

# ASSOCIATION OF THROMBOCYTOPENIA AND MORTALITY IN CRITICALLY ILL CHILDREN ADMITTED TO PICU IN TERTIARY HOSPITAL IN BIRATNAGAR

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## ABSTRACT

### Introduction

Thrombocytopenia is a clinical condition characterized by decrease in number of platelets below the normal range. It is associated with bleeding tendency, hemodynamic instability, impaired inflammatory process and thus affecting host defense mechanism. There has been only few studies published till date in pediatric intensive care units suggesting thrombocytopenia is associated with increased mortality.

### Objectives

To determine the prevalence of thrombocytopenia in the critically ill children and its relationship with mortality in Pediatric intensive care unit (PICU) admitted children.

### Methodology

A prospective observational study was performed over a period of 12 months on 102 critically ill children admitted in PICU who fulfilled the criteria. Two patients left the study due to financial problems and as outcome could not be assessed on them, they were excluded from the study. Platelet count was noted at the time of admission and consecutively for the initial four days at PICU. Thrombocytopenia was defined as platelet count less than 150/nL. Mortality in PICU was recorded as primary outcome.

### Results

The prevalence of thrombocytopenia during consecutive 4 days was 34% (n=34) and at the time of admission in PICU was 16% (n=16) among 100 children analysed in the study. The mortality in the PICU was 27% (n=27). Mortality among thrombocytopenic children was 61.7% (n=21) as compared to 7.6% (n=5) in non-thrombocytopenic children ( $p < 0.001$ ). Mortality was 18 times more for those who were thrombocytopenic at the time of admission as compared to those who subsequently developed thrombocytopenia during course of stay in PICU.

### Conclusion

Thrombocytopenia has significant association with increased mortality. Thrombocytopenic children at the time of admission have more likelihood of mortality than non-thrombocytopenic children in intensive care units.

## KEYWORDS

Mortality, platelets, thrombocytopenia

## INTRODUCTION

Platelets are non-nucleated cellular fragments produced by megakaryocytes within the bone marrow and other tissues. They circulate with a life span of 10-14 days. The normal platelet count is  $150-450 \times 10^9/L$ .<sup>1</sup> They play a pivotal role in normal hemostasis and thrombus formation, which can be beneficial as well as potentially harmful. In sepsis, they aggregate at sites of inflammation leading to impaired microcirculation and organ dysfunction. Beneficial effects include reducing vascular permeability, mediating inflammatory processes, promoting wound healing and host defense mechanisms. This is attributed to bioactive molecules they release on activation such as ADP (adenosinediphosphate), ATP (adenosine triphosphate),  $Ca^{2+}$ , coagulation factors, prostaglandins, thromboxane A<sub>2</sub>, histamine and serotonin.<sup>1-3</sup>

Thrombocytopenia refers to a reduction in platelet count to  $<150/nL$ .<sup>1</sup> Various causes have been identified for the occurrence of thrombocytopenia like presence of disseminated intravascular coagulation, increased destruction by immune/non-immune mechanisms, reduced production due to congenital/acquired causes, increased consumption or abnormal sequestration of platelets within an enlarged spleen or other organ or a combination of these.<sup>1,4</sup> Certain drugs also cause thrombocytopenia for example heparin, antibiotics (Linezolid, Vancomycin, betalactams, Trimethoprim/ sulphamethoxazole, Fluroquinolone, Rifampin) and anticonvulsants (Phenytoin, Diazepam, Valporic acid) which are commonly used in intensive care units.<sup>4</sup> Thrombocytopenia is associated with worse outcomes in patients with acute respiratory distress syndrome, which is most commonly caused by infection and marked by alveolar-capillary barrier disruption. However, the mechanisms by which platelets protect the lung alveolar-capillary barrier during infectious injury remain unclear.

Thrombocytopenia is common among patients admitted to the intensive care unit (ICU). Multiple pathophysiological mechanisms may contribute, including thrombin-mediated platelet activation, dilution, hemophagocytosis, extracellular histones, ADAMTS13 gene mutation and complement activation. From the clinical perspective, the development of thrombocytopenia in the ICU usually indicates serious organ system derangement and physiologic decompensation rather than a primary hematologic disorder. Thrombocytopenia is associated with bleeding, transfusion, and adverse clinical outcomes including death, though few deaths are directly attributable to bleeding. The assessment of thrombocytopenia begins by looking back to the patient's medical history and presenting illness. This past information, combined with careful observation of the platelet trajectory in the context of the patient's clinical course, offers clues to the diagnosis and prognosis.<sup>5</sup>

Thrombocytopenia reflects the severity of dysfunction in blood-clotting systems. A low platelet count is one indicator of organ dysfunction in intensive care unit (ICU) scoring

systems, such as the Sequential Organ Failure Assessment (SOFA) score. Platelet count is also used in the diagnosis of sepsis-induced coagulopathy and disseminated intravascular coagulation.<sup>6</sup> Furthermore, the clinical significance of platelet count had increased because of recent changes in the definition of sepsis, with organ dysfunction now required for diagnosis. However, the precise mechanism of thrombocytopenia and its association with disease severity and outcome in sepsis remains unclear.<sup>7</sup>

Thrombocytopenia is commonly seen in critically ill patients. In addition, some patients, such as those with uremia or vWD, may have dysfunctional platelets despite normal counts. When mild, thrombocytopenia may not increase the bleeding risk substantially, but severe thrombocytopenia is associated with both increased bleeding risk and higher mortality. As the most common coagulopathy in the ICU, the etiology of low platelet counts is often multifactorial resulting from the underlying disease state, medications, or as a result of consumption of thrombi. Although thrombocytopenia often improves with treatment of the underlying illness, an in-depth understanding of the causes of thrombocytopenia and subsequent action may raise platelet counts and prevent unnecessary deferment of invasive procedures or exposure to platelet transfusion risks in critically ill patients.<sup>5,8</sup>

Thrombocytopenia is one of the most common laboratory abnormalities in intensive care unit patients with an incidence range of 15% to 50%.<sup>5,6,8-12</sup> Thrombocytopenia can be a life-threatening condition encountered in the ICU as it has been associated with spontaneous bleeding requiring platelets and fresh frozen plasma which ultimately results in significant morbidity and mortality.<sup>7</sup> Platelet count been studied for being an independent prognostic risk factor in ICU patients and linked to increased mortality, morbidity, and length of stay, independent of severity of illness or the number of dysfunctional organs at baseline.<sup>6,7</sup> The advantage of using platelets as a predictor of ICU outcome, is the dynamic nature of daily platelet counts which takes the disease progression into account in contrast to various mortality scores which use only the worst parameters within first 24h after admission or at admission like PRISM and PIM. Serial platelet counts can be used to complement scoring systems such as pediatric risk of mortality (PRISM) score and pediatric index of mortality (PIM) score, as the information is dynamic and reflective of the evolution of the disease process. In addition, it is universally available, simple investigation and, unlike scoring systems does not involve calculations or algorithms.<sup>7</sup>

Thrombocytopenia is consistently associated with increased risks of bleeding, transfusion, and death; however, the effectiveness of platelet transfusion to stop bleeding, reduce transfusion of other blood components, or improve clinical outcomes is uncertain. The need for evidence addressing this uncertainty is especially relevant in the ICU. Past practices of liberally correcting abnormal laboratory values (eg, hemoglobin, albumin) or aggressively supporting deranged physiologic parameters that are recognized to be



associated with poor prognosis.<sup>7</sup>

A lot of studies has been carried out in adult medical intensive care unit regarding implication of platelet count and its outcome.<sup>5,6,9,12-14</sup> There are few studies in pediatric population and especially in our part of world.<sup>8,12</sup> Hence this study was conducted in our setup to establish a relationship between the platelet counts and outcome in critically ill children admitted in PICU as there is paucity of such studies in Nepal.

## METHODOLOGY

This is a hospital based prospective observational study conducted in Nobel medical college and teaching hospital, Biratnagar, Nepal conducted over a period of one year from August 2017 to July 2018. After ethical clearance from institutional review committee, data was collected from 102 consecutively admitted cases in PICU during the study period except those meeting the exclusion criteria. The sample size was calculated based on a similar research conducted in India by Agrawal S et al.<sup>10</sup> By mortality rate comparison, estimated sample size for two-sample comparison of proportions sample size was determined to be 102. Two patients left the study due to financial problems and as outcome could not be assessed were excluded from the study.

After the admission of the patient in PICU, informed consent was taken from the parents/caretakers after explaining about the study. Patient particulars and demographic information were collected according to the prepared performa. The patients who failed to give consent, left PICU against medical advice or were diagnosed cases of hematological malignancy were excluded.

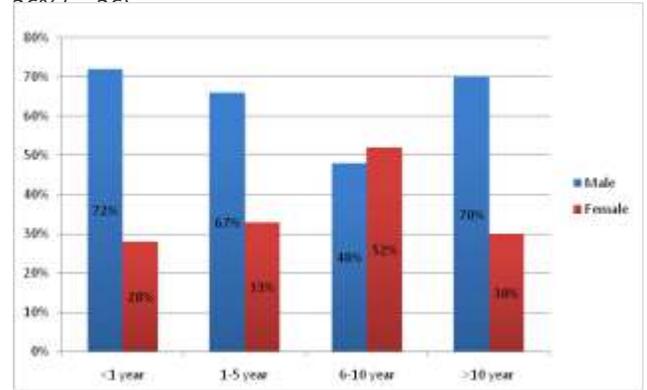
Laboratory investigations were done at the time of admission including complete blood count, renal function test, random blood sugar and other relevant investigations. Platelet count at the time of PICU admission was recorded and similarly daily platelet counts for initial 4 days were recorded. Platelet count was done by hematology automated analyzer Duri bcc-3000B Tokyo, Japan. Thrombocytopenia was defined as platelet count less than 150 n/L and graded as mild, moderate, severe and very severe if platelet count <150 n/L, <100 n/L, <50n/L and <20 n/L respectively.<sup>11</sup>

The collected data was coded and entered into Microsoft excel and transferred to statistical package for social sciences (SPSS) version 20 for analysis. Differences in proportion between the groups were analyzed with Chi-Square test. *p* value <0.05 was considered significant.

## RESULTS

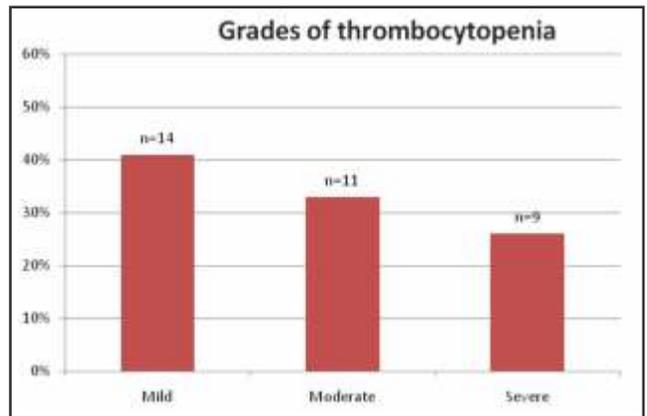
In the study a total 102 children admitted in the pediatric intensive care unit were analyzed. Among these children 80 got admitted from ER whereas 22 from pediatric ward. There was male preponderance in our study with 62%(n=62) males and 38% (n=38) females. Largest group

of patients were between 1 to 5 years accounting 30% (n=30) and smallest group of age between 6 to 10 years being 21% (n=21), while less than 1 year age group consisting of 23% (n=23) and more than 10 years of age group being 20% (n=20).



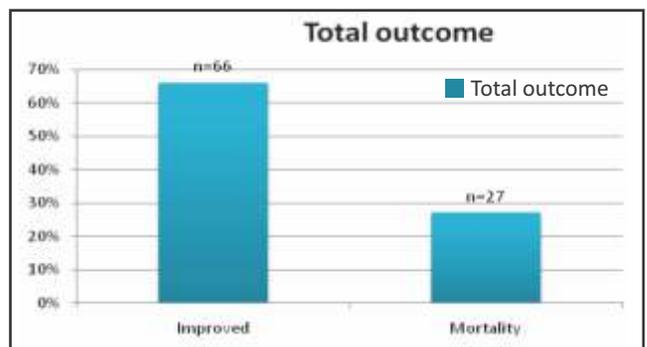
**Figure 1:** Age and sex distribution of patients admitted in PICU.

Among 102 patients admitted to our PICU, 16% of them had thrombocytopenia at the time of admission, and 34 % had thrombocytopenia including those who were thrombocytopenic at admission and those who developed thrombocytopenia by fourth day of admission.



**Figure 2:** Grades of thrombocytopenia during 4 days of admission

Among thrombocytopenic patients 41.17%(n=14) developed mild thrombocytopenia, 32.3%(n=11) moderate, 26.4%(n=9) developed severe thrombocytopenia.



**Figure 3:** Overall outcome among study group

The overall mortality in the PICU was found to be 27% (n=27).

**Table 1:** Comparisons of mortality among patient with thrombocytopenia vs. no thrombocytopenia

Outcome	Thrombocytopenia		Non-thrombocytopenia		Pvalue
	N	%	N	%	
Survivors	13	38.2	61	92.4	<0.001
Death	21	61.7	5	7.6	
Total	34	100	66	100	

There was significant mortality among patient with thrombocytopenia vs no thrombocytopenia with p value <0.001.

**Table 2:** Risk estimation among Thrombocytopenic vs Non-thrombocytopenic patients

Risk Estimate	Value	95%Confidence interval	
		Lower	Upper
Odds Ratio for Thrombocytopenia	18.092	5.747	56.960

There was 18 times more risk of mortality among thrombocytopenic patient compared to non thrombocytopenic as odd ratio was 18 at 95%CI.

Increase in mortality with increase in severity of thrombocytopenia is seen in the present study. Mortality of 18.1%, 36.3%, 45.4% [% within grade] respectively was observed in patients with mild, moderate and severe thrombocytopenia. No survivors were observed in patients with severe thrombocytopenia, P value being 0.018

severity	Mortality		Improved		p value
	N	%[with in grade]	n	%[with in grade]	
Mild	4	18.1	10	83.33	0.018
Moderate	8	36.3	2	16.66	
Severe	10	45.4	0	0	
Total	22	64.7	12	35.2	

## DISCUSSION

The present prospective observational study was conducted to determine a relationship between platelet count and outcome in critically ill children admitted in PICU Nobel Medical Teaching Hospital, Biratnagar, Nepal. In the present study 102 patients consecutively admitted to PICU were studied. Among them 62(62%) were male and 38(38%) were female(Male: Female ratio = 1.6:1). A similar study done by Agrawal S *et al* revealed male: female ratio of 1.76:1.<sup>10</sup>

In the present study,16% patients had thrombocytopenia at the time of admission which was similar to the study done by Agrawal S *et al*.<sup>10</sup> In contrast, a similar study carried out by Olmez *et al* observed only 9.3% with thrombocytopenia at the time of admission.<sup>11</sup> The difference in the prevalence may be due to the exclusion of heparin and other medications related thrombocytopenia in that retrospective study.

Mortality rate of our PICU was 27% which was less than a study done in PICU at Turkey (37.2%) by Yilmaz S *et al*.<sup>15</sup>

Similar study performed Olmez I *et al*<sup>11</sup> in PICU at Maimonides Infants and Children's Hospital, New York shows mortality rate of 8.8%. The lower mortality rate in PICU of developed countries as compared to developing countries could be because of standardized treatment guidelines and availability of sophisticated diagnostic and therapeutic tools in their institute.

Mortality was 61.7% among those who were thrombocytopenic compared to 7.5% who were not thrombocytopenic (p value < 0.001). A study done by Agrawal S *et al*<sup>10</sup> in PICU at Sir Ganga Ram Hospital, New Delhi, India revealed thrombocytopenia was associated with increased mortality compared to non-thrombocytopenia (66.6% vs 33%, p = 0.00). Similar findings were observed in various other studies.<sup>6,8</sup>

Mortality of 26%, 75%, 88% [% within grade] respectively was observed in patients with mild, moderate and severe thrombocytopenia respectively (p=0.011). Similar results were observed with increase in mortality rates by severity:12% for mild, 47% for moderate, 56% for severe, and 67% for very severe thrombocytopenia in a study done by Strauss R *et al*.<sup>6</sup>

## CONCLUSIONS

In this prospective observational study, platelet counts <150.0/nL was found to be common laboratory finding in PICU. Thrombocytopenic children had higher mortality than non-thrombocytopenic children admitted in PICU. Thrombocytopenic children at the time of admission to PICU had 18 times more likelihood of mortality in comparison to non-thrombocytopenic children.

## LIMITATIONS OF THE STUDY

Limitations of the present study are the confounding factors and treatment strategies not taken into consideration as scoring systems such as PRISM and PIM couldn't be applied due to lack of resources in our PICU which could identify the severity of illness. The present study has demonstrated an association between thrombocytopenia and worsened outcome;however, no assumption regarding causation is implied.

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## CONFLICT OF INTEREST

We declare no conflict of interests.

## FINANCIAL DISCLOSURE

None



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