Original Article

Decline in Platelet Count as A Prognostic Marker in Critically Ill Children

Sunil Mhaske*, Bipin Rathod**, Liza Bulsara**, Sham Tarde***

Author's Affiliation:
*Professor & Head, **Resident,
***Associate Professor,
Department of Paediatrics,
PDVVPF's Medical College,
Ahmednagar, Maharashtra.

Reprint Request:
Liza Bulsara,
Resident, Department of
Paediatrics, PDVVPF's Medical
College, Vilad Ghat, Ahmednagar,
Maharashtra 414111
E-mail:
liza.bulsara@gmail.com

Abstract

Objectives: To study the variation in platelet count in critically ill children and correlate its association with their outcomes. *Methods:* This was a prospective cross-sectional analysis of 150 critically ill children admitted in PICU of our tertiary care hospital over period of 1 year. Laboratory data was collected with daily platelet counts from day of admission till death or discharge whichever was earlier in all patients. The study population was grouped as thrombocytopenic (platelet count < 150 x 10^9/L) and non-thrombocytopenic. They were compared with each other with respect to laboratory parameters and risk factors. Survivor and non survivors were compared with variation in platelet count. Decline in platelet count was correlated with mortality. Chi-square test, median test, ROC curve and forward stepwise binary logistic regression was used for statistical analysis. *Results:* Forty eight (32%) children had thrombocytopenia. They had significantly higher mortality [14(29.16%) vs 14(13.72%)] and bleeding tendency [13(28.08%) vs 4(3.92%)] than non- thrombocytopenic children. Admission thrombocytopenia was not found to be risk factor for mortality. Though survivors and non-survivors had decline in platelet count in first four days, non-survivors had significantly higher drop. Platelet counts decline >30% at 72 hours was independent risk factor (odds ratio 4.126) for mortality with high sensitivity(91.7%) and specificity (84.4%) with area under ROC curve of 0.898 which was associated with PRISMII. *Conclusion:* Decline in platelet count can be used as prognostic marker of poor outcome in critically ill children.

Keywords: Thrombocytopenia; Decline in Platelet Count; Paediatric Intensive Care Unit.

Introduction

Low platelet count is very common laboratory finding in critically ill adults , children and neonates in intensive care units. Incidence of thrombocytopenia has been reported from 13 to 58% in prior studies, depending on type of population and threshold used to define thrombocytopenia.

Thrombocytopenia was associated with increased mortality in several studies [1-6]. In addition to participation in coagulation and thrombosis, platelets play an increasingly recognized physio-pathological role in the [7-8] mediation of inflammation and infection. The dynamic nature of daily platelet counts gives prognostic information of the outcome of critically [8-9] ill patients. Platelet count is now considered to be predictor of outcome in ICU setting as independent parameter and various mortality have included it [10]. Many ICU patients do not have thrombocytopenia at admission but experience decreases in platelet count in ICU falling short of criteria for thrombo- cytopenia. The pathophysiological and prognostic significance of these decline in platelet count is unclear. After major surgical procedure or trauma platelet count decrease, then recover and overshoot the normal range with in few days [11-13]. Little is known about platelet count

decline after ICU admission for other reasons. Potential association between decline in platelet count and survival has been assessed in many adult studies. [14-17]. But these are few studies in paediatric critical care populated to [18-19] support the data. Hence we decided to study the incidence and the factors associated with thrombocytopenia in PICU setting and to study the correlation between the variation in platelet counts and subsequent outcome in critically ill children.

Material and Methods

This was a prospective, cross-sectional analysis of case records of critically ill children at an eight bedded Pediatric Intensive Care Unit of our tertiary care hospital over a period of one year from January 2014 to December 2015. Thrombocytopenia was defined as a platelet count of < 150.0/nL. Mild, moderate and severe thrombocytopenia was defined as platelet counts of <150/nL, <100/nL and <50/nl respectively. All consecutive critically ill children admitted staying for a minimum of 48 hours, were included in the study and followed up till discharge or death. The patients were followed-up prospectively. A detailed history and examination was carried out in every patient. Besides patient's demographical data, primary diagnosis, source of admission, presence or absence of sepsis, bleeding tendency, use of central venous catheter, use of inotropes and mechanical ventilation were recorded. Pediatric Risk of Mortality Score (PRISM II) at admission was used to assess severity of illness. Laboratory data collected at admission included complete blood count (CBC), blood urea nitrogen (BUN), serum creatinine, serum bilirubin, Blood Sugar Level (BSL), coagulation profile, Arterial Blood Gas (ABG) analysis. These were also repeated with the occurrence of thrombocytopenia. Daily platelet counts was done for all patients and if collection was done more than once in 24 hours, the lowest value was recorded for analysis. Low platelet counts were confirmed by direct examination of the blood smear. Variation in platelet counts was calculated at 24 hrs interval with respect to admission platelet count. Decline in platelet count was calculated by ratio of difference in platelet count to base line admission platelet level and presented as percentage drop. For the purpose of this study, thrombocytopenia was defined as platelets less than 150 X10^3/L. The study population of 150 patients was grouped as thrombocytopenic (those with platelet count <150x10^3/L) and non-thrombocytopenic (those with 3 platelet count > 150 x 10/L). They were compared with each other to determine the relationship of thrombocytopenia with particular age, sex, source of admission, ventilation, shock, bleeding tendencies, transfusion, CPR, ICU stay, PRISM score, INR, total leucocyte count, bilirubin and sepsis. Survivors and non-survivor were compared with respect to decline in platelet count. Sepsis was defined in patients with documented or assumed infection in presence of positive acute phase reactants and total leukocyte counts (TLC); (as defined by the American College of Chest Physicians and Society of Critical Care Medicine) [20].

Bleeding tendency was defined as an episode resulting in a drop in hemoglobin of >2 g/dL within 24h, episodes requiring transfusions within 24h, and any intracranial hemorrhage. Multiple bleeding events at the same site were counted only once for each patient. Shock was defined as the need for vasoactive drugs for at least one hour (>5¼g/ kg/mt dopamine/ dobutamine or any dose of epinephrine/ nor-epinephrine). No informed consent was taken, as the study was purely observational. The hospital ethics and review board's approval was taken before undertaking the study. Statistical Analysis of data was done by using SPSS 19.0 Statistics software. Normally distributed continuous variables were compared with Student's t-test and categorical variables were compared with Chi-square test or Fisher's exact test. For non- normally distributed (skewed) data median was used instead of mean and was compared using "median test". After determination of individual factors with mortality by univariate analysis, a binary logistic regression model of significant factors associated with mortality was developed. The results of regression model were presented as adjusted odds ratio with 95% confidence interval. Wald's chi square value was used to test unique contribution of each predictor. Regression model adequacy was tested by Omnibus test of model coefficients, Negelkerke R square and Hosmer and Lameshow chi square test. Receiver Operating Characteristic Curve analysis was used to find out the cut-off values for drop in platelet count from the baseline and for PRISM II score to validate predicted probabilities of death p< 0.05 was considered statistically significant.

Results

During study period of one year, out of 206 total admissions 150 critically ill children who stayed for more than 48 hours were included in study. Fifty six children were excluded because of their stay less than

48hrs.Median age of study population was 69 months (range 2-92 months) with male to female ratio 1.58. Forty eight (32%) children were thrombocytopenic and rest 102 (68%) were non-thrombocytopenic. Both groups were comparable with respect to demographic variables like age, weight, sex and severity of illness [Table 1]. Among thrombocytopenic children 43 (89.5%) had thrombocytopenia at admission while rest 5(11.5%) had developed it eventually during hospital stay. Mild, moderate, and severe thrombocytopenia was present in 18(37.5%), 12(25%), and 18(37.5%) of patients respectively. For the given effect and alpha (0.05,2 tailed) statistical power was 0.975. Source of admission, shock, use of inotropes, total leucocytes count(TLC > 15000) , blood urea nitrogen (BUN > 20 mg/dl), serum creatinene >1.2mg.dL had no correlation with thrombo cytopenia. But presence of Sepsis, use of central line, mechanical ventilation, cardio-pulmonary resuscitation (CPR), INR>1.5, Total leucocytes count(TLC < 4000) and serum bilirubin >1.5 were significantly associated with the development of thrombocytopenia[Table 1]. After regression analysis, bleeding tendencies (Odds ratio 5.076), CPR (Odds ratio 3.80), Bilirubin > 1.5(Odds ratio 2.44),Ventilation(Odds ratio 2.27) and Sepsis (Odds ratio 2.11) found to have significant correlation with thrombocytopenia [Table 3].

Bleeding tendency [13(28.08%) vs 4(3.92%)] and mortality [14(29.16%) vs 14 (13.72%)] were significantly higher in thrombocytopenic than non-thrombocytopenic children. There was no significant difference of mean length of stay in PICU (4.77±1.79 vs3.76±1.57) between two groups [Table 2]. Twenty eight (18.66%) children expired. PRISMII score (6.28±2.64 vs11.79±5.188) was significantly higher in non survivors. Use of mechanical ventilation, inotropes and presence of sepsis were significantly associated with mortality [Table 4]. Median

admission platelet count (290500 vs 256500), minimum platelet count median (199500 vs 153000), admission thrombocytopenia [34(27.86%) vs 9(32.14%)] or overall thrombocytopenia [38(31.15%) vs 10(35.71%)] was not significantly higher in non survivors [Table 4]. Platelet counts decreased significantly in the initial four days of PICU stay in both survivors and non- survivors [Table 5]. Absolute platelet counts were lowest on day 4. Though absolute platelet count between survivors and non survivors was not different significantly except on day 3, the decline of platelets was significantly higher in non-survivors till first 96 hrs [Table 6]. Change in the platelet count was monitored daily and drop in platelet count was studied by receiver operator curve analysis and was compared with that of PRISMII. The values for Area under curve (AUC) for drop of platelet at 24 hrs (0.749), at 48hrs(0.860) ,at 72hrs (0.898) and at 96 hrs (0.803) were comparable with PRISMII score (0.888) [Table 7][Fig 1]. As AUC for Drop at 72 hrs for criteria >31.7 had highest sensitivity and specificity closely matching with respective value of PRISM II score. Rounded figure of drop more than 30% at 72 hrs as an independent risk factor for mortality was studied with multivariate analysis by using forward stepwise method of binary logistic regression.Values of Omnibus model coeffient(35.23.p-0.000 at df=4) Nagelkerke R square (0.388) and Hosmer and Lemeshow test (chi-square1.92 at df-7, sig.964) indicated strong predictive value and overall fitness of the regression model. Drop of platelet >30% at 72hrs (odds ratio 4.126,wald-5.391,p-0.02) and PRISM II score (odds ratio1.422 ,wald-11.882,p- 0.001) were independently associated with increased risk of death, while use of inotropes(odds ratio 1.772,wald-0.892, p-0.345)and mechanical ventilation(odds ratio0.534 ,wald-1.091, p-0.296) were not found to be independent predictors of mortality[Table 8].

Table 1: Comparative demography in thrombocytopenic verses non-thrombocytopenic children

Parameter	thrombocytopenic (n=48)	Non- thrombocytopenic (n=102)	Pvalue
Mean Age in months		62.12±45.99	0.379
Male/female	26/22	66/36	0.141
Weight in kg	12.68±6.93	13.84±7.12	0.688
Admission source- Ward/ICU	10/38	35/67	0.093
INR>1.5	9	6	0.02
TLC >15000	7	25	0.115
TLC< 4000	8	2	0.012
BUN >20	10	11	0.132
Serum creatinine>1.2	3	7	0.888
CPR n (%	13(27.08)	4 (3.92)	0.000
Serum bilirubin >1.5	19	12	0.000
Use of inotropes n (%)	13(27.08)	34 (33.34)	0.572
Ventilation n (%)	16 (33.34)	16 (15.68)	0.019
PRISMII score(mean)	7.71±3.717	7.07±3.68	0.321
Shock n (%)	10 (20.83)	13(12.74)	0.228
Central line n (%)	12 (25)	8 ((7.83)	0.005
Sepsis n (%)	23(47.91)	15 (14.70)	0.000

CPR=cardiopulmonary resuscitation, PRISM II: Pediatric Risk of Mortality Score II

Table 2: Comparison of morbidity and mortality between thrombocytopenic verses non thrombocytopenic children

Parameter	Thrombocytopenic (n=48)	Non- thrombocytopenic (n=102)	Pvalue
Mean PICU stay in days	4.17±1.79	3.76±1.57	0.454
Mortality n (%)	14(29.16)	14 (13.72)	0.023
Bleeding Tendency n (%)	13(28.08)	4(3.92)	0.000

Table 3: Significant risk factors associated with thrombocytopenia (Regression Analysis)

Variable	Odds Ratio	95% CI
Bleeding tendencies	5.0763	1.3382 to 19.2570
CPR	3.8055	0.9533 to 15.1915
Bilirubin > 1.5	2.4413	0.8782 to 6.7865
Ventilation	2.4413	0.2405 to 21.5445
Sepsis	2.1146	0.7815 to 5.7215
INR >1.5	0.6702	0.1320 to 3.4030
Central line	0.6140	0.0921 to 4.0952
PRISM II > 8	0.3210	0.1005 to 1.0250

Table 4: Comparison between survivor and non survivors

Variables	Survivors (n=112)	Non-survivors (n=28)	P-value
Age in months(median)	48	39	0.503
Weight in kg	13.75±8.97	14.05±6.712	0.888
Sex n (% of male)	73 (59.8%)	18(64.3%)	0.792
PRISMII score	6.28±2.64	11.79±5.188	0.003
Mechanical ventilation n (%)	17(13.9%)	15(53.6%)	0.004
Inotropes use n (%)	31(25.4%)	16(57.1%)	0.008
Admission platelet count median(/L)	290500	256000	0.675
Admission thrombocytopenia (%)	34(27.86%)	9(32.14%)	0.652
Minimum platelet count median	199500	153000	0.063
Overall thrombocytopenia (%)	38(31.15%)	10(35.71%)	0.658

PRISM II: Pediatric Risk of Mortality Score II

Table 5: Comparison of platelet count between survivors and non-survivor

Day of platelet count	Median Platelet Count Survivors (n=122)	Non-Survivors (n=28)		Chi square (median test	Degree of freedom	p- value
Day-1	256500	290500	150	1.098	1	0.209
Day-2	218500	210000	150	2.810	1	0.094
Day-3	198000	142500	128	8.960	1	0.003
Day-5	221000	163000	48	1.395	1	0.238

Table 6: Comparison of drop in Platelet count between survivors and non-survivors

Time	Drop in Platelet Count %(median)			Chi square (median test)	Degree of freedom	p- value
	Survivors (n=122)	Non-Survivors (n=28	N			
24 hrs	7.04	25.88	150	12.69	1	0.000
48 hr	3.97	43.8	128	24.18	1	0.000
72 hrs	2.6	49.55	76	8.016	1	0.009
96hrs	0.23	45.68	48	7.111	1	0.006

Table 7: ROC curve analysis of factors associated with mortality

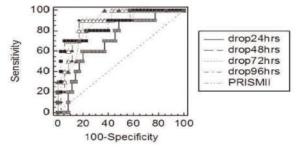| Variable	AUC	SE	P value	95%CI	sensitivity	specificity	criterion
%Drop of platelets 24hrs	0.749	0.0512	0.0001	0.672to 0.816	64.3%	77.9%	>21.23
%Drop of platelets 48hrs	0.860	0.0447	0.0001	0.788 to 0.915	85.7%	85%	> 27.4
%Drop of platelets 72hrs	0.898	0.0475	0.0001	0.805 to 0.956	91.7%	84.4%	> 31.17
%Drop of platelets 96hrs	0.803	0.0475	0.0001	0.805 to 0.956	58.3%	91.7%	> 46.62
PRISM2 score	0.888	0.0279	0.0001	0.826 to0.933	92.9%	95.4%	>7

Null hypothesis area=0.5, criterion based on predicted probability, AUC: Area under curve; SE: Standard error;
PRISM II: Pediatric Risk of Mortality Score II; CI: Confidence interval; ROC: Receiver operating characteristic

Table 8: Multivariate analysis of factors associated with mortality by logistic regression

Variable	Wald	DF	P value	Odds ratio
PRISM II score	11.882	1	0.001	1.422
>30% drop at 72 hours	5.391	1	0.020	4.126
Inotropes use	0.892	1	0.345	1.772
Mechanical ventilation	1.091	1	0.296	0.534

PRISM II: Pediatric Risk of Mortality Score II; df: Degree of freedom

Fig. 1:

Discussion

The relationship between drop in platelets counts during PICU stay and mortality in critically ill children was analyzed in this study. In a large group of medical and surgical ICU patients the prognostic importance of platelet counts extends well beyond initial changes. A total of 48 children (32%) had at least one platelet count <150 × 109/L, this incidence of thrombocytopenia is comparable to Vanderschueren S et al, Strauss et al, Agrawal et al and Mussa et al studies [2,15,18,19]. Large difference in study population, different inclusion criteria and definitions used in various studies reflects great variation in incidence of thrombocytopenia ranging [1,6] from 13-58%. Sepsis was found to have association with thrombocytopenia. Platelets play a complex role in sepsis, they are able to modulate not only their own function but also cells around them. [9] cardio- pulmonary resuscitation has been quoted as risk factor for development of thrombocytopenia by Strauss et al. [15]. We found similar association. Though association of shock with thrombo- cytopenia is well established in Vanderschueren S et [2] al, we were not able to demonstrate it. Our finding was consistent with Agrawal et al. [18]. Similarly low total leucocyte count (TLC <4000) and disturbed biochemical markers in the form of elevated serum bilirubin>1.5mg/dl and INR >1.5 were also predictive of thrombocytopenia [18,19]. Mechanical ventilation and central line insertion were described [12,15] as independent risk factor for thrombocytopenia although this may only reflect disease severity and local ICU preference. INR>1.5

was another factor associated with thrombocytopenia, which was comparable to the significant association of DIC in the evolution of thrombocytopenia found by Strauss [15] et al . This finding was consistent with Agrawal et al [18] but contrast to Mussa et al [19] Thrombocytopenic children had significantly higher mortality found in our study was consistent with prior studies [2,3,15,18,19]. In consistent with [18] Agrawal et al admission thrombocytopenia was not associated with risk of death in our study, signifying that predictive value of low platelet count does take disease progression in account. Bleeding tendency was found to be a significant predictor of morbidity associated with thrombocytopenia in our study. Bleeding can be both a risk factor and cause for thrombocytopenia and this was not elaborated sufficiently in the present study, though most of the patients had bleeding secondary to thrombo- cytopenia rather than vice-versa so per se thrombocytopenia is not a significant factor for high morbidity or mortality. Agrawal et al [18] found similar results.Similar to findings by Mussa et al [19] we also could not find prolonged PICU stay in thrombocytopenic children. Absolute platelet count at admission was lower in non survivors than survivor and remained lower throughout PICU stay in Mussa et al study [19] In our study admission platelet count and counts during PICU stay were not significantly different between two group except on day three, which can be explained by significantly higher drop of platelets on day 3. Very few studies evaluated link between declining platelet count and outcome in ICUs. We found that platelet counts decreased significantly in the initial four days of PICU stay in both survivors and non-survivors. Absolute platelet counts were lowest on day 4. In their adult studies [14] [16] Moreau et al and Akca S demonstrated decline in platelet count from day one reaching lowest on day four, but differed significantly between survivors and non- survivors only on day 7. Similar [18] finding was observed by Agrawal et al. We were not able to study the rise in platelet count at stabilization of platelets after day 5 as majority [24(85.7%)] of death occurred within this period [18]. Agrawal et al found drop of platelets >27% with [14] increased mortality risk. Moreau et al and Strauss[15] et al have found >30% decline in platelet count as

independent predictor of death with odds ratio 1.54 and 3.73 respectively. With similar decline of >30% in platelets we found odds ratio of 4.126 which was quite comparable with Moreau et al [14] and Strauss et [15] al.

Limitations of Study

The study is not powered to actually work out the cause and effect and can only suggest an association between various factors. Besides small size, various confounding factors are present in sick children at any given point of time, which cannot be controlled. We did not study the mechanisms that lead to decreased platelet count. Many pre-existing condition or drugs may influence platelet count, which were not studied in present cohort. Results needs to be validated in larger study population as limited number of patients in certain groups doesn't allow more precise estimation of odds ratio.

Conclusions and Recommendation

Thrombocytopenia is common in pediatric intensive care unit as in adult ICUs. Thrombocytopenic children have higher incidence of bleeding and higher mortality. Sepsis, mechanical ventilation and cardiopulmonary resuscitation increase probability of thrombocytopenia. Serial measurements of platelet counts are better predictors of disease progression than one-time values. Decline in platelet count irrespective of thrombocytopenia can be used as prognostic marker of poor outcome in critically ill children. Similar studies are required with larger number of patients in the critically ill pediatric population to further consolidate the present study's findings.

References

1. Baughman RP, Lower EE, H C Flessa HC and Tollerud DJ. Thrombocytopenia in the intensive care unit. Chest. 1993; 104: 1243-1247.

2. Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med. 2000; 28: 1871–1876.

3. Crowther MA, Cook DJ, Meade MO, Griffith LE, Guyatt GH, Arnold DM, et al. Thrombocytopenia in a medical-surgical critically ill patients:prevalence, incidence and risk factors. J Crit Care. 2005; 20: 348-53.

4. Guida JD, Kunig AM, Leef KH, McKenzie SE, Paul DA. Platelet counts and sepsis in very low birth weight neonates: Is there an organism specific response? Pediatr. 2003; 111: 1411-5.

5. Christensen RD, Henry E, Wiedmeier SE, Stoddard RA, Sola Visner MC, Lambert DK, et al. Thrombocytopenia among exteremely low birth weight neonates: Data from a multihospital healthcare system. J Perinatol. 2006; 26: 348-53.

6. Roberts I, Murray NA. Neonatal thrombo- cytopenia: Causes and management. Arch Dis Child Fetal Neonatal Ed. 2003; 88: 359-64.

7. Levi M. Platelets. Crit Care Med 2005; 33: 523–525.

8. Levi M, Opal SM. Coagulation abnormalities in critically ill patients. Crit Care. 2006; 10: 222–228.

9. Vincent JL, Yagushi A, Pradier O. Platelet function in Sepsis. Crit Care Med. 2002; 30: 5313-7.

10. Pollack MM, Patel KM, Ruttiman UE. PRISM III: An updated pediatric risk of mortality score. Crit Care Med. 1996; 24: 743-52.

11. Stephan F, Hollande J, Richard O, Cheffi A, Maier-Redelsperger M, Flahault A. Thrombocytopenia in a surgical ICU. Chest. 1999; 115: 1363– 1370.

12. Aissaoui Y, Benkabbou A, Alilou M, Moussaoui R, El Hijri A, Abouqal R, et al. Thrombocytopenia in surgical intensive care unit, incidence, risk factors and effects on outcome. Press Med 2007; 36: 43-9.

13. Hanes SD, Quarles DA, Boucher BA. Incidence and risk factors of thrombocytopenia in critically ill trauma patients. Ann Pharmacother. 1997; 31: 285–289.

14. Moreau D, Tinsit JF, Vesin A, Garrouste-Oryeas M, de Lassence A, Zahar JR, et al. Platelet count decline: An early prognostic marker in critically ill patients with prolonged intensive care unit stays. Chest 2007; 313: 735-41.

15. Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med. 2002; 30: 1765–1771.

16. Akca S, Haji Michael P, de Medonca A, Suter PM, Levi M, Vincent JL. The time course of platelet counts in critically ill patients. Crit Care Med. 2002; 30: 753–756.

17. Nijsten MW, ten Duis HJ, Zijlstra JG, Porte RJ, Zwaveling JH, Paling JC, et al. Blunted rise in platelet count in critically ill patients is associated with worse outcome. Crit Care Med. 2000; 28: 3843-6.

18. Agrawal S, Sachdev A, Gupta D, et al. Platelet counts and outcome in the pediatric intensive care unit. J Crit Care. 2008; 12: 102-108.

19. Russul F. Mussa, Adeba A. Al- Al-Alyasiri and Jasim M. Al-Marzoki. Prognostic Value of Platelet Count in Paediatric Intensive Care Unit. Medical Journal of Babylon. 2012; 9: 833-42.

20. Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus   conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005; 6: 2-8.