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Research article

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Thrombocytopenia and its effect on mortality and morbidity in the intensive care unit

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Ethics Committee Approval
The study was approved by Bezmialem University non-interventional research ethics committee with the number 2011-KAEK-42 2016703-01. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Thrombocytopenia is a common hematological abnormality among patients in the intensive care unit (ICU). The development of thrombocytopenia in the ICU usually indicates severe organ system dysfunction rather than a primary hematological disorder. We aimed to determine the incidence, causes, and clinical results of thrombocytopenia in patients followed up in ICU.
Methods: In this retrospective cohort study, 165 patients who were followed up in the ICU with thrombocyte counts below 150,000 /uL were included and causes of thrombocytopenia, along with its effects on mortality and intensive care stay were investigated.
Results: Thrombocytopenia was determined in 30.1% of the patients in the ICU. The cause of thrombocytopenia was sepsis in 33 (20.0%) of the patients and disseminated intravascular coagulation (DIC) in 20 (12.1%) patients. During the study period, 115 (69.7%) of 165 thrombocytopenic patients and 173 (45.1%) of 383 patients without thrombocytopenia died. Mortality was significantly higher in patients with thrombocytopenia. Mortality significantly increased when platelet count decreased, even with similar APACHE II scores.
Conclusion: The most common causes of thrombocytopenia in the ICU were sepsis and DIC. Thrombocytopenia is common in the ICU and increases mortality rates.

Keywords: APACHE II, Intensive care, Mortality, Sepsis, Thrombocytopenia

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Introduction

Thrombocytopenia is defined as blood platelet count remaining below the accepted normal limits [1]. Values below 150,000/uL are considered thrombocytopenia [1-3]. It is a common hematological abnormality among patients admitted to the intensive care unit (ICU). From a clinical perspective, the development of thrombocytopenia in the ICU usually indicates severe organ system dysfunction and physiological decompensation rather than a primary hematological disorder. Thrombocytopenia is associated with adverse clinical outcomes, including bleeding, transfusion, and death. Few deaths can be directly attributed to bleeding [3,4], the risk of which is inversely proportional to the platelet count [5,6]. Its management is directed primarily at the underlying disorder [5]. Bleeding is not expected in platelet values above 100,000/uL, including major surgical interventions [6]. Major bleeding risk increases with values below 20.000/uL, and there is a risk of life-threatening bleeding at values below 10,000/uL.

Thrombocytopenia is a quite common laboratory disorder in intensive care patients. The incidence of thrombocytopenia varies between 35-44% in studies previously conducted on ICU patients [7, 8]. Identifying the underlying cause of thrombocytopenia is vital in determining patient management and treatment regimens. In the light of all these results, we aimed to determine the incidence of thrombocytopenia in ICU patients, the underlying causes, and clinical consequences, and investigate its contribution to mortality and morbidity, considering that the presence and severity of thrombocytopenia may be a prognostic marker in patients in the intensive care unit.

Materials and methods

Study design

Patients admitted to the ICU of Izmir Metropolitan Municipality Esrefpasa Hospital and University of Health Sciences, Okmeydanı Training and Research Hospital between April 2016 and December 2019 were included in the study. The study was approved by Bezmialem University non-interventional research ethics committee with the number 2011-KAEK-42 2016703-01 and signed informed consent forms were obtained from the relatives of all patients participating in the study.

Patients

Adult patients over 18 years of age who were followed up for at least one day in the ICU were included in the study. A platelet count of <150,000 /μL indicated thrombocytopenia. Patients with thrombocytopenia at admission to the intensive care unit or those who developed thrombocytopenia during ICU hospitalization were included in the study. Peripheral blood smears were examined, and Wright-Giemsa staining was used as the peripheral smear dye. Thrombocyte, white blood cell count, hemoglobin, INR, aPTT values, the lowest platelet count, D-Dimer, and Fibrinogen values of the patients with suspicion of consumption coagulability and the APACHE II score calculated during the hospitalization of each patient were recorded. The age and gender of the patients, reasons for intensive care admission, underlying chronic diseases, if any, whether they were thrombocytopenic during admission to intensive care, the cause of thrombocytopenia, and the length of stay in the ICU of those who were discharged or transferred to the wards were noted. Complete blood count, peripheral blood smear, coagulation parameters, fibrinogen, D-dimer, urea and creatinine, blood electrolytes, liver enzymes, and bilirubin levels, hepatitis markers, autoimmune markers from suspected patients, and bone marrow aspiration and/or biopsy results, if present, were examined. Bone marrow biopsies of 95 patients and aspirates of 119 patients were assessed. Neither of these procedures were performed in patients currently unfit for the procedure, who died before they could be performed, those with drug or heparin-related thrombocytopenia whose condition improved after the suspicious agent was discontinued, and those with suspected pseudo-thrombocytopenia. According to the recommendations of the Turkish Hematology Association regarding the patients' platelet count, the patients were divided into five groups as follows: Those with platelet counts between 100,000-149,000 uL/mm^3, 50,000-99,000 uL/mm^3, 20,000-49,000 uL/mm3, 10-19,000 uL/mm^3 and <10,000 uL/mm3. A platelet count below 50.00 uL/mm^3 was defined as severe thrombocytopenia.

Scale

APACHE scoring is one of the systems used in determining the mortality rate in the ICU and evaluating treatment efficiency. APACHE II, a version of the APACHE system, has been used in ICUs since 1985. For APACHE II, the worst values of the following variables within the first 24 hours of intensive care admission are used: Age, fever, respiratory rate, heart rate, mean arterial blood pressure, Glasgow coma scale, serum creatinine value, hematocrit, white blood cell count, arterial blood pH, sodium, potassium, and alveolo-arterial pressure gradient. While calculating, a score is determined according to the presence of chronic organ failure, immunosuppression status, emergency or elective surgical operation status, and the presence of acute renal failure, and the expected mortality of the patient is estimated. In our study, the APACHE II score of the patients was calculated by the intensive care physician team. The patients were divided into four groups according to their APACHE II scores as below 10, between 10-24, between 25-34, and those above 35.

Statistical analysis

SPSS 17.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum - maximum where necessary). Chi-square test or Fisher's test were used for comparison of categorical variables. In the comparison of continuous measurements between the groups, the normality of distributions was checked. Student-t test or One-way Analysis of Variance were used for normally distributed parameters, and Mann Whitney U test or Kruskal Wallis test were used for non-normally distributed ones. Spearman correlation test was used to check for correlation between variables. Risk factors for mortality were determined by Logistic Regression analysis. $P<0.05$ was considered statistically significant in all tests.

Results

During the study period, 548 patients (325 males, 223 females) with a mean age of 57.2 (16.4) (min: 18, max: 91) years

were followed in the ICU. Thrombocytopenia was observed in 165 (61 female, 104 male) patients (30.1%). While 134 (81.2%) of these patients had thrombocytopenia during admission to ICU, 31 (18.8%) developed thrombocytopenia during hospitalization. Clinical features of patients who had thrombocytopenia in the ICU are summarized in Table 1.

Table 1: Clinical features of patients with thrombocytopenia

Variable	n=165	%
Gender		
Male	104	63.0
Female	61	37.0
Pre-admission thrombocytopenia		
Yes	134	81.2
No	31	18.8
Malignancy		
Yes	66	40.0
No	99	60.0
APACHE II score		
10-24	20	12.1
15-19	49	29.7
20-24	58	35.2
25-34	26	15.8
<34	12	7.3
The lowest number of thrombocytes		
Below 10,000 / uL	14	8.5
Between 10-19,000 / uL	30	18.2
Between 20 and 49,000 / uL	62	37.6
Between 50 and 99,000 / uL	46	27
Between 100 and 149,000 / uL	13	7.9

The median APACHE II score calculated on the first day of admission to ICU was 22 (min: 10, max: 42). The distribution of APACHE II scores and the lowest number of thrombocyte counts of the patients are summarized in Table 1.

In 27 patients (16.3%), thrombocytopenia was due to known hematological malignancies, in 33 patients (20.0%) due to sepsis, in 13 patients (7.8%) due to cytotoxic chemotherapy, 20 (12.1%) patients had drug-related thrombocytopenia and 20 (12.1%) had thrombocytopenia due to DIC. Seventeen patients (10.3%) had thrombocytopenia due to hypersplenism and 7 patients (4.2%) had immune-thrombocytopenia (primary or secondary). Eight patients (4.9%) had thrombocytopenia because of solid tumor metastasis to the bone marrow. Six patients (3.6%) were evaluated as TTP. Five patients (3.0%) had heparin-associated thrombocytopenia. The cause of thrombocytopenia could not be determined in nine patients (5.4%).

The laboratory data analyzed at the admission and during discharge from the ICU are summarized in Table 2.

Table 2: The laboratory data analyzed at the admission and during the discharge from the ICU

Variable	Mean (SD)	Median (min-max)	*P*-value
Platelet (first)	99.6 (120.8)	67 (5-846)	0.001
Platelet (discharge)	61.1 (68.7)	46 (4-560)	
Platelet (lowest)	45.4 (33.3)	37 (4-163)	0.001
WBC (first)	15.1 (41.4)	8 (0-510)	0.030
WBC (discharge)	10.0 (9.30	7 (0-41)	
Hemoglobin (first)	9.4 (2.1)	9 (5-17)	0.360
Hemoglobin (discharge)	9.3 (1.8)	9 (5-14)	
INR (first)	1.6 (0.7)	1.4 (0.9-7)	0.332
INR (discharge)	1.8 (1.6)	1.4 0.9-17)	
APTT (first)	38.1 (19.4)	33 (14-141)	0.001
APTT (discharge)	47.4 (29.2)	37 12-148)	

The mean platelet count of the patients included in the study at the time of hospitalization was 67,000 /μL and the mean lowest platelet count during hospitalization in ICU was 37,000 /μL. A statistically significant decrease in the platelet count was observed in patients during hospitalization (*P*=0.001). The mean white blood cell count and aPTT values were also altered significantly (*P*=0.03); however, hemoglobin, or INR levels did not significantly change during hospitalization in the ICU (Table 2).

In this study, 115 (69.7%) of 165 thrombocytopenic patients and 173 (45.1%) of 383 patients without thrombocytopenia died. Accordingly, mortality was significantly higher in patients with thrombocytopenia (*P*=0.020). While the mean length of stay of all patients transferred to the ward or discharged during the study was 5.9 (1.3 days), the mean length of stay for those with thrombocytopenia was 6.1 (3.7) days. There was no statistically significant difference between thrombocytopenic and non-thrombocytopenic ICU patients regarding the length of stay in ICU (*P*=0.064).

Table 3: Comparison of patients with and without malignancy

	Malignancy				
	Present (n:66)		Absent (n:99)		
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	*P*-value
Age	58.5 (17.2)	60 (20-91)	55.2 (15.0)	57.5 (18-84)	0.136
PLT first	109.8 (132.6)	76 (6-846)	84.2 (99.6)	52.5 (5-601)	0.114
PLT last	73.1 (83.2)	55 (4-560)	43.1 (29.9)	34.5 (5-129)	0.002
PLT lowest	51.1 (34.9)	41 (4-163)	36.8 (29.0)	26 (5-123)	0.005
WBC first	10.9 (7.8)	9 (0-37)	21.3 (64.5)	8 (0-510)	0.469
WBC last	9.9 (8.2)	8 (0-41)	10.2 (10.7)	6 (0-37)	0.286
Hgb first	9.5 (2.1)	10 (5-17)	9.3 (2.1)	9 (5-14)	0.409
Hgb last	9.4 (1.6)	9 (5-14)	9.1 (1.9)	9 (5-14)	0.155
INR first	1.6 (0.7)	1.4 (0.9-7)	1.5 (0.5)	1.4 (0.9-3.4)	0.967
INR last	1.7 (1.0)	1.3 (0.9-8.2)	1.9 (2.1)	1.4 (0.9-17)	0.518
aPTT first	37.3 (17.1)	34 (17-104)	39.3 (22.7)	32 (14-141)	0.993
aPTT last	49.9 (32.1)	38 (17-148)	43.7 (23.8)	36 (12-135)	0.446
APACHE II	21.3 (6.4)	20 (12-40)	22.9 (5.5)	22.5 (10-42)	0.026

When patients with and without an underlying malignant disease were compared, no significant difference was found between the platelet values, coagulation parameters, hemoglobin, and white blood cell values during admission (Table 3). The mean lowest platelet values and mean last measured platelet counts of patients with and without malignancy were significantly different.

The mean APACHE II score of patients with malignancy was significantly higher (*P*=0.026). The results of patients with or without malignancy are summarized in Table 3.

Some laboratory data of survivors and non-survivors are compared in Table 4.

Table 4: Comparison of laboratory data of alive or death patients

	Non-survivors	Survivors	*P*-value
The lowest platelet values detected	30.000 / uL (5000-563000)	57.500 (4.000-138.000)	0.001
The last platelet count	37.000 / uL (4000-533000)	70.000 / uL (4000-563.000)	0.001
The last INR	1.4 (0.9 - 8.8)	1.3 (0.9 - 17)	0.040
The last aPTT	42 sec (12- 148)	32 sec (19- 81)	0.030
APACHE II	24 (13- 42)	18 (10- 30)	0.001

Twenty-seven (87.09%) of 31 patients who had no thrombocytopenia at admission, but developed thrombocytopenia during ICU stay, died. In the same period, while the ICU overall mortality was 52.5%, the mortality of non-thrombocytopenic patients was 45.1% (173/383 patients), and the mortality of thrombocytopenic patients included in our study was 69.7%. Accordingly, the mortality of patients who did not have thrombocytopenia at admission but developed thrombocytopenia while in the ICU was significantly higher than the others (*P*=0.001).

Seventy-eight (61.4%) of 127 patients with APACHE II scores between 10-24, 25 (96.2%) of 26 patients with APACHE II scores between 25-34, and all 12 patients (100%) with APACHE II score of 35 and above died. Accordingly, the mortality of the patients examined in our study significantly increased with APACHE II scores (*P*=0.001).

In our study, no significant relationship was found between the APACHE II score, genders, and the lowest platelet

value. However, mortality significantly increased as the lowest platelet count decreased (P=0.003), and as the platelet count decreased in patient groups with the same APACHE II score (P=0.002).

Discussion

Thrombocytopenia is quite common in ICU patients, and important in terms of determining the underlying causes, predicting clinical results, and determining treatment regimens. In numerous studies, thrombocytopenia rates in the ICU varies between 35-45% and approximately half of these patients developed thrombocytopenia during intensive care hospitalization [9,10]. In the studies of Provan et al. and Strauss et al., this rate was between 35% and 44%, and in the study conducted by Singh et al., thrombocytopenia rate was between 20-40% [11-13]. In our study, the rate of thrombocytopenia in the ICU was 30%, which was similar to the previous studies [14-17]. In the study of Singh et al., the rates of patients with thrombocyte count below 100,000 / uL varied between 20-40% [13]. In the studies conducted by Knöbl et al. [17] and Hanes et al. [18] the rates of those with a thrombocyte level below 100.000 /uL and 50.000 /uL were between 20-25% and 12-15%, respectively. In our study, thrombocytopenia rates were similar to those in the literature, but the rate of patients with severe thrombocytopenia was 65%, which was higher than previously reported.

In a study by Provan et al. [11], while the overall mortality of patients in the ICU was 19.5%, and the mortality of patients with and without thrombocytopenia were 33% and 9.3%, respectively. The mortality of patients with thrombocytopenia at admission to the ICU was 34%, and the mortality of those who developed thrombocytopenia during ICU hospitalization was 31.9%. In the study conducted by Hoogendoorn et al. [20], the intensive care mortality of thrombocytopenic patients was 1.6%, that of non-thrombocytopenic patients was 4.4%. In the same study, the hospital mortality of thrombocytopenic patients was 22.1%, and that of non-thrombocytopenic patients was 7.8%. According to the results of our study, the overall mortality in the ICU, and the mortality of thrombocytopenic and non-thrombocytopenic patients were higher than those previously reported in the literature. In our study, as in other studies, the mortality of patients with thrombocytopenia was significantly higher than overall mortality and that of non-thrombocytopenic patients.

Acute Physiology and Chronic Health Evaluation (APACHE) scoring is one of the systems used in determining the mortality rate and evaluating treatment efficiency in intensive care units [21, 22]. Warren et al. [16] found the APACHE II score as 26.9 (6.9) in patients who died and 23.5(5.4) in patients who survived, and reported that the higher the score, the higher the mortality. In another study, it was observed that 50% and 72.2% of patients with APACHE II scores of ≥15 and ≥20, respectively, did not survive [23]. It is noteworthy that mortality increases significantly in patients with APACHE II scores between 21-25 [24, 25]. In our study, as the APACHE II score increased, so did mortality significantly, and the APACHE II score was significantly higher among non-survivors.

In our study, the mortality of patients who did not have thrombocytopenia at the beginning but developed thrombocytopenia during ICU hospitalization was significantly higher than that of the other patients. There was a positive correlation between the lowest level of platelets and mortality, and the lowest platelet values reached in patients with malignancy were significantly lower. In our study, no significant relationship was found between the APACHE II score and the lowest platelet value obtained. As platelet count decreases, mortality increases significantly in patients with similar APACHE II scores, which suggested that thrombocytopenia may be an independent marker for mortality. Moreover, even if the severity of the underlying disease and the general condition of the patients were similar, the patients with thrombocytopenia were more mortal and as thrombocytopenia deepened, mortality increased. Thrombocytopenia may be an independent predictive marker for mortality in intensive care patients. We think that our study contributes to the literature in this respect.

Limitations

The first limitation of this study is its retrospective nature, and secondly, we analyzed the results of all thrombocytopenic patients without analyzing the underlying causes, which may also affect mortality.

Conclusions

Thrombocytopenia was highly prevalent in the ICU in our study, with sepsis as etiology in the first place, and DIC in the second place. The mortality of patients with thrombocytopenia was significantly higher than the overall mortality and mortality of non-thrombocytopenic patients, and as thrombocytopenia deepened, mortality increased. This was independent of the APACHE II score. Patients who did not have thrombocytopenia at the beginning but developed thrombocytopenia during intensive care follow-ups had higher mortality than those with thrombocytopenia during intensive care admission. However, studies and meta-analyses in a larger series will contribute to the subject.

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