Original Article

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Reliability of Thrombocytopenia in Sepsis as a Predicting Tool for ICU Mortality

Internal Medicine Section

AKASH SHRIDHARANI[1], LABANI GHOSH[2], JYOTI MANNARI[3]

ABSTRACT

Introduction: There are many easy reproducible scores used in Intensive Care Unit (ICU) to predict mortality. But these need to be reassessed on a regular basis. There are many variables used to calculate these scores. But there can be some loss of data as the scores are repeated 24-48 hours apart and have many parameters which may make the process less user friendly.

Aim: To study the predictive value of new onset thrombocytopenia as an effective tool in predicting mortality in septic patients.

Materials and Methods: In this prospective observational study, 200 patients with thrombocytopenia at admission or at any time during ICU hospitalisation between 1st February 2015 to 1st November 2016 were selected; patients hospitalised for less than 24 hours were excluded. Thrombocytopenia is defined as a platelet count lower than 150,000/mm^3, and recovery is defined as returning to levels above 150,000/mm^3 after showing thrombocytopenia. Admission prognosis variables Acute Physiology, Age and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) Score and platelet counts during the hospitalisation and outcomes were assessed using descriptive statistics, Chi-square test and One-way Analysis of Variance (ANOVA).

Results: Out of 200 patients included, overall incidence of thrombocytopenia was 29.83%. The mean age was 49 (SD 18.24) years and mean duration of stay was 8.85 (SD 6.58) days. Maximum patients belonged to the age group of 18-30 years and 51-60 years. Total 89 (44.5%) of the 200 had sepsis and out of them 24 patients died, therefore, mortality rate among those in sepsis with thrombocytopenia was 27%. Mean SOFA score and APACHE II scores were 6.32 (SD 3.44) and 14 (SD 7.89), respectively. In the patients with thrombocytopenia and poor outcomes in the form of death or Discharge Against Medical Advice (DAMA), the SOFA scores were 9.04 and 6.96, respectively (p=0.0438). Similarly, patients with sepsis and thrombocytopenia who had either died or given DAMA the mean APACHE II scores were 18.66 and 17.96, respectively (p-value 0.0492).

Conclusion: There was a significant association between, APACHE II and SOFA scores with new onset thrombocytopenia. Therefore, it can be used as an independent individual variable to predict mortality in patients of sepsis with thrombocytopenia.

Keywords: Co-morbidity, Platelet count, Prognosis, Septic patients

INTRODUCTION

Sepsis is currently a major concern; however, assessing the prognosis of sepsis remains difficult. Assessing the prognosis of diseases and therapies is part of regular medical care. Mastering this challenge is largely related to the art of medical practice and leads to more objective care of the patient [1]. Prognostic scores like APACHE II and SOFA have been shown to be effective for the assessment of septic patients in numerous studies [2,3]. Observing the platelet counts, to check for new onset thrombocytopenia, may be very useful for assessing critical patients, especially those with sepsis. However, one-time platelet count is less valuable than sequential platelet counts throughout the course of sepsis [2,3].

There are many validated scoring systems which can be used to predict mortality in ICU. But they consist of several variables which need to be accounted for at the time of scoring and rescoring later at 24 and 48 hours. Therefore, there are chances of loss of data and faulty scores. Using a single variable like thrombocytopenia can reduce in loss/repetition of data. Platelets have a pivotal role in haemostasis in septic patients, significant drop in platelets acts as an independent factor for predicting morbidity and mortality [2,3].

Thrombocytopenia occurs in 20-50% of patients in intensive-care settings [4,5]. Thrombocytopenia or the non-resolution of thrombocytopenia is associated with the poor outcome [6]. In more recent study done by Lee KH et al., platelet count was not found to be an independent risk factor as against the present study. The presence of Disseminated Intravascular Coagulation (DIC) surprisingly was not an independent risk factor as well, in the mentioned study which correlates to present study [7].

Hence, the present study was conducted to study the predictive value of new onset thrombocytopenia as an effective tool in predicting mortality in septic patients.

MATERIALS AND METHODS

The present study was a prospective observational study which was conducted in ICU of Shri Krishna Hospital, between 1st February 2015 to 1st November 2016. Institutional Ethical clearance was obtained with approval letter number-HMPCMCE: HREC/2015/OUT. No. 169/15 (Human research Ethics Committee, HM Patel centre for Medical Care and Education, Karamsad, Gujarat, India).

Inclusion criteria: All individuals above 18 years of age having platelet count <1,50,000/μL or a fall in platelet count ≥500% from the ICU admission value were included.

Exclusion criteria: Patients less than 18 years of age and with platelet count >1,50,000/μL were excluded.

Sampling: Total number of admissions in critical care from 1st February 2015 to 1st November 2016 were 8055. Out of them there were 2403 patients who had thrombocytopenia (29.83%). Out of 2403 patients, 200 were those who had thrombocytopenia and sepsis. These 200 patients were taken in the study.

All patients with thrombocytopenia on admission or anytime during the stay in ICU were evaluated clinically and haematologically, after obtaining required consent. In case of patients developing thrombocytopenia after admission to ICU, the day of development of thrombocytopenia was considered as day one and was evaluated for the next days in ICU till the final outcome.

The data included demographic details of the patient, history of present illness, drug history, cause of admission to ICU, length of

ICU stay as well as total hospitalisation (in number of days), complete blood count, kidney function tests, liver function tests, coagulation profile and general examination data.

Subsequent platelet counts were done on various days after admission to ICU and thrombocytopenia was considered as a platelet count of <150,000/μL. Thrombocytopenia is classified as very severe thrombocytopenia (platelet count ≤10,000/μL), severe thrombocytopenia (platelet count >10,000/μL but ≤50,000/μL) moderate thrombocytopenia (platelet count >50,000/μL but ≤1,00,000/μL) and mild (1,00,000-1,50,000/ μL) [8]. Sepsis is defined by the presence of infection and two or more signs suggesting reduced organ perfusion. In case of availability of more than one platelet count of a patient on a single day, the lower value was taken into consideration. Regarding drug-induced thrombocytopenia, the following general criteria was used for suspecting the presence of drug-induced thrombocytopenia [8].

The drug should bear a direct relationship with thrombocytopenia, usually within a week after beginning it for the first time [8].

- The platelet count should be less than 20,000 to 30,000/μL.
- There should not be an alternative explanation for the thrombocytopenia that is more highly probable than Drug Induced Thrombocytopenia (DITP).

After data collection and analysis, the rate of occurrence of thrombocytopenia in patients admitted to medical ICU was calculated. Mortality or recovery or prolonged hospitalisation was correlated with thrombocytopenia.

STATISTICAL ANALYSIS

Descriptive statistics {Mean (SD), Frequency (%)} were used to depict characteristics of study population. Associations of different explanatory variables with thrombocytopenia at univariate level were evaluated using Chi-square/t-test depending on nature of the variables. The ANOVA was used to compare SOFA [9] and APACHE II [10] scoring systems. Epi InfoVersion 7 was used to collect data.

RESULTS

Mean age of the patients was 49 (SD 18.24) years and mean duration of hospital stay was 8.85 (SD 6.58) days. Maximum number of patients belonged to 18-30 and 51-60 years with 48 patients each. Out of 200, 115 (57.5%) were males and 85 (42.5%) were females [Table/Fig-1].

Age group (years)	Male	Female	Total
18-30	21	27	48
31-40	14	10	24
41-50	11	9	20
51-60	29	19	48
61-70	21	14	35
>70	19	6	25
Total	115	85	200

[Table/Fig-1]: Age and gender distribution.

Total 99 (49.5%) patients presented with fever, 15 (7.5%) presented with bleeding from any site and 11 (5.5%) had presented with trauma. In the patients who had come with bleeding from any site as a presenting symptom, 4 (26.67%) patients had very severe thrombocytopenia (platelet count ≤10,000/μL), 8 (53.33%) patients had severe thrombocytopenia (platelet count >10,000/μL but ≤50,000/μL) and 3 (20%) patients had moderate thrombocytopenia (platelet count >50,000/μL but ≤1,00,000/μL). In patients who had major trauma (11 patients out of 200) had developed thrombocytopenia secondary to platelet consumption.

Majority of the patients had severe thrombocytopenia 72 (36%), 17 patients had very severe thrombocytopenia [Table/Fig-2].

Severity/μL	No. of patients	Percentage (%)
Very severe ≤10000	17	8.5
Severe 10000-50000	72	36
Moderate 50000-100000	59	29.5
Mild 100000-150000	52	26

[Table/Fig-2]: Distribution of thrombocytopenia according to severity.

There were 72 (36%) patients with deranged liver functions, 73 (36.5%) had deranged renal functions and 59 (29.5%) had deranged coagulation profile. Total 17 (8.5%) cases had chronic liver disease and 6 (3%) cases of patients who had thrombocytopenia had underlying chronic kidney disease. Total 89 (44.5%) of the 200 had sepsis and out of them 24 patients died, therefore, mortality rate among those with sepsis in thrombocytopenia was 27%. Mean SOFA score and APACHE II scores were 6.32 (SD 3.44) and 14 (SD 7.89), respectively.

[Table/Fig-3] shows a significant association between sepsis scoring systems and patient outcomes (SOFA p=0.0438, APACHEII p=0.0492).

	Death	DAMA	Discharge	DOR	p-value (t-test)
SOFA (Mean Score) in Sepsis with Thrombocytopenia N=200	9.04	6.96	6.66	6.2	0.0438
APACHE II (Mean Score) in Sepsis with Thrombocytopenia n=200	18.66	17.96	14.4	11.8	0.0492
Days of Stay (Mean) in those with Sepsis and Thrombocytopenia	8.37	9.33	12.6	14.8	0.1293

[Table/Fig-3]: Association between patient outcome, sepsis scoring systems, thrombocytopenia and days of stay.
DAMA: Discharge against medical advice; DOR: Discharged on request

Out of 200 patients, 45 developed thrombocytopenia due to some medication/drug. Most commonly implicated drugs were chemotherapeutic agents [Table/Fig-4].

Medications	No. of patients n=45	Percentage (%)
Heparin	2	4.444
Linezolid	5	11.111
Beta Lactams	9	20
Valproate	3	6.666
Phenytoin	2	4.444
Chemotherapy	24	53.333

[Table/Fig-4]: Distribution of thrombocytopenia in patient with various medications.

DISCUSSION

According to a study by Chakraverty R et al., medical and surgical Intensive Care Units (ICUs) had found platelet counts less than 100,000/μL in 20-40% of patients at some point during their stay in the unit, whereas severe thrombocytopenia (platelet counts <50,000/μL) occurred in 10-20% of patients [11]. The present study included all the critical care units in the hospital, and it revealed an overall incidence of thrombocytopenia of 29.83%. The mean age of the patients was 49 years with the minimum age being 18 years and maximum age being 86 years.

In this study, the mortality rate of patients with sepsis having thrombocytopenia was 27%. The association of chronic kidney disease and chronic liver disease in the thrombocytopenic patients was studied and concluded that 8.50% (n=17) cases had chronic liver disease and 30% (n=6) cases of patients who had thrombocytopenia had underlying chronic kidney disease, hence the association of thrombocytopenia and chronic liver disease was stronger than chronic kidney disease (p<0.001). This is comparable to the study by Afdhal N et al., which associates thrombocytopenia

(platelet count, 50,000/μL-75,000/μL) with chronic liver disease (cirrhosis) occurring in approximately 13% of patients [12]. A 99v (49.5%) patients had presented with fever, 15 (7.5%) patients had presented with bleeding from any site and 11 (5.5%) patients had presented with trauma. In the patients who had come with bleeding from any site as a presenting symptom, four patients had very severe thrombocytopenia eight patients had severe thrombocytopenia and three patients had moderate thrombocytopenia. In patients who had major trauma (11 patients out of 200) and had developed thrombocytopenia secondary to platelet consumption, nadir of thrombocytopenia was day 3 or 4 (Mean day of nadir of thrombocytopenia-3.45) after which thrombocytopenia gradually recovered. Similar patterns of platelet count courses were described by Nijsten MW et al., in ICU patients after various surgeries [13].

Forty-five (22.5%) patients had a suspected DITP. Most commonly implicated drugs were chemotherapeutic agents, Linezolid, Valproate, Phenytoin, Beta-lactam and Heparin. Chemotherapy induced thrombocytopenia was seen in 24 (53.33%) patients out of 45. Heparin induced thrombocytopenia was seen in 2 (4.44%) patients. 89 (44.5%) patients had sepsis induced thrombocytopenia followed by viral haemorrhagic fever and consumptive coagulopathy 13.5% each. Similar study was done by Lee KH et al., which had 107 subjects in critical care out of which 53 patients were septic of which 31 patients developed thrombocytopenia. It was observed that majority of the patients in critical care had severe thrombocytopenia 72 (36%) patients and very severe thrombocytopenia was seen in only 17 patients (8.5%) among all the thrombocytopenic patients. Various studies found thrombocytopenia in 35%-45% of ICU patients, with a somewhat greater variability of 5%-20% for severe thrombocytopenia [7,14,15].

The study had used SOFA and APACHE II scores for assessment of severity of illness in thrombocytopenic patients in critical care, mean values (±SD) of both these scores were 6.32 (±3.44) and 14 (±7.89). The level of association between length of stay and outcome was not significant (p=0.1293) [Table/Fig-3]. In thrombocytopenic patients with sepsis, those patients who had poor outcome had the highest mean SOFA score of 9.04 (death) and 6.96 (DAMA) respectively. Whereas those with good outcomes had a mean SOFA score of 6.66 (discharge) and 6.20 (DOR) respectively (p=0.0438). Similarly, the association between APACHE II and outcome in sepsis with thrombocytopenia was also very significant (p=0.0492). A retrospective cohort study by Balci C et al., analysed data collected from patients admitted to a postoperative ICU. Patients were divided in two groups: Thrombocytopenic patients (P group) and non-thrombocytopenic (C group). The APACHE II score did not show statistically significant difference between groups in their study. The evaluation of the SOFA score, rather than APACHE II, correlates better with the outcomes in patients with sepsis and thrombocytopenia [16].

Limitation(s)

The limitation of this study was the small sample size. If the trend of platelet count could be obtained for all the subjects in the study it would have given a better understanding of trends and patterns of thrombocytopenia due to various causes.

CONCLUSION(S)

Considering the results of this study, it was concluded that platelet counting is a simpler and more affordable method when treating septic patients. A daily assessment of thrombocytopenia should be considered as an important prognostic factor in sepsis, although authors have validated lengthy scores like SOFA and APACHE II to predict mortality. When treating thrombocytopenia in septic patients, interfering with platelet function, physician should treat the cause of thrombocytopenia to reduce the mortality.

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PARTICULARS OF CONTRIBUTORS:
1. Resident, Department of Medicine, Pramukh Swami Medical College, Karamsad, Gujarat, India.
2. Associate Professor, Department of Medicine, Pramukh Swami Medical College, Karamsad, Gujarat, India.
3. Professor, Department of Medicine, Pramukh Swami Medical College, Karamsad, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Labani Ghosh,
Bunglow 6, Nilamber Aarcon, Vadodara, Gujarat, India.
E-mail: labanigmg@gmail.com

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