Platelet transfusion and mortality in patients with sepsis-induced thrombocytopenia: A propensity score matching analysis

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Abstract

Background and Objectives: Thrombocytopenia is common among sepsis patients. Platelet transfusions are frequently administered to increase platelet counts, but their clinical impacts remain unclear in sepsis-induced thrombocytopenia. The goal of this study was to explore the association between platelet transfusion and mortality in patients with sepsis-induced thrombocytopenia.

Materials and Methods: The study was based on the Medical Information Mart for Intensive Care (MIMIC) III database. Septic patients with severe thrombocytopenia (a platelet count ≤ 50/nl) were included in the study and were divided into two groups: a platelet transfusion group (PT group) and a no platelet transfusion group (NPT group). The primary outcome was in-hospital mortality, and the secondary outcomes were the length of intensive care unit (ICU) stay (LOS-ICU) and 90-day mortality. Propensity score matching multivariable logistic regression was used to reduce the imbalance.

Results: A total of 1733 patients were included: 296 patients were included in the PT group and 1437 patients were included in the NPT group. After propensity score matching, 296 paired patients constituted each group. Crude hospital mortality was significantly higher in the PT group than in the NPT group (145 [48.99%] vs. 567 [39.46%], p = 0.002). In the extended multivariable logistic models for hospital mortality, the odds ratio (OR) of receiving a platelet transfusion was consistently significant in all six models (OR range, 1.340–1.525, p < 0.05 for all). In the following subgroups, platelet transfusion was associated with increased in-hospital mortality: age > 60 years; sex: female; sequential organ failure assessment score ≤ 8; simplified acute physiology score ≤ 47; platelet count > 29/nl and the complication of congestive heart failure. However, there were no significant differences in the 90-day mortality rate (170 [57.43%] vs. 741 [51.57%], p = 0.066) or the LOS-ICU (5.84 [2.68–11.78] vs. 4.94 [2.18–12.72], p = 0.442) between the two groups. All these results remained stable after adjustment for confounders and in the comparisons after propensity score matching.

Conclusions: The propensity score-matched analysis showed that platelet transfusion was associated with increased in-hospital mortality in septic patients with severe thrombocytopenia (a platelet count ≤ 50/nl). However, it was not associated with 90-day mortality or the length of ICU stay.

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Keywords
90-day, mortality, platelet transfusion, propensity score matching, sepsis-induced thrombocytopenia

Highlights
- Platelet transfusion was associated with increased in-hospital mortality in septic patients with severe thrombocytopenia (a platelet count ≤50/nl).
- With regard to age (>60 years), sex (female), sequential organ failure assessment score (≤8), simplified acute physiology score (≤47), platelet count (>29) and comorbidities (congestive heart failure), subgroup analyses showed that platelet transfusion was associated with increased in-hospital mortality.
- Patients with sepsis-induced thrombocytopenia might not benefit from platelet transfusion regarding 90-day mortality or length of intensive care unit stay.

INTRODUCTION

Sepsis is the most common disease in the intensive care unit (ICU), defined as a life-threatening syndrome of organ dysfunction caused by a dysregulated host response to severe infection [1], and it has been considered a major cause of health loss worldwide. According to a recent scientific publication, there were approximately 48.9 million cases and 11 million sepsis-related deaths worldwide in 2017, which accounted for almost 20% of all global deaths [2].

Clinically, a decrease in platelet count is common among patients with sepsis who are admitted to the ICU. The incidence of sepsis-induced thrombocytopenia is approximately 25% on ICU admission [3] and approximately 55% during the hospital stay [4]. Studies have confirmed that platelets play a crucial role in the inflammatory balance, immune responses, tissue repair, and regeneration, in addition to their important role in haemostasis and thrombosis [5–7]. Based on recent studies, thrombocytopenia is closely associated with multiple organ dysfunction syndromes, prolonged ICU stay and high mortality in sepsis patients [8]. In addition, thrombocytopenia is an early prognostic marker for septic shock onset in ICU patients in the first 24 h [9]. Nonresolution of thrombocytopenia is associated with increased 28-day mortality in this population [3].

In general, the recovery of thrombocytopenia in septic patients is always accompanied by the control of infection and improvement of the patient’s condition. Recently, several studies have explored the impact of platelet-elevating drugs (recombinant human thrombopoietin, rhTPO) on sepsis-induced thrombocytopenia, which showed that rhTPO could lead to the quick recovery of the platelet count and improve the prognosis of patients with severe sepsis-induced thrombocytopenia [10–12]. Platelet transfusions are the most common clinical therapy to increase platelet counts. However, platelet transfusion is limited in clinical practice and does not have a precise indication in sepsis patients [13, 14]. There are no large prospective clinical trials exploring the impact of platelet transfusion on sepsis-induced thrombocytopenia. Two of the main challenges with performing a randomized controlled trial are (1) challenges in recruiting participants from this relatively uncommon and acutely ill patient group and (2) obtaining buy-in from clinicians.

A recent large registry study showed that platelet transfusion was not associated with an increased risk of death in critically ill patients [15]. Nonetheless, there is no large study based on platelet transfusion in severe sepsis-induced thrombocytopenia investigating whether platelet administration influences the prognosis of sepsis patients. In this study, we aimed to determine the potential association between platelet transfusion and clinical outcomes in sepsis patients. We hypothesized that platelet transfusions in this population are associated with worse clinical outcomes, including in-hospital mortality, 90-day mortality and length of ICU stay.

METHODS

Database

This was a retrospective study based on the online international Medical Information Mart for Intensive Care III (MIMIC III) database [16]. The MIMIC III database is a large, single-centre database comprising information related to patients admitted to the critical care units at the Beth Israel Deaconess Medical Center, which is a fully integrated medical centre that provides adult care, with over 1250 full-time medical staff managing more than a half a million outpatient visits each year. The database contains information for 46,520 patients admitted to the critical care units between 2001 and 2012. All the patients included in the database were deidentified, and the need for informed consent was waived. One author (A.Z.) obtained access to this database (certification number 35752875) and was responsible for data extraction.

Study population and definitions

Septic patients with a platelet count level ≤50/nl were eligible for inclusion in our study. Sepsis was defined according to the third
sepsis definition [1], which was defined as a suspected infection and an acute change in patients with a total sequential organ failure assessment (SOFA) score ≥2 points. For patients who were readmitted to the ICU, only data from the first ICU admission were included. Patients younger than 18 years or older than 89 years were excluded. The primary outcome was in-hospital mortality. The secondary outcomes were 90-day mortality and the length of ICU stay (LOS-ICU).

Propensity score matching

Propensity score matching (PSM) was used to minimize the imbalance of the confounding factors between the PT and no platelet transfusion (NPT) groups. A one-to-one nearest neighbour matching algorithm was applied with a calliper width of 0.05 in our study. The following variables were selected to generate the propensity score: age, sex, SOFA score, simplified acute physiology score II (SAPS II), platelet count, diabetes mellitus, hypertension, chronic pulmonary disease, congestive heart failure, cancer, obesity, anaemia, haemorrhage, minimum haemoglobin (Hb_min) and maximum activated partial thromboplastin time (APTT_max).

The management of missing data

Variables with missing data are common in the MIMIC III database. For C-reactive protein, serum lactate, albumin and procalcitonin values, more than 20% were missing and were removed from this analysis. For other continuous variables with missing values less than 5%, the missing values were replaced by the mean or median values.

Statistical analysis

Continuous variables are depicted as medians with interquartile ranges. Student's t-test, analysis of variance, the Wilcoxon rank-sum test or the Kruskal–Wallis test was used as appropriate. Categorical data are shown as frequencies and proportions, and they were compared using the χ² test. The association between platelet transfusion and in-hospital mortality was determined by logistic regression, including the baseline as a covariate and the group as a fixed factor. An extended logistic model approach was used for adjusting the following covariates, and subgroup analysis was performed as described above: platelet count, age, sex, SOFA score, SAPS II score, comorbidities (chronic pulmonary disease, congestive heart failure and anaemia) and minimum haemoglobin (Hb_min). The survival outcome comparisons between the groups were analysed by the log-rank test. PSM was used to minimize the imbalance between groups. A two-tailed test was performed, and p < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using the R package (version 3.6.3).

Ethics statement

The use of the MIMIC III database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and informed consent were waived for this manuscript.

RESULTS

Baseline characteristics

The data of 1733 patients were included. The flow chart of patient selection is presented in Figure 1. The overall 90-day mortality rate was 52.6%. The comparisons of the baseline characteristics are listed in Table 1. Patients in the PT group were younger than those in the NPT
Comparisons of the baseline characteristics between patients with and without platelet transfusion

Note

Abbreviations: APTT_max, maximum of activated partial thromboplastin time; Hb_min, minimum of haemoglobin; ICU, intensive care unit; LOS-ICU, length of ICU stays; PT_max, maximum of prothrombin time; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment.

The results of the univariable analysis showed that platelet transfusion was associated with higher in-hospital mortality (OR, 1.473; 95% CI, 1.146–1.894; p = 0.002). After the confounders (platelet count, SOFA score, SAPS II score, age, sex, comorbidities [chronic pulmonary disease, congestive heart failure, anaemia] and minimum haemoglobin [Hb_min]) were adjusted, platelet transfusion was also associated with increased mortality in patients with the following characteristics: age > 60 years (OR, 1.599; 95% CI, 1.055–2.422; p = 0.018), a platelet count > 29/nl (OR, 1.671; 95% CI, 1.138–2.454; p = 0.009), a SAPS II score ≤ 47 (OR, 1.585; 95% CI, 1.086–2.312; p = 0.017), a platelet count > 29/nl (OR, 1.815; 95% CI, 1.108–2.971; p = 0.018), and the complication of congestive heart failure (OR, 1.599; 95% CI, 1.055–2.422; p = 0.027). However, there was no significant difference in survival at 90 days between the groups according to Kaplan–Meier survival estimates (Figure 3).

### Table 1

| Variables | No platelet transfusion (n = 1437) | Platelet transfusion (n = 296) | p-value |
|-----------|----------------------------------|------------------------------|---------|
| Age (years), median (IQR) | 61.66 (51.00–72.79) | 57.16 (48.49–68.92) | 0.001* |
| Male, n (%) | 784 (54.56) | 168 (56.76) | 0.489 |
| Comorbidities, n (%) | | | |
| Diabetes mellitus | 311 (21.64) | 71 (23.99) | 0.376 |
| Hypertension | 199 (13.85) | 44 (14.86) | 0.646 |
| Chronic pulmonary | 239 (16.63) | 29 (9.80) | 0.003* |
| Congestive heart failure | 311 (21.64) | 87 (29.39) | 0.004* |
| Cancer | 225 (15.66) | 44 (14.86) | 0.732 |
| Obesity | 65 (4.52) | 8 (2.70) | 0.156 |
| Anaemia | 179 (12.46) | 53 (17.91) | 0.012* |
| Haemorrhage | 29 (2.02) | 11 (3.72) | 0.076 |
| Disease severity scores, median (IQR) | | | |
| SOFA score on ICU admission | 8.00 (6.00–11.00) | 8.00 (6.00–11.00) | 0.806 |
| SAPS II on ICU admission | 47.00 (37.00–57.00) | 46.00 (37.00–55.00) | 0.534 |
| Biochemical indices, median (IQR) | | | |
| Platelet count | 31.00 (19.00–41.00) | 20.00 (11.00–33.00) | <0.001* |
| Hb_min | 7.60 (6.80–8.40) | 7.50 (6.80–8.03) | 0.012* |
| PT_max | 20.40 (16.20–28.90) | 19.90 (16.10–27.15) | 0.368 |
| APTT_max | 58.40 (38.90–115.50) | 59.30 (38.70–150.00) | 0.493 |
| Clinical outcomes | | | |
| LOS-ICU (day), median (IQR) | 4.94 (2.18–12.72) | 5.84 (2.68–11.78) | 0.442 |
| In-hospital mortality, n (%) | 567 (39.46) | 145 (48.99) | 0.002* |
| Mortality of 90 days, n (%) | 741 (51.57) | 170 (57.43) | 0.066 |

Note: Values are shown as medians with interquartile ranges (IQRs) unless otherwise indicated. p values comparing platelet transfusion group (PT group) to no platelet transfusion group (NPT group).

Abbreviations: APTT_max, maximum of activated partial thromboplastin time; Hb_min, minimum of haemoglobin; ICU, intensive care unit; LOS-ICU, length of ICU stays; PT_max, maximum of prothrombin time; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment.

*p < 0.05.

The platelet count was significantly lower in patients who received platelet transfusions (20.00 [11.00–33.00] vs. 31.00 [19.00–41.00], p < 0.001). The SOFA score on admission was similar in the PT group and the NPT group (8.00 [6.00–11.00] vs. 8.00 [6.00–11.00], p = 0.806). Patients in the PT group were more likely to have congestive heart failure (87 [29.39%] vs. 311 [21.64%], p = 0.004), while more patients in the NPT group were complicated with chronic pulmonary disease, congestive heart failure, anaemia and minimum haemoglobin (Hb_min) were adjusted, platelet transfusion was also associated with increased mortality in patients with the following characteristics: age > 60 years (OR, 1.599; 95% CI, 1.055–2.422; p = 0.009) (Figure 2). In the extended multivariable logistic models (Table 2), we found that the OR of platelet transfusion was consistently significant in all six models (OR range, 1.340–2.971; p < 0.05 for all). Subgroup analysis was performed according to age, sex, SOFA score, SAPS II score, platelet count and congestion heart failure (Figure 2). In the subgroup analysis, platelet transfusion was significantly associated with increased mortality in patients with the following characteristics: age > 60 years (OR, 1.599; 95% CI, 1.055–2.422; p = 0.027), female sex (OR, 1.563; 95% CI, 1.022–2.391; p = 0.040), a SOFA score ≤ 8 (OR, 1.671; 95% CI, 1.138–2.454; p = 0.009), a SAPS II score ≤ 47 (OR, 1.585; 95% CI, 1.086–2.312; p = 0.017), a platelet count > 29/nl (OR, 1.815; 95% CI, 1.108–2.971; p = 0.018), and the complication of congestive heart failure (OR, 1.599; 95% CI, 1.055–2.422; p = 0.027). However, there was no significant difference in survival at 90 days between the groups according to Kaplan–Meier survival estimates (Figure 3).

### Association between platelet transfusion and patient outcomes

The results of the univariable analysis showed that platelet transfusion was associated with higher in-hospital mortality (OR, 1.473; 95% CI, 1.146–1.894; p = 0.002). After the confounders (platelet count, SOFA score, SAPS II score, age, sex, comorbidities [chronic pulmonary disease, congestive heart failure, anaemia] and minimum haemoglobin [Hb_min]) were adjusted, platelet transfusion was also associated with increased mortality in patients with the following characteristics: age > 60 years (OR, 1.599; 95% CI, 1.055–2.422; p = 0.027), female sex (OR, 1.563; 95% CI, 1.022–2.391; p = 0.040), a SOFA score ≤ 8 (OR, 1.671; 95% CI, 1.138–2.454; p = 0.009), a SAPS II score ≤ 47 (OR, 1.585; 95% CI, 1.086–2.312; p = 0.017), a platelet count > 29/nl (OR, 1.815; 95% CI, 1.108–2.971; p = 0.018), and the complication of congestive heart failure (OR, 1.599; 95% CI, 1.055–2.422; p = 0.027). However, there was no significant difference in survival at 90 days between the groups according to Kaplan–Meier survival estimates (Figure 3).
Outcomes after propensity score matching

After PSM, 296 patients from each group were matched by a 1:1 matching algorithm (Table 3). For assessing the overall quality of the matched sample, the standardized difference of the means and the ratio of the variances between the propensity scores of both groups were compared, and the propensity scores between the groups were also inspected. There was no significant difference between the two matched groups with regard to any of the 15 covariates (age, sex, SOFA score, SAPS II score, platelet count, diabetes mellitus, hypertension, chronic pulmonary disease, congestive heart failure, cancer, obesity, Hb_min, APTT_max, anaemia and haemorrhage). Among the
296 propensity-matched pairs, we found that the hospital mortality rate in the PT group was higher than that in the NPT group (145 [48.99%] vs. 121 [40.88%], \( p = 0.047 \)). However, the 90-day mortality rate was not different between the groups (170 [57.43%] vs. 155 [52.36%], \( p = 0.215 \)), and similar results were shown for LOS-ICU (5.84 [2.68–11.78] vs. 5.90 [2.35–14.70], \( p = 0.594 \)) (Table 3).

### DISCUSSION

The present study demonstrated that platelet transfusion was associated with increased in-hospital mortality in sepsis patients with severe thrombocytopenia. This result was robust in the PSM analysis after adjustment for covariates and remained consistent in the extended multivariable logistic models. Additionally, for patients with sepsis-induced thrombocytopenia, platelet transfusion was not associated with an increased risk of 90-day mortality or increased LOS-ICU. According to our findings, platelet transfusion was associated with worse clinical outcomes in sepsis patients with severe thrombocytopenia (a platelet count \( \leq 50/\text{nl} \)).

According to previous research, nearly 35%–59% of patients with sepsis develop thrombocytopenia [17, 18], which has been recognized as an independent risk factor for mortality and a marker for disease severity [19]. The mechanisms of sepsis-induced thrombocytopenia are complex and probably correlate with various factors. For instance, endothelial dysfunction is a major consequence of sepsis and plays a crucial role in platelet activation and consumption [20]. This activation, which results in aggregation, is increased locally by cytokine production [21]. In addition, altered thrombopoiesis and/or hae-mophagocytosis are the major causes of thrombocytopenia, which is potentiated by sepsis mediators [22]. In addition, fluid resuscitation and surgical operation may influence platelet count.

Sepsis patients with platelet count less than 50/nl are considered to have sepsis-induced thrombocytopenia [23], which has high mortality and poor prognosis. It has been reported that the nonresolution of thrombocytopenia was associated with increased 28-day mortality instead of thrombocytopenia itself [3]. In our study, the in-hospital mortality rate was 41.08% and the 90-day mortality rate was 52.57%, which were higher than those in other studies [24]. A lower platelet count level (the median value was 29/nl) and a higher disease severity score (the median SOFA score value was 8 and the median SAPS II score value was 47) were the two main reasons for the high mortality rate in our study. Currently, there is no effective treatment for this condition. Infection control, organ support therapy, and immune

### Table 3 Comparisons of the covariates after propensity score matching

| Variables | No platelet transfusion (n = 296) | Platelet transfusion (n = 296) | \( p \)-value |
|-----------|----------------------------------|---------------------------------|--------------|
| Age (years), median (IQR) | 56.86 (45.21–67.63) | 57.16 (48.49–68.92) | 0.260 |
| Male, n (%) | 163 (55.07) | 168 (56.76) | 0.679 |
| Comorbidities, n (%) | | | |
| Diabetes mellitus | 57 (19.26) | 71 (23.99) | 0.162 |
| Hypertension | 30 (10.14) | 44 (14.86) | 0.082 |
| Chronic pulmonary | 19 (6.42) | 29 (9.80) | 0.132 |
| Congestive heart failure | 97 (32.77) | 87 (29.39) | 0.375 |
| Cancer | 41 (13.85) | 44 (14.86) | 0.725 |
| Obesity | 8 (2.70) | 8 (2.70) | 1.000 |
| Anaemia | 40 (13.51) | 53 (17.91) | 0.142 |
| Haemorrhage | 7 (2.36) | 11 (3.72) | 0.338 |
| Disease severity scores, median (IQR) | | | |
| SOFA score on ICU admission | 8.50 (6.00–11.00) | 8.00 (6.00–11.00) | 0.860 |
| SAPS II on ICU admission | 47.00 (36.00–56.25) | 46.00 (37.00–55.00) | 0.571 |
| Biochemical indices, median (IQR) | | | |
| Platelet count | 23.00 (13.00–35.00) | 20.00 (11.00–33.00) | 0.113 |
| Hb_min | 7.50 (6.80–8.30) | 7.50 (6.80–8.03) | 0.256 |
| PT_max | 19.05 (15.70–25.63) | 19.90 (16.10–27.15) | 0.118 |
| APTT_max | 59.95 (38.55–134.50) | 59.30 (38.70–150.00) | 0.702 |
| Clinical outcomes | | | |
| LOS-ICU (day), median (IQR) | 5.90 (2.35–14.70) | 5.84 (2.68–11.78) | 0.594 |
| In-hospital mortality, n (%) | 121 (40.88) | 145 (48.99) | 0.047* |
| Mortality of 90 days, n (%) | 155 (52.36) | 170 (57.43) | 0.215 |

Abbreviations: APTT_max, maximum of activated partial thromboplastin time; Hb_min, minimum of haemoglobin; ICU, intensive care unit; LOS-ICU, length of ICU stays; PT_max, maximum of prothrombin time; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment.

* \( p < 0.05 \).
response regulation remain the mainstream treatments. In recent years, several studies have suggested that rhTPO could rapidly lead to a recovery of the platelet count, increase the number of survival days and reduce the 28-day mortality rate in sepsis patients with severe thrombocytopenia [10, 12]. Nevertheless, another study found that rhTPO was efficacious in increasing the patients’ platelet counts, resulting in a shorter ICU stay (9.20 ± 5.38 vs. 10.88 ± 6.82 days, \( p = 0.047 \)) for patients with severe thrombocytopenia and patients with severe sepsis, while there was no significant difference in 28-day mortality (rhTPO group: 25.0% vs. control group: 34.1%, \( p = 0.158 \)) [25]. Therefore, the question of whether patients with sepsis-induced thrombocytopenia can benefit from rhTPO therapy still remains according to the controversial results.

Platelet transfusion is a regular clinical practice in thrombocytopenic patients for preventing and treating haemorrhages. Approximately 1,937,000 platelet component transfusions were given in the United States in 2017 [26]. Several pieces of evidence suggest that platelet transfusion is associated with adverse effects, such as infection [27]. Some experts believe that conventional platelet transfusion therapy may worsen patients’ procoagulant and anticoagulant disorders. A prospective nonrandomized observational study revealed that prophylactic platelet transfusion was associated with an increased risk of thrombosis and mortality [28]. Another publication found that platelet transfusion was associated with higher risks of arterial thrombosis and mortality among thrombotic thrombocytopenic purpura (TTP) and heparin-induced thrombocytopenia (HIT) patients [29]. A cross-sectional study reported that platelet transfusion was associated with increased mortality and comorbidities in premature infants with thrombocytopenia [30]. In addition, platelet transfusion rates were associated with hospital mortality (adjusted relative risk per 5 ml/kg/d increase: 1.12; 95% CI 1.02–1.23, \( p = 0.02 \)) among neonates receiving extracorporeal membrane oxygenation (ECMO) [31]. In our study, we found nearly the same results among sepsis patients with thrombocytopenia: platelet transfusion was associated with an increased risk of in-hospital mortality. This might have something to do with the influence of platelet transfusion that promotes the formation of microthrombi in sepsis patients and thus aggravates microcirculatory obstructions. Moreover, subgroup analysis revealed that platelet transfusion was significantly associated with increased mortality in patients with the following characteristics: age > 60 years, female sex, a SOFA score ≤ 8, a SAPS II score ≤ 47, a platelet count >29/nl and the complication of congestive heart failure. It is known that both older age (age > 60 years) and the complication of congestive heart failure are risk factors for venous thromboembolism (VTE). Platelet transfusion might not be suitable for patients with these two features, which would increase the risk of VTE and lead to a worse outcome. According to our findings, platelet transfusion may be harmful to patients with sepsis-induced thrombocytopenia. It seems that platelet transfusion is not an effective rescue therapy and does not improve the prognosis in patients with sepsis-induced thrombocytopenia.

There are still several limitations to the present study. First, as a retrospective design, the adjustment of missing relevant data was not allowed. Although we did perform propensity score matching to reduce the imbalance, the estimation of the propensity score could only be based on the acquirable data. Second, bacterial species and sources were not recorded in our data, and the purpose of platelet transfusion was also unknown. Thus, these two aspects could not be included in the analysis. Third, other outcomes (such as bleeding, thrombosis, and infection) were absent, and further hypotheses about the reasons for the observed association were not possible. Last, since this was an observational study, the association between platelet transfusion and clinical outcomes was not a causality. Therefore, well-organized prospective randomized clinical trials are required to verify the role of platelet transfusion in sepsis-induced thrombocytopenia.

In conclusion, platelet transfusion is associated with increased inhospital mortality in septic patients with severe thrombocytopenia (a platelet count ≤ 50/nl). However, it may not be associated with 90-day mortality or the length of ICU stay. Further prospective studies will be needed in the future to confirm these results.

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A.Z. conceived the study and extracted the data. A.Z. and S.W. performed the statistical analyses. A.Z. and S.W. wrote the manuscript. J.P. and Q.C. reviewed the data analysis and interpretation and revised the manuscript for the final version. All authors read and approved the final manuscript. We thank Dr. Xianwei Zhang (The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China) and Dr. Jiejie Cai (The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang) for their help in this revision.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT
The datasets are available in the MIMIC III database (https://physionet.org/works/MIMICIII/).
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