables and the dependent variable (mortality). Variables with a P-value of less than 0.1 in the bivariate analysis were entered into the multivariate logistic regression model for final analysis. Multivariate analysis was done using forward logistic regression method. Odds ratios were calculated to determine independent predictors of in-hospital mortality. P-value less than 0.05 was considered to determine the statistical significance.

Receiver operating characteristic (ROC) curve method was used to compare the discriminatory power of platelet count and the scoring system (pSOFA, PRISM III) for the prediction of mortality. Youden's J-statistic was used to evaluate the optimal cutoff of the platelet count, PRISM III and SOFA scores to discriminate dead or alive.

The study protocol was approved by The Science and Technology Board of Can Tho Children's Hospital and The Institutional Review Board of Can Tho University of Medicine and Pharmacy. The need for informed consent was waived.

III. RESULTS

A total of 62 pediatric patients with septic shock were admitted to the PICU of Can Tho Children's Hospital from January 2018 to May 2019.

Major sources for sepsis included pneumonia (28 patients), gastro-intestinal tract (22 patients), central nervous system infection (5 patients) and unknown source (6 patients).

Thrombocytopenia (≤ 100 x 109/L) was observed in 68.3% (43/62) of the patients during the first 24 hours at the onset of septic shock. Of the 43 thrombocytopenic patients, 33 (76.7%) had severe thrombocytopenia (≤ 50 x 109/L). The 28 day in-hospital mortality rate was 66% (41/62). Age, gender did not differ significantly in survivors and non-survivors.

Non-survivor patients had significantly lower platelet count, WBC count, GCS, Pa O2/FiO2 ratio, blood glucose, but had significantly higher PaCO2, serum potassium, serum total bilirubin, serum creatinine, blood urea nitrogen and more prolonged PT, APTT than those who survived. Blood gas showed more acidosis (decreased pH and increased PaCO2 in non-survivors.

DIC occurred in 38.1% (8/21) in survivors and 53.7% (22/41) in non-survivors but the difference was not statistically significant.

Finally, PRISM III and pSOFA scores, which reflect disease severity, were significantly greater in the non-survivors than in survivors (Table 1).

Table 1. Demographic characteristics, clinical and laboratory findings in 62 pediatric patients with septic shock

Variable†	All patients	Survivors (n = 21)	Non-survivors (n = 41)	P value
Age (year)	2 (1 - 6)	2 (1 - 7.5)	3 (1 - 5.5)	.837
Male (%)	34 (54.0%)	12 (57.1%)	22 (53.7%)	.794
Heart rate (beat/mn)	170 (160 - 180)	164 (153 - 184)	170 (160 - 180)	.988
Temperature > 400C	3 (4.8%)	2 (9.5%)	1 (2.4%)	.263
Systolic BP (mmHg)	65 (0 - 76)	65 (60 - 75)	65 (0 - 80)	.443
MAP (mmHg)	46 (0 - 56)	46 (45 - 58)	46 (0 - 56)	.380
GCS (mean ± SD)	10.6 ± 2.6	12.5 ± 1.4	9.6 ± 2.6	.000
Fixed pupils >3mm	6 (9.5%)	0 (0%)	6 (14%)	.088
Ph	7.30 (7.13 - 7.38)	7.35 (7.29 - 7.42)	7.20 (7.10 - 7.5)	.004
PCO2 (mmHg)	29 (20 - 37)	25 (18 - 32)	34 (23 - 40)	.017
HCO3 (mmol/L)	15.6 (12 - 18)	15 (16 - 19)	14 (12 - 17)	.413
PaO2 (mmHg)	152 (92 - 194)	152 (113 - 187)	136 (74 - 195)	.246
PaO2/FiO2	210 (116 - 326)	331 (226 - 387)	163 (108 - 263)	.002
Glucose (mmol/L)	5.7 (3.9 - 7.7)	7.2 (5,8 - 9,4)	4.5 (2.7 - 6.5)	.000
Total bilirubin (mg/dL)	1.5 (1.0 - 4.0)	1.0 (0.75 - 1.50)	2.1 (1.0 - 4.0)	.006

Variable†	All patients	Survivors (n = 21)	Non-survivors (n = 41)	P value
Potassium (mmol/L) (mean ± SD)	3.6 ± 1.0	3.3 ± 0.7	3,8 ± 1.0	.053
Creatinine (mg/dL)	0.79 (0.67-1.01)	0.70 (0.60 - 0.80)	0.85 (0.70 - 1.11)	.004
BUN (mg/dL)	15.0 (10.3-23.7)	11.8 (10.0 - 14.8)	19.3 (11.2 - 27.0)	.014
PT (sec)	16.4 (13.5-25.8)	14,0 (13 - 20)	17,8 (14,8 - 27,5)	.050
APTT (sec)	46.5 (39.7-59.4)	42,0 (33,5 - 44,9)	50,0 (44,5 - 68,8)	.000
Lactate (mmol/L)	5.3 (3.4-8.8)	3.4 (3 - 4.4)	6.8 (4.3 - 10.0)	.001
WBC (x 109/L)	11.2 (6.5-21.6)	15.9 (8.4 - 21,9)	10.0 (5.3 - 16.8)	.056
Platelets (x109/L)	48.5 (34-155)	207 (100 - 355)	36 (30 - 50)	.000
DIC	30 (48.4%)	8 (38.1%)	22 (53.7%)	.246
pSOFA score	12 (9-14)	7 (6 - 11)	14 (12 - 15)	.000
PRISM III score	12.5 (8-20)	8 (5 - 12)	16 (10 - 26)	.000

†All continuous variables were presented as median and IQR (interquartile range) or mean ± SD and categorical variables were presented by number and percentages

BP = Blood pressure; MAP=Mean arterial pressure; GSC = Glasgow coma score; PT = Prothrombin time; APTT = Activated partial thromboplastin time; BUN = Blood urea nitrogen; WBC = White blood cell; SD = Standard deviation; DIC: Disseminated Intravascular Coagulation

The multivariate analysis using forward logistic regression method revealed that GCS, glucose, prothrombin time and platelet count were independent predictors in association with mortality in pediatric patients with septic shock (Table 2).

Table 2. Multivariate analysis for predicting factors of mortality in 62 pediatric patients with septic shock

Variables	Adjusted OR	95% CI	P value
GSC	0.23	0.07 - 0.76	.016
Glucose	0.55	0.32 - 0.97	.039
Prothrombin time	0.87	0.76 - 1.00	.059
Platelet count	0.96	0.94 - 0.99	.007

OR = Odds ratio; 95% CI = 95% Confidence interval; GSC = Glasgow Coma

Using Youden's J-statistics, we calculated the optimal cutoff of platelets, PRISM III score and pSOFA score for predicting mortality in pediatric patients with septic shock.

The optimal cutoff of platelets, PRISM III score, and pSOFA were 50 x 109/L, 12 points and 12 points, respectively.

Comparing the significance of platelets, PRISM III score and pSOFA score to discriminate between survivors and non-survivors using ROC curves were shown in Table 3.

Table 3. Sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for platelets, pSOFA and PRISM scores

Variables	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Platelets	50 x 109/L	0.93 (0.87 - 0.99)	96.9	95.2	20.18	0.03
PRISM III	12 points	0.81 (0.70 - 0.92)	82.8	71.4	2.89	0.24
pSOFA	12 points	0.92 (0.85 - 1.00)	94.5	90.4	9.40	0.06

Thrombocytopenia was the same discriminative value for mortality prediction as pSOFA score, but greater than PRISM III score on ROC curve. (Figure 1)

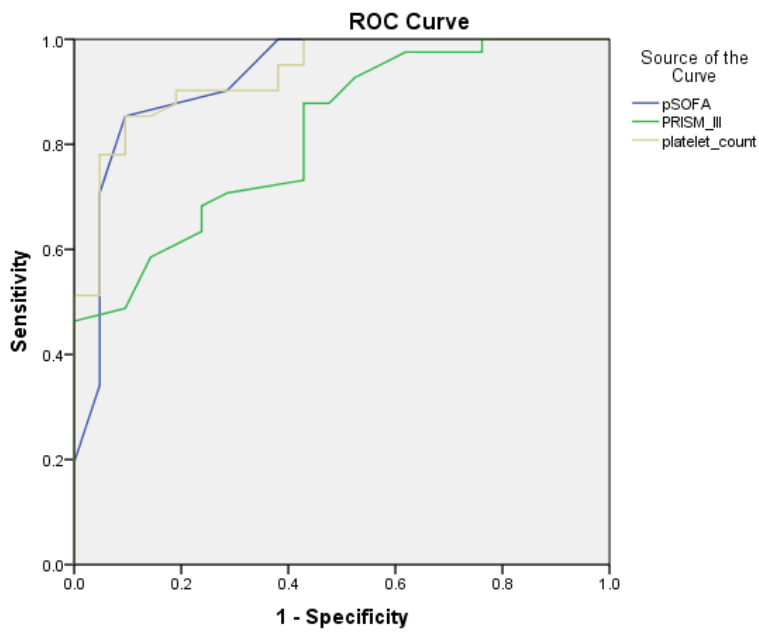

Figure 1. The area under the Receiver Operating Characteristic curve of pSOFA score, PRISM III score and platelets to predict mortality

IV. DISCUSSION

In this study, we observed a higher incidence of thrombocytopenia in pediatric patients with septic shock. Thrombocytopenia (≤ 100 x 109/L) was observed in 68.3% of the patients at the time of admission to the PICU, in which 76.7% (33/43) had severe thrombocytopenia (≤ 50 x 109/L). We also found that patients with severe thrombocytopenia were associated with increased mortality than in patients without thrombocytopenia.

Adult studies have demonstrated that both levels of thrombocytopenia (< 50 x109/L and <100 x 109/L) were independently associated with increased 28-day mortality in patients with severe sepsis/septic shock; however, the risk of mortality increased in patients with platelet counts below 50x 109/L.[14] Claushuis et al. observed that very low platelet counts were associated with elevated plasma levels of interleukin (IL)-8 and IL-10, elevated endothelial activation biomarkers, reduced vascular integrity, and increased coagulation activity.[14] Thrombocytopenia is associated with DIC, which is a frequent and major complication of sepsis. In the present study, DIC was occurred in higher proportion in non-survivors (53.7%) as compared to survivors (38.1%), but the difference was not statistically significant (P=0.246). In a recent cohort study of 980 adults with septic shock in Canada, the authors found that thrombocytopenia (<100 x 109/L) was associated with increased length of stay, longer duration of organ support, major bleeding events, and mortality.[5]

In children, thrombocytopenia was common in critically ill patients in PICU and was associated with increased mortality[6,7,15] however, the association between thrombocytopenia and mortality in pediatric patient septic shock patients has been unclear. To date, few studies have investigated the link between platelet count and mortality in children with sepsis/septic shock. In one previous study by Choi et al.[8], which included 83 children with septic shock, the authors reported that 25.3% of patients died within 28 days of hospital admission and the mean platelet count was significantly lower in non-survivors than in survivors (46.1 $\pm$ 44.1 x109/L vs 146.6 $\pm$ 133.7 x109(/L , P = 0.000). They also found that platelet count was predictive of mortality, with an AUROC of 0.85, a sensitivity of 85.7%, and a specificity of 78.9%.[4] . These results were also consistent with our study in which thrombocytopenia had a high predictive value of mortality with a sensitivity of 96.9% and a specificity of 95.2%. In adult, Tsigotis et al.[4] also found that thrombocytopenia (AUROC was 0.84, P < 0.001) was the best marker for predicting of mortality in adult patients with severe sepsis/septic shock.

In this study, we observed that thrombocytopenia, high PRISM III or high pSOFA scores were significantly associated with increased 28-day hospital mortality. Platelet count had the same sensitivity and specificity for predicting mortality as those of pSOFA scores but higher than those of PRISM III score. As compared to the scoring system (PRISM, pSOFA) with many variables to be measured, platelet count is a simple, inexpensive and easily available to pediatric practitioners.

This study has several limitations. First, small sample size in this study does not allow great precision in the estimation of odds ratio and we may have missed some important risk factors. Second, this is a single-center study; the results may not be generalizable to other institutions. Third, we do not consecutively measure the platelet count to assess the non-resolution of thrombocytopenia because some authors notified thrombocytopenia itself was not associated with increased mortality. Fourth, we measured HCO_3 as a surrogate for total CO_2 content in PRISM III score. Finally, some medications, particularly beta-lactam antibiotics may affect platelet count; the result of which is unlikely to be controlled.

V. CONCLUSION

Thrombocytopenia was associated with mortality in pediatric patients with septic shock and provides similar prognostic information as the more complex PRISM III and pSOFA scores.

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Disclosure

The authors declare no conflict of interest.

Author contributions

NNR: study conceptualization, statistical analysis, drafting the manuscript;
PHC: prepared protocol, data collection, drafting the manuscript.

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