

## Original Research Article

# A study to evaluate the prognostic significance of thrombocytopenia among critically ill children

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## ABSTRACT

**Background:** Pediatric critical care differs from Adult critical care not only in age but also in the outcomes. There are no studies regarding thrombocytopenia in the pediatric population. Therefore, in the current study, our objective was to study the prevalence and, the severity of thrombocytopenia, clinical features, and prognostic significance of low platelet count as an independent predictor of mortality and prolonged hospital and ICU stay.

**Methods:** This was a prospective observational study conducted at tertiary care paediatric intensive care unit in India. Children between 1 month to 18 years admitted to the Pediatrics intensive care unit with thrombocytopenia due to any cause at admission were involved in the study. Detailed history was documented. Haemoglobin levels, total leucocyte counts, platelet counts, and platelet indices were recorded on the first and fourth day of admission. Outcomes were analysed in term of survivors and non-survivors and duration of ICU and hospital stay.

**Results:** The study group consisted of 150 children with mean age of 8.458(± 5.604) years. Majority of children in the study group had severe thrombocytopenia 77 (51.3%). Moderate and mild thrombocytopenia was seen in 35(23.3%) and 38(25.4%) children respectively. Infection (50.66%) was the most common cause of thrombocytopenia, followed by sepsis (10.66%). Sepsis (27.5%) was observed to be the most common cause of mortality. Rise in platelet count on the fourth day among survivors, and no survivors were observed in 79.1% and 15.9% respectively. Failure of the rise in platelet count on the fourth day of admission was significantly associated with mortality (p value=0.001). The severity of thrombocytopenia does not correlate with duration of hospital and ICU stay.

**Conclusions:** Platelet counts and indices at the time of admission to a critical care unit have limited use as a prognostic marker for predicting mortality in children.

**Keywords:** Outcome, Pediatrics intensive care unit, Platelet counts, Platelet course, Prognosis, Thrombocytopenia

## INTRODUCTION

Platelets are versatile cells. They participate in the inflammatory process, wound healing, angiogenesis, tissue regeneration and in endothelial barrier function.<sup>1</sup> This multi-functionality explains the frequent finding of low platelet count among critically ill children.

Thrombocytopenia is a well-known complication in children admitted to pediatric intensive care unit and receive platelet transfusions frequently.<sup>2-6</sup> Causes of thrombocytopenia among critically ill children are numerous, but usually, it develops because of decreased formation, increased utilization, destruction of platelet, abnormal sequestration or a combination of any or all of

these.<sup>7-10</sup> Prevalence of thrombocytopenia varies between 13% to 58% among different ICU settings.<sup>11</sup> Critically ill children admitted under intensive care, who have persisting thrombocytopenia are at higher risk for prolonged bleeding manifestation, prolonged duration of ICU or hospital stay, and even mortality.<sup>11</sup> Thrombocytopenia is considered as a strong and independent predictor of a poor outcome among critically ill children.

The bleeding manifestation was initially thought to be directly related to the severity of thrombocytopenia. However, a study by Greinacher A et al, observed that bleeding is not only depended on platelet count but also on other additional factors like underlying pathology, disease process, vascular status, platelet function, anticoagulant medication and other plasma factor involved in coagulation.<sup>7</sup> According to the studies done previously, single platelet count done at admission has lesser prognostic importance than a change of platelet count over time for predicting the outcome among critically ill children.<sup>11</sup>

Several studies have confirmed dynamic nature of platelet in critically ill children. Among critically ill children, platelet count decreases during the initial four days of the illness both in survivors and in no survivors and reaches a nadir on day four. This initial decline in platelet count is later followed by an increment.<sup>12,13</sup> The decline in platelet count or failure of the rise in platelet count can be used as a prognostic marker for determining outcome among critically ill children.<sup>14,15</sup> This study was conducted to evaluate prognostic importance of thrombocytopenia among critically ill children.

## METHODS

This observational study was conducted in a kasturba medical college, Manipal, Karnataka, a tertiary care center. All children aged 1 month to 18 years admitted from August 2015 to July 2017 with thrombocytopenia at admission in pediatric intensive care unit were included in the study.

A child was included in the study if at admission platelet count was less than 1.5 lakh. Detailed history including demographic data, history of bleeding manifestation, and other associated symptoms, striking examination findings and the provisional diagnosis was recorded. Hemoglobin, White blood cell count (WBC) counts, RBC (Red blood cell) indices, Platelet count, PDW (platelet distribution width), Mean platelet volume and platelet crit as given by automated blood cell analyzer (Beckmann Coulter) was noted in all cases of thrombocytopenia.<sup>16,17</sup> To avoid discrepancy with the Colter method, the platelet counts were confirmed by a peripheral smear by a pathologist. Platelet counts on the first and fourth day of admission were analyzed. Children were followed up to check for improvement or worsening in condition, need for platelet or other blood product transfusion, ventilator or inotropic

support requirement.<sup>8,18</sup> The outcomes were measured as child survival or death and length of ICU / hospital stay.

## Statistical analysis

Data was analyzed with statistical package for social sciences (SPSS) 15. Mean or median was used for continuous variables depending on the distribution of values. Associations between the outcome of critically ill children and various variables were estimated using Fisher's Exact Test and Chi-Square Tests or Mann Whitney test. A p value of <0.05 was considered to be statistically significant.

## RESULTS

### Characteristics of children with thrombocytopenia

The total number of children admitted to Pediatrics intensive care unit (PICU) during the study period was 1574. Of these 1574 children, 195 had thrombocytopenia at admission. Among these 195 children, 45 were excluded because 19 children had malignancy, 19 died within 48hrs of admission, four children had received platelet transfusion within one week before admission, two children were post-operative cases, and one child had platelet disorder. In the present study 150 children with thrombocytopenia were studied, among them 77(51.3%) were male, and 73(48.7%) were female children. Male to female ratio was 1.05:1 and the mean decimal age of the study population was 8.458±5.604 (Table 1).

**Table 1: Baseline characteristics of the study population (n=150).**

Parameters	Variable	n (%)
Decimal age	Mean±SD	8.458±5.604
Gender	Male	77 (51.3)
	Female	73 (48.7)
Type of admission	Shifted from ward to PICU	32 (21.3)
	Admitted directly to PICU	118 (78.7)
Etiology	Infective	122 (81.3)
	Non-infective	28 (18.7)
Outcome	Survivor	121 (80.7)
	Non-survivor	29 (19.3)

Among 150 children 51.3% children had severe thrombocytopenia, 23.4% had moderate and 25.3% children had mild thrombocytopenia. (Supplemental Digital content Table 1) fourth-day platelet count and indices were not available for 25 children due to missing data.

### Diagnosis of children with thrombocytopenia

In the present study, 122 children had an infectious cause, and 28 children had non-infectious cause of

thrombocytopenia. Among infectious causes for thrombocytopenia, 56 (49.5%) children had dengue fever (Table 2 and 3).

**Table 2: Diagnosis in children admitted with thrombocytopenia (infectious cause).**

Diagnosis	N	%
Dengue	56	45.9
Scrub typhus	18	14.7
Sepsis	16	13.1
LRTI	14	11.4
Meningitis/acute necrotizing encephalitis	6	4.9
Hepatitis	5	4
Infection associated haemophagocytosis	2	1.6
Leptospirosis	2	1.6
Gastroenteritis	2	1.6
Malaria	1	0.8

**Comparison between survivors and non-survivors outcome among children**

Among 150 children, 121 survived, and 29 succumbed due to the illness. The mean decimal age for survivors was  $8.476 \pm 5.615$  and among no survivors was  $8.385 (\pm 5.659)$ . Among 121 survivors 64 (52.89%) were male and 57 (47.1%) were female children (Male: Female=1.18:1).

Among 29 children who succumbed 13 (44.82%) were male and 16 (55.17%) were female children with a male to female ratio of 0.8:1. The median (IQR) platelet count observed among survivors and no survivors on the 1<sup>st</sup> day of admission were  $49000/\text{mm}^3$  (22000, 101000) and  $57000/\text{mm}^3$  (27000, 95000,) respectively. In the current study, there was no statistical difference in platelet count at admission among survivors and non-survivors ( $p > 0.05$ ).

**Table 3: Diagnosis in children admitted with thrombocytopenia (non-infectious cause).**

System	N	%
<b>Hematological (n=9)</b>		
Anemia	6	32.1
Atypical HUS	3	
<b>Seizure disorder</b>	5	17.8
<b>Liver diseases (n=5)</b>		
Wilson disease	1	17.8
Extra hepatic portal hypertension with variceal bleed	1	
Hepato renal syndrome with hepatic encephalopathy	1	
Reye syndrome	2	
<b>GIT</b>		
Duodenal ulcer with bleeding	1	3.5
<b>Others (n=8)</b>		
Diesel poison	1	28.5
Camphor consumption	1	
Snake bite	2	
SLE	4	

**Comparison of platelet count and platelet indices between survivors and no survivors on 1<sup>st</sup> and day 4<sup>th</sup> of admission**

The median platelet count observed among survivors and non-survivors on the 4th day of admission was  $130500/\text{mm}^3$  (59500, 189750,) and  $44000/\text{mm}^3$  (22000, 102000,) respectively and the difference was statistically significant ( $p=0.001$ ). Rise in platelet count among survivors, and non-survivors were 79.1% and 15.9% respectively ( $p=0.001$ ). Failure of the rise in platelet count on the 4th day of admission was significantly associated with mortality ( $p=0.001$ ) (Table 4 and 5).

**Table 4: Platelet count and platelet indices of the study population at admission (n=150).**

Laboratory parameters median (IQR)	Survivors (n=121)	Non-survivors (n=29)	p value
Platelet count at admission $/\text{mm}^3$	49000 (22000, 101000)	57000 (27000, 95000)	0.663
Mean platelet volume (fl)	9.3 (8.6, 10.1)	9.2 (8.4, 10.1)	0.782
Plateletcrit (%)	0.460 (0.021, .086)	0.600 (0.029, 0.093)	0.386
Platelet distribution width (%)	17.5 (16.7, 18.1)	17.6 (16.7, 18.1)	0.636

**Table 5: Platelet count and platelet indices on day 4 of admission (n=125).**

Laboratory parameters median (IQR)	Survivors (n=104)	Non survivors (n=21)	p value
Platelet count ( $/\text{mm}^3$ )	130500 (59500, 189750)	44000 (22000, 102000)	0.001
Mean platelet volume (fl)	9.0 (8.3, 9.9)	9.7 (8.5, 10.0)	0.245
Plateletcrit (%)	0.105 (0.172, 0.532)	0.045 (0.021, 0.098)	0.002
Platelet distribution width (%)	17.8 (17.1, 18.3)	17.3 (16.4, 18.1)	0.170

**The outcome of children with thrombocytopenia**

Of total 150 children, 121(80.7%) survived, and 29(19.3%) children succumbed. Among 29 children who died, sepsis (27.5%) was the most common cause. (Supplemental digital content Table 2). Severity of thrombocytopenia had no significance with the duration of ICU/hospital stay in the present study( $p=0.160$ ) (Table 6).

**Table 6: Comparison of outcome with severity of thrombocytopenia (n=150).**

Duration of stay	Mild to moderate (n=73)	Severe (n=77)	P value
Median duration of PICU stay (IQR)	4 (6,2)	3 (5,2)	0.160
Median duration of hospital stays (IQR)	10 (12,6.5)	8 (11.75,6.25)	

**DISCUSSION**

Thrombocytopenia is a frequently encountered hematological abnormality among critically ill children. Various studies have shown the prevalence of thrombocytopenia ranging from 22% in neonatal ICU to 23% to 41% in adult ICUs. In the present study incidence of thrombocytopenia in the children admitted in PICU was 12.38% which is lower than the study by Amarpreet K et al and Jambunathan KMD et al, where it was 32.4% and 25.3% respectively.<sup>2,19</sup> Among 150 children with thrombocytopenia studied in the present study 77 were males (51.3%) and 73 were females (48.7%). Male to female ratio was 1.05:1. The mean decimal age of the study population was  $8.458 \pm 5.604$ .

Majority of children had severe thrombocytopenia at admission (51.3%). Etiology of thrombocytopenia among children being admitted to PICU was broadly categorised into infective and noninfective causes. Among infective cause majority of children had dengue fever (45.9%). Thrombocytopenic children are at a higher risk for prolonged bleeding manifestation, prolonged duration of ICU or hospital stay, and even mortality.

Platelets play an important role in several diseases, affecting different organ and organ systems. It is an early marker of organ impairment and hence a better prognostic marker.<sup>20</sup> Platelet count analysis is now used as a prognostic marker in ICU. The advantage of using platelet as a predictor of ICU outcome is the dynamic nature of daily platelet count which takes the disease progression into account in contrast to various mortality scores which use only the worst parameter within first 24 hours after admission or at admission.<sup>11</sup> The decline in

platelet count irrespective of initial platelet count is a better prognostic marker in the critical care unit. Nearly all studies observed that thrombocytopenia to be a prognosis marker in ICU and found an inverse correlation of platelet count with risk for prolonged ICU stay and mortality. Thrombocytopenia is a known negative prognostic indicator for adverse clinical outcomes in ICU children. The decline in platelet count or failure of rising in platelet count can be used as a prognostic marker for determining outcome among critically ill children.<sup>12</sup> Both a low platelet count on the fourth day of illness and decline in platelet count predicts outcome in critically ill children.<sup>11-14</sup> According to a study by Vanderscheueren S et al, change in platelet during hospital stay carries greater prognostic significance than the absolute count in children with acute illness at admission.<sup>21</sup>

In the study done by Moreau D et al and Strauss R et al, >30% decrease in platelet count by the fourth day was an independent predictor of mortality.<sup>15,22</sup> In a study by Agrawal S et al, drop in platelet count by >27% was associated with increased mortality rate.<sup>11</sup> In a study by Patki K, Vinayaka et al, decreased count by >30% at 72 hours was independently associated with mortality.<sup>23</sup> In the present study, also there was no statistically significant difference in platelet count and platelet indices among survivors and non survivors. However, platelet count and platelet crit value were significantly different among survivor and non-survivors on day 4<sup>th</sup> of admission. In the present study rather than a decrease in platelet count on day 4 of admission, platelet count increased both in survivors and in non-survivors, but the proportionate increase was different between both groups. Rise in platelet count among survivors and non-survivors was 79.1% and 15.9% respectively.

The failure of the rise in platelet count on day 4<sup>th</sup> of admission was significantly associated with mortality ( $p=0.001$ ). Hence, serial monitoring of platelet count is a better predictor of outcome in children admitted to PICU than one-time values. Thrombocytopenia is a danger marker rather than a cause of mortality in intensive care unit, independent of severity of illness or number of dysfunction organ at the base. In a study by Agrawal S et al, the incidence of mortality was 33% and 66.6% in non-thrombocytopenic and thrombocytopenic children respectively.<sup>11</sup> In a study by Amarpreet K et al, mortality in thrombocytopenic patients was higher (29.21%) in comparison to non-thrombocytopenic children (15.05%).<sup>2</sup> The main limitations of this study were smaller sample size, and the study being done in a single setting.

**CONCLUSION**

Platelet counts and indices at the time of admission to a critical care unit have limited use as a prognostic marker for predicting mortality in children. Failure of the rise in platelet count following admission may be a better predictor of mortality warranting further research in the field using serial or daily platelet count monitoring.



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