

Platelet Transfusion is Not Associated with the Better Outcomes of Patients with Sepsis-Induced Thrombocytopenia: A Propensity Score-Matching Analysis.

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Research

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Abstract

Background: The association of platelet transfusion and short-term mortality in patients with sepsis-induced thrombocytopenia remains unclear. Therefore, we intended to explore whether platelet transfusion could make a difference for patients with sepsis-induced thrombocytopenia.

Methods: The study was based on the Medical Information Mart for Intensive Care (MIMIC) III database. Sepsis patients were divided into those with or without platelet transfusion (Platelet Transfusion group [PT group] and No Platelet Transfusion group [NPT group], respectively) during hospital stay. The primary outcome was 28-day all-cause mortality, and secondary outcomes were length of ICU stay (LOS-ICU) and survival days of 28. Propensity-score matching was used to reduce the imbalance.

Results: We included 1733 patients: 296 patients in the PT group and 1437 patients in the NPT group. Overall, 655 patients died by day 28. After propensity score matching, 294 paired patients constituted each group. 28-day mortality did not decrease in PT patients comparing to NPT patients (120 [40.54%] vs. 535 [37.23%] deaths; $P=0.29$). LOS-ICU was similar between PT group and NPT group (5.84[2.68-11.78] vs. 4.94[2.18-12.72]; $P=0.44$). After confounders were adjusted for, it showed no difference between PT group and NPT group in 28-day mortality (hazard ratio [HR], 1.28;95% confidence interval [CI], [0.96, 1.17]; $P=0.09$) or LOS-ICU (odd ratio [OR], 0.09; 95%CI, [-1.45, 1.62]; $P=0.91$). Survival at 28 days showed no difference between the groups according to Kaplan-Meier survival estimates. After propensity score matching, platelet transfusion was also not associated with 28-mortality or LOS-ICU.

Conclusions: In the propensity score-matched analysis, there is no evidence that platelet transfusion is beneficial for patients with sepsis-induced thrombocytopenia, neither 28-mortality nor LOS-ICU.

Background

Sepsis is the most common disease in the intensive care unit (ICU), defined as a life-threatening syndrome of organ dysfunction caused by dysregulated host response to a severe infection(1), 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 decreased is very common among patients with sepsis 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 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 syndrome, prolonged ICU stay and high mortality in sepsis patients(8, 9). Besides, thrombocytopenia was an early prognostic marker for ICU patients in the first 24h of septic shock onset(10). And non-resolution of thrombocytopenia was associated with increased 28-day mortality in this population (9).

In general, accompanied by control of infection and improvement of the patient's conditions, sepsis-induced thrombocytopenia is gradually returning to be normal. Recently, several studies 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(11–13). 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 $20 \times 10^9/L$. However, because of resource scarcity, transfusion-related immune and infectious complications, platelet transfusion is limited in clinical practice and has a rigorous indication in sepsis patients(14, 15), which in return restricts large prospective clinical trials conducted to explore the impact of platelet transfusion on sepsis-induced thrombocytopenia.

According to a recent large registry study, it showed that platelet transfusion were not associated with increased risk of death in critically ill patients(16). Nonetheless, there has been no large study of platelet transfusion in severe sepsis-induced thrombocytopenia to investigate whether platelet administration can improve the prognosis of sepsis patients. Therefore, in this study, we aimed to determine the possible association between platelet transfusion with outcomes including 28-day mortality and length of ICU stay.

Methods

Database introduction

This was a retrospective study based on an online international database, Medical Information Mart for Intensive Care III (MIMIC III), comprising the information of 46,520 critically ill patients admitted to the Beth Israel Deaconess Medical Center from 2001 to 2012(17).

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.

Study Population And Definitions

Septic patients with a platelet count level $\leq 50 \times 10^9/L$ 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 total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points. 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 28-day mortality. The secondary outcome was length of ICU stay (LOS-ICU).

Propensity Score Matching

PSM was used to minimize the imbalance of the confounding factor between the PT and NPT groups. A one-to-one nearest neighbor matching algorithm was applied with a caliper width of 0.02 in our study. The following variables were selected to generate the propensity score: age, gender, SOFA, Simplified Acute Physiology score II (SAPSI), platelet count, platelet transfusion, diabetes mellitus, hypertension, chronic pulmonary, congestive heart failure, cancer.

Management Of Missing Data

Variables with missing data are common in the MIMIC III database. For C-response 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 were expressed as means with standard deviations or medians with interquartile ranges (IQRs), as appropriate. 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 compared using the X² test. The association between platelet transfusion and 28-day mortality was determined by logistic regression including the baseline as the covariate and the group as a fixed factor. 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).

Results

Baseline characteristics

Data on 1733 patients were included. The flow chart of patient selection is presented in Additional file 1. The overall 28-day mortality rate was 38.9%. The comparisons of the baseline characteristics are listed in Additional file 2. Patients in PT group were younger than those in NPT group [58.17 ± 14.56 vs. 61.00 ± 15.14 , $P = 0.001$]. The platelet count was significantly lower in patients with platelet transfusion [22.37 ± 12.84 vs. 29.60 ± 13.35 , $P < 0.001$]. The SOFA score on admission was similar in PT group and NPT group [8.81 ± 3.84 vs. 8.79 ± 3.98 , $P = 0.81$]. Patients in PT group were more likely to combining with congestive heart failure [87(29.39%) vs. 311(21.64%), $P = 0.004$], while more patients in NPT group were complicating with chronic pulmonary [29(9.80%) vs. 239(16.63%), $P = 0.003$]. The mortality of 28 days had no significant difference between the PT group and NPT group [120(40.54%) vs. 535(37.23%), $P = 0.29$].

Association Between Platelet Transfusion And Patient Outcomes

On univariable analysis, risk of 28-day mortality was similar between the PT group and NPT group [hazard ratio (HR), 1.15(0.89–1.48), $P = 0.29$]. After confounders including platelet count and SOFA score, were adjusted for, platelet transfusion was also not associated with overall 28-day mortality [HR, 1.28(0.96,1.71), $P = 0.09$] (Additional file 3, 5) or LOS-ICU [odds ratio (OR), 0.08(-1.45, 1.61), $P = 0.92$] (Additional file 3). Also, there was no significant difference on survival at 28 days between the groups, according to Kaplan-Meier survival estimates (Additional file 6).

Outcomes After Propensity Score Matching

After PSM, 294 cases from each group were matched by a 1:1 matching algorithm (Additional file 2). The overall quality of the matched sample was assessed by comparing the standardized difference of the means and the ratio of the variances between the propensity scores of both groups as well as by graphically inspecting the propensity scores between the groups. There was no significant difference between the two matched groups with regards to all eleven covariates, including age, gender, SOFA, SAPSII, platelet count, platelet transfusion, diabetes mellitus, hypertension, chronic pulmonary, congestive heart failure, cancer (Additional file 2). Among the 294 propensity-matched pairs, we found that the 28-day mortality had no evident difference between the groups [119(40.48%) vs. 107(36.40%), $P = 0.309$] (Additional file 2, 4, 7), and LOS-ICU was comparable [5.73(2.68–11.76) vs. 5.90(2.33–14.26), $P = 0.606$] (Additional file 2, 4).

Discussion

The present study demonstrates that platelet transfusion in sepsis patients with severe thrombocytopenia is not associated with 28-day mortality or LOS-ICU. This result was robust in the PSM analysis after adjustment for covariates including platelet counts and SOFA scores. According to our findings, it seems that platelet transfusion is not a reasonable choice to correct sepsis-induced thrombocytopenia, aiming at improving the prognosis of sepsis patients with severe thrombocytopenia.

A low platelet count, thrombocytopenia, commonly occurs in sepsis patients. According to previous research, nearly 35–59% of patients with sepsis develop thrombocytopenia(18, 19), which has been recognized as an independent risk factor for mortality and a marker for disease severity(20). Moreover, it is also an important index to evaluate the prognosis of patients(21). Sepsis patients with a low platelet count or dynamic thrombocytopenia show a poor prognosis and increased mortality (22). There are several main mechanism of developing thrombocytopenia in sepsis patients: 1) bacteria and their products directly inhibit bone marrow hematopoietic function and destroy megakaryocytes, which results in decreased platelet production; 2) platelet aggregation and destruction are increased due to the host's own immunity and other factors, such as nonspecific platelet-associated antibodies and cytokine-driven

hemophagocytosis of platelets (23); 3) activated platelet mediate the reaction between leukocytes and endothelial cells by secreting cytokines, which amplifies the host inflammatory response and further reduces the number of platelet in the circulation via positive feedback; 4) fluid resuscitation and surgical operation may have an influence on platelet count.

Sepsis patients with platelet counts less than $50 \times 10^9/L$ are considered to have sepsis-induced thrombocytopenia (24), which has a high mortality and poor prognosis. It was reported that non-resolution of thrombocytopenia was associated with increased 28-day mortality, instead of thrombocytopenia itself (9). 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 (11). In another research, it suggested that 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 (25). 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 patients with sepsis-induced thrombocytopenia can 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 some 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. However, the other study noted that platelet transfusion was not associated with increased mortality or infective complications following first cardiac surgery (29). A recent publication by Ning S and colleagues reported that platelet transfusions were not associated with increased risk of death in critically ill patients neither in ICU (HR, 0.78; 95%CI, 0.60–1.02; $p = 0.41$) nor in hospital (HR, 0.89; 95%CI, 0.68–1.09; $p = 0.41$)(16). In our study, we found nearly the same result among sepsis patients with thrombocytopenia, that platelet transfusion was not associated with increased risk of 28-day mortality or LOS-ICU. Regarding to our negative finding, platelet transfusion cannot benefit patients with sepsis-induced thrombocytopenia, which may also put patients into a potential risk of infection, it is 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 that were not recorded in our data 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 analyze the role of platelet transfusion in sepsis-induced thrombocytopenia and identify patients most likely to benefit from platelet transfusion.

Conclusions

In our study, we found that there is no evidence that platelet transfusion is beneficial for patients with sepsis-induced thrombocytopenia, neither 28-mortality nor LOS-ICU. However, this is a retrospective study, and more further prospective studies will be need in the future to address the benefits and harms of platelet transfusion in sepsis patients with thrombocytopenia, to distinguish different subtypes of sepsis for which platelet transfusions may be of benefit, and to develop optimal platelet transfusion thresholds to better guide clinical treatment.

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

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Availability of data and materials

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

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.

Ethics approval and consent to participate

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.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–10.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395:200–11.
3. Chakradhar Venkata R, Kashyap JC, Farmer B, Afessa. Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. *J Intensive Care*. 2013;1:1–10.
4. Sharma B, Sharma M, Majumder M, Steier W, Sangal A, Kalawar M. Thrombocytopenia in septic shock patients—a prospective observational study of incidence, risk factors and correlation with clinical outcome. *Anaesth Intensive Care*. 2017;35:874–80.
5. Cedervall J, Hamidi A, Olsson A-K, Platelets. NETs and cancer. *Thromb Res*. 2018;164:148–52.
6. Sreeramkumar V, Adrover JM, Ballesteros I, Cuartero MI, Rossaint J, Bilbao I, et al. Neutrophils scan for activated platelets to initiate inflammation. *Science*. 2014;346:1234–8.
7. Jenne CN, Kubers P. Platelets in inflammation and infection. *Platelets*. 2015;00:1–7.

8. Greco E, Lupia E, Bosco O, Vizio B, Montrucchio G. Platelets and Multi-Organ Failure in Sepsis. *Int J Mol Sci.* 2017;18:2200.
9. Venkata C, Kashyap R, Farmer JC, Afessa B. Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. 2013;1:1–10.
10. Thiery-Antier N, Biquet C, Vinault S, Meziani F, Boisramé-Helms J, Quenot J-P. Is Thrombocytopenia an Early Prognostic Marker in Septic Shock? *Crit Care Med.* 2016;44:764–72.
11. MD QW, FACS JRM, MD XW, MD GW, MD GG, MD SL, et al. Recombinant human thrombopoietin improves platelet counts and reduces platelet transfusion possibility among patients with severe sepsis and thrombocytopenia: A prospective study. *J Crit Care.* 2014;29:362–6.
12. Zhou Z, Feng T, Xie Y, Huang P, Xie H, Tian R, et al. The effect of recombinant human thrombopoietin (rhTPO) on sepsis patients with acute severe thrombocytopenia: a study protocol for a multicentre randomised controlled trial (RESCUE trial). *BMC Infect Dis.* 2019;19:1–7.
13. Zhou Z, Feng T, Xie Y, Zhang X, Du J, Tian R, et al. Prognosis and rescue therapy for sepsis-related severe thrombocytopenia in critically ill patients. *Cytokine.* 2020;136:155227.
14. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med.* 2017;45(3):486–552.
15. Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program.* 2007;2007:172–8.
16. Ning S, Liu Y, Barty R, Cook R, Rochweg B, Iorio A, et al. The association between platelet transfusions and mortality in patients with critical illness. *Transfusion.* 2019;9999:1–9.
17. Johnson AEW, Pollard TJ, Shen L, Lehman L-WH, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. *Sci Data.* 2016;3:1–9.
18. Levi M, Löwenberg EC. Thrombocytopenia in critically ill patients. *Semin Thromb Hemost.* 2008;34:417–24.
19. Yasser Sakr MB, BCh P, PhD J-LVM, MD ER, MD MP, MD EI, MD KR, et al. Sepsis and organ system failure are major determinants of post-intensive care unit mortality. *J Crit Care.* 2008;23:475–83.
20. Claushuis T-AM, Vught L-A, Scicluna B-P, Wiewel M-A, Klouwenberg P-MC, Hoogendijk A-J, et al. Thrombocytopenia is associated with a dysregulated host response in critically ill sepsis patients. *Blood.* 2016;127(24):3062–72.
21. Levi M. Platelets in Critical Illness. *Semin Thromb Hemost.* 2016;42:252–7.
22. Sacha F, de Stoppelaar C, van't Veer TAM, Claushuis, Bregje JA, Albersen, Joris JTH, Roelofs. Tom van der Poll. Thrombocytopenia impairs host defense in gram-negative pneumonia-derived sepsis in mice. *Blood.* 2014;124(25):3781–90.
23. Laursen MA, Larsen JB, Larsen KM, Hvas A-M. Platelet function in patients with septic shock. *Thromb Res.* 2019;185:33–42.

24. Guclu E, Durmaz Y, Karabay O. Effect of severe sepsis on platelet count and their indices. *Afr Health Sci.* 2013;13:333–8.
25. Zhou Z, Feng T, Xie Y, Zhang X, Du J, Tian R, et al. Prognosis and rescue therapy for sepsis-related severe thrombocytopenia in critically ill patients. *Cytokine.* 2020;136:155227–7.
26. Liu Y, Jin G, Sun J, Wang X, Guo L. Recombinant human thrombopoietin in critically ill patients with sepsis-associated thrombocytopenia: A clinical study. *Int J Infect Dis.* 2020;98:144–9.
27. Jefferson M, Jones, Mathew RP, Sapiano AA, Savinkina KA, Haass ML, Baker RA, Henry, et al. Slowing decline in blood collection and transfusion in the United States-2017. *Transfusion.* 2020;9999:1–9.
28. Aubron C, Flint AW, Bailey M, Pilcher D, Cheng AC, Hegarty C, et al. Is platelet transfusion associated with hospital-acquired infections in critically ill patients? *Crit Care.* 2017;21:1–8.
29. Ninkovic S, McQuilten Z, Gotmaker R, Newcomb AE, Cole-Sinclair MF. Platelet transfusion is not associated with increased mortality or morbidity in patients undergoing cardiac surgery. *Transfusion.* 2018;58:1218–27.

Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Figures

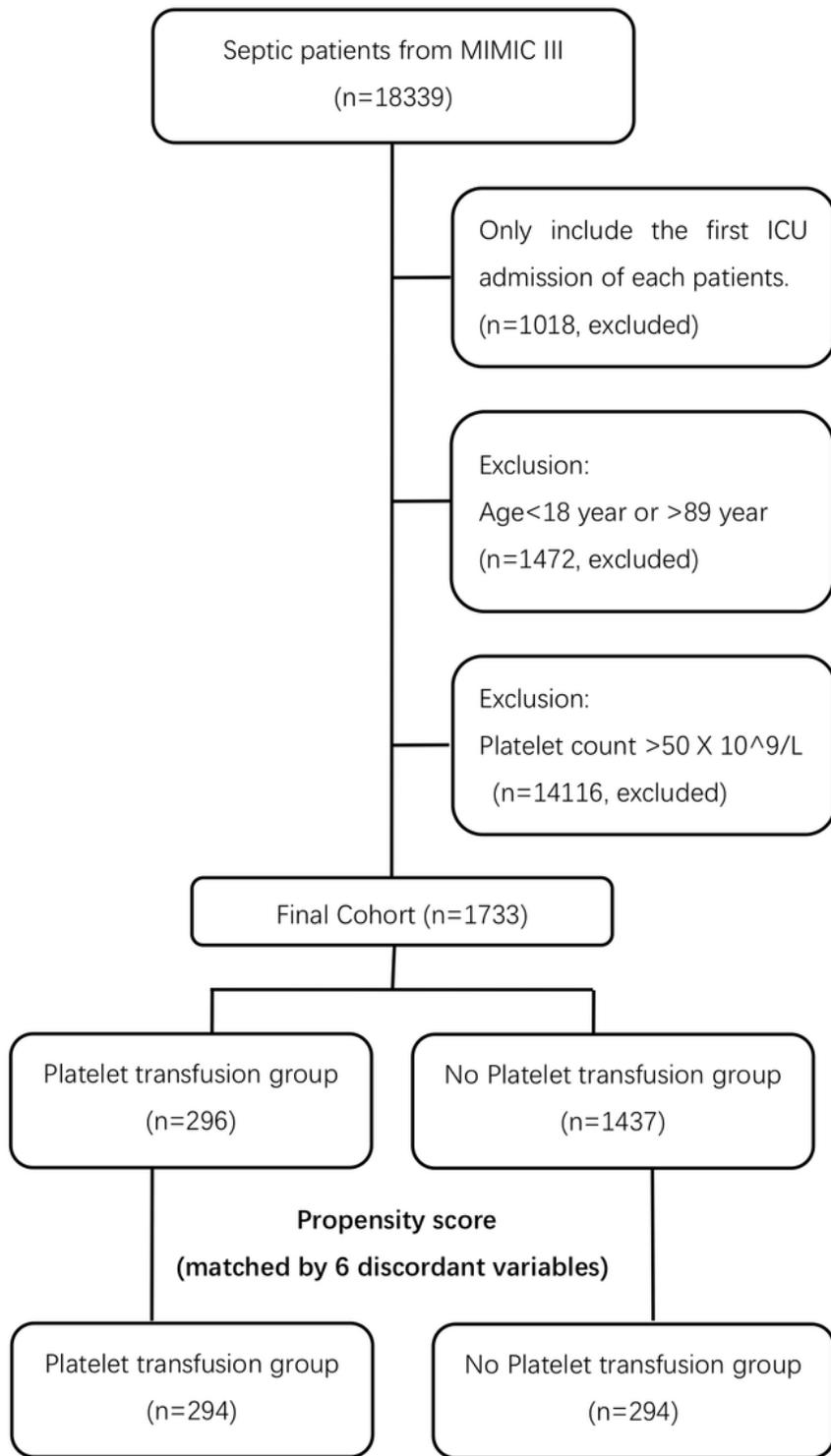


Figure 1

Flow chart of patient selection from the MIMIC III database

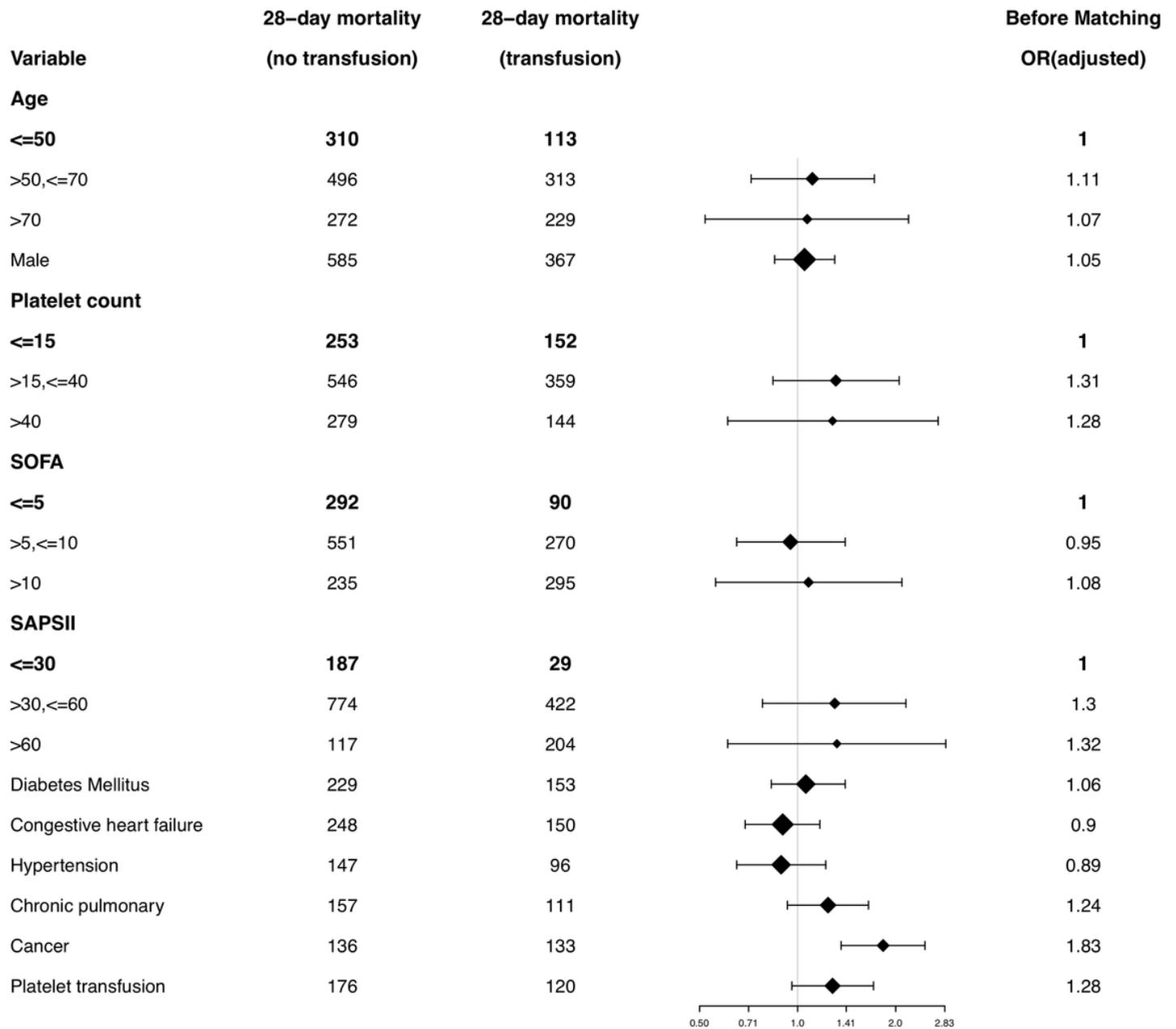
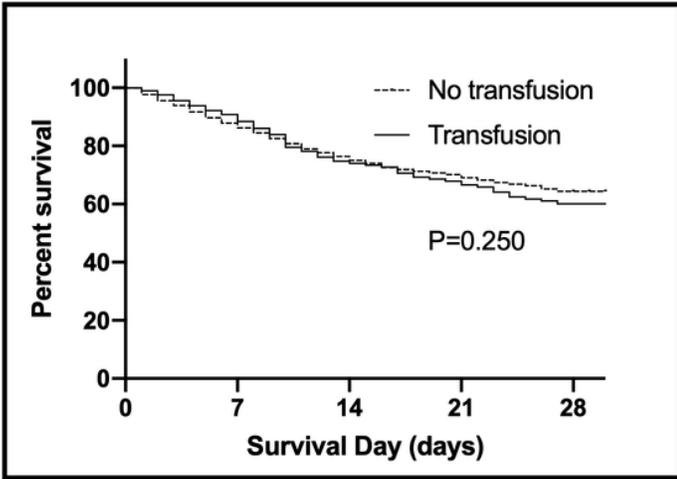
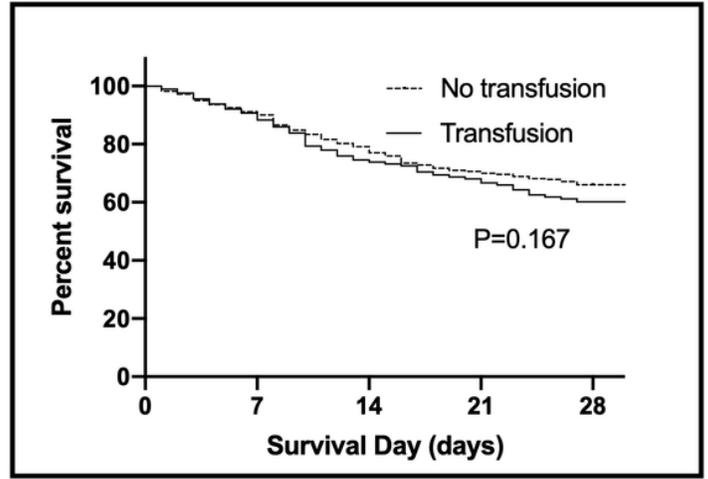


Figure 2

Analysis of the association between platelet transfusion and 28-day mortality before PSM Description: OR: Odds ratio; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score. OR was adjusted by age, male, platelet count, SOFA, SAPSII, Diabetes Mellitus, Congestive heart failure,



Before PSM



After PSM

Figure 3

The 28-day survival curves of the Platelet transfusion and No Platelet Transfusion groups before and after PSM

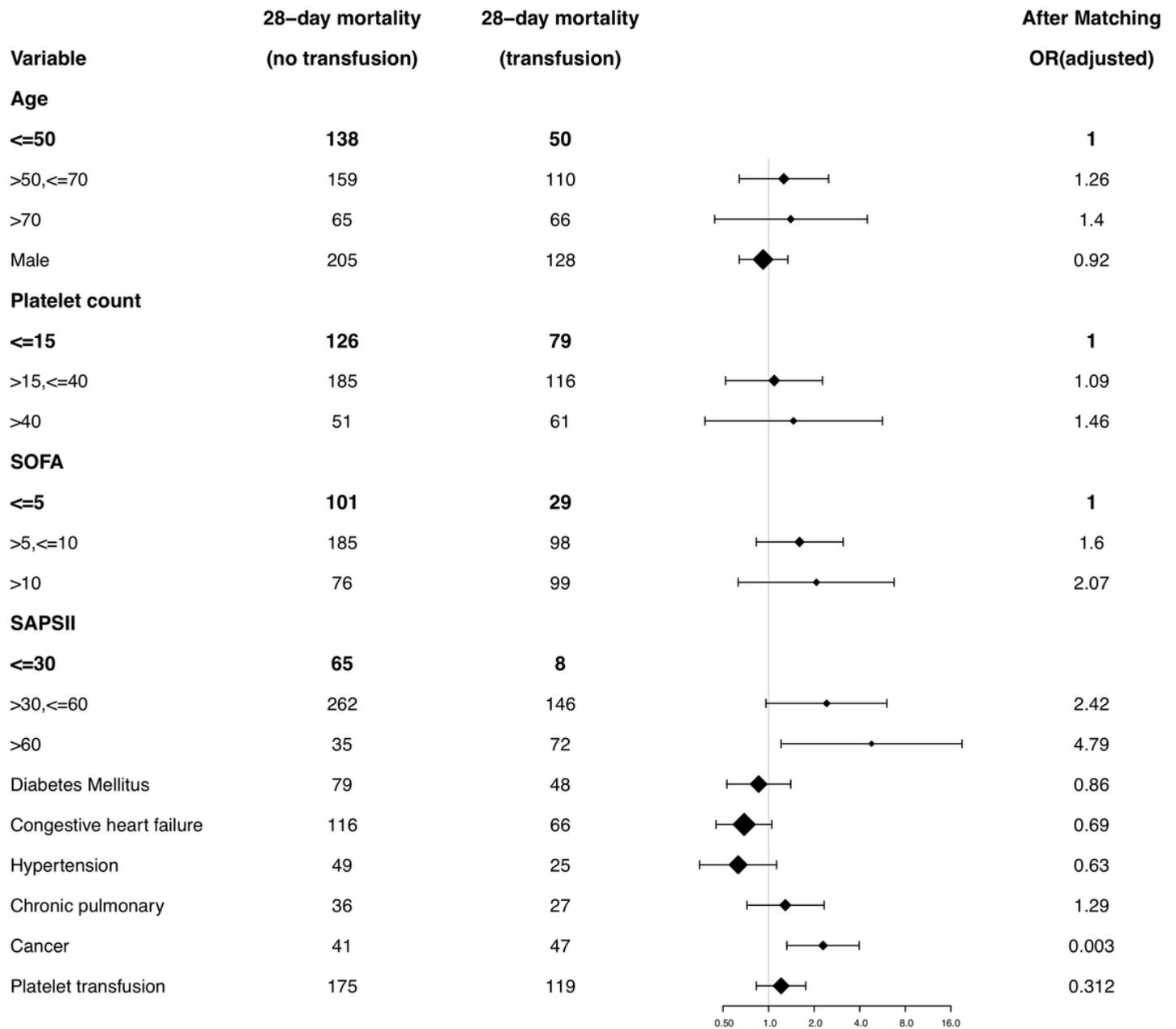


Figure 4

Analysis of the association between platelet transfusion and 28-day mortality after PSM Description: OR: Odds ratio; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score. OR was adjusted by age, male, platelet count, SOFA, SAPSII, Diabetes Mellitus, Congestive heart failure, Hypertension, Chronic pulmonary, Cancer.

Supplementary Files

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- Additionalfile2Table1Baseline.tiff
- Additionalfile3Table2BeforeMatch.tiff
- Additionalfile4Table3AfterMatch.tiff
- TableS1LOSICUBeforeMatch.tiff
- TableS2LOSICUAfterMatch.tiff