

Thrombocytopenia upon Admission in Pediatric Septic Patients is Associated with a Higher Vasopressors Requirement

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Abstract

Background: Thrombocytopenia has been identified as a reliable predictor of increased morbidity and mortality in critically ill patients admitted to the pediatric intensive care unit (PICU). In this study, we assessed the clinical outcomes of patients admitted to the PICU with sepsis and concomitant thrombocytopenia.

Methods: A retrospective chart review was performed focusing on patients admitted to the PICU at a tertiary care institution with a documented diagnosis of sepsis, severe sepsis or septic shock between January 1st, 2011 and June 30th, 2015. Patients were divided into two groups: those with a normal platelet count on admission (platelet count $\geq 150,000/\mu\text{L}$) and those with thrombocytopenia ($<150,000/\mu\text{L}$).

Results: 138 charts were reviewed and a total of 71 sepsis admissions were analyzed. Of these, 28 (39.5%) had thrombocytopenia. We determined that patients with thrombocytopenia had a higher need for vasopressors as compared to those with normal platelet counts. (22.5% vs 15.5% respectively; $p<0.01$) This association was especially significant in patients with gram-negative sepsis. The overall mortality in our study population was 6.9% (n=5). The mortality for septic patients with thrombocytopenia was 10.7% (n=3) versus 4.7% (n=2) for septic patients with a normal platelet counts. This difference was not statistically significant.

Conclusions: Thrombocytopenia on admission in septic pediatric patients is associated with a higher vasopressor requirement. This association is even stronger in patients with gram-negative sepsis and concomitant thrombocytopenia.

Keywords: Thrombocytopenia; Sepsis; Children; Critical care; Pediatrics; Vasopressors

Abbreviations: PICU: Pediatric Intensive Care Unit; PRISM III: Pediatric Risk of Mortality-III; DIC: Disseminated intravascular coagulation; LOS: Length of stay

Background

Thrombocytopenia has been identified as a reliable predictor of mortality in critically ill patients admitted to intensive care units [1,2]. Several studies, performed in both adult and pediatric populations, reported that a drop-in platelet count of 30% or more is an independent predictor of mortality. It has also been demonstrated that the rate of progression of thrombocytopenia correlates with a worsening outcome, regardless of the patients' primary diagnosis. Furthermore, thrombocytopenia is a key component of the Pediatric Risk of Mortality -III (PRISM III) score, the only validated predictor of outcome in the Pediatric Intensive Care Unit (PICU) [3-12].

Sepsis is one of the most common diagnoses requiring PICU admission and is associated with severe morbidity and mortality. Platelets play a crucial role in both hemostasis and inflammation. Their role in the pathogenesis of sepsis is well

documented as they influence both innate and adaptive immune responses. Platelets catalyze the development of hyper-inflammation, disseminated intravascular coagulation (DIC) and micro-thrombosis, which subsequently leads to multiple organ failure.

As an acute-phase reactant, a physiologic elevation of platelet count has been described in patients with sepsis; paradoxically, severe infections can also induce thrombocytopenia. This paradox is often described during the course of sepsis when associated with DIC and is often associated with a fatal outcome. Septic patients with DIC have a described 28-day mortality rate of 45% as compared to 25% mortality in septic patients without DIC [13,14]. It is unclear if the effect on mortality associated with sepsis and thrombocytopenia, is related to the impact of thrombocytopenia on intravascular thrombosis and hemorrhage or to the impairment of the host immune response. A recent study, using a mouse sepsis model, showed that animals with gram-negative pneumonia-derived sepsis caused by *Klebsiella pneumoniae* presenting with thrombocytopenia had a higher mortality rate as compared to the animals with normal platelet counts [15].

The clinical significance of thrombocytopenia at the time of PICU admission of septic children has not yet been clearly established. In this study, we assess the clinical outcome of patients admitted to the PICU with sepsis and concomitant thrombocytopenia. Our hypothesis is that septic patients with thrombocytopenia on admission have an increased need for cardiovascular support. We also examined any potential association between thrombocytopenia and specific microorganisms.

Methods

We conducted a retrospective chart review from January 1st, 2011 to June 30th, 2015. Our study was reviewed and approved by the University of Miami Institutional Review Board (IRB). We included in our cohort all patients between birth and age 21 years, with a documented diagnosis of sepsis, severe sepsis or septic shock in the medical records. These patients were admitted to the PICU at Holtz Children's Hospital-Jackson Memorial Medical Center, a tertiary care teaching hospital. For the purposes of analysis, the diagnosis needed to fulfill the criteria defined by the 2012 Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock. Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion, and septic shock is defined as sepsis-induced hypotension, persisting, despite adequate fluid resuscitation. Patients less than 100 days-post bone marrow transplant were excluded from the study [16].

Eligible patients were divided into two groups: those who, on admission to the PICU, had a normal platelet count (platelet count $\geq 150,000/\mu\text{L}$) and those with thrombocytopenia (platelet count $<150,000/\mu\text{L}$). Pertinent data including

demographic information such as age and gender, baseline diagnosis and/or diagnosis prior to PICU admission were collected. Other analyzed data included PICU admission diagnosis, complete blood count including platelet count, the PRISM – III score, and the organism isolated on admission blood cultures.

The primary outcome analyzed was the need for vasopressor support (dopamine, norepinephrine, epinephrine, dobutamine, vasopressin) and the number of days these vasopressors were administered. The secondary measured outcomes were the length of stay (LOS) in the PICU, defined from date of admission to the PICU, until the date of discharge from PICU or death, and mortality during PICU admission.

Continuous variables are expressed as mean and standard deviations (SD); categorical variables are expressed as absolute values. T-test was used to compare and evaluate association for continuous variables and Chi-square was used to compare and to evaluate for associations of categorical variables. The statistical analysis was done using IBM SPSS statistics, version 22.0, the significant p-value was set to less than or equal to 0.05.

Results

We reviewed 138 charts of patients admitted to our PICU with a diagnosis of sepsis and/or bacteremia. Of those, 38 patients met the inclusion criteria, but 12 accounted for multiple admissions. For analysis purposes, we considered each new admission as a separate event. A total of 71 admissions were then analyzed.

Of those 71 events, 43 (60.5%) had normal platelet counts and 28 (39.5%) had thrombocytopenia. Of the patients with thrombocytopenia, 8 (11.3%) had severe thrombocytopenia, with platelet counts less than $50,000/\mu\text{L}$; 12 (16.9%) had moderate thrombocytopenia with platelet counts between $50,000$ to $99,000/\mu\text{L}$ and 8 patients (11.3%) had mild thrombocytopenia with platelet counts ranging between $100,000$ to $149,000$ units/ μL .

When analyzing associated underlying comorbidities within the thrombocytopenic group, the most common associated diagnoses were gastrointestinal pathologies including, but not limited to, liver failure, biliary atresia and short gut syndrome. These accounted for 41 (57.7%) of the admissions, while 20 (28.3%) had a history of visceral transplant (intestinal, liver, kidney). The third most common comorbidity was oncologic pathologies encountered in 4 (5.6%) of the events. Six admissions (8.5%) did not have an identified significant underlying pathology.

Table 1 describes the basic characteristics of both groups including age, PRISM scores, hemoglobin and white blood cell counts. There was no statistically significant difference between the ages of the patients in months, p 0.56. The PRISM-III score was found to be higher on admission in the thrombocytopenia group (11.3 ± 5) as compared to those with a normal platelet count (6.7 ± 6); $p < 0.01$. Since PRISM-III score includes thrombocytopenia as one of the variables, we

reanalyzed these results after excluding the platelet count as one of the predetermined variables (2 points for platelets between 100,000 to 200,000/ μ L, 4 points for platelets between 50,000 to 99,000/ μ L and 5 points for platelets <50,000/ μ L). The difference in the modified PRISM-III score between the septic patients with and without thrombocytopenia showed no statistical significance. The modified PRISM score in the thrombocytopenia group was 7.5

\pm 4.5 versus 6.3 ± 6 , in the normal platelet count group, p 0.37. We analyzed the presence of anemia, defined as a hemoglobin less than 11 g/dl and leukocytosis, defined as a white blood cell count (WBC) higher than 12,000/ μ L, and the association with normal platelet count or thrombocytopenia, and found no statistically significant association, $p=0.93$, and, $p=0.43$ respectively.

Table 1 Patient’s characteristics and clinical correlates.

Demographics and admission variables	Normal plateletcount	Thrombocytopenia	P-value
Admissions (n=71)	43	28 Mild 8 (11.3%) Moderate 12 (16.9%) Severe 8 (11.3%)	
Age (months)	53 \pm 58	61 \pm 53	0.56
Prism-iii score	6 \pm 5	11 \pm 5	<0.01
Modified prism-iii*	6 \pm 6	7.5 \pm 4	0.37
Hemoglobin<11 g/dl	35 (49%)	23 (32%)	0.93
WBC >12,000/ μ l	15 (21%)	7 (33%)	0.43
Mild thrombocytopenia=platelet count between 100,000 to 150,000 units/ μ l. Moderate thrombocytopenia=platelet count between 50,000 to 99,000 units/ μ l. Severe thrombocytopenia=platelet count<50,000 units/ μ l. Wbc=white blood cell count *without platelets			

A total of 27 (38%) events required vasopressor support. We were able to determine that patients with thrombocytopenia had a higher need for vasopressors 22. 5% (n=16) than those with normal platelet counts 15.5% (n=11); Odds ratio 3.88 CI 1.4 – 10.7, $p=0.01$. The number of days requiring this support was not statistically significant (patients with normal platelet counts required vasopressors for 4.4 ± 2.2 days versus 3.6 ± 2.5 days for patients with low platelet count ($p=0.39$). There was no statistically significant difference found with regards to length of PICU stay when comparing the two groups. Those patients with normal platelet counts on admission stayed 14.5 ± 17.9 days versus 14.2 ± 17 days for patients with thrombocytopenia, ($p=0.95$). The overall mortality rate for our

study population was 6.9% (n=5). Of the septic patients with thrombocytopenia on admission 10.7% (n=3) died vs. 4.7 % (n=2) of the septic patients with a normal platelet count. One of those patients accounted for multiple admissions to the PICU. The PRISM scores for the patients that died was higher than 11. There was no statistically significant association between death and thrombocytopenia ($p=0.33$). All patients that died required vasopressors as part of their management. The length of PICU stay for the patients that died ranged from 4 to 42 days. Of the three patients in the thrombocytopenic group that died, one had mild thrombocytopenia, one had moderate thrombocytopenia and the third, had severe thrombocytopenia. These results are detailed in **Table 2**.

Table 2 Outcomes measured.

Clinical Outcomes	Normal platelet count	Thrombocytopenia	P-value
Admissions on pressors (n=27)	11	16	0.01 OR 3.88 CI (1.4 – 10.7)
Days on pressors, mean (n=27)	4.4 \pm 2.2	3.6 \pm 2.5	0.39
Los mean (days)	14.5 \pm 17.9	14.2 \pm 17	0.95
Mortality	2	3	0.33
Admissions with gram negative bacteremia requiring pressors (n=12)	1	11	0.04
Mortality during picu admission. Los length of stay; or odds ratio; ci confidence interval			

We identified 55 (77%) admissions with a positive blood culture. Of those, 28 (51%) grew a Gram-negative organism. The remainder of the positive blood cultures were divided between Gram-positive organisms 14 (26%), mixed Gram-negative and Gram-positive 4 (7%) and fungal organisms 9

(16%). Of the 28 admissions with Gram-negative bacteria, 17 had thrombocytopenia on admission and 11 had a normal platelet count which is statistically significant, $p < 0.02$ as shown in **Table 3**.

Table 3 Positive blood cultures (n=55) results in association with platelet count.

Blood culture results (n=55)	Normal platelet count	Thrombocytopenia	P-value
Gram-positive bacteria (n=14)	11 (20%)	3 (6%)	0.12
Gram-negative bacteria (n=28)	11 (20%)	17 (31%)	<0.02
Mixed organisms* (n=4)	2 (3.5%)	2 (3.5%)	0.65
Fungal organisms (n=9)	6 (11%)	3 (%)	0.68

*mixed organisms: gram positive and gram-negative blood positive cultures.

Of the 28 encounters with gram-negative bacteremia, 12 required vasopressor supports; interestingly there was a higher association between gram-negative sepsis with thrombocytopenia and vasopressor need upon admission to the PICU 11 (91.6%) vs 1 (8.4%) as compared to patients with gram-negative sepsis and no need for vasopressor support ($p=0.04$). There was no statistical difference in mortality rate when analyzed by type of microorganism. Two of the 5 patients that died had gram-negative bacteremia, 2 had gram-positive bacteremia and one patient had no isolated organisms.

Discussion

Thrombocytopenia has been associated with higher morbidity and mortality rates in patients admitted to intensive care units regardless of diagnosis. However, the role of platelets during sepsis in pediatric patients is not yet fully understood. Our study provides evidence that thrombocytopenia is associated with an increased need for vasopressor support in septic children admitted to the PICU and confirms the higher association of thrombocytopenia with gram negative sepsis.

Despite only 38% of our analyzed admissions requiring vasopressors, our results found a statistically significant association between thrombocytopenia on admission and the need for vasopressors. More importantly, there was a stronger correlation with vasopressor requirement when the subgroup of patients with gram-negative bacteremia and concomitant thrombocytopenia was analyzed. These results confirm the findings described in two previous reports, one in adults and the other in children. In his study, Sharma et al. reported that adults with septic shock and thrombocytopenia (n=38) required a higher dose of norepinephrine [17]. The study done by Krishnan et al. that included all patients admitted to the pediatric critical care unit with thrombocytopenia but not necessarily with sepsis, revealed that 71% of patients with thrombocytopenia required vasoactive medications [3]. Because of the small number of admissions analyzed, it is difficult to determine if the need for vasopressors is in fact

independently associated with thrombocytopenia. The clinical relevance of our findings is that we describe a higher need for intensive hemodynamic support in patients with sepsis and thrombocytopenia.

The association between gram-negative bacteremia and thrombocytopenia has been reported in prior studies that reached conflicting conclusions. In a study by Thierry-Antier et al., there was no correlation between gram-negative bacteremia and thrombocytopenia [18]. On the other hand, Arif et al. reported that gram-negative bacterial sepsis was more frequently associated with severe thrombocytopenia, though this study was limited by a small number of patients with positive cultures [8]. Manzoni et al. published a larger study trying to define an association between specific organisms and thrombocytopenia in neonatal sepsis but were unable to find a statistically significant association with any particular organism. Manzoni's study was also limited by a small sample population [6]. Recent studies in animal models analyzing the role of platelets in sepsis concluded that the clinical course is worse in those animals with concomitant thrombocytopenia and gram-negative sepsis [15]. Based on our results, we can conclude that patients presenting with sepsis and thrombocytopenia on admission will require a higher level of care (i.e., vasopressors) and the results support the use of timely initiation of broad-spectrum empiric antibiotics [16].

Length of stay is a common clinical parameter used to determine severity of illness in the critical care setting. We did not find an association between thrombocytopenia and PICU LOS. In 2008, Krishnan et al. published a study assessing the clinical implications of thrombocytopenia in the pediatric critical care unit; of the 294 patients analyzed, the investigators found a significant association between thrombocytopenia and a higher mortality rate as well as a longer length of stay. Nevertheless, it is important to mention that this study did not exclusively focus on patients with sepsis [3]. Interestingly, a recently-published large study by Claushuis et al., examining the clinical outcomes and molecular biomarkers involved in septic adult patients admitted to the ICU concluded that there was no association between LOS and

presence of thrombocytopenia. They found that thrombocytopenia was independently associated with a more disturbed host immune response, validating the important role of platelets in sepsis as has been previously shown in animal models [19]. These results conflict with a paper by Thiery-Antier, who studied the implications of platelet count in ICU patients with sepsis using a larger cohort (n=1468). Thiery-Antier et al. found a statistically significant correlation between LOS and degrees of thrombocytopenia [18]. These two adult studies are the largest descriptive studies focusing on sepsis and thrombocytopenia. Both studies confirmed the association between thrombocytopenia and worse clinical outcome as measured by mortality but presented conflicting data regarding the association with LOS. Our results may be due in part to the retrospective nature of our study and the lack of standardized pre-existing discharge criteria.

Our study found no statistically significant association between sepsis with thrombocytopenia and mortality. This lack of statistical significance with respect to mortality is likely due to the small number of analyzed admissions. A larger study would be necessary to determine the association of mortality and thrombocytopenia in septic patients. Our overall mortality for this population of patients is lower than those reported in other cohorts that examined mortality in sepsis. Our study excluded patients who were less than 100 days post bone marrow transplantation because of the inability to determine if thrombocytopenia could be accurately attributed to sepsis rather than delayed engraftment. Inclusion of these patients in other published series, resulted in a higher mortality rate.

Some studies have demonstrated that maintaining an elevated or near normal platelet count by transfusions and/or the use of thrombopoietin may result in better clinical outcomes. Unfortunately, these studies are small, and larger randomized control trials are needed [20,21]. The platelet count threshold supporting platelet transfusions in septic pediatric patients has not yet been fully determined. There is a recent descriptive study suggesting that patients transfused with platelets experience multiple organ failure and higher mortality [22]. Other studies have reported that there exists molecular and laboratory evidence supporting the pro-inflammatory role of platelets in specific organs, leading to worse end-organ damage and multiple organ failure states. For this reason, some researchers hypothesize that the use of platelet inhibitors, specifically in sepsis, may be beneficial; the proposed mechanism being the blocking of platelet receptors associated with the inflammatory process during a septic event [12,19,23]. Further studies are needed to better characterize this mechanism.

Platelet count is an important component of the comprehensive physiologically - validated PRISM III score [1]. In our review, thrombocytopenia was associated with a higher PRISM-III score as expected. When we tried recalculating the PRISM-III score without the platelet count, we did not find a statistically significant difference between patients with normal platelet counts versus those with thrombocytopenia. In our cohort of septic patients with thrombocytopenia, our

modified version of PRISM had a mean of 3.8 points less than the standard PRISM-III. This finding confirms the importance of platelets as a marker of severity of illness in critically ill pediatric patients.

We analyzed the association of anemia or leukocytosis and thrombocytopenia in septic patients, without finding a statistically significant result. Thrombocytopenia in the setting of anemia could be explained by bone marrow suppression. The fact that there was no significant association makes bone marrow suppression a less likely cause of thrombocytopenia. Leukocytosis is a common marker for bacterial infection, yet our patients with sepsis and thrombocytopenia did not present with leukocytosis. Interestingly, Kitazawa et al. examined the impact of changes in platelet volume during sepsis and found that this measure was an important prognostic factor [24,25].

The limitations of our study include the small number of cases identified that fulfilled the criteria for sepsis, and the reality that some patients accounted for multiple admissions, potentially adding a selection bias to the analysis. The ideal primary measure to assess clinical outcome in ICU patients should be 28-day mortality rates but this would require a more extensive and larger study. A larger population would allow stratification of the population by diagnosis and analysis of the results with clinical confounders. It would also be interesting to determine the impact of thrombocytopenia and associated molecular markers in pediatric sepsis patients on prognosis.

Conclusion

To our knowledge this is the first pediatric study investigating the clinical significance of thrombocytopenia in pediatric septic patients upon their admission to the PICU. We have demonstrated that the presence of thrombocytopenia is associated with a higher requirement for vasopressors. This is particularly true in those patients with proven gram-negative sepsis. Further studies are necessary to investigate this association.

Declarations

Authors information: AP participated in this study as a medical student at Miller School of Medicine, University of Miami. ACM and CRM participated in this study during their training as fellows in Pediatric Critical Care Medicine and Pediatric Hematology-Oncology, respectively, at Holtz Children's Hospital, Jackson Health System, University of Miami. MN, JD and FCM mentored ACM and CRM during this process.

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