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

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Research Article

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Abstract

Thrombocytopenia is common among sepsis patients. Platelet transfusion is frequently administered to increase platelet counts but its 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 based on the Medical Information Mart for Intensive Care (MIMIC) III database. In this study, we included 1733 patients with sepsis-induced thrombocytopenia, and these patients were divided into two groups: platelet transfusion group (PT group) and no platelet transfusion group (NPT group). Propensity-score matching was used to reduce the imbalance. We found that patients in the PT group had a higher in-hospital mortality as compared with the NPT group. Furthermore, in the subgroup of age (>60 years), gender (female), sequential organ failure assessment score (≤8), simplified acute physiology score (≤47), platelet count (>27/nL), congestive heart failure, platelet transfusion was associated with increased in-hospital mortality. However, there was no significant difference in the 90-day mortality and the length of ICU stays (LOS-ICU) between these two groups. All these results remain stable after adjustment for confounders and in the comparisons after propensity score matching. In conclusion, platelet transfusion was associated with increased in-hospital mortality in patients with sepsis-induced thrombocytopenia.

1. Introduction

Sepsis is the most common disease in the intensive care unit (ICU), defined as a life-threatening syndrome of organ dysfunction which was caused by the 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 about 48.9 million cases and 11 million sepsis-related deaths worldwide in 2017, which accounted for almost 20% of all global deaths [2].

Clinically, platelet count decrease is common among patients with sepsis who are admitted to the ICU. The incidence of sepsis-induced thrombocytopenia is around 25% on ICU admission [3] and approximately 55% during the hospital stay [4]. Studies have confirmed that platelets play a crucial role in inflammatory balance, immune responses, tissue repair, and regeneration, beyond their important role in hemostasis 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]. Besides, thrombocytopenia is an early prognostic marker for ICU patients in the first 24h of septic shock onset [9]. And non-resolution of thrombocytopenia is associated with increased 28-day mortality in this population [3].

In general, after controlling the infection and improving the patient's conditions, sepsis-induced thrombocytopenia is gradually returning to be normal. Recently, several studies have showed that recombinant human thrombopoietin (rhTPO) can lead to the quick recovery of the platelet count and improve the prognosis of patients with sepsis-induced severe thrombocytopenia [10-12]. And platelet transfusion is the most common clinical therapy to increase platelet counts. In theory, one standard unit

dose of platelet transfusion can elevate platelet counts by 2010^9/L. However, platelet transfusion is limited in clinical practice and has a rigorous indication in sepsis patients [13,14] because of resource scarcity, transfusion-related immune, and infectious complications. Thus, large prospective clinical trials are restricted in the exploration of the platelet transfusion impact on sepsis-induced thrombocytopenia.

According to a recent large registry study, it showed that platelet transfusion was not associated with the 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 could influence the prognosis of sepsis patients. In this study, we aimed to determine the potential association between platelet transfusion and clinical outcomes including in-hospital mortality, 90-day mortality and the length of ICU stays (LOS-ICU).

2. Methods

2.1 Database

This was a retrospective study based on an online international database, Medical Information Mart for Intensive Care III (MIMIC III), compromising the information of 46,520 critically ill patients who have been admitted to the Beth Israel Deaconess Medical Center from 2001 to 2012[16]. All the patients in the database were de-identified, and the need for informed consent was waived. One author (AZ) obtained access to this database (certification number 35752875) and was responsible for data extraction.

2.2 Study population and definitions

Septic patients with a platelet count level $\leq$ 50/nL were eligible for inclusion in our study. And sepsis was defined according to the third sepsis definition [1], which was extracted as suspected infection and an acute change in cases that total Sequential Organ Failure Assessment (SOFA) score $\geq$ 2 points. For patients who were readmitted to the ICU, only the first ICU admissions were included. For patients younger than 18 years or older than 89 years were excluded. The primary outcome was in-hospital mortality. The secondary outcome was 90-day mortality and the length of ICU stay (LOS-ICU).

2.3 Propensity score matching

PSM was used to minimize the imbalance of the confounding factor between the PT and the NPT groups. A one-to-one nearest neighbor matching algorithm was applied with a caliper width of 0.05 in our study. The following variables were selected to generate the propensity score: age, gender, SOFA, Simplified Acute Physiology score II (SAPS II), platelet count, diabetes mellitus, hypertension, chronic pulmonary, congestive heart failure, cancer, obesity, anemia, hemorrhage, minimum of hemoglobin (Hb_min), maximum of activated partial thromboplastin time (APTT_max).

2.4 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.

2.5 Statistical analysis

Continuous variables were depicted as medians with interquartile ranges (IQRs). Student's *t* test, analysis of variance, Wilcoxon rank-sum test, or Kruskal-Wallis test were used, as appropriate. Categorical data were shown as frequencies and proportions, and they were compared using the $\chi 2$ test. The association between platelet transfusion and in-hospital mortality was determined by logistic regression including the baseline as the covariate and the group as a fixed factor. An extended logistic model approach was used for covariate adjustment: platelet count, age, gender, SOFA score, SAPSII score, etc. The survival outcomes comparisons between the groups were analyzed 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).

3. Results

3.1 Baseline characteristics

The data of 1733 patients were included. The flow chart of patient selection is presented in Fig. 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 group (57.16(48.49-68.92) vs. 61.66(51.00-72.79), p=0.001). The platelet count was significantly lower in patients with platelet transfusion (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 combine with congestive heart failure (87(29.39%) vs. 311(21.64%), p=0.004), while more patients in the NPT group were complicating with chronic pulmonary (29(9.80%) vs. 239(16.63%), p=0.003). The hospital mortality was significantly higher in the PT group comparing to the NPT group (145(48.99%) vs. 567(39.46%), p=0.002). However, there were no significant difference in the 90-day mortality rate (170(57.43%) vs. 741(51.57%), p=0.066) and the LOS-ICU (5.84(2.68-11.78) vs. 4.94(2.18-12.72), p=0.442) between the PT group and the NPT group.

Table 1 Comparisons of the baseline characteristics between patients with and without platelet transfusion

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
Anemia	179 (12.46)	53 (17.91)	0.012 *
Hemorrhage	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

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).

SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score; Hb_min: minimum of hemoglobin; PT_max: maximum of prothrombin time; APTT_max: maximum of activated partial thromboplastin time; LOS-ICU: length of ICU stays.

3.2 Association between platelet transfusion and mortality

On univariable analysis, we observed that platelet transfusion was associated with higher in-hospital mortality (OR, 1.473; 95%CI, 1.146-1.894; p=0.002). After confounders (platelet count, SOFA score, SAPSII score, age, gender, etc.) were adjusted, it revealed that platelet transfusion was also associated with the hospital mortality (OR, 1.473; 95%CI, 1.113-1.948; p=0.007) (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 1.340-1.525, p<0.05 for all). Subgroup analysis was performed according to the age, gender, SOFA score, SAPSII score, platelet count, congestive heart failure (Figure 2). In the subgroup analysis, platelet transfusion was significantly associated with increased mortality in patients with these characteristics: age >60 years (OR, 1.599; 95%CI, 1.055-2.422; p=0.027), female (OR, 1.563; 95%CI, 1.022-2.391; p=0.040), SOFA score ≤8 (OR, 1.671; 95%CI, 1.138-2.454; p=0.009), SAPSII ≤47 (OR, 1.585; 95%CI,

1.086-2.312; p=0.017), platelet count >29/nL (OR, 1.815; 95%CI, 1.108-2.971; p=0.018), and complicated with congestive heart failure (OR, 1.599; 95%CI, 1.055-2.422; p=0.027). However, there was no significant difference on the survival days at 90 days between the groups according to Kaplan-Meier survival estimates (Figure 3).

Table 2 Association between platelet transfusion and hospital mortality using an extended model approach

	Odds ratio of platelet transfusion	95% confidence interval	P
Model 1	1.473	(1.146-1.894)	0.002 *
Model 2	1.340	(1.036-1.732)	0.026 *
Model 3	1.397	(1.077-1.811)	0.012 *
Model 4	1.525	(1.156-2.012)	0.003 *
Model 5	1.467	(1.109-1.941)	0.007 *
Model 6	1.473	(1.113-1.948)	0.007 *

Adjusted covariates: Model 1 = platelet transfusion. Model 2 = Model 1 + (platelet count). Model 3 = Model 2 + (gender, age). Model 4 = Model 3 + (SOFA score, SAPSII score). Model 5 = Model 4 + (Chronic pulmonary, Congestive heart failure, Anemia). Model 6 = Model 5 + (Hb_min).

3.3 Outcomes after propensity score matching

After PSM, 296 cases from each group were matched by a 1:1 matching algorithm (Table 3). To assess 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 was also inspected. There was no significant difference between the two matched groups with regards to all fifteen covariates (age, gender, SOFA, SAPSII, platelet count, diabetes mellitus, hypertension, chronic pulmonary, congestive heart failure, cancer, obesity, Hb_min, APTT_max, anemia, hemorrhage). Among the 296 propensity-matched pairs, we found that the hospital mortality in the PT group was higher than in the NPT group (145(48.99%) vs. 121(40.88%), p=0.047). However, the 90-day mortality rate had no evident difference between the groups (170(57.43%) vs. 155(52.36%), p=0.215), and LOS-ICU showed the similar results (5.84(2.68-11.78) vs. 5.90(2.35-14.70), p=0.594) (Table 3).

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
Anemia	40 (13.51)	53 (17.91)	0.142
Hemorrhage	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

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).

SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score; Hb_min: minimum of hemoglobin; PT_max: maximum of prothrombin time; APTT_max: maximum of activated partial thromboplastin time; LOS-ICU: length of ICU stays.

4. 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 increased risk of the 90-day mortality or the LOS-ICU. According to our findings, it seems that platelet transfusion is not a reasonable choice to rescue sepsis-induced thrombocytopenia for improving the prognosis of sepsis patients with severe thrombocytopenia.

A low platelet count, thrombocytopenia, commonly occurs in sepsis patients. According to previous research, nearly 35% to 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]. Moreover, it is also an important index to evaluate the prognosis of patients [20]. Sepsis patients with a low platelet count or dynamic thrombocytopenia show a poor prognosis and increased mortality [21]. The mechanisms of sepsis-induced thrombocytopenia are complex and probably involve various factors. For instance, endothelial dysfunction is a major consequence of sepsis and plays a crucial role in platelet activation and consumption [22]. This activation which results in aggregation is increased locally by cytokine production [23]. Besides, altered thrombopoiesis and/or hemophagocytosis is the major causes of thrombocytopenia, which would be potentiated by sepsis mediators [24]. In addition, fluid resuscitation and surgical operation may have an influence on platelet count.

Sepsis patients with platelet counts less than 50/nL are considered to have sepsis-induced thrombocytopenia [25], which has a high mortality and poor prognosis. It has been reported that non-resolution of thrombocytopenia was associated with increased 28-day mortality, instead of thrombocytopenia itself [3]. Currently, there is no effective treatment for this condition. Infection control, organ support therapy and immune response regulation remain the mainstream treatments. In recent years, recombinant human thrombopoietin (rhTPO) was reported improving platelet count and reducing platelet transfusion possibility among patients with severe sepsis and thrombocytopenia in a prospective study [10]. In another research, it suggested that the rescue therapy with rhTPO could rapidly lead to a recovery of the platelet count, increase survival days and reduce the 28-day mortality in sepsis patients with severe thrombocytopenia [12]. Nevertheless, Yu Liu et al. found that rhTPO is efficacious in increasing the patients' platelet counts, resulting in a shorter ICU stay time (9.20±5.38 vs 10.88±6.82, p=0.047) for patients with severe thrombocytopenia or patients with severe sepsis, while there was no significant difference in 28-days mortality (rhTPO group: 25.0% vs. control group: 34.1%, p=0.158) between the two groups [26]. Therefore, whether can patients with sepsis-induced thrombocytopenia benefit from rhTPO therapy still remains a question according to the controversial results.

Platelet transfusion is a regular clinical practice in thrombocytopenic patients for preventing or treating hemorrhages. Approximately 1,937,000 platelet component transfusions are given in the United States in 2017[27]. There are several evidences suggesting that platelet transfusion is associated with adverse effects including infection [28]. Some experts believe that conventional platelet transfusion therapy may worsens patient's procoagulant and anticoagulant disorders. In a prospective nonrandomized observational study, it revealed that prophylactic platelet transfusion was associated with increased risk of thrombosis and mortality [29]. Another publication found that platelet transfusion was associated with higher risks of arterial thrombosis and mortality among TTP and HIT patients [30]. In a cross-sectional study, it reported that platelet transfusion was associated with increase mortality and comorbidities in premature infants with thrombocytopenia [31]. Besides, platelet transfusion rates were associated with hospital mortality (adjusted relative risk per 5ml/kg/d increase: 1.12; 95%CI 1.02-1.23, p=0.02) among neonates receiving extracorporeal membrane oxygenation (ECMO) [32]. In our study, we found nearly the same results among sepsis patients with thrombocytopenia, that platelet transfusion was associated with increased risk of in-hospital mortality. Moreover, subgroup analysis revealed that platelet transfusion was significantly associated with increased mortality in patients with these characteristics: age >60

years, female, SOFA score ≤8, SAPSII ≤47, platelet count >29/nL, and complicated with congestive heart failure. Regarding to our findings, platelet transfusion may be harmful for patients with sepsis-induced thrombocytopenia. And it seems to be reasonable to avoid unnecessary transfusions.

In present study, there are still several limitations. Firstly, as a retrospective design, the adjustment of relevant but missing data was not allowed. Although we did perform propensity score matching to reduce the imbalance, estimation of the propensity score could only be based on the acquirable data. Secondly, bacteria 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. Thirdly, patients who have been administrated with β-lactam or sulfa antibiotics, which may result in antibiotic-induced thrombocytopenia, did not excluded in this study. Lastly, well-organized prospective randomized clinical trials are required to verify the role of platelet transfusion in sepsis-induced thrombocytopenia.

5. Conclusions

In conclusion, platelet transfusion is associated with increased in-hospital mortality in patients with sepsis-induced thrombocytopenia. However, it maybe not associated with 90-day mortality and the length of ICU stay. And further prospective studies will be needed in the future to confirm these results.

Abbreviations

MIMIC III: Medical Information Mart for Intensive Care III; PT group: Platelet Transfusion group; NPT group: No Platelet Transfusion group; ICU: Intensive Care Unit; LOS-ICU: length of ICU stay; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score II; CI: Confidence interval; HR: hazard ratio; OR: odd ratio; rhTPO: recombinant human thrombopoietin; PSM: propensity score matching; IQRs: interquartile ranges.

Declarations

Authors' contributions

AZ designed the study, extracted the data and performed all statistical analyses. SW wrote the draft of the manuscript. JP, QC, LC review the data analysis and interpretation, and revised the manuscript for the final version. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

The datasets are available in the MIMIC III database (https://physionet.org/works/MIMICIIIClinicalDatabase/files/).

Ethics approval and consent to participate

The MIMIC III database was approved by the Massachusetts Institute of Technology (Cambrige, 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.

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Figures

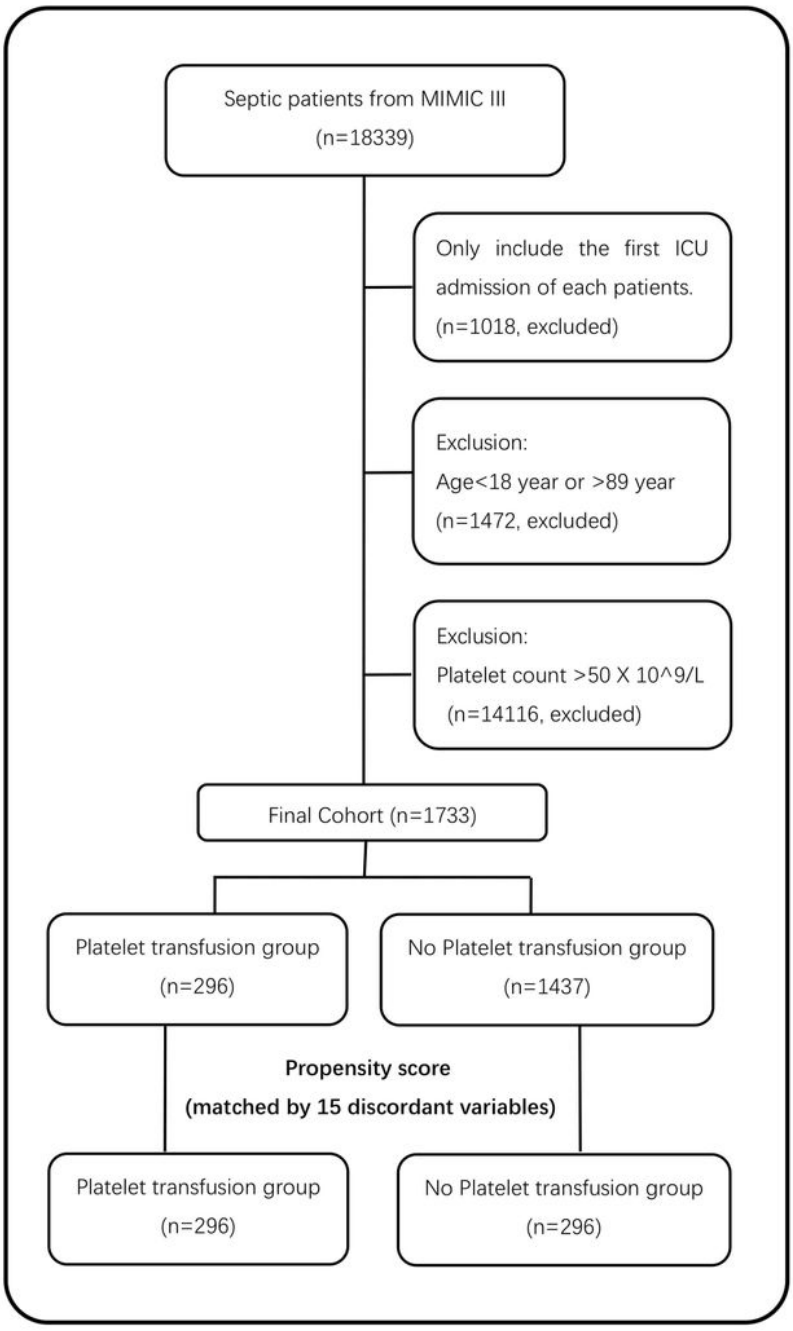

Figure 1

Flow chart of patient selection from the MIMIC III database

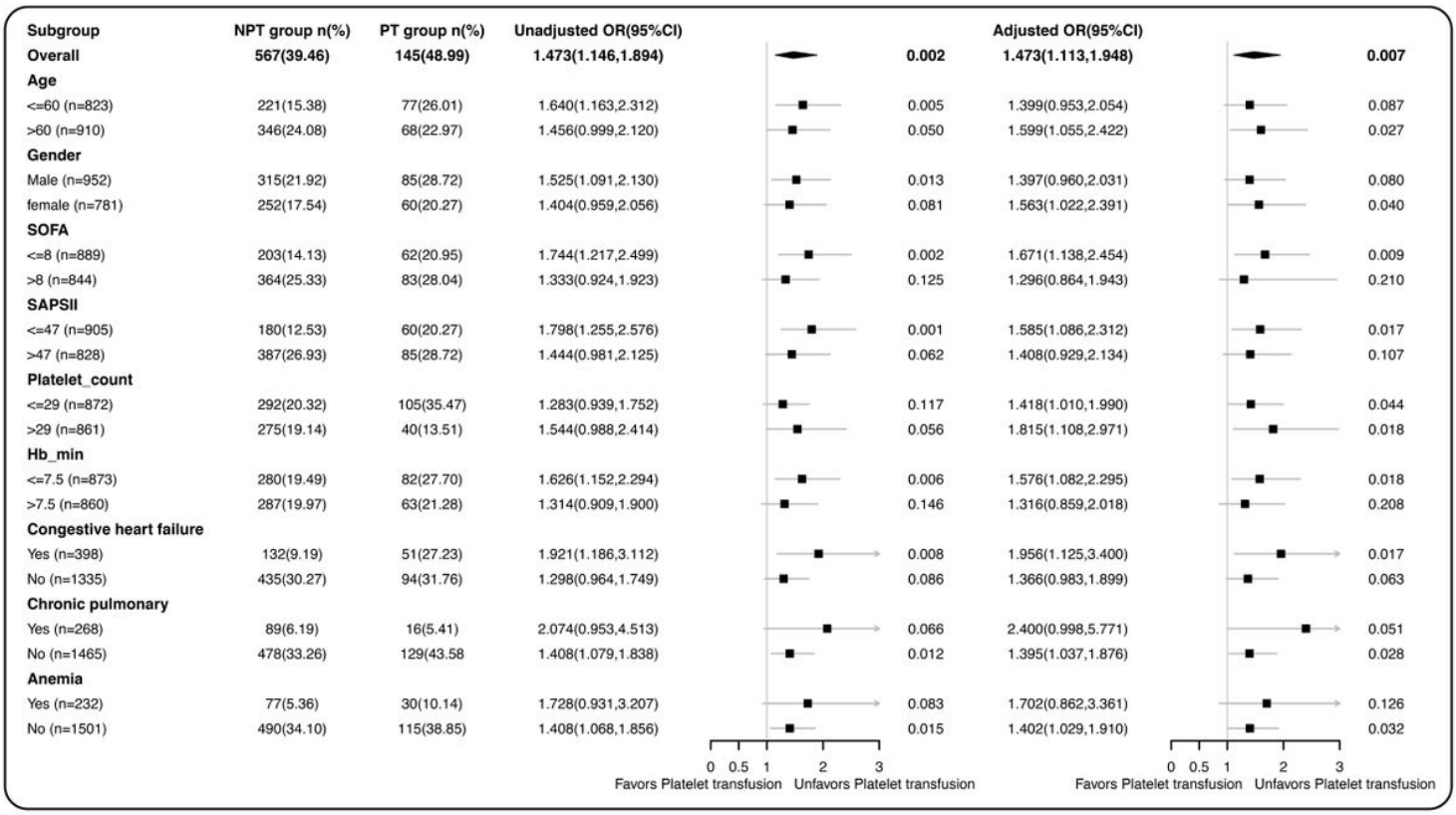

Figure 2

Subgroup analysis of the association between hospital mortality and platelet transfusion. CI: Confidence interval; OR: Odds Ratio; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score.

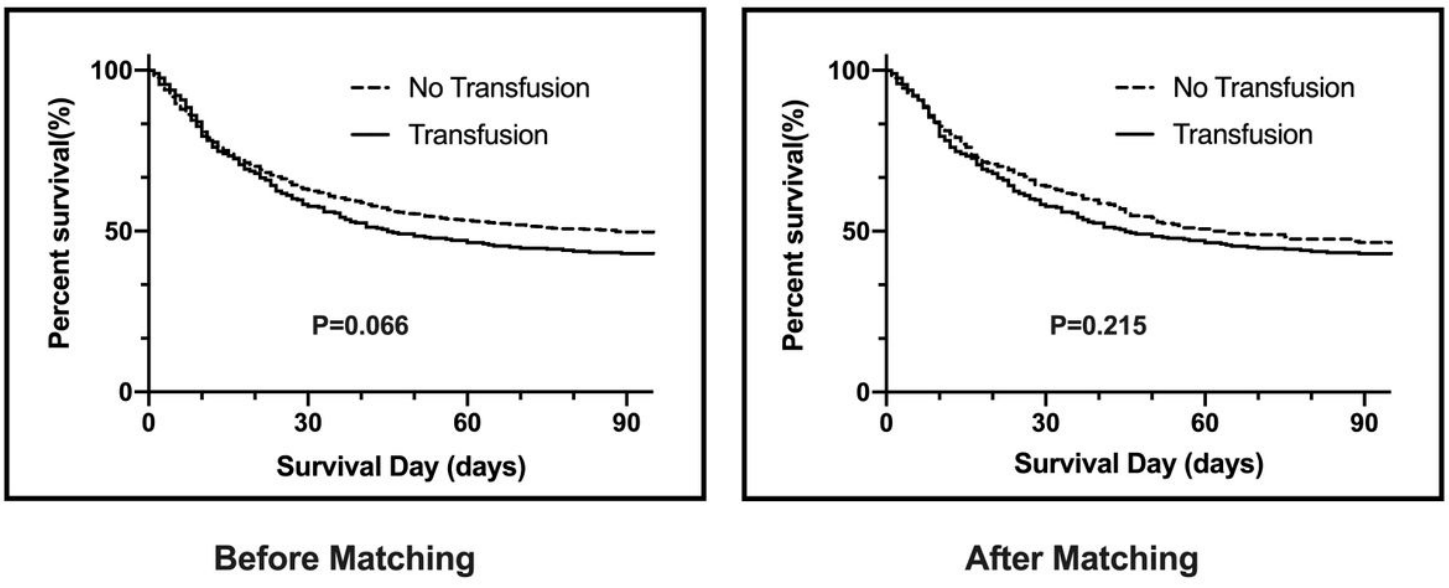

Figure 3

The 90-day survival curves of the Platelet transfusion group (PT group) and No platelet transfusion group (NPT group).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile2Table1Baseline.tiff
- Addtionalfile3Table2BeforeMatch.tiff
- Additionalfile4Table3AfterMatch.tiff