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ORIGINAL INVESTIGATION

Thrombocytopenia: A Risk Factor of Mortality for Patients with Sepsis in the Intensive Care Unit

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Abstract

OBJECTIVES: The objective of this study was to evaluate the intensive care unit (ICU) and long-term mortality in sepsis patients with/without thrombocytopenia on the fifth day of ICU admission.

MATERIALS AND METHODS: The retrospective observational cohort study was performed in a teaching hospital, and patients with sepsis who stayed more than 4 days in the ICU between January 2012 and December 2012 were included. Patients were divided into two groups according to thier platelet count at fifth day of ICU stay: Group 1, < 150.000/µL; Group 2, >150.000/µL. Patients having thrombocytopenia on admission were excluded. The patients' characteristics, comorbid diseases, body mass index, arterial blood gas analysis and blood biochemistry results, SIRS criteria, Acute Physiological and Chronic Health Evaluation Score II (APACHE II), implication of invasive and non-invasive mechanical ventilation, use of sedation, nutrition information, and culture results of microbiological samples were recorded. The groups were compared according to the recorded data. Logistic regression analysis was performed for ICU mortality; the Kaplan–Meier test was used to evaluate 12-month survival after ICU discharge.

RESULTS: During the period, 1003 patients were admitted to the ICU; 307 sepsis patients were included in the study. Group 1 (n= 67) and Group 2 (n=240) had similar patient characteristics and sepsis findings. The groups had similar ICU and hospital stays; mortality was higher in Group 1 than in Group 2 (40.3% vs. 17.5%, respectively, p< 0.001). Fifth day thrombocytopenia, septic shock, male gender, and low albumin levels were found to be risk factors of ICU mortality; the respective odds ratios, 95% confidence intervals, and p values for these factors were 3.03, [1.15-7.45], p= 0.025; 4.97, [1.79-13.86], p= 0.002; 3.61, [1.27-10.23], p= 0.001; and 0.19, [0.07-0.52], p= 0.001. Follow-up after a year indicated that 124 out of 238 (52.1%) patients died, and 50% of the deaths occurred in the first 2 months. Kaplan-Meier analysis revealed no statistically significant effects of thrombocytopenia at ICU day 5 on 12-month mortality after ICU discharge.

CONCLUSION: Higher rates of septic shock and mortality were seen in sepsis patients with thrombocytopenia in the ICU. The measurement of thrombocytopenia in the ICU, which is easy and low-cost, may help to predict mortality. Thus, precautions can be taken early in patient treatment and follow-up. As we know, early intervention is crucial in the approach to sepsis.

KEY WORDS: Thrombocytopenia, sepsis, mortality, intensive care unit

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INTRODUCTION

Various immunological changes induced by mediators involved in the pathogenesis of sepsis lead to organ failure and subsequent organ dysfunction. Once circulatory failure and shock have developed, the mortality rate among patients with severe sepsis increases to > 50% [1]. As an indicator of hematological system failure, thrombocytopenia reflects an increase in the mortality rate and severity of sepsis; therefore, it is included in the Sepsis-related Organ Failure Assessment (SOFA) score [2]. A limited number of studies have evaluated the relationship between sepsis and reduction in platelet count despite the fact that thrombocytopenia is equally as important as circulatory failure [3,4].

Determination of the most appropriate therapeutic agent and rapid initiation of treatment allow for the reversal of the damage that occurs during early pathogenesis. Because the causative microorganism cannot be identified in approximately half of the patients with sepsis, treatment is directed at developing organ failure. Although improvement in the treatment of patients with sepsis was ensured by the Surviving Sepsis Campaign and other published guidelines, thrombocytopenia remains a major problem for these patients in the ICU [5]. Few studies have

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investigated survival during and after an ICU stay among patients with sepsis and the worsening of thrombocytopenia with the passage of time post-admission [6,7].

In the present study, we hypothesized that the development of thrombocytopenia due to sepsis, particularly on day 5 of hospitalization, may be associated with a worse prognosis of patients in the ICU and after ICU discharge than in non-thrombocytopenic patients with sepsis.

MATERIALS AND METHODS

This study was approved by the Internal Review Board of Kartal Lütfi Kırdar Teaching Hospital-İstanbul. It was conducted in accordance with the ethical principles stated in the Declaration of Helsinki [8]. This retrospective cohort study was performed in a 22-bed respiratory ICU of a single tertiary training and research hospital. All patients were followed up by the same pulmonary specialist team (n= 8) from 1 January 2012 to 31 December 2012.

Patients

All patients with sepsis who were admitted to our ICU and stayed more than 4 days were enrolled in the study. Patients having thrombocytopenia on admission were excluded. All patients had pulmonary-origin sepsis (pneumonia, infective bronchitis, bronchiectasis, and other conditions). It is known that in heparin-induced thrombocytopenia (HIT), the platelet count usually falls 5-14 days after heparin is first administered. To exclude HIT, patients were stratified into two groups according to their fifth day thrombocyte count. Group 1 comprised patients with a thrombocyte count of ≤ 150,000/mL or that had decreased to ≥ 50% of the ICU admission count on their fifth day in the ICU. Group 2 comprised patients with a thrombocyte count of > 150.000 or that had decreased by < 50% of the ICU admission count on their fifth day in the ICU.

Definitions

The systemic inflammatory response syndrome (SIRS) criteria were defined as follows:

- Core body temperature of > 38°C or < 36°C,
- Heart rate of ≥ 90 bpm,
- Respiratory rate of ≥ 20/min (or $PaCO_2$ of < 32 mmHg),
- White blood cell count of ≥ 12.000/μL or ≤ 4000/μL or > 10% immature forms.

Sepsis was defined as the presence of at least two SIRS criteria [9] caused by a known or suspected infection. Patients with organ dysfunction and/or hypoperfusion abnormalities were considered to have severe sepsis. Shock was defined as the need for vasoactive drugs (> 5 μg/kg/min of dopamine, dobutamine, or norepinephrine at any dose) for at least 1 h [9]. Septic shock was diagnosed when shock was associated with a documented or assumed infection without any other identifiable cause of shock [9].

Data Collection

The pre-ICU locations and date of ICU admission were recorded for all patients. Demographic data, comorbid diseases (diabetes, cardiovascular disease, chronic renal disease, and chronic respiratory disease), body mass index (BMI, kg/m^2), arterial blood gas analysis and blood biochemistry results, SIRS criteria [9], APACHE II [10], and other ICU outcomes (implication for and durations of invasive and non-invasive mechanical ventilation, lengths of ICU and post-ICU hospital stay, use of sedation, and nutrition information) were gathered from the patients' ICU files. Hemogram parameters, including thrombocyte levels, white blood cell levels, hemoglobin levels, biochemical blood analysis results, activated partial thromboplastin time, and international normalized ratio, were noted on days 1 and 5 of ICU admission. All agents isolated from culture samples were documented. All patients were treated according to established guidelines [11].

We followed the Modified Protocol for Surviving Sepsis [3] and Early Directed Goal Therapy protocol [12]. Invasive mechanical ventilation (IMV) with a moderate tidal volume [13] was performed if the patient was unresponsive to or had a contraindication for non-invasive mechanical ventilation (NIMV) [14]. Moderate-dose steroids [15] were administered at 20 mg three times daily for 7 days in patients without contraindications. A glucose control protocol [16] was followed to maintain blood glucose levels between 110 and 140 mg/dL (< 150 mg/dL). A sedation protocol was applied during mechanical ventilation. The Richmond Agitation-Sedation Scale was used for the determination of infusions and assessment of the daily need for sedation [17].

Microbiology

Bronchial secretions were collected via deep tracheal aspiration in intubated patients. Sputum was collected in a sputum Petri dish in non-intubated patients. A blood culture was obtained and incubated in aerobic culture media in patients with hyperthermia or hypothermia (< 36°C or > 38°C, respectively).

Statistical Analysis

Descriptive statistics were used to define the characteristics of the study population. All recorded data were compared between the two groups. We further divided the patients with severe sepsis into two subgroups according to mortality. Data were compared using the Mann-Whitney U test and Student's t-test for nonparametric and parametric variables, respectively. All nonparametric values are presented as median with interquartile range (25%-75%). We used the chi-square test to compare categorical variables (sex, comorbidities, and IMV and NIMV status) between the two groups.

Logistic regression analysis was performed to evaluate the multivariate associations between risk factors and mortality. The multivariate model was adjusted for baseline severity (SOFA score on admission to the ICU). Odds ratios, 95% confidence intervals, and p values were reported. Patients were followed for 12 months after ICU discharge, and mortality status was recorded during this period. The long-term survival analysis of the two groups after ICU discharge according to the fifth day of thrombocytopenia was analyzed using the Kaplan-Meier curve. Data were analyzed using the Statistical Package for the Social Sciences 15.0 (SPSS, Inc., Chicago, IL, USA). A p value of < 0.05 was considered to indicate statistical significance.

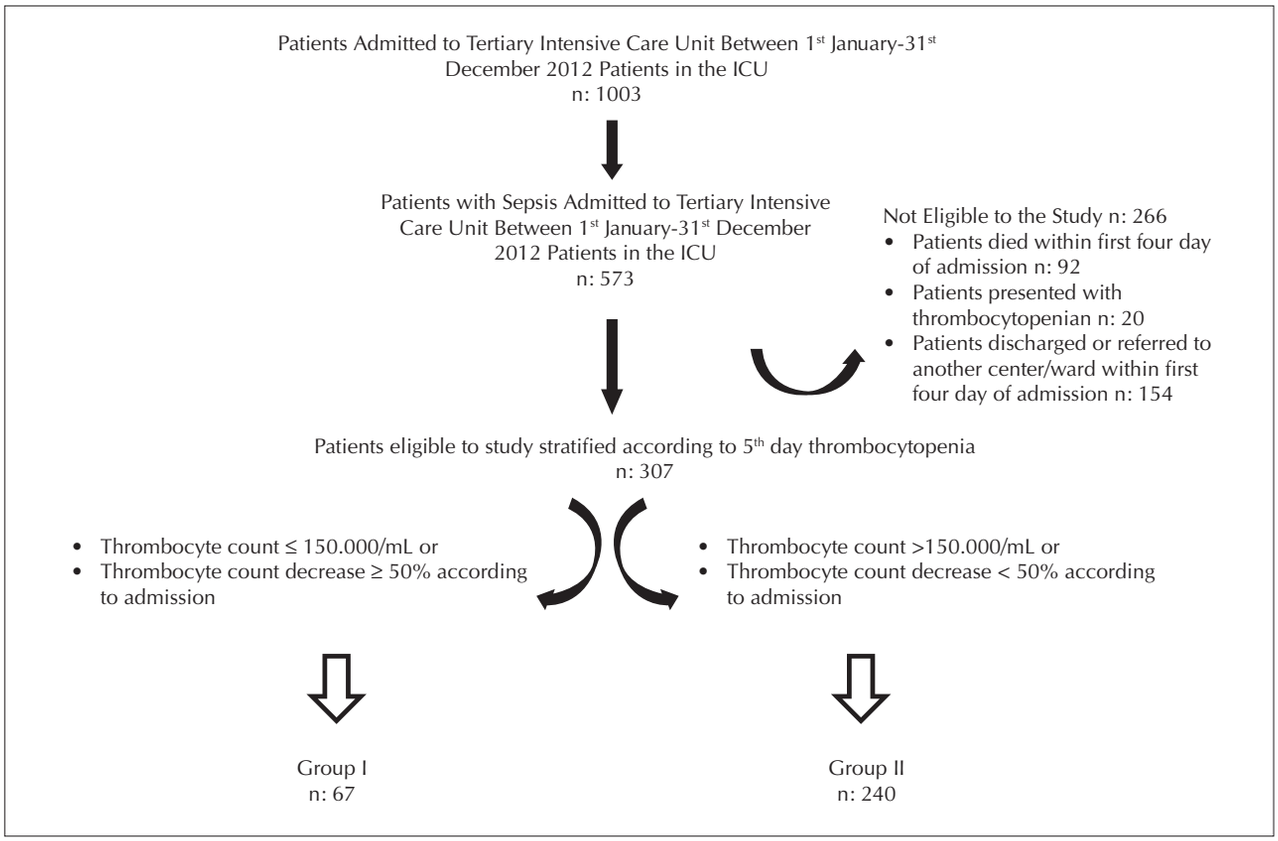

Figure 1. CONSORT diagram showing patient enrolment and stratification.

RESULTS

Patient enrolment and stratification are shown in the CONSORT diagram in Figure 1. Sepsis criteria were present in 573 (57.1%) of all 1003 patients admitted to the ICU during the study period. Septic shock was observed in 120 (39.1%) of the patients with sepsis.

Demographic characteristics, comorbidities, the performance of long-term oxygen therapy, and the performance of NIMV were compared between the two groups (Table 1). Most patients were male and > 65 years old. The characteristics of both groups were similar, except that the thrombocytopenic group had a significantly higher incidence of cancer as a comorbidity (p= 0.001). There were no significant differences in the number and frequency of SIRS signs between the two groups.

Laboratory values, APACHE II scores, and BMIs at admission as well as the patients' pre-ICU locations are shown in Table 2. Patients in Group 1 had significantly higher APACHE II scores and were more frequently transferred from other centers.

Microbiological samples were taken from 237 patients (77%). An agent was isolated in 92 (38.8%) of these patients. Gram-negative agents constituted most of the isolated pathogens. The most frequent were *Acinetobacter baumannii* (n= 40, 28.9%), *Pseudomonas aeruginosa* (n= 16, 11.6%), and *Klebsiella pneumoniae* (n= 15, 10.9%).

The application of mechanical ventilation, lengths of ICU and post-ICU hospital stay, and mortality rates of the two groups are shown in Table 3. The mortality, septic shock, and IMV rates were significantly higher in Group 1.

The application of mechanical ventilation and ICU outcomes are summarized in Figure 2. Group 1 patients who underwent direct IMV without NIV had a mortality rate of 73.3% (11 of 15 patients), which was significantly higher than that in Group 2 (p= 0.001).

Sex, APACHE II score at admission, serum albumin level, thrombocyte level on ICU days 1 and 5, presence of septic shock, serum CRP level, isolated pathogens, comorbidities, application of IMV and NIMV, and length of ICU stay were added to the logistic regression model to analyze the risk of mortality among patients with severe sepsis staying more than 4 days in the ICU. Thrombocytopenia on ICU day 5, the presence of septic shock, male sex, and a low albumin serum level were associated with an increased mortality rate of 80.1% in the regression model (Table 4).

A 12-month follow-up of 238 patients discharged from the ICU revealed that 124 (52.1%) of these patients had died. Half of the patients died within the first 2 months of discharge. Kaplan-Meier analysis revealed no statistically significant effects of thrombocytopenia on ICU day 5 (Figure 3).

DISCUSSION

This study showed that thrombocytopenia on the fifth day of ICU admission is a risk factor for ICU mortality, but not for long-term mortality, among patients with sepsis and acute

Table 1. Demographics, co-morbidities, presence of long-term oxygen therapy, and NIV

	Group 1 (n= 67)	Group 2 (n= 240)	p
Age, mean ± SD	68 ± 11	67 ± 13	0.67
Female %	26.8	24.5	0.71
APACHE II score, mean ± SD	25 ± 7	22 ± 7	0.003
Body mass index, kg/m^2, median (IQR)	25 (20-29)	23 (20-28)	0.35
C-reactive protein, mg/L, median (IQR)	97.3 (37.8-134.0)	79.1 (31.8-144.0)	0.79
Comorbidities, n (%)			
COPD	30 (44.8)	136 (56.7)	0.08
Diabetes mellitus	17 (25.4)	48 (20.0)	0.34
Hypertension	25 (37.3)	69 (28.8)	0.18
CAD	4 (6.0)	31 (12.9)	0.11
CRF	4 (6.0)	9 (3.8)	0.43
CVA	1 (1.5)	12 (5.0)	0.21
Malignancy	20 (29.9)	27 (11.2)	0.001
Respiratory support before ICU, n (%)			
Long-term oxygen therapy	28 (43.1)	118 (50.0)	0.32
Home NIMV	12 (18.5)	53 (22.6)	0.48

SD: standard deviation; APACHE: acute physiology and chronic health evaluation; IQR: interquartile ratio; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CRF: chronic renal failure; CVA: cerebrovascular accident; NIMV: non-invasive mechanical ventilation.

Table 2. Pre-ICU length of stay/location and laboratory data of the two groups at ICU admission

	Group 1 (n= 67)	Group 2 (n= 240)	p
Pre-ICU length of hospital, days, median (IQR)	5 (1-10)	4 (1-8)	0.99
Pre-ICU location, n (%)			
Medical ward	34 (50.7)	108 (45.0)	0.037
Surgical ward	1 (1.5)	9 (3.8)	
Outer center	17 (25.4)	34 (14.2)	
Emergency	15 (22.5)	89 (37.1)	
Hemogram values			
Leucocyte, 10^3/µL, mean ± SD	13.6 ± 7.3	14.5 ± 6.8	0.35
Hemoglobin, g/dL, mean ± SD	11.5 ± 2.6	11.8 ± 2.2	0.33
Thrombocyte, 10^3/µL, median (IQR)	165 (122-267)	273 (220-349)	0.001
Biochemistry values			
Glucose, mg/dL, median (IQR)	142 (115-195)	149 (119-191)	0.45
Blood urea nitrogen, mg/dL, mean ± SD	38 ± 21	28 ± 16	0.001
Creatinine, mg/dL, median (IQR)	1.13 (0.78-1.56)	0.79 (0.65-1.09)	0.001
SGOT, U/L, median (IQR)	28 (19-65)	24 (18-39)	0.067
SGPT, U/L, median (IQR)	27 (16-49)	23 (14-43)	0.27
Sodium, mmol/L, mean ± SD	137 ± 8	138 ± 6	0.87
Potassium, mmol/L, mean ± SD	4.5 ± 0.8	4.5 ± 0.7	0.77
INR, mean ± SD	1.35 ± 0.48	1.26 ± 0.50	0.19
Arterial blood gas analysis			
pH, mean ± SD	7.31 ± 0.13	7.33.13	0.29
$PaCO_2$, mmHg, mean ± SD	63.0 ± 29.2	65.7 ± 26.2	0.47
PaO_2/FiO_2, median (IQR)	155 (106-229)	160 (123-216)	0.58
HCO_3, mmol/L, mean ± SD	29.0 ± 9.2	33.5 ± 24.5	0.14

ICU: intensive care unit; IQR: interquartile ratio; SD: standard deviation; CRP: C-reactive protein; µL: microliter; mg/dL: milligram/deciliter; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamate pyruvate transaminase; U/L: units/liter; mmol/L: millimoles per liter; INR: international normalized ratio; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; mmHg: millimeter of mercury; PaO_2: partial pressure of oxygen in arterial blood; PaO_2/FIO_2: pressure of arterial oxygen to fractional inspired oxygen concentration; HCO_3: bicarbonate.

respiratory failure. Additional risk factors for ICU mortality were male gender, the presence of septic shock, and a low serum albumin level.

The mechanism of thrombocytopenia in sepsis is not completely clear. Hemophagocytosis may occur, consisting of active phagocytosis of megakaryocytes and other hematopoietic cells by monocytes and macrophages, hypothetically due to stimulation with high levels of macrophage colony-stimulating factor (M-CSF) in sepsis. Platelet consumption may also play an important role in patients with sepsis because of the ongoing generation of thrombin (which is the most potent activator of platelets *in vivo*) [18].

Studies of patients with sepsis hospitalized in the ICU have reported an overall mortality of 20%-30% [19,20]. Sepsis combined with septic shock is known to increase mortality. Many studies have shown that mortality associated with shock ranges from 20%-70%. This wide range varies according to factors such as underlying diseases, sex, and the presence of acute respiratory distress syndrome (ARDS) [19-21]. Therefore, the Surviving Sepsis Campaign aims to prevent the development of sepsis and shock and to treat shock as soon as possible once it develops. The overall mortality rate in patients with sepsis in our study was 42.5%, while the mortality rate in patients with septic shock was 22.3%. These rates are consistent with those reported worldwide [21,22]. In total, 51.7% of patients had sepsis criteria among those hospitalized in the ICU during the study period. Meanwhile, septic shock was observed in 23.1% of these patients during application of the sepsis protocol. The overall incidence of septic shock in our patients was 11.9%, which is compatible with data reported worldwide. Previous

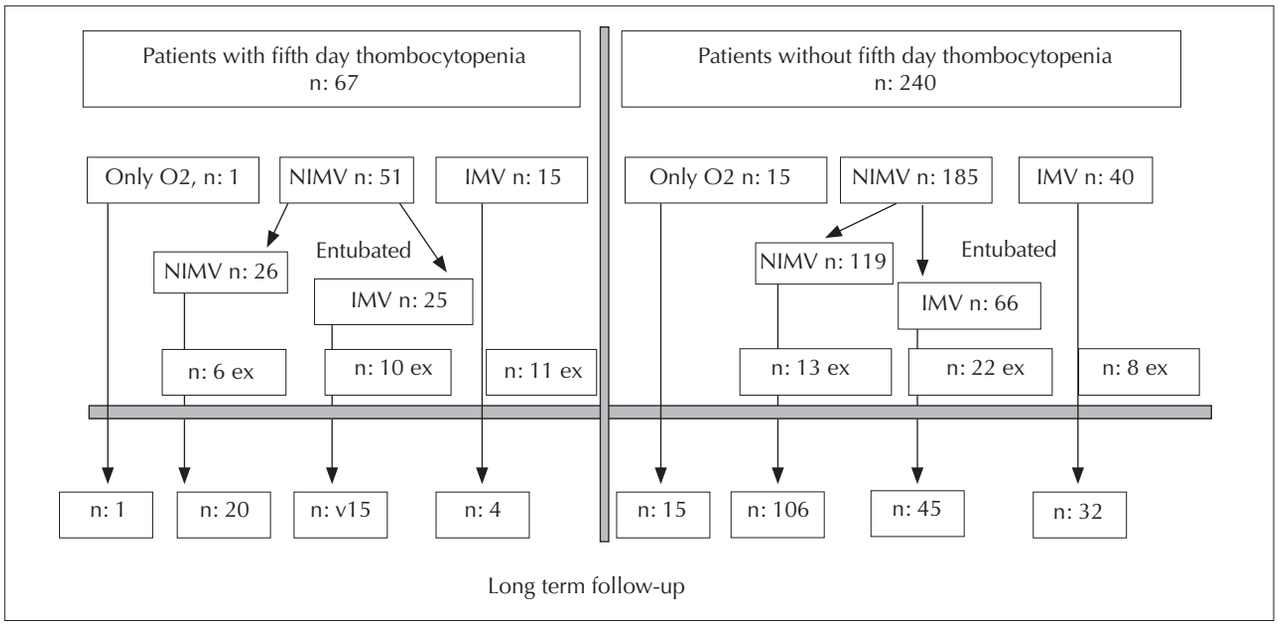

Figure 2. Mechanical ventilation in severe sepsis patients with/without fifth day thrombocytopenia.
NIMV: non-invasive mechanical ventilation, IMV: invasive mechanical ventilation.

Table 3. ICU mortality rate, application of mechanical ventilation, length of stay at ICU and hospital after ICU of the two groups

	Group 1 (n= 67)	Group 2 (n= 240)	p
MV support, n (%)	66 (98.5)	225 (93.8)	0.12
NIMV, n (%)	51 (76.1)	185 (77.1)	0.87
NIMV, day, median (IQR)	6 (2-10)	5 (3-7)	0.46
IMV, n (%)	40 (59.7)	106 (44.2)	0.024
IMV, day, median (IQR)	6 (3-8)	5 (2-8)	0.27
Presence of septic shock, n (%)	36 (53.7)	84 (35.0)	0.005
ICU length of stay, day, median (IQR)	9 (7-12)	8 (6-11)	0.067
ICU mortality, n (%)	27 (40.3)	42 (17.5)	0.001
Post-ICU length of hospital stay, day, median (IQR)	7 (4-10)	8 (5-12)	0.53

MV: mechanical ventilation; NIMV: noninvasive mechanical ventilation; IQR: interquartile ratio; IMV: invasive mechanical ventilation; ICU: intensive care unit.

Table 4. Mortality risk factors for patients with severe sepsis after logistic regression analysis

	Odds ratio	95% confidence interval	p
Fifth day thrombocytopenia at ICU	3.03	1.15-7.45	0.025
Presence of septic shock	4.97	1.79-13.86	0.002
Male gender	3.61	1.27-10.23	0.001
Low albumin level at ICU admission	0.19	0.07-0.52	0.001

ICU: intensive care unit.

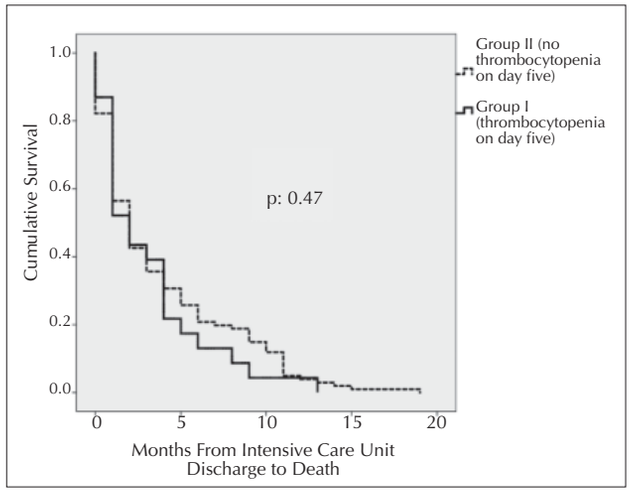

Figure 3. Long-term survival analysis of groups using Kaplan-Meier analysis after ICU discharge.

studies have reported that patients with septic shock are usually > 65 years old, male, and have comorbidities that suppress the immune system, particularly cancer [21,23]. Septic shock and male gender increased the risk of mortality 4.9- and 3.6-fold, respectively, in the present study. Because the average age of the patients in our study was 67 years, we could not demonstrate that age > 65 years is a risk factor for mortality.

Thrombocytopenia is a sepsis marker in patients with hematologic organ dysfunction [2]. It is also a significant predictor of mortality in patients with blood infections, pneumonia, and ARDS [24,25]. In a similar study performed 22 years ago with a smaller sample size than ours, a 58% incidence of thrombocytopenia and a 51% mortality rate were found among patients with sepsis [26]. Using the current sepsis protocol, we found a 40% mortality rate in the present study. In a systematic review of 6894 patients in

different ICUs (internal medicine, surgical, mixed, and trauma), the incidence of thrombocytopenia at ICU admission ranged from 8.3% to 67.6% [27]. Additionally, thrombocytopenia persisted in 13%-44% of patients during their ICU stay and was a risk factor for mortality in six of eight studies included in the review. The incidence of thrombocytopenia was 21.8% on the fifth day of the ICU stay in our study population. These variations can be explained by the differences in the definitions of thrombocytopenia; we used a definition of < 150.000/μL in the present study. Other studies have used cut-off values of 30.000, 50.000, and 100.000/μL. Worsening of thrombocytopenia during the ICU stay, particularly from day 4 to 7 of the ICU stay, has been reported as a risk factor for mortality in previous studies [6,27]. The mortality rate was two times higher in patients with severe sepsis and thrombocytopenia on the fifth day of the ICU stay in our study. Additionally, septic shock developed in half of the patients with thrombocytopenia and in one-third of the patients without thrombocytopenia. Various mediators involved in the pathogenesis of sepsis and endothelial permeability are also likely to be effective in the production of platelets and their function. Further study of platelet function and production may lead to new approaches in the treatment of septic shock.

Although few data are available on the long-term post-ICU mortality of patients with sepsis, a retrospective study showed that the life expectancy of patients who were admitted to the ICU with septic shock and survived for at least 30 days after discharge decreased from 8 to 4 years [28]. In our study, after a 12-month follow-up of patients with sepsis, male patients with septic shock were found to have shorter survival times; however, the difference was not statistically significant. Two articles published in 2004 and 2009 reported mortality rates of 36% and 37%, respectively, after prospective follow-up of patients with sepsis for 12 months; these rates were lower than the mortality rate in the present study (52.1%) [29,30]. Additionally, half of our patients died within the first 2 months of ICU discharge. This can be explained by the fact that nearly half of our patients were admitted with a diagnosis of end-stage chronic obstructive pulmonary disease (COPD).

In the present study, 61.3% of patients had positive culture results, and the rate of culture positivity was identical in the thrombocytopenic and non-thrombocytopenic groups. The most frequently isolated agents were *A. baumannii* (28.9%), *P. aeruginosa* (11.6%), *K. pneumoniae* (10.8%), and *Staphylococcus aureus* (5.1%). In an international multicentre study that examined 13.796 patients, culture specimens were taken from 51% of patients, and 70% of these cultures were positive [31]. In this same multicentre study, Gram-negative agents were mostly isolated in 62% of cases [31]. The high rate of culture isolation of *A. baumannii* in our patients may have been associated with their pre-ICU location and clinical features. Most patients were admitted to the ICU from the ICU of another center or ward. Additionally, these patients had a history of broad-spectrum antibiotic use as well as frequent and prolonged hospital admissions, which increases susceptibility to resistant pathogen growth. The higher rate of isolation of resistant pathogens in the thrombocytopenic group suggests that throbocytopenia is induced by uncontrolled infection due to these pathogens.

In this study, NIV and IMV were applied in approximately 95% of patients, while 47.6% were followed up with IMV. However, IMV was applied two-thirds more frequently in patients with thrombocytopenia on day 5 of the ICU stay. NIV was applied at a similar rate in both groups of patients. The mortality rate of patients with thrombocytopenia on day 5 was higher among those patients who underwent IMV directly upon admission than in those who underwent IMV after NIV failure (73.3% vs. 40.0%, respectively). The mortality rate in patients who underwent only NIV treatment was lower. Thus, the presence of thrombocytopenia adversely and significantly affects the response to applied mechanical ventilation and to the mortality rate. Application of NIV to clinically unstable patients with shock and ARDS is controversial and has a low success rate [32]. Because most of our patients were diagnosed with COPD, NIV might be regarded as the first-line mechanical ventilation application unless a specific contraindication exists. Additionally, because most of our patients had COPD, intubation may have been performed in worse clinical conditions, explaining the poorer prognosis.

There were several limitations to our study. First, this was a retrospective, single-center study. However, the follow-up and treatment of patients and the data collection were performed by the same physician group using the same optimized computer-based program; thus, our study provides significant international data. Second, the study was conducted in a respiratory ICU and included only patients with severe sepsis and respiratory disease. The results may differ in a different population; however, it should be noted that sepsis with a pulmonary origin constitutes the clinical condition in half of the patients in general ICUs. Third, we did not perform microbiological examinations in half of our patients. In our respiratory ICU, we routinely perform endotracheal aspiration to obtain culture specimens from intubated patients. However, sputum expectoration is not always possible in patients who are not intubated, and contamination from the oropharynx is also a problem in these patients. Finally, we could not exclude patients with possible HIT because we could not detect antibodies directed against the PF4/heparin complex in our laboratory. However, the incidence of HIT is low in ICU patients. In a large prospective study comprising 5.949 ICU patients (2.751 after cardiac surgery and 3.198 after thoracic surgery), HIT was clinically suspected in 1.7% at a median of 5 (range, 4-9) days after ICU admission [33]. Most of the studies investigating thrombocytopenia and ICU mortality exclude HIT patients using the presence of clinical criteria suggestive of HIT and the presence of platelet factor-4 antibodies [34,35]. On the other hand, in patients with HIT, the platelet count usually falls 5-14 days after heparin is first administered, and we divided our patients in two groups according to the platelet count on the fifth day because of the absence of the immunologic test. By this method, we likely eliminated patients with heparin-induced thrombocytopenia.

As far as we know, this is the first retrospective study in which patients were classified according to the fifth day thrombocyte count.

This study also had several strengths. It is one of only a few comprehensive studies investigating the long- and short-term outcomes of patients with thrombocytopenia and sepsis in the ICU. Using a current sepsis protocol, the impact of thrombocytopenia on the prognosis of sepsis was investigated in broad and specific patient populations. Patients were treated by the same intensivists and pulmonary specialists working in the ICU with 7/24 shifts, thus minimizing implementation differences.

In conclusion, this study found that thrombocytopenia on the fifth day of the ICU stay increases ICU mortality threefold. The need for IMV and frequency of septic shock were greater in these thrombocytopenic patients admitted to our ICU. We showed that male sex, a low blood albumin level, and the presence of septic shock and thrombocytopenia on day 5 of the ICU stay increased the risk of mortality to 80%. Application of IMV upon admission to the ICU significantly increases mortality. The measurement of thrombocytopenia in the ICU, which is easy and low-cost, may help to predict mortality. Thus, precautions can be taken early in patient treatment and follow-up. As we know, early intervention is crucial in the approach to sepsis.

Ethics Committee Approval: Ethic committee approval of this study was received from Internal Review Board of Kartal Lütfi Kırdar Teaching Hospital.

Informed Consent: Because of retrospective nature of study consent form was not taken from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.K., B.B., C.S., E.A.Ö., H.B.T.; Design - B.B., C.S., Z.K., H.B.T., F.K., G.H., A.Y., G.G., Ö.M.; Supervision - Z.K., B.B., A.Y., H.B.T.; Resources - B.B., F.K., G.H., E.A.Ö., Z.K., C.S., Ö.M., N.A.; Materials - B.B., E.A.Ö., H.B.T., G.H., A.Y., N.A., G.G.; Data Collection and/or Processing - C.S., B.B., E.A.Ö., N.A., Ö.M., H.B.T.; Analysis and/or Interpretation - Z.K., C.S., B.B., N.A., G.G., Ö.M., H.B.T.; Literature Search - B.B., C.S., Z.K., E.A.Ö., G.H., A.Y., F.K.; Writing Manuscript - B.B., C.S., Z.K., G.G., Ö.M., N.A., F.K.; Critical Review - B.B., Z.K., G.G., N.A., Ö.M., F.K.; Other - B.B., G.G., F.K., N.A., H.B.T.

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