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Profile of Thrombocytopenia in Pediatric ICU Patients and its Role as a Prognostic Marker in Children Aged 2 Months to 12 Years at Tertiary Care Hospital in Central India

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Abstract

Background: Platelets play an important role in normal homeostasis and thrombus formation. Thrombocytopenia is defined as platelet count less than 150×10^9/L. It is associated with bleeding tendency, hemodynamic instability, impaired inflammatory process and thus affecting host defence mechanism.Aim: To investigate prevalence of thrombocytopenia, platelet transfusions requirement, categorise thrombocytopaenia according to the severity and relationship between thrombocytopenia and mortality.**Material and Methods:**This was a retrospective study over a period of 2 years in a tertiary care hospital in central India. Two hundred and thirty three patients of age 2 month–12 years, critically ill, admitted in PICU or transferred from paediatric ward were enrolled. Those, who had thrombocytopaenia during admission or during PICU stay, were marked as 'Thrombocytopaenia' group, while the remaining patients were grouped as 'Non thrombocytopaenia' group.**Results:**The prevalence of thrombocytopaenia in PICU was 21.03%.Category wise44.90%, 28.57%, 16.33% and 10.20% of patients had mild, moderate, severe and very severe thrombocytopaenia, respectively. Mean duration of stay in PICU was more in patients with severe and very severe thrombocytopaenia, followed by moderate and mild thrombocytopaenia, which was statistically significant (P = 0.0004). The 43 patients having severe thrombocytopenia received platelet transfusion and out of these 43 patients 24 (55.81%) received more than one transfusion and 18 (41.86%) of the transfused patients expired. There is a statistically significant association between thrombocytopenia and mortality. Mortality was significantly higher in thrombocytopenic group as compared to non-thrombocytopenic patients, with P value being 0.0162.**Conclusion:**Severity of thrombocytopenia correlates with duration of stay in Hospital. Mortality rate is higher in thrombocytopenic patients.

Keywords: Thrombocytopaenia, Prevalence, Paediatric Intensive Care Unit (PICU).

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Introduction

Thrombocytopaenia results from underproduction or overconsumption of platelets. Some common causes that might affect both platelet production and consumption i.e., sepsis and malignancy. The prevalence of thrombocytopenia varies in PICUs ranging from 13% to 60%. [1-4]

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Disseminated intravascular coagulation, increased destruction, reduced production, increased consumption and abnormal sequestration are mechanism of thrombocytopaenia. Thrombocytopaenia is a common complication in patients admitted to PICUs and may require transfusions. [5-9] 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.

Some of the drugs such as beta-lactams, linezolid, vancomycin and anticonvulsants such as phenytoin and valproic acid also cause decrease in platelet counts. [10-13]Platelet count can also be used in the diagnosis of sepsis- induced coagulopathy and disseminated intravascular coagulation.[14] 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 for thrombocytopenia and its association with disease severity and outcome in sepsis still remains unclear.[15] 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 dependent 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.[16]

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.[14,15] 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 24 hour after admission or at admission like PRISM and PIM. Serial platelet counts can be used to complement scoring systems such as paediatric risk of mortality (PRISM) score and paediatric 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.[15]

Implications of platelet count and its outcome have been studied in adult medical intensive care units but there are few studies and scarce data available, as regards prevalence of thrombocytopaenia and its outcome in paediatric intensive care units (PICU), particularly in Indian setup; hence, this study was planned. Outcome of this study finding may add to the existing literature.

Material and Methods

This study was a retrospective study of over a period of 2 years (from 1 January 2018 to 31 December 2019) in a tertiary care center in Central India. The study was approved by the 'Institutional Ethics Committee' and a written informed consent from the parent/guardian of enrolled patients were obtained. A total of 233 patients were enrolled, out of which 22 expired. Parents of patients who did not give consent or who took their kids LAMA, were excluded from the study. While those patients who had deranged coagulation profile, platelet function disorder and received platelet transfusion, were also excluded from the study. Patient particulars and demographic information were collected according to the prepared proforma.

Platelet counts were performed as a part of routine investigations at the time of admission and as per treating physician but it was ensured that minimum of two investigations was done during the entire PICU stay. Any discrepancy in platelet count was counter confirmed by expert faculty. Patients with any of the platelet counts showing thrombocytopaenia during the

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duration of PICU stay were grouped into 'Thrombocytopaenic' group while the remaining patients who did not develop thrombocytopaenia during PICU stay duration were grouped into 'No thrombocytopaenic' group. Data were entered into predesigned proforma. The lowest platelet counts on admission or during PICU stay was used to grade the severity of thrombocytopaenia.

Results

Table 1: Table depicting Grading of Thrombocytopenia

S.No.	Grade of Thrombocytopenia	Platelet Count (µL)
1.	Mild	1.0 lac -1.5 lac
2.	Moderate	50 k -1.0 lac
3.	Severe	20 k -50 k
4.	Very Severe	Less than 20 k

Table 2: Table Showing Prevalence of Thrombocytopenia

Thrombocytopenia	Total number of patients	Percentage
Present	49	21.03%
Absent	184	78.97%

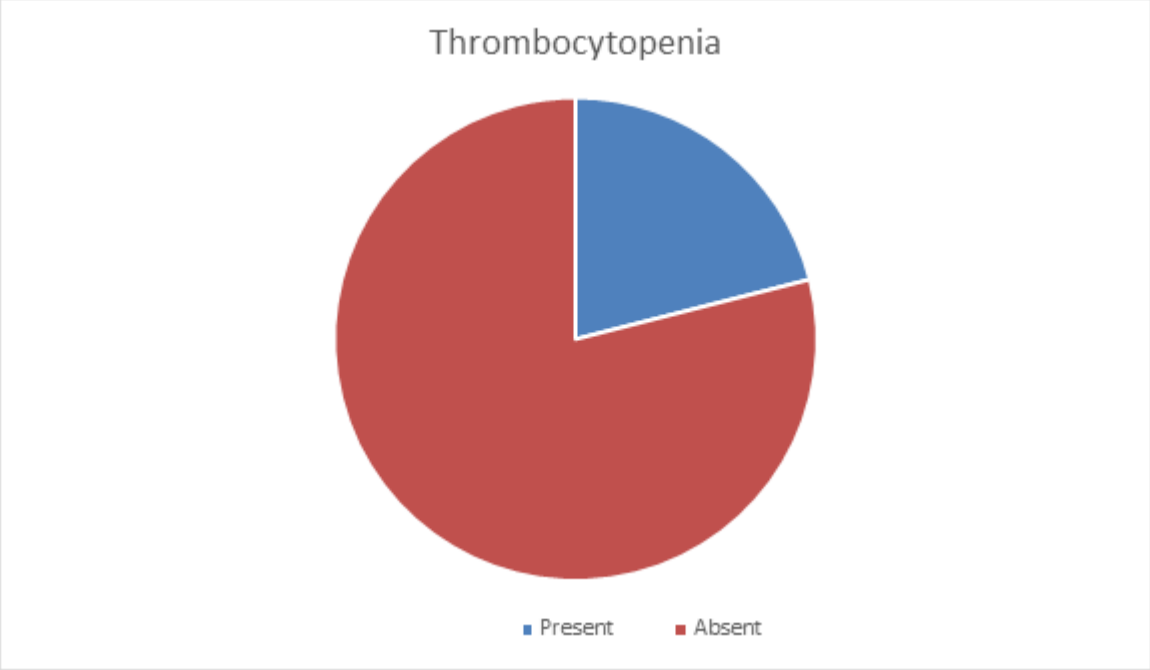

Figure 1: Prevalence of Thrombocytopenia-

Table 3: Gender wise Distribution of Thrombocytopenia

Gender	Thrombocytopenic Patients	Total	%
Male	31	151	20.53
Females	18	82	21.95
Total	49	233	21.03

P Value 0.7992

Table 4: Age Wise Distribution of Thrombocytopenia -

Age in years	Number of cases	Total	%
2 months to 1 year	4	26	15.38
1 year to 5 years	17	75	22.67

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5 to 10 years	20	87	22.99
10 to 12 years	8	45	17.78

P Value 0.7753

Table 5: Table Showing Severity of Thrombocytopenia

S.No.	Severity of Thrombocytopenia	Number of Patients	Percentage
1.	Mild	22	44.90%
2.	Moderate	14	28.57%
3.	Severe	8	16.33%
4.	Very Severe	5	10.20%

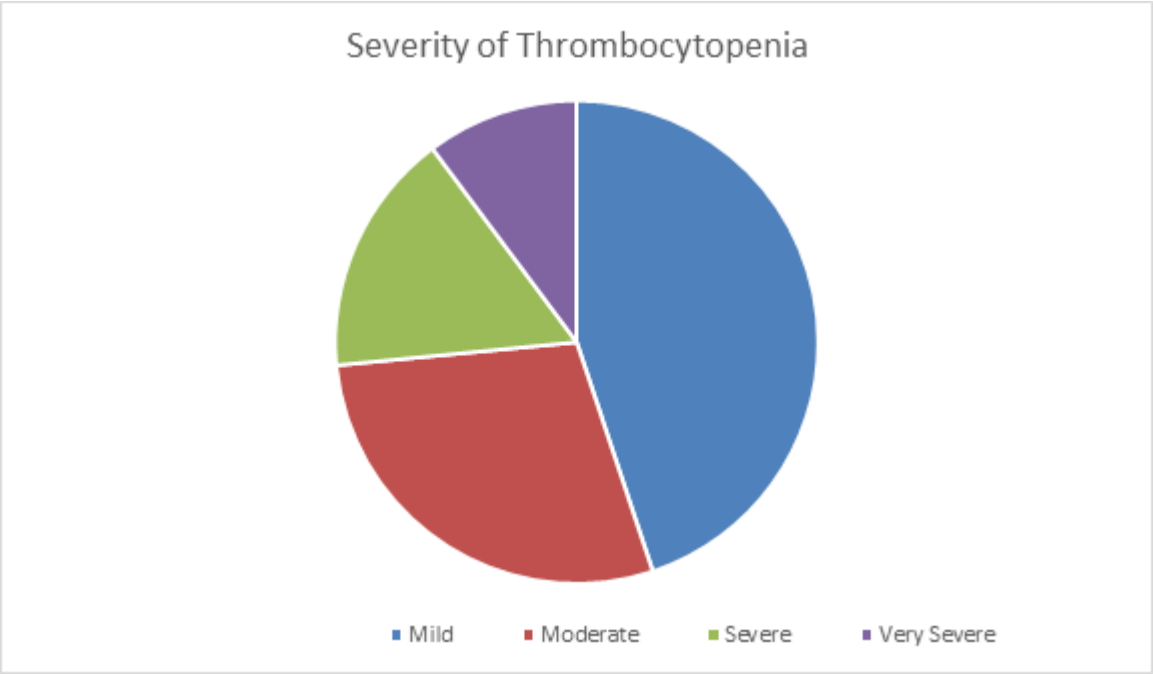

Figure 2: Figure Depicting Severity of Thrombocytopenia

Table 6: Table Describing Duration of PICU Stay as a Risk Factor of Thrombocytopenia

Duration of PICU stay	Total Number	Percentage	Thrombocytopenia			
			Present	Percentage	Absent	Percentage
<3 days	80	34.34%	11	22.45%	69	37.50%
3-7 Days	120	51.50%	24	48.98%	96	52.17%
>7 Days	33	14.16%	14	28.57%	19	10.33%
Total	233	100%	49	100.00%	184	100.00%

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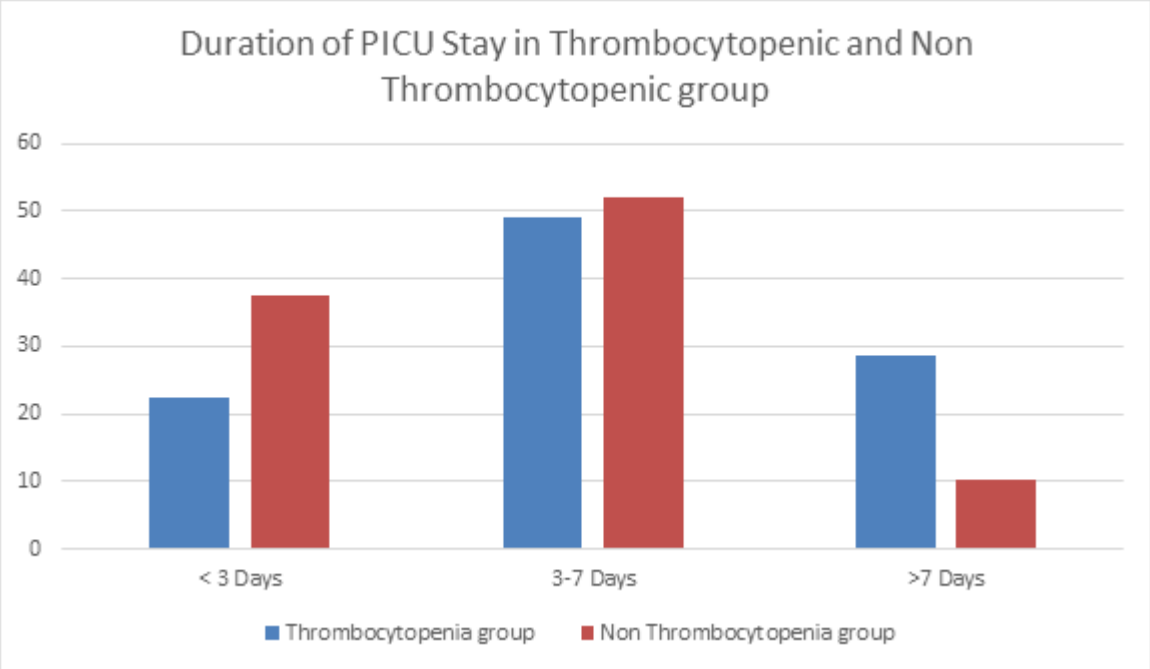

Figure 3: Figure Showing Comparison of Duration of PICU Stay in Thrombocytopenic and Non-Thrombocytopenic Patients

Table 7: Comparison of Mean Duration of PICU Stay Between Thrombocytopenic and Non-Thrombocytopenic Patients

S.no.	Thrombocytopenia	Number of Patients	Mean +- SD
1.	Present	49	6.02 +- 3.86
2.	Absent	184	4.13 +- 3.12
3.	Total	233	4.53 +- 3.37

P value is 0.0004

Table 8: Association of Mean Duration of PICU Stay and Severity of Thrombocytopenia

S.No.	Severity of Thrombocytopenia	Number of Patients	Mean Stay of Duration
1.	Mild	22	4.14 +- 2.51
2.	Moderate	14	6.07 +- 3.99
3.	Severe	8	9.75 +-3.32
4.	Very Severe	5	8.20 +- 4.66

P Value 0.0003

Table 9: Outcome of Admitted Patients

S.No.	Outcome of Patients	Number of patients	Percentage
1.	Survived	211	90.55%
2.	Expired	22	9.44%

Table 10: Association of Thrombocytopenia with Mortality

S.No.	Outcome	Thrombocytopenia		Total
		Yes	No	
1.	SurvivedNumber %	40	171	211
2.	ExpiredNumber %	9	13	22
3.	Total Number %	49	184	233

P value 0.0162

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The classification of thrombocytopaenia is as shown in Table 1 reflecting the grading of thrombocytopenia based on platelet counts. As shown in Table 2 and Figure 1, out of the 233 patients studied, 49 patients (21.03 %) had thrombocytopaenia at least on a single occasion, while the duration of PICU stay, whereas 184 patients (78.96 %) had platelet counts within the normal range. The prevalence of thrombocytopaenia was observed to be 21.03% (i.e., 49 patients out of 233). Out of 233 patients, 156 patients (51.11%) were males and 77 patients were females (48.89%) [Table 3]. Male predominance was observed with M: F ratio of 2.02:1. The majority of the patients 74 (31.75%) were in the age group of 2–12 months, followed by 6–10 years (28.75%) then 1–5 years with 49 patients (21.03%) and lastly age group 11-12 years with 43 patients (18.45%) [Table 4]. Mean age of the study population was 5.61±3.66.

As shown in Table 5 and Figure 2, 49 patients had thrombocytopaenia, out of 233 patients enrolled, 22 patients (44.90 %) had mild thrombocytopaenia, 14 patients (28.57 %) had moderate thrombocytopaenia, 8 patients (16.33%) had severe thrombocytopaenia and 5 patients (10.20 %) had very severe thrombocytopaenia. Mean duration of PICU stay was 4.53 ±3.37 days. The study population was divided into three groups, with PICU stay lesser than 3 days, 3 to 7 days and more than 7 days and majority that is, 124 patients (53.22%) had 3 to 7 days of PICU stay. 58 patients (24.89 %) had PICU stay of <3 days whereas 51 patients (21.89%) had PICU stay of more than 7 days [Table 6 and Figure 3].

As shown in Table 7, the mean duration of PICU stay for patients with thrombocytopaenia was 6.02±3.86, while it was 4.13±3.12days in patients without thrombocytopaenia. Statistically significant difference was observed on comparison of mean PICU stay between the two groups (P = 0.0004); hence, mean PICU stay was longer in thrombocytopaenic patients as compared to non-thrombocytopaenic patients.

As shown in Table 8, mean PICU stay duration was more in severe thrombocytopaenia (9.75 ±3.32 days) followed by very severe thrombocytopaenia (8.20±4.66 days). There was statistically significant difference (P = 0.0003) observed on comparison of mean PICU stay with severity of thrombocytopaenia. Hence, the mean PICU duration is more for patients with severe and very severe thrombocytopaenia as compared to patients with mild and moderate thrombocytopaenia.

[Table 9] reflects that overall mortality observed in this study was 9.44 % (22 patients out of total 233 patients studied). From the 211 patients (90.55 %) that survived during the period of this study. Gender and age were not found to be statistically significant, as risk factors for thrombocytopaenia, as p value for both was 0.7992 and 0.7753, respectively.

[Table 10] depicts that 18.37% of thrombocytopaenic patients expired, while only 7.07 % of non-thrombocytopaenic patients expired. Statistically significant difference was observed on comparison of mortality and thrombocytopaenia. Hence, mortality was more in patients with thrombocytopaenia as compared to patients without thrombocytopaenia.

Statistical analysis:

The sample size was calculated as per the average annual admissions in the PICU. The level of significance was 95%. The sample size calculated was 233 for the present study. Qualitative data were presented in the form of frequency (number) and percentage. Association between 'Thrombocytopaenia' and 'No thrombocytopaenia' with the qualitative variables was assessed by Chi-square test for 2 × 2 tables along with Yates correction and Fisher's exact test where Chi-square was not valid because of small counts. This analysis was done with the help of OpenEpi software. Quantitative data were represented by mean ± SD. For more than 2 rows and columns, R X C table for Chi-square testing was used for statistical analysis in OpenEpi software. Independent t-test and ANOVA test were applied for the

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evaluation of quantitative data wherever applicable. Odds ratio was applied for the evaluation of association between thrombocytopaenia and risk factors. Results were graphically represented where deemed necessary. Statistical analysis was done by MS Excel 2007, OpenEpi software (version 3.01) and SPSS 20 software. Graphical representation was done in MS Word 2007 and MS Excel 2007. P value < 0.05 was considered statistically significant and confidence interval was at 95% confidence limit.

Discussion

The Prevalence of thrombocytopenia ranges from 26 to 60% in various studies. In our study the prevalence was recorded as 21.03%. This is similar to the results seen in the studies conducted by Krishnan et al. [13] (25.3%) and Agrawal et al. [17] (25%). Relatively higher prevalence was observed in the studies conducted by Sah et al,[18] Kaur et al,[5]Divechaet al. [2] Yilmaz et al. [1] and Mussaet al. [19] where the prevalence was 34%, 32.36%, 60.3%, 59.57% and 44.61% respectively. The difference in the prevalence of thrombocytopaenia may be attributed to the differing inclusion criteria of different studies.

The mean age of the patients in the present study was 5.61±3.66 which is similar to the studies conducted by Mittal et al. [20] and Mussaet al. [19] The range of age groups of the study population in this study was 2 months–12 years, which is similar to that of the study by Mundkuret al. [20] who had included patients from 1 month to 18 years of age. In this study, maximum patients 22 out of total 49 thrombocytopaenic patients that is, 44.90 % had mild thrombocytopaenia followed in decreasing order by moderate thrombocytopaenia 28.57%, severe thrombocytopaenia 16.33% and very severe thrombocytopaenia 10.20%. Similar results were observed in the study conducted by Sahet al. [18] where maximum 41.7% patients had mild thrombocytopaenia followed by 32.3% of patients with moderate thrombocytopaenia and 26.4% of patients with severe thrombocytopaenia. Studies conducted by Mundkuret al. [21] and Kaur et al. [5] showed higher prevalence of severe thrombocytopaenia 51% whereas the study by Yilmaz et al. [1] showed lower prevalence 7.45% of severe thrombocytopaenia as compared to our study. Thus, there is varying prevalence of severity of thrombocytopaenia.

In this study, the mean duration of PICU stay was found to be 4.53±3.37 days. The majority of patients (53.22%) had PICU stay duration of 3 to 7 days whereas 24.89% had PICU stay duration of less than 3 days and 21.89% had more than 7 days of PICU stay. The study conducted by Mundkuret al. [21] showed that the median duration of PICU stay in mild and moderate thrombocytopaenia was 4 days and in severe thrombocytopaenia was 3 days. The median duration of PICU stay was 8 days (3–120 days) in the study by Yilmaz et al. [1] In the study by Mussa et al.,[19] PICU stay duration was divided into <7 days, 7–14 days and >14 days with 56.2%, 25.4% and 18.5% of study population, respectively. The duration of PICU stay would depend on the type of diagnosis of the patients admitted in the PICU, treatment protocols and the outcome.

In this study as well as studies by Yilmaz et al,[1]Mussa et al,[19] Agrawal et al, [17] and Krishnan et al,[13] longer duration of stay was observed in thrombocytopaenia group as compared to non-thrombocytopaenia group, which was statistically significant whereas in a study of Mittal et al,[19] this difference was insignificant. Mortality was 9.44 % in this study, which was comparable to Sahet al. [18] (26%), Mittal et al,[19] (20%) and Kaur et al,[5] (19.64%), whereas it was 37.2% and 53.07% in Yilmaz et al. [1] and Mussa et al,[19] study. The difference may be attributed to the different diagnosis of the patients and admission criteria in different studies.

In this study, 18.36 % of thrombocytopenic patients expired while only 7.06 % of non-thrombocytopenic patients expired and this was statistically significant. Similarly, statistically significant association between mortality and thrombocytopaenia was observed in

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various studies as shown in table below. Kaur et al,[5] and Mittal et al,[19] observed that mortality among thrombocytopenic and non- thrombocytopenic patients was similar to this study. Higher mortality was observed among thrombocytopenic patients in the studies by Sah et al,[18] Yilmaz et al,[1]Mussa et al,[19] and Agrawal et al,[17] while lower mortality was seen among thrombocytopenic patients in studies by Mundkur et al,[21] and Krishnan et al,[13]Sah et al,[18] observed that there were 18 times more risk of mortality among thrombocytopenic patient compared to non-thrombocytopenic patients with odds ratio 18 at 95% CI. Mortality including this study was statistically significant in thrombocytopenic group as compared to non-thrombocytopenic group in all studies.

Conclusion

Thrombocytopenic children had higher mortality than non-thrombocytopenic children admitted in PICU. Duration of Hospital stay was found to be significantly higher in thrombocytopenic group as compared to non- thrombocytopenic group, thus platelet counts are an important predictor of mortality and prognosis, and should be performed in all patients getting admitted to PICU as aroutine investigation.

Limitation of the study:

Limitations of the present study are the confounding factors and treatment strategies not taken into consideration. The present study has demonstrated an association between thrombocytopenia and worsened outcome; however, no assumption regarding causation is implied.

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