

Frequency of ICU mortality and thrombocytopenia in patients with sepsis

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Abstract

Introduction: Thrombocytopenia in patients with sepsis was found to be associated with a poorer outcome. Rationale of this study was to gather data in our settings to assess the association between thrombocytopenia and intensive care unit (ICU) mortality in such patients. This will help us in devising proactive management guidelines for improving the outcomes in these patients.

Objectives: To determine the frequency of thrombocytopenia in patients with sepsis and to compare the frequency of ICU mortality in patients with sepsis with and without thrombocytopenia

Materials and Methods: A total of 200 patients irrespective of gender between ages of 18-75 years who admitted to the ICU with sepsis was included to the study. Frequency of thrombocytopenia was measured and ICU mortality was compared between patients with and without thrombocytopenia.

Results: 64.5% (n=120) of patients were males and 35.5% (n=71) of patients were females. 59.9% (n=118) of patients had thrombocytopenia and overall mortality study subjects was 64.5% (n=129). In patients with thrombocytopenia, mortality was significantly higher (72.9% versus 52.4%) as compare to patients without thrombocytopenia ($P<0.05$). Gender and age based stratification showed mortality was higher in males and older age group with thrombocytopenia ($P<0.05$).

Conclusion: Significant percentage (59.9%) of patients admitted with sepsis in ICU were found to have thrombocytopenia. Mortality was significantly higher in these patients as compared to those patients recruited in group who did not have thrombocytopenia.



Introduction

Sepsis is a major health problem affecting millions of people and causing the death of every one in four and increasing in incidence (1). Sepsis is basically a life threatening complication of an infection. It occurs when cytokines are released in to the blood stream by tissue macrophages, monocytes, mast cells, platelets and endothelial cells to fight the infection and trigger an inflammatory response throughout the body. This leads to a cascade of changes that can damage multiple organ systems.

Thrombocytopenia is commonly seen in critically ill patients admitted to the intensive care unit (ICU). The main cause of thrombocytopenia in ICU setting is sepsis and septic shock (2). Several mechanisms are included like endothelial sequestration, destruction of the platelets, immune mediated destruction, bone marrow suppression

Core tip

In a study on 200 patients between ages of 18-75 years who admitted to the ICU with sepsis, we found a significant percentage (59.9%) of patients admitted with sepsis in ICU were found to have thrombocytopenia. Mortality was significantly higher in these patients as compared to those patients recruited in group who did not have thrombocytopenia. Thrombocytopenia in patients with sepsis was found to be associated with a poorer outcome. Rationale of this study was to gather data in our settings to assess the association between thrombocytopenia and ICU mortality in such patients. This will help us in devising proactive management guidelines for improving the outcomes in these patients.

and hemophagocytosis. Thrombocytopenia is a part of an early inflammatory response of the body to infection and as the response be-

comes severe thrombocytopenia worsens leading to DIC (3). However, a single platelet count is not as valuable as sequential platelet counts throughout the course of sepsis. A trend of the platelet count is of more prognostic value than a single measurement (4). Thrombocytopenia is associated with a poor prognosis and increased mortality in ICU patients.

The mortality rate of patients with sepsis in ICU is 62.5%. Thrombocytopenia is a frequent laboratory abnormality in critically ill patients with sepsis. The prevalence of thrombocytopenia in ICU patients with sepsis is 60.7% and the mortality rate is 76.4%. However, the mortality rate of patients with sepsis who did not develop thrombocytopenia is 40.9% (5).

The rationale of my study is to determine the role of thrombocytopenia on the disease course of critically ill patients with sepsis. This will help the intensive care physicians at our hospital to counsel the patient's attendants and family in a better way about the disease course of sepsis and outcome in terms of mortality. The measurement of the platelet count is a daily routine laboratory investigation done in the ICU and would prove to be a marker of predicting the course and outcome of illness in critical patients with sepsis.

Objectives

1. To determine the frequency of thrombocytopenia in patients with sepsis
2. To compare the frequency of ICU mortality in patients with sepsis with and without thrombocytopenia

Patients and Methods

Thrombocytopenia

It is defined as platelet count of less than $150 \times 10^3/\mu\text{L}$. It will be measured within seven days of admission to ICU with sepsis.

ICU mortality

It is defined as death of the patient while admitted to the ICU within 7 days.

Sepsis

It is defined as known or the suspected infection whose signs and symptoms fulfill at least two of the criteria mentioned increased heart rate of more than 90 beats per minute

- Body temperature either more than $100^\circ\text{F}/38^\circ\text{C}$ or lower than $98^\circ\text{F}/36^\circ\text{C}$
- Increased respiratory rate equal to or more than 20 per minute or an arterial partial carbon dioxide pressure of less than 32 mm Hg
- An abnormal white blood cell count $>12 \times 10^3/\mu\text{L}$ or $<4 \times 10^3/\mu\text{L}$ or less than 10% band cells (an immature type of white blood cells)

Study design

Descriptive case series.

Duration

Six months (27-01-2015 to 26-07-2015).

Sample size

Confidence level: 95%; Anticipated population: 60.7% (5); Absolute precision: 0.07; Sample size: 200 patients.

Sample technique

Non probability consecutive sampling technique.

Inclusion criteria

Patients aged 18-75 years of both the genders admitted to the ICU with sepsis.

Exclusion criteria

- Patients who stayed in the ICU for less than 1 day
- Patients on un-fractionated heparin in the last 10 days as it can lead to heparin induced thrombocytopenia
- Patients with a history of taking aspirin in the last three days as it can cause thrombocytopenia
- Patients with a history of idiopathic thrombocytopenic purpura as it is an autoimmune non-septic cause of thrombocytopenia
- Patients with a history of decompensated chronic liver disease.
- Patients with a history of hematological malignancies

Data collection procedure

After taking approval from hospital's ethical committee, informed consent from patients' next of kin for patients' record was taken to be used in this study. Patients were enrolled who were admitted to the ICU with the diagnosis of sepsis as per operational definition. A venous blood sample for platelet measurement was taken on daily basis for platelets measurement for a maximum of seven days. The platelet count was documented if it is $<150\,000 \times 10^3/\mu\text{L}$ on any single day and correspondingly thrombocytopenia were entered as present for that patient. Similarly, the patient who had sepsis but the platelet count of that particular patient was $>150\,000$ were documented. The enrolled patients were followed over a period of maximum seven days and outcome in terms of mortality and survival was documented.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained and the research was approved by the Ethics Committee of Shifa Research Center.

Statistical analysis

SPSS version 17.0 used for analyzing the data. For quantitative variables, mean & standard deviation (SD) values for age was calculated. Frequency and percentages were calculated for qualitative variables like gender, thrombocytopenia and mortality. Chi-square test was used to compare qualitative variables like mortality among the two groups. P value < 0.05 considered significant. Effect modifier like

age and gender were controlled by stratification. Post stratification chi-square test was applied.

Results

Demography of the selected population

A total of 200 patients were recruited in this study after the informed consent from every patient. All adult patients irrespective of gender between ages 18-75 years admitted to the ICU with sepsis were included in the study. Patients who stayed in the ICU for less than 24 hours, who were on un-fractionated heparin for the last 10 days, who had idiopathic thrombocytopenic purpura as it is an autoimmune non-septic cause of thrombocytopenia, who had decompensated chronic liver disease and patients who had history of hematological malignancies were excluded from the study. Data was collected using designed proforma. 64.5% (n = 129) of patients were males with the mean age of 57.4 years \pm 11.2 SD and 35.5% (n = 71) of patients were females with mean age of 54.0 years \pm 12.7 SD. Cumulative mean age was 56.1 years \pm 11.9 SD (Table 1). There were 25.5% (n = 51) of patients who were between 18-50 years of age and 74.5% (n = 149) were between 51-75 years of age (Table 2).

Overall frequency of thrombocytopenia and mortality in study sample

In our study overall study sample, 59.9% (n = 118) of patients were diagnosed to have thrombocytopenia as per our operational definition (Table 3). Overall ICU mortality among study subjects was 64.5% (n = 129) as per our operational definition (Table 4).

Comparison of mortality in two groups (with and without thrombocytopenia)

In patients with thrombocytopenia, mortality was found to be 72.9% (n = 86) while it was 52.4% (n = 43) among patients who did not have thrombocytopenia. *P* value was 0.003 (<0.05) implicating mortality was significantly higher in patients with thrombocytopenia. Results are shown in Table 5.

Stratification based on gender and age

In males who had thrombocytopenia, mortality was found to be 82.6% (n = 57) while the percentage was 55.8% (n = 2)

in males who did not have thrombocytopenia. *P* value was 0.001 (<0.05) implicating mortality was significantly raised in male with thrombocytopenia as compared to other group of males who did not have thrombocytopenia. In females who had thrombocytopenia, mortality was found to be 59.2% (n = 29) while the percentage was 46.7% (n = 14) in females who did not have thrombocytopenia. *P* value was 0.278 (>0.05) implicating no significant difference in mortality in females with or without thrombocytopenia. Results are shown in Table 6.

In age group 18-50 years who had thrombocytopenia, mortality was found to be 56.7% (n = 17) while the percentage was 42.9% (n = 9) in patients who did not have thrombocytopenia. *P* value was 0.332 (>0.05) implicating no significant difference in mortality between younger age groups with or without thrombocytopenia. In age group 51-75 years who had thrombocytopenia, mortality was found to be 78.4% (n = 69) while the percentage was 55.7% (n = 34) in patients who did not have thrombocytopenia. *P* value was 0.003 (<0.05) implicating mortality was significantly higher in older age group with thrombocytopenia (Table 7).

Discussion

Sepsis is termed as a clinical syndrome resulting from an inflammatory response to an infection, which is usually non-resolving and detrimental, leading to organ dysfunction. Sepsis may be defined as the presence (probable or documented) of infection along with systemic manifestations due to this infection. The rate of severe sepsis during hospitalization has almost doubled during the last 11 years and is considerably greater than what was previously predicted. Mortality from this severe sepsis has also increased significantly (6). It has been observed that thrombocytopenia is commonly seen in such critically ill patients that are admitted to the intensive care units. The main cause

Table 3. Frequency of thrombocytopenia in study sample

Thrombocytopenia	Frequency	Percent	Cumulative percent
Present	118	59.0	59.0
Absent	82	41.0	100.0
Total	200	100.0	

Table 4. Frequency of mortality in study sample

Mortality	Frequency	Percent	Cumulative percent
Present	129	64.5	64.5
Absent	79	35.5	100.0
Total	200	100.0	

Table 5. Comparison of mortality in patients with and without thrombocytopenia*

Mortality	Thrombocytopenia	
	Present	Absent
Present	86 (72.9%)	43 (52.4%)
Absent	32 (27.1%)	39 (47.6%)
Total	118 (100.0%)	82 (100.0%)

**P* value (chi-square) = 0.003

Table 1. Demographic profile of the study population (age and gender distribution)

Gender	Frequency	Percent	Mean age \pm SD (Years)
Males	129	64.5	57.4 \pm 11.2
Females	71	35.5	54.0 \pm 12.7
Total	200	100	56.1 \pm 11.9

Table 2. Demographic profile of the study population (age groups)

Variables	Frequency	Percent	Cumulative percent
Age groups (years)			
18-50	51	25.5	25.5
51-75	149	74.5	100.0
Total	200	100.0	

Table 6. Gender wise stratification (mortality)

Gender		Thrombocytopenia	
		Present	Absent
Males ^a			
Mortality, yes	Count	57	2
	% Within groups	82.6%	55.8%
Mortality, no	Count	12	23
	% Within groups	17.4%	44.2%
Total	Count	30	21
	% Within groups	100.0%	100.0%
Females ^b			
Mortality, yes	Count	29	14
	% Within groups	59.2%	46.7%
Mortality, no	Count	20	16
	% Within groups	40.8%	53.3%
Total	Count	49	30
	% Within groups	100.0%	100.0%

^a*P* value (chi-square) = 0.001; ^b*P* value (chi-square) = 0.278.

Table 7. Age wise stratification (mortality)

Age groups		Thrombocytopenia	
		Present	Absent
18-50 years ^a			
Mortality, yes	Count	17	9
	% Within groups	56.7%	42.9%
Mortality, no	Count	13	12
	% Within groups	43.3%	57.1%
Total	Count	30	21
	% Within groups	100.0%	100.0%
51-75 years ^b			
Mortality, yes	Count	69	34
	% Within groups	78.4%	55.7%
Mortality, no	Count	19	27
	% Within groups	21.6%	44.3%
Total	Count	88	61
	% Within groups	100.0%	100.0%

^a*P* value (chi-square) = 0.332; ^b*P* value (chi-square) = 0.003.

of this thrombocytopenia in intensive care setting is a result of sepsis and septic shock (2). During sepsis, pathologically body undergoes several mechanisms like endothelial sequestration, destruction of the platelets, immune mediated destruction, bone marrow suppression and hemophagocytosis (3). Although thrombocytopenia in such critical care patients has found to be associated with a poor prognosis and increased mortality, the accurate relationship has not yet been defined (4). Rationale of this study is to gather data in our setting in order to assess the association between thrombocytopenia and ICU mortality. This will help us in devising a proactive guideline for improving the outcomes in such patients. The objective of the study is to determine the frequency of thrombocytopenia in patients with sepsis and to compare this frequency of ICU mortality with sepsis with and without thrombocytopenia. A total of two hundred (n=200) patients irrespective of gender between age 18-75 admitted to the ICU with sepsis were taken as the sample population. *P* value < 0.05 (chi-square) was considered significant. 64.5% (n = 120) of

patients were males and 35.5% (n = 71) of patients were females. 59.9% (n = 118) of patients had thrombocytopenia and overall mortality study subjects were 64.5% (n = 129). In patients with thrombocytopenia, mortality was significantly higher (72.9% versus 52.4%) as compare to patients without thrombocytopenia (*P*<0.05). Gender and age based stratification showed mortality was higher in males and older age group with thrombocytopenia (*P*<0.05).

Our results are similar to an already published data on the same hypothesis. Strauss et al (7) in their prospective observational study that determined prevalence, risk factors, and outcome of thrombocytopenia in medical intensive care patients. They enrolled all consecutively admitted patients with normal platelet count at admission and an intensive care unit stay of >48 hours during a 13-month period (n = 145). Their results indicated that the prevalence of intensive care unit-acquired thrombocytopenia (platelet count, <150×10³/μL) was 64 of 145 patients (44%).

Mortality was observed to be higher in patients with a lowest platelet count of <100×10³/μL (*P*<0.001) and in patients with a drop in platelet count of ±30% (*P*<0.001). In non-survivors, the decrease in platelet count was greater (*P*<0.001), the lowest platelet count (*P*<0.001), and the duration of thrombocytopenia longer (*P*=0.008) than in survivors. Authors concluded that that thrombocytopenia is usually common in medical intensive care unit patients. At admission, disseminated intravascular coagulation, signs of organ failure and cardiopulmonary resuscitation are predictors of intensive care unit-acquired thrombocytopenia, which must be checked.

Boechat et al (5) aimed to demonstrate an association between thrombocytopenia and platelet trends in predicting mortalities in such septic patients. Patients with criteria for sepsis on admission or at any time during hospital stay were chosen; patients hospitalized for <24 hours were excluded. Thrombocytopenia is defined as a platelet count lower than 150×10³/μL, where as a recovery was defined as returning of levels above 150.000/mm³ after showing thrombocytopenia. Their results indicated that out of the 56 patients that were included, 34 developed thrombocytopenia during sepsis (group 1) and had a 76.4% of mortality rate. The mortality rate among patients not showing thrombocytopenia (group 2) was about 40.9% (RR: 1.87; 95% CI: 1.12-3.12; *P*=0.0163). In 44.1% of group 1 patients, the platelet counts drops by more than 50% as compared to the initial admission counts; 93.3% of these patients eventually died (RR: 1.48; 95% CI: 0.93-2.36; *P*=0.0528). Amongst the group 1 patients showing recovered platelet counts, 53.3% survived; 100% of the patients who could not revive from this thrombocytopenia eventually passed away (RR: 2.14; 95% CI: 1.35-3.39; *P*=0.0003). Amongst the patients with APACHE II scores >22, the thrombocytopenic patients had an 81.8% of mortality rate (*P*=0.25), while no mortalities took place amongst the non-thrombocytopenic patients. For the patients with APACHE II scores ≤22, the mortality rate for these thrombocytopenic patients was about 74% (*P*=0.0741), versus 42.8% for the non-thrombocytopenic patients. Authors

concluded that thrombocytopenia and its advancement or failure to recover to a reasonable platelet count, were shown to be markers of poor prognosis.

Vanderschueren et al (8) in their prospective observational cohort study aimed to study the incidence and prognosis of thrombocytopenia in adult intensive care patients. Data of 329 patients was analyzed. Overall intensive care mortality rate was 19.5%. 136 patients in total (41.3%) had at least one platelet count $<150 \times 10^9/L$. These patients also had a higher multiple organ dysfunction score (MODS).

Akca et al (9) in their prospective, observational cohort analysis aimed at describing the time course of the platelet count in relation to the mortality rate in critically ill patients. Data was collected from all intensive care admissions in a 1-month period, excluding patients younger than 12 years of age and those who stayed in the ICU for less than 48 hours after uncomplicated surgery. A total of 1449 critically ill patients were selected, including 257 who stayed in the ICU for more than 2 weeks. Platelet counts were collected daily throughout the ICU stay, together with other parameters of organ dysfunction. Thrombocytopenia was defined as a platelet count of $<150 \times 10^3/\mu L$. A gradual increase in the platelet count was considered as a 25% increase above the initial admission value, along with an absolute platelet count of $\geq 150 \times 10^3/\mu L$. Authors found that for the entire population, the platelet count was lower in those 313 subjects who were non-survivors than in the 1131 survivors throughout the ICU course. Of the 257 patients who stayed in the ICU for more than 2 weeks, 187 (64%) survived. The platelet count decreased significantly in the first few days after admission to reach a nadir on day 4 in both survivors and non-survivors. In the survivors, the platelet value returned to the admission value at the end of first week and continued to rise to become noteworthy greater than the admission value by day 9. In the non-survivors, the platelet also come back to normal value after 1 week of treatment which was same at the time of admission, but there was no noteworthy increase in platelet count. In a total of 138 (54%) patients, all of them had thrombocytopenia on day 4, and these patients had a greater mortality rates than other patients (33% vs. 16%; $P < 0.05$). On day 14, 51 (20%) patients had thrombocytopenia, and these patients had a greater mortality rate than the other patients (66% versus 16%; $P < 0.05$). Thrombocytopenia was less common on day 14 than on day 4 (20% versus 54%; $P < 0.05$), but the mortality rate observed was greater in these thrombocytopenic patients on day 14 than those who were thrombocytopenic on day 4 (66% versus 33%; $P < 0.05$). The ICU mortality rate of non-thrombocytopenic patients on day 14 was also significantly lower in patients with, than without, a relative increase in platelet count on day 14 (11% versus 30%; $P < 0.05$). Authors concluded that platelet count in the critically ill have a biphasic pattern that is different in survivors and non-survivors. Late thrombocytopenia is more predictive of death than in case of early thrombocytopenia in subjects. A relative increase in platelet count after thrombocytopenia was observed in survivors but not in non-survivors. For pre-

dicting outcome single count of platelet measured is not enough, changes in platelet count over time are related to patient outcome.

Venkata et al (10) in their retrospective analysis investigated the incidence, prognostic importance of thrombocytopenia and its risk factors in adult patients admitted under ICU with sepsis. A total of 304 patients were included in the study. The patients' mean (\pm SD) age was 68.8 (\pm 15.8) years. Thrombocytopenia developed in 145 patients (47.6%). The association of non-resolution of thrombocytopenia and death of such patients remained noteworthy after adjusting for age, APACHE III score and compliance with a sepsis resuscitation bundle ($P < 0.01$). Authors concluded that thrombocytopenia is common in patients that are admitted to the intensive care with severe sepsis and septic shock. Patients with thrombocytopenia had more major bleeds, increased incidence of acute kidney injury, and prolonged ICU stay (11,12).

Moreau et al (13) evaluated possible links between deteriorating platelet counts initial in the ICU visit and survival. They enrolled all patients who were admitted to the ICU for at least 5 days and had no thrombocytopenia at the time of admission. A multivariable logistic regression model, with hospital mortality as the outcome variable, was built. A total of 1077 patients were included in the study.

Conclusion

Significant percentage (59.9%) of patients admitted with sepsis in intensive care units was found to have thrombocytopenia. Mortality was significantly higher in these patients as compare to ones who did not have thrombocytopenia. Thrombocytopenia may be considered as an important prognostic factor in patients with sepsis. Further larger scale studies are needed in order to prove this hypothesis.

Limitations of the study

Small sample size was the main limitation of our investigation.

Authors' contribution

AAK, AT and AB; data gathering, data interpretation, and manuscript preparation (Thesis work). CMJN and HT; study design, interpretation of data and patients support.

Conflicts of interest

None to be declared.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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