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Research Article

Thrombocytopenia in Critical Care: Incidence, Risk Factors and Prognostic Factors

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Abstract

Thrombocytopenia is a frequent hematologic anomaly in the critical care. Its etiologies are multifactorial, many studies investigated thrombocytopenia in critical care with different results.

As the incidence of thrombocytopenia, identify risk factors associated with the occurrence and determine the prognostic.

A prospective cohort study in the emergency surgical critical department in a university hospital during a period of 9 months.

296 patients were included in the study, 40 presented with a thrombopenia during their ICU stay, with an incidence of 13,5%. The etiologies of the thrombopenias were mostly linked to sepsis and septic shock (66,7%). The only statistically significant risk factor for development of thrombocytopenia in multivariate analysis was a low platelet count on admission. Advanced age at the lowest platelet count were both independent bad prognostic factors in thrombocytopenia patients (age of the dead patients 54,40 ± 16,77, versus 45,50 ± 17,51 for survivors, p = 0,023, OR = 1,084, CI95% = [1,031 - 1,141]).

So, our incidence is 13,5%. The only independent risk factor for thrombocytopenia is the platelet rate on admission. The mortality rate of thrombopenic patients is 50%. Advanced age and the lowest platelet count were bad prognostic factors in thrombopenic patients.

Keywords: *Thrombocytopenia; Critical Care; Risk Factors; Mortality; Sepsis*

Introduction

Thrombocytopenia is defined as a platelet number < 150.000/mm^3, some authors use a threshold lower than 100.000/mm^3 do define thrombopenic patients [1]. Thrombocytopenia is frequent in critical care departments with a reported incidence varying between 8,3 and 67,6% according to studies [2]. Many studies investigated thrombocytopenia in the critical care environment, with different results depending on studied populations and varying methodologies.

Aim of the Study

The goal of this study is to assess the incidence of thrombocytopenia in an emergency surgical critical care department, to identify risk factors associated with its occurrence and to determine its prognostic significance.

Materials and Methods

The present work is a prospective cohort study in the Emergency Surgical Critical Care Department of a University hospital during a time period of 9 months (from September 25th 2020 to May 16th 2021). Patients included were aged of at least 16 years and were hospitalized in the critical care department for over 48 hours. Exclusion criteria were any known hemopathy, long term anticoagulation, anticancerous chemotherapy (including corticosteroids) and patients with thrombocytopenia on admission. Recruited patients were followed clinically and biologically with daily complete blood counts from admission till they were transferred from critical care or died.

Reported characteristics were age, gender, cause of admission in the critical care, the Charlson score and the IGS 2 score. The presence of an intravascular catheter, hemorrage, transfusion, sepsis and septic shock (as defined per the SSC 2021 guidelines), hepatic failure, mechanical ventilation with it's duration, and medications were analyzed when they occurred before or at the time of discovery of thrombocytopenia. The duration of hospitalization and mortality (were also analysed in the study).

Thrombocytopenia was defined as a platelet count lower than 150.000/mm^3 or a fall of more than 50% from the initial value. False thrombocytopenia was eliminated due to EDTA-dependent antibodies by confirming thrombocytopenia on blood smears. When thrombocytopenia occurred, the platelet count on admission, the timing of thrombocytopenia, its duration and the lowest platelet rate (were reported). The severity of thrombocytopenia was defined as mild when the platelet rate was less than 150.000/mm^3, moderate when less than 100.00/mm^3, severe when less than 50.000/mm^3 and profound when less than 20.000/mm^3. Studied risk factors were only considered when they occurred before or during the discovery of the thrombocytopenia.

We considered as significant hemorrhage any macroscopic upper or lower gastrointestinal bleeding, hematuria, intracranial hemorrage, any hemorrhage requiring surgical intervention, or responsible of a drop in hemoglobin rate of at least 2 g/dl in 24 hour or requiring a transfusion. Coagulopathy was defined by a prothrombin rate lower than 50% or an International normalized ratio over 1.5.

Statistical analysis

Statistical analysis was conducted using the SPSS for Windows program (Version 20, SPSS, Inc, Chicago, IL, USA). Results were expressed as numbers and percentages for qualitative variables and as means ± standard deviations, and they were compared using the x^2 test and the Fisher's exact test. Quantitative variables were expressed as medians and quartiles and were compared as per their distribution by the Student's t test or the Mann Whitney test. Variables considered as thrombocytopenia risk factors in univariate analysis were entered in a linear logistic regression model to make a multivariate analysis. The odds ratios (OR) were expressed as confidence intervals (IC) of 95%. Statistical significance was reached with a p value of 0.05.

Results

During the period of the study, 487 patients were hospitalized at the Emergency Surgical Critical Care department. 191 patients were excluded from the study: 178 because of a hospitalization lasting less than 48 hours, 13 patients because of thrombocytopenia on admission or because of interfering medications. 296 patients were included in the study.

Patient characteristics	Number (%)
Age	49.8 +/- 17.96
Gender (Male)	164 (55.4)
IGS 2	22.54 +/- 10.269
Trauma Patient	144 (48.6)
Emergency digestive surgery	152 (51.4)
Septic shock	105 (35.5)
Hemorragic shock	98 (19.6)
Hepatic failure	65 (22)
Transfusion	178 (60.1)
Intravenous catheter	219 (74)
Ventilated patients	193 (65.2)
Mechanical ventilation duration (in days)	7.86 +/- 5.4
Hospitalisation duration	9.05 +/- 33
Thrombocytopenia incidence	40 (13.5)
Global mortality	136 (45.9)

Table 1: *Included patient characteristics.*

Thrombocytopenia characteristics

Thrombocytopenia occurred in 40 patients during their hospitalization which represents 13.5% of patients. Thrombocytopenia occurred at 2,10 ± 1.95 days (extremes from 1 to 8 days). 25 patients (62.5%) became thrombopenic in the 48 hours following their admission in critical care, 5 patients among them were hospitalized in a surgery ward before their admission in critical care for at least 5 days.

The mean platelet rate of the thrombopenic patients at the time of inclusion in the thrombocytopenia group was 75000 ± 14870/mm^3 (extremes from 42.000 to 138.000/mm^3). The mean lowest platelet rate in thrombopenic patients was 67700 ± 15749//mm^3.

Eight patients presented a severe thrombocytopenia (20%), the remaining 32 patients had mild or moderate thrombocytopenia (80%). No profound thrombocytopenia was reported. In 38 patients the platelet rate returned to normal on discharge or at the time of death. The mean duration of thrombocytopenia was 3,82 ± 1,46 days.

Characteristics	Number (%)
Thromboytopenia incidence	40 (13,5)
Platelet rate on admission	273 610 ± 96 160
Platelet rate at the time of inclusion of thrombopenic patients	75 200 ± 14 870
Lowest platelet count in thrombopenic patients	67 700 ± 15 749
Thrombopenia timing	2,10 ± 1,95
Thrombopenia duration	3,82 ± 1,46

Table 2: *Characteristics of the thrombocytopenias.*

Thrombocytopenia were mostly linked to sepsis and septic shock (66,7% cases) and hemorrhagic shock (25%). One case was due to sodium valproate, in this case the thrombocytopenia resolved after the medication was withdrawned.

Etiology of the thromboepnia	Number of cases (%)
Sepsis-septic shock	28 (66,7)
Hemorrhagic shock	10 (25)
Medication	1 (2,5)
Not identified	1 (2,5)

Table 3: *Factors associated with thrombocytopenias.*

A binary linear regression analysis (was conducted) to identify the thrombocytopenia risk factors, then a multivariate analysis. When comparing thrombopenic and non thrombopenic patients, a statistically significant difference was found between two risk factors: IGS 2 score on admission was 25,63 ± 8.32 versus 22,06 ± 10,47 (p = 0,041), and septic shock 23 (57,5%) versus 82 (32%) p = 0.002. When comparing haematologic data between both groups, there was a statistically significant difference in platelet count on admission (297,25 ± 78,13 versus 168,14 ± 27,76 p < 0,001). Regarding medications, the association of an aminoside plus imidazole antibiotic was found statistically significant p = 0,014.

On multivariate analysis, when adjusting for other risk factors (IGS2, septic shock and aminoside plus imidazole association), the platelet count on admission remained the sole major independent predictive factor of thrombocytopenia occurrence in intensive care.

Impact of thrombocytopenia on mortality

The global patient mortality during the study period was 30.8%. The mortality of patients included in the study was 45,9%. Mortality was higher in thrombopenic patients compared to non thrombopenic patients, respectively 50% versus 45.3%, without reaching statistical significance p = 0.58, meaning that thrombocytopenia was not a prognostic factor in the patient sample. Patient survival was found to be similar in both groups when comparing it using the Kaplan Meier curves.

Compared to IGS2 score, the platelet rate on admission and the lowest platelet rate had a lower association with mortality, the area under the curve being 0,424 and 0,462 for platelet counts compared to 0,616 for IGS2.

When analyzing the factors linked to mortality in thrombopenic patients, the platelet rate on admission and the hemoglobin rate at 24h were found to be protective factors with the odds ratio being 0,339 for both. Advanced age and the lowest platelet count were both independently associated with mortality.

Characteristic	P value	Odds-ratio	Confidence interval at 95%
Age	0,002	1,084	1,031 - 1,141
Hemoglobin rate at 24h	0,001	0,339	0,183 - 0,628
Platelet count on admission	0,001	0,967	0,948 - 0,987

Table 4: *Multivariate analysis of prognostic factors in thrombocytopenia patients.*

Discussion

Thrombocytopenia is the most frequent hemostatic disorder encountered in intensive care patients. A systematic review of 24 studies enrolling 6894 patients from medical, surgical, mixed cardiac or trauma ICUs found a thrombocytopenia prevalence (thrombocytopenia present before ICU stay) varying from 8,3% to 67,6% of patients, while incident thrombocytopenia (thrombopenia occurring during the ICU stay) occurred in 13% to 44,1% of patients [2]. This disparity is probably due to the absence of homogenous biological criteria in studies, to the varying type of intensive care departments where the studies took place and to whether patients who were thrombopenic on admission were included or not.

Thrombocytopenia is defined as a platelet count < 150 G/l. Some authors use a lower threshold of 100 G/l in the intensive care unit. The time course of platelet counts, including the absolute counts and nadir is also relevant, since a decrease > 50% from baseline in the second week of ICU stay is considered abnormal even within a normal platelet range, with a possible prognostic significance, while this decrease can be normal after cardiac surgery. The absence of platelet count rise within 5 days of ICU admission may also be considered abnormal [3]. A threshold of 150 G/L (was used) to define thrombocytopenia, a lower value of 100 G/l may have selected more severe patients without analyzing the multifactorial facets of thrombocytopenia in the ICU.

Patients who were thrombopenic on admission were excluded (1,7% of studied patients). The incidence of thrombocytopenia in our study was 13,5%. Cawley., *et al*. investigated the incidence of thrombocytopenia in mixed patients (medical, surgical and trauma patients) using a threshold of 100 G/L to define thrombocytopenia, and found an incidence of 13% [4].

Thrombocytopenia is often multifactorial in the critically ill (patient). The mechanisms implied include hemodilution, increased platelet consumption, sequestration and destruction, or decreased production. In the setting of sepsis, these mechanisms can coexist, with peripheral mechanisms being preponderant, through consumption by disseminated intravascular coagulation and thrombin mediated platelet activation, and aggregation and adhesion to endothelial cells, immune-mediated destruction and acquired hemophagocytic

lymphohistiocytosis. Interestingly, platelet count is a part of the Sepsis-related Organ Failure Assessment (SOFA) score, representing the hematologic component of organ dysfunction in critically ill patients [5].

Thrombocytopenia may precede the diagnosis of sepsis by 24 - 48h. Sepsis was twice more frequent in thrombopenic patients than in non thrombopenic patients in a study by Aissoui., *et al* [6]. In a study by Masrouki., *et al*. sepsis multiplied the risk of death by 34 in thrombopenic patients [7]. The present study found an association between sepsis and thrombocytopenia in univariate analysis, this is in line with 8 studies reviewed by P Hui., *et al* [2]. A study by Zhao., *et al*. found a correlation between abnormal platelet level and long-term prognosis in septic patients, with Thrombocytopenia being associated with respiratory, circulatory, coagulation, kidney and hepatic failure [8]. Whether thrombocytopenia reflects disease severity or is a cause of death, its occurrence should be considered a risk marker and prompt an evaluation and correction of the underlying cause.

Drug induced thrombocytopenia is a frequent diagnosis in intensive care medicine where patients are on multiple medications. The challenge is to identify the responsible therapeutic agent. The mechanism can be either direct cytotoxicity or immunologic through drug dependent antibodies. The present study, among catecholamines, antibiotics, steroids, heparin and anticonvulsants, sodium valproate was found to be associated with the development of thrombocytopenia. It is known that thrombocytopenia can occur in 5 - 18% of patients on sodium valproate, with risk factors being female gender, high doses and advanced age. The mechanisms of sodium valproate induced thrombocytopenia may be direct bone marrow toxicity or autoantibodies formation [9]. The association of gentamicin with an imidazole antibiotic was also a thrombocytopenia risk factor in univariate analysis. In a study by Lfach., *et al*. 82 out of 118 patients (70%) developed thrombocytopenia under gentamicin therapy. Among them, 32 were tested for drug dependent antibodies, with 12 patients (38%) testing positive, whereas no gentamicin associated platelet antibodies where (were) found in non thrombopenic patients treatment with gentamicin [10]. Metronidazole was reported in the database for BloodCenter of Wisconsin for positive drug dependent antibodies. Lew., *et al*. reported one patient who became thrombopenic under cefepime, metronidazole and vancomycin therapy, with drug dependent antibodies being strongly positive to metronidazole and weakly positive to vancomycin. The patients (of) thrombocytopenia resolved after switching antibiotics to daptomycin and moxifloxacin, suggesting that metronidazole may be a cause of drug induced-thrombocytopenia [11]. Unfortunately there was lack of lacked laboratory data to support this, and whether metronidazole and gentamicin taken together increase the risk of drug-dependent thrombocytopenia occurrence needs further investigation.

A lower platelet count on admission was the sold independent risk factor for the development of thrombocytopenia in this study. A study by Stephan., *et al*. investigated the incidence of thrombocytopenia in a surgical ICU, and found a platelet count > 185000 to be a protective factor against thrombocytopenia. This was probably due to the platelet count reflecting the importance of the surgical procedure and the intensity of bleeding, as 56% of their patients were admitted for postoperative management, GI bleeding or trauma [12]. In the study by Strauss., *et al*. that took place in a medical ICU, a higher baseline platelet count was also protective against the development on thrombocytopenia, with platelet counts on admission being higher in non thrombocytopenia patients [13].

Most of studies show that mortality in intensive care increases with thrombocytopenia [12,14-16]. The retrospective study of Masrouki., *et al*. showed that the mortality rate of thrombopenic patients was 53% and that dead patients were significantly older than survivors. Another study [6] showed that the mortality rate was higher in thrombopenic patients than in non thrombopenic patients 31% versus 21%.

Vanderschueren., *et al*. showed that thrombocytopenia was a mortality predictor in intensive care [15]. On the other hand, in a study by Stephan., *et al*. thrombocytopenia didn't worsen patients prognosis in intensive care. A falling platelet count or a low increase in platelet count were bad prognostic factors [7]. In a recent study by Moreau D and Trimist J-F, a platelet fall over 30% compared to the initial rate was predictive of mortality [17].

In this study, the mortality rate was higher in the thrombopenic patients compared to the non-thrombopenic patients without reaching statistical significance. The correction of a thrombocytopenia seemed to be a good prognostic factor, as we found in the present study. Among the thrombopenic patients who survived, we noticed higher transfusion rates and a higher hemoglobin rate at 24 hours.

Most of studies show an association between thrombocytopenia and a longer ICU stay. This wasn't the case in this study (7,05 ± 5,29 days in thrombopenic patients versus 7,05 ± 5,7 days in non-thrombopenic patients, p = 0.99).

The prognostic significance of thrombocytopenia is pejorative since it is associated with a longer ICU stay, an increase in hemorrhagic or thrombotic events, an increased consumption of blood products and an increase of mortality risk. A decrease in the platelet count or the persistence of thrombocytopenia were also predictive of mortality.

Conclusion

Thrombocytopenia is often encountered in the ICU environment. Many risk factors are described in the literature but are largely dominated by sepsis. The sole independent risk factor we found in the present study was the baseline platelet count on admission, reflecting probably the initial severity of disease. Advanced age and the lowest platelet count were predictive of mortality in thrombopenic patients. Identifying the underlying mechanism is important to treat the thrombocytopenia as its resolution seems to be protective against mortality.

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