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IMPACT OF PLATELET TRANSFUSION THRESHOLDS ON OUTCOMES OF PATIENTS WITH SEPSIS: ANALYSIS OF THE MIMIC-IV DATABASE

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ABSTRACT—**Background:** The benefits of platelet thresholds for transfusion remain unclear. This study assessed the effect of two transfusion thresholds on the survival outcomes of patients with sepsis and thrombocytopenia. **Methods:** In this retrospective cohort study, data of patients with sepsis admitted to an intensive care unit (ICU) and who had received platelet transfusion were extracted from the Medical Information Mart for Intensive Care IV database. Patients were classified into the lower-threshold group (below 20,000/μL) and higher-threshold group (20,000–50,000/μL), based on thresholds calculated from their pretransfusion platelet count. The endpoints included 28- and 90-day mortality, red blood cell (RBC) transfusion, ICU-free days, and hospital-free days. **Results:** There were 76 and 217 patients in the lower-threshold and higher-threshold groups, respectively. The higher-threshold group had a higher rate of surgical ICU admission (35.0% vs. 9.2%) and lower quick Sequential Organ Failure Assessment (qSOFA) score than the lower-threshold group. In the higher-threshold group, 94 (43.3%) and 132 (60.8%) patients died within 28 and 90 days, compared to 51 (67.1%) and 63 (82.9%) patients in the lower-threshold group (adjusted odds ratio, 1.96; 95% confidence interval, 1.16 to 3.03; $P = 0.012$; adjusted odds ratio, 2.04; 95% confidence interval, 1.16 to 3.57; $P = 0.012$, respectively). After stratification by mortality risk, the subgroup analysis showed a consistent trend favoring higher-threshold transfusion but reached statistical significance only in the low-risk group. There were no differences in red blood cell transfusion, ICU-free days, and hospital-free days between the groups. The E-value analysis suggested robustness to unmeasured confounding. **Conclusions:** In patients with sepsis and thrombocytopenia, platelet transfusion at a higher threshold was associated with a greater reduction in the 28- and 90-day mortalities than that at a lower threshold.

KEYWORDS—Intensive care unit, outcomes, platelet, platelet transfusion, sepsis, thresholds

INTRODUCTION

Sepsis is a global public health concern; annually, the number of persons affected by sepsis is above 30 million, with approximately 6 million deaths (1). Sepsis outcomes have improved over time due to the advances in early goal-directed therapy (2). However, patients with sepsis would still experience multisystem complications (3), and in the intensive care unit (ICU) treatment of sepsis, higher demand of medical resources is required (4). Thrombocytopenia is a hematologic complication of sepsis that occurs in approximately 15% of patients with severe sepsis in the critical care unit (5). In addition, the mortality of patients with sepsis and thrombocytopenia is higher than that of patients with sepsis without thrombocytopenia (6, 7). Hence, the correction of thrombocytopenia is key for clinicians.

Platelet transfusions are commonly used in managing thrombocytopenia in ICU patients with sepsis. The proportion of patients in the ICU receiving platelets as prophylaxis for hemorrhage ranges from 9% to 30% (8, 9). Although the platelet utilization rate is high, the platelet transfusion criteria and optimal platelet threshold in critically ill patients with sepsis remain unclear. Previous studies on the recommended platelet threshold of patients with sepsis and concurrent thrombocytopenia revealed controversial findings (5, 9). The 2016 Surviving Sepsis Campaign guidelines recommend platelet transfusion when platelet counts are <10,000/μL in the absence of apparent bleeding. If thrombocytopenia is accompanied by a significant risk of bleeding or active bleeding, surgery, and invasive procedures, the recommended transfusion threshold is a platelet concentration of less than 20,000/μL or 50,000/μL, respectively (6). However, the above recommendations are based on low-quality evidence and are for patients with therapy-induced thrombocytopenia (usually leukemia and stem cell transplant) (10, 11).

With the limited knowledge on platelet transfusion criteria, the optimal platelet transfusion threshold for patients with sepsis and concurrent thrombocytopenia remains unknown. Using a large cohort of critically ill patients with sepsis (the Medical Information Mart for Intensive Care IV database, MIMIC IV) (12), this study aimed to investigate the platelet transfusion practice in patients with sepsis and thrombocytopenia, with the goal of identifying platelet levels that are correlated with the outcomes of optimal survival and length of hospital stay.

MATERIALS AND METHODS

Study design and setting

This was a retrospective cohort study of patients with sepsis admitted to an ICU where they received platelet transfusion. Data were extracted from the MIMIC-IV database (12). The database included records of 53,423 adult patients admitted at the ICUs of Beth Israel Deaconess Medical Center between 2001 and 2019. One author (Chenyu Fan) had full access to the database and completed the data extraction (certification number 27252652). Informed consent was waived since the data were obtained from publicly available sources. Authorization was obtained from the Massachusetts Institute of Technology Affiliates for the use of the data.

Participants' and individual's platelet transfusion threshold

Patients aged 18 years or older who fulfilled the criteria for sepsis and underwent platelet transfusion were eligible for inclusion. Sepsis was diagnosed using the Sepsis-3 criteria; specifically, if patients presented with documented or suspected infection and a change of ≥ 2 points in the total Sequential Organ Failure Assessment (SOFA) score, they were considered as having sepsis (1). Since thrombocytopenia occurs mostly within 10 days of sepsis onset, the timing of platelet transfusions was restricted to the first 14 days of ICU admission (5). Only patients who met the two eligibility criteria were used to define the individualized platelet transfusion thresholds. For patients who received one platelet transfusion, the threshold was defined as a platelet nadir 2 days before the transfusion. For patients who received multiple platelet transfusions, the threshold was the mean of the single transfusion thresholds; this was to include information from each transfusion.

The participants were divided into two transfusion threshold groups ($<20,000/\mu L$ and $20,000-50,000/\mu L$) with well-known cut-off points recommended in the sepsis guidelines. The exclusion criteria were: had a threshold $> 50,000/\mu L$; were pregnant or breastfeeding; died within 48 h of admission to the ICU; had active hematological or autoimmune disorders; primary hospital discharge diagnosis of thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or heparin-induced thrombocytopenia (HIT); received platelet transfusions after 2 weeks; and had a history of a red blood cell (RBC) transfusion before the platelet transfusion or a decrease in the hemoglobin level of more than 20 g/L. For multiple admissions of the same patient, only data from the last ICU admission were analyzed.

Variables

The patients' baseline characteristics of interest included sex, race, ICU type (medical [MICU] or surgical [SICU]), severity score at admission measured by the SOFA score (mSOFA, devoid of the platelet component), quick SOFA (qSOFA) score, and comorbidities (diabetes mellitus, renal failure, liver disease, and coagulopathy). For the patients' medication history, medications that could affect platelet function or could increase the risk for spontaneous bleeding (e.g., aspirin, clopidogrel, and warfarin) were noted. Furthermore, the sites of infection (respiratory, urinary, gastrointestinal, and others) for each patient were identified using the ninth edition of the International Classification of Diseases (13). Data on advanced life support measures used during the patients' ICU stay, such as invasive mechanical ventilation, administration of vasopressors, and renal replacement therapy, were also collected. For recipients, in addition to documenting the platelet counts after the last platelet transfusion, we collected the number of each RBC transfusion as well.

Outcomes

The primary outcomes were 28-day and 90-day all-cause mortalities. The secondary outcomes were RBC transfusion, ICU-free days, and hospital-free

days. ICU-free days were defined as the number of days between the day of discharge from the ICU and Day 28 of ICU admission. If the patient died before 28 days of admission or stayed in the ICU for more than 28 days, ICU-free days were scored as 0. Hospital-free days were defined as the number of days between the day of discharge from the hospital and Day 28 of ICU admission. When RBC transfusion was administered after the platelet transfusion, it was considered a secondary outcome. The mean number of RBC units transfused in the two groups was analyzed.

Statistical analysis

All normally distributed and skewed continuous variables are presented as mean (SD) or median (interquartile range [IQR]). Categorical variables are presented as frequencies (%). The descriptive data of the two groups were explored. Differences in continuous data were analyzed using Student's *t* test or the exact Mann–Whitney *U* test. Frequencies were analyzed using Chi-square test or Fisher's exact test.

Second, the adjustment variables were identified. All baseline and intervention variables were considered to be associated with exposure, and the outcomes were considered as confounding variables. To achieve model parsimony and taking into account the relatively small sample size, variables with no significant contribution to the model were eliminated. These variables included:

1. those with a C-statistic that did not change by more than 0.01 units and
2. those that were not accompanied by a reduction in the Akaike information criteria (AIC) (14).

A logistic regression model was developed using the eligible variables to predict the risk of mortality. To evaluate the discriminative capacity of the logistic regression model, the C-index was calculated.

Third, logistic regression was used to estimate the association between two different platelet transfusion thresholds and 28-day mortality after adjusting for the aforementioned variables. Through the logistic regression model, the patients were ranked according to their predicted risk and categorized into three risk tertiles (low-, moderate-, and high-risk). For each tertile, the absolute-risk differences between the high- and low-threshold groups were assessed. The absolute-risk difference and confidence interval for each risk group are presented. The heterogeneity of platelet transfusion on 28-day mortality was assessed in accordance with the interaction between platelet transfusion and ICU type (SICU and MICU), organ dysfunction (impaired liver or renal function), and with or without aggressive medical interventions (use of vasopressors, mechanical ventilation, and renal replacement therapy).

Finally, the potential impact of unmeasured confounding between the two different transfusion thresholds and 28-day mortality was assessed by calculating E-values. The E-value quantified the required magnitude of an unmeasured confounder that could rebut the association between low-threshold transfusion and 28-day mortality (15).

A two-sided $P < 0.05$ was considered statistically significant. Analyses were performed using R (mgcv and boot packages, R version 3.3) (16).

RESULTS

Figure 1 shows the flow chart of the study. A total of 945 patients with platelet transfusion were identified. Of those, 464 patients were excluded because they died within 48 h (n = 165), received platelet transfusions after 2 weeks (n = 97), received RBC transfusion or decreased in hemoglobin more than 20 g/L before platelet transfusion (n = 101), had active hematological or autoimmune disorders (n = 76); or had TTP, HUS, or HIT (n = 25). After the exclusion of 188 patients with the threshold of over $50,000/\mu L$, a total of 293 patients were included in the final cohort. We divided them into two groups based on their mean platelet count before transfusion: the lower-threshold group (n = 76) and the higher-threshold group (n = 217).

The patients' mortality distribution according to platelet count is shown in Figure 2. Tests for linear trend suggested negative linear relationships of platelet with mortality hazard overall ($R^2 = 0.7788$, $P = 0.048$). Mortality increased as platelet count decreased, which is in line with previous findings (17).
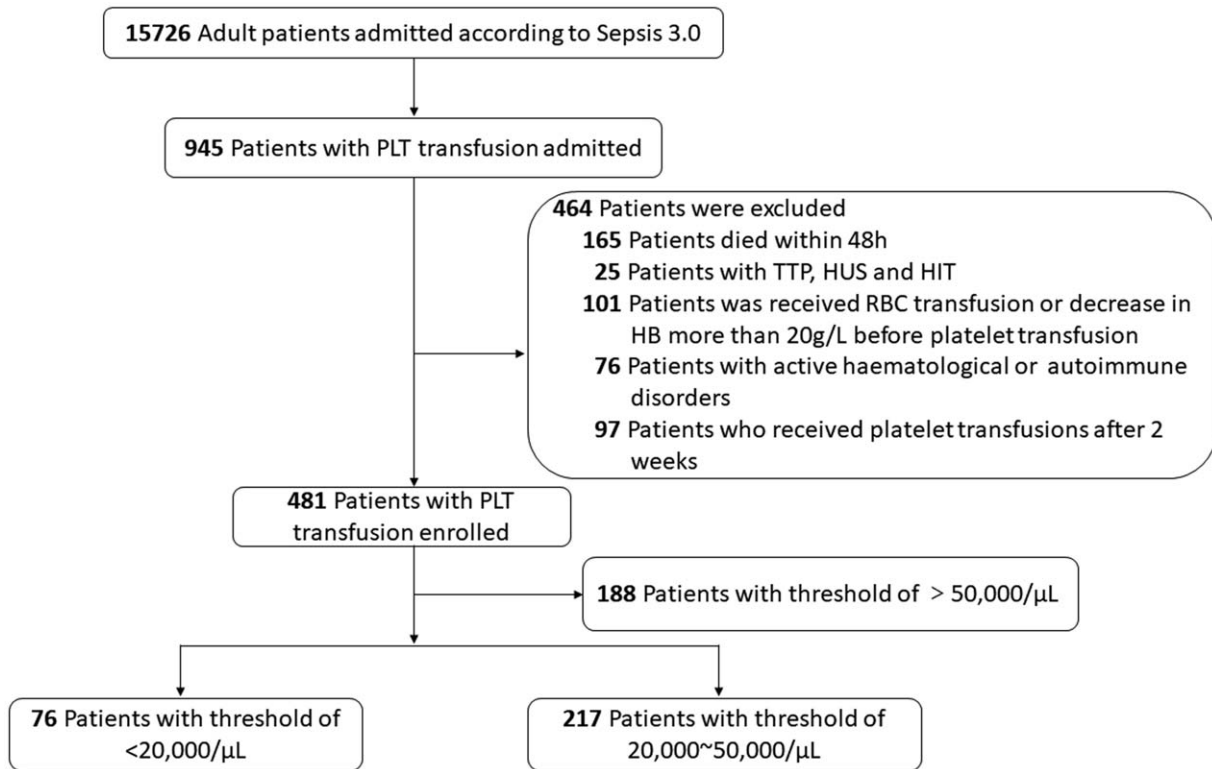
FIG. 1. **Study population flow diagram.** HIT indicates heparin-induced thrombocytopenia; HUS, hemolytic uremic syndrome; PLT, Platelets; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

Comparisons of the platelet count at onset and within 14 days of the transfusion are shown in Figure 3. This confirmed that platelet transfusion could be considered as an intervention in this cohort study. The differences in the baseline platelet count between the lower-threshold group and the higher-threshold group were significant (23.67 ± 13.53 vs. 41.76 ± 16.66, $P < 0.001$). The changes in platelet counts within 14 days are shown in Figure 3; there was a significant increase in the platelet count on the first day (30.12 ± 26.56 vs. 33.29 ± 29.45, $P < 0.001$) after the transfusion compared to baseline, which gradually leveled off in the following days. Thirty patients had no
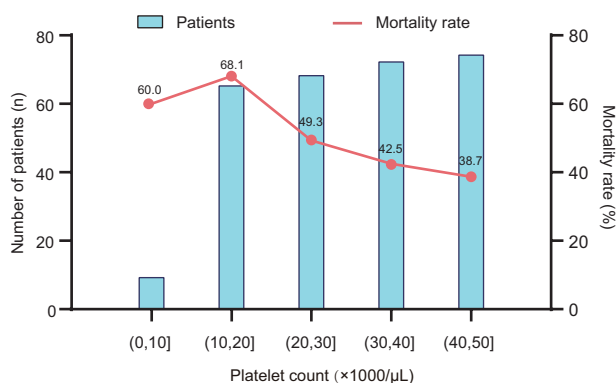

FIG. 2. **Distribution of patients by platelet counts and mortality rate of patients at different platelet-transfusion threshold.** Shown are bar plots illustrating the number of patients who received platelet transfusion at different platelet counts. The broken line represents mortality rate in different platelet transfusion threshold.

increase in platelets after platelet transfusion. The adjusted 28-day (66.7% vs. 47.5%; odds ratio [OR], 2.87; 95% confidence interval [CI], 1.22–6.76; $P = 0.016$) all-cause mortality rates in the PLT not increasing group were higher than those in the PLT increasing group (sTable 3 in Additional file1, http://links. lww.com/SHK/B389).

Baseline characteristics of the two groups are shown in Table 1. Of the patients in this study, most received a median of three platelet transfusions during their admission, 60.4% received mechanical ventilation, and 40.3% received vasoactive drugs. There were no differences in demographic data, comorbidities, aggressive medical interventions, admission scores, and laboratory examination findings. In addition, patients in the higher-threshold group had a higher rate of SICU admission (35.0% vs. 9.2%, $P < 0.001$) and lower qSOFA score (1.93 ± 0.60 vs. 2.09 ± 0.55, $P = 0.036$) than those in the lower-threshold group.

In addition, to adjust for confounders, a multi-factor logistic regression model was constructed with death as the outcome variable and seven risk factors (lactate level, last platelet count, international normalized ratio, qSOFA score, mSOFA score, age, and ICU type). The max C-index of the model was 0.730. The model with the lowest AIC (368.28) was the most stable one (sTable 1 in Additional file1, http://links.lww.com/SHK/ B389).

Comparisons of the outcomes between the lower-threshold group and the higher-threshold group are shown in Table 2. The adjusted 28-day (67.1% vs. 43.3%; odds ratio [OR], 1.96; 95% confidence interval [CI], 1.16–3.03; $P = 0.012$) and 90-day
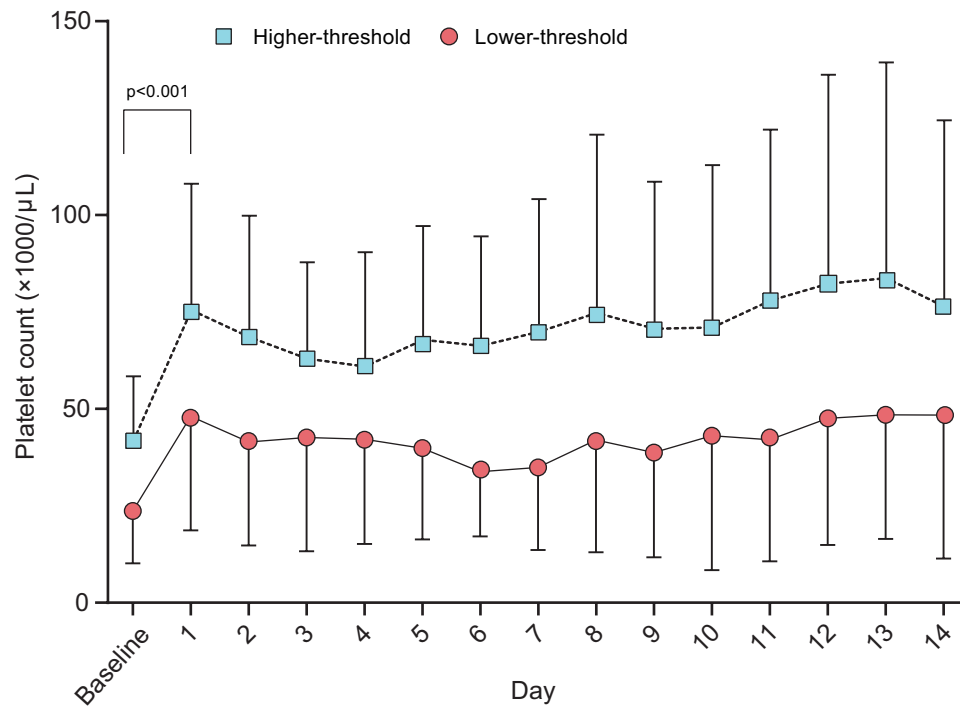
Fig. 3.   **Separation of platelet levels after transfusion between the lower-threshold group and the higher-threshold group.** Platelet levels in the Lower-threshold group and Higher-threshold group were recorded until 14 days after platelet transfusion. Threshold values were the mean counts by summing all single pretransfusion thresholds. The bar indicates one standard deviation.

Table 1.   **Baseline characteristics of lower-threshold group and higher-threshold group**

Baseline characteristics	Lower-threshold group (n = 76)	Higher-threshold group (n = 217)	P
Average platelet count (×1000/μL), mean (SD)	14.03 (3.72)	35.41 (8.84)	<0.001
Last platelet count (×1000/μL), mean (SD)	23.67 (13.53)	41.76 (16.66)	<0.001
Elevation of platelet count (×1000/μL), mean (SD)[‡]	30.12 (26.56)	33.29 (29.45)	<0.001
Number of platelet transfusion (IQR)[*]	4 (2, 8)	2 (1, 5)	0.024
Age (year), mean (SD)	58.52 (16.42)	59.26 (15.57)	0.728
Sex, male, n (%)	38 (50.0)	135 (62.2)	0.084
Ethnicity, white, n (%)	22 (28.9)	65 (30.0)	0.985
ICU type, SICU, n (%)	7 (9.2)	76 (35.0)	<0.001
Infection site, n (%)			0.264
Respiratory	38 (50.0)	96 (44.2)	
Gastrointestinal	9 (11.8)	45 (20.7)	
Urinary	6 (7.9)	23 (10.6)	
Other	23 (30.3)	53 (24.4)	
Diabetes mellitus, n (%)	17 (22.4)	40 (18.4)	0.564
Renal failure, n (%)[#]	8 (10.5)	29 (13.4)	0.660
Liver disease, n (%)[#]	16 (21.1)	61 (28.1)	0.293
Coagulopathy, n (%)[#]	26 (34.2)	75 (34.6)	0.999
Renal replacement therapy, n (%)	9 (11.8)	25 (11.5)	0.999
Mechanical ventilation, n (%)	39 (51.3)	138 (63.6)	0.081
Vasopressor use, n (%)	30 (39.5)	88 (40.6)	0.977
SOFA score, mean (SD)	9.93 (3.72)	9.86 (3.82)	0.879
mSOFA score, mean (SD)	6.66 (3.91)	7.21 (3.86)	0.284
qSOFA score, mean (SD)	2.09 (0.55)	1.93 (0.60)	0.036
Creatinine (mg/dL), mean (SD)	1.77 (1.34)	2.11 (1.61)	0.105
Hemoglobin (g/dL), mean (SD)	8.66 (1.69)	8.54 (1.80)	0.613
Lactate (mmol/L), mean (SD)	4.33 (4.19)	4.95 (4.16)	0.291
INR, mean (SD)	2.36 (2.24)	2.22 (1.27)	0.525
Antiplatelet drug use, n (%)[†]	8 (10.5)	40 (18.4)	0.155

[*]Data are presented as median (interquartile range).
[†]Antiplatelet drug included aspirin, clopidogrel.
[‡]It means difference of platelet count between first day after transfusion and baseline.
[#]Renal failure, Liver disease, Coagulopathy was identified by ICD-9-CM code.
INR indecates international normalized ratio; mSOFA, modified sequential organ failure assessment; qSOFA, quick sequential organ failure assessment; SICU, surgical intensive care unit; SOFA, sequential organ failure assessment.

TABLE 2. **Primary and secondary outcomes of patients in different groups**

	Lower-threshold group (n = 76)	Higher-threshold group (n = 217)	Adjusted OR or mean difference (95%CI)	P
Primary outcome				
28-day mortality, n (%)	51 (67.1)	94 (43.3)	1.96 (1.16, 3.03)[*]	0.012[†]
			2.46 (1.33, 4.55)[‡]	0.004[†]
90-day mortality, n (%)	63 (82.9)	132 (60.8)	2.04 (1.16, 3.57)[*]	0.012[†]
Secondary Outcome				
RBC Transfusion, n (%)	32 (42.1)	73 (33.6)	1.14 (0.68, 1.88)[*]	0.626[†]
ICU-free days[§]	15.85 (9.03)	15.84 (9.09)	0.01 (−2.36, 2.39)	0.991[∥]
Hospital-free days[§]	10.10 (8.29)	10.83 (8.56)	−0.74 (−2.97, 1.49)	0.516[∥]

[*]Logistic regression model adjusted for Lactate, INR, Last Platelet count, mSOFA, qSOFA, Age, and ICU type.
[†]Estimate and *P*-value comes from logistic regression model.
[‡]Logistic regression model adjusted for Lactate, INR, Elevation of Platelet count, mSOFA, qSOFA, Age, and ICU type.
[§]ICU-and hospital-free days at Day 28 and data are presented as mean (SD).
[∥]Estimate and *P*-value comes from generalized linear mixed model.
OR indecates odds ratio; RBC, red blood cell.

(82.9% vs. 60.8%; OR, 2.04; 95% CI, 1.16–3.57; $P = 0.012$) all-cause mortality rates in the lower-threshold group were higher than those in the higher-threshold group. The 28-day all-cause mortality rates (OR, 2.46; 95% CI, 1.33–4.55; $P = 0.004$) was also adjusted by elevation of platelet count and other risk factors from previous logistic regression model, which lead to the same conclusion as before. The rates of RBC transfusion (42.1% vs. 33.6%) were not significantly different between the two groups ($P = 0.626$). Regarding other secondary outcomes, ICU-free days (15.85 ± 9.03 vs. 15.84 ± 9.09 days, $P = 0.991$) and hospital-free days (10.10 ± 8.29 vs. 10.83 ± 8.56 days, $P = 0.516$) were not significantly different.

Figure 4A shows that, in all three tertile of baseline mortality risk, the 28-day mortality rate observed among patients in the higher-threshold group were lower than the mortality rate in the lower-threshold group. After a chi-square test, rates of mortality in both groups remain difference in low-risk group ($P < 0.001$); however, no significant difference in mortality was detected between the moderate- and high-risk groups ($P = 0.494$, and $P = 0.289$, respectively). The absolute risk difference between two threshold groups of the three mortality risk subgroups was calculated in Figure 4B, which indicated a protective effect of higher-threshold group in all three tertile of baseline risk, varying from an absolute-risk difference of 40% in the lowest tertile to 11.1% in the highest tertile of baseline risk. Similar to the conclusions reached earlier, the absolute risk difference of 90-day death in the lower-threshold group was increased in all the risk groups (sFigure 1 in Additional file 1).
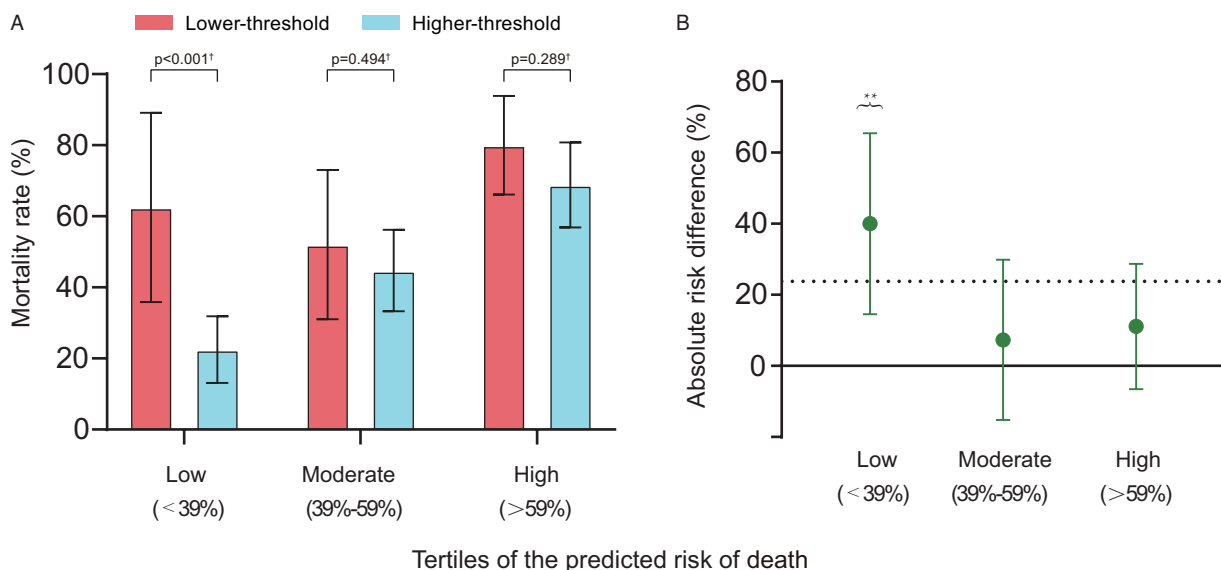

FIG. 4. **Comparison of the occurrence of all-cause mortality at 28 days.** The data are expressed as observed mortality rate (A) and absolute risk differences (B) for the septic patents with receiving platelet transfusion in each of the three tertiles of their predicted risks (low, <39%; moderate, 39%−59%; and high, >59%). Vertical lines represent 95% CI. (A) In all three tertiles of predicted risk, the event rates of 28-day mortality among patients in the higher-threshold group were lower than the event rates in the lower-threshold group. (B) In all three tertiles of predicted risk, the risk differences (incidence in the lower-threshold group vs. the higher-threshold group) and a horizontal line indicating the mean result (27% absolute-risk difference). The absolute risk difference indicated harm of the lower-threshold group in all three tertiles of predicted risk, which was most pronounced among patients with the low risk. *P* values < 0.05 indicate that the effect of risk differs significantly in the subgroup, while *P* values ≥ 0.05 indicate no difference in the effect of risk in the subgroup. [†] *P*-value comes from Chi-square test. [**] *P* < 0.001.

Results of the stratified analysis are shown in sTable 2, Additional file 1, http://links.lww.com/SHK/B389, indicating the association between lower-threshold group for 28-day mortality and higher-threshold group was consistently present in various subgroups with stratification according to ICU type, infection site, organ injury, mechanical ventilation, and vasopressor use.

We generated an *E*-value to assess the sensitivity to unmeasured confounding. The *E*-Value was OR 3.31 (95% CI, 2.85–3.77), meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association ≥3.31 with both 28-day mortality and lower-threshold platelet transfusions.

DISCUSSION

Thrombocytopenia is frequently encountered in the ICU. Platelet transfusions are commonly used to manage patients with sepsis and thrombocytopenia. This study included patients with different platelet transfusion thresholds. After multiple sensitivity analyses, our findings were not consistent with previous sepsis guideline recommendations (1). In this study, the number of deaths and ICU stay was higher in the lower-threshold group (<20,000/μL) than in the higher-threshold group (20,000–50,000/μL). Our study findings support this statement that in cases where platelet transfusion is necessary, it may not be beneficial at lower thresholds.

Thrombocytopenia is a poor prognostic marker for critically ill patients (18). It is used as a marker for organ impairment because of the platelets' unique pathophysiological function in the human body: they help in thrombosis and hemostasis, participate in the inflammatory response, enhance the endothelial barrier function, and promote tissue regeneration for wound healing (19, 20). In sepsis, thrombocytopenia can result from multiple causes including hypersplenism, bone marrow failure, use of heparin or other platelet-inducing drugs, and hemodilution (21, 22). Due to the clinical importance of platelets, clinicians are concerned about acute complications from thrombocytopenia and try to correct platelet reduction in the early stages with platelet transfusion.

Platelet transfusion can correct thrombocytopenia and improve body function (17). Several studies have confirmed that there is a short-term increase of platelet counts after platelet transfusion (23, 24). Platelet counts can increase by approximately 30,000/μL after transfusing two units of platelets (23). There are also some patients whose platelet counts do not respond to platelet transfusions or even continue to decrease. In our study, the platelet counts increased similarly in the two threshold groups; this is consistent with previous studies. A retrospective study reported that increasing platelet counts could improve survival and reduce mortality; however, in that study, recombinant human thrombopoietin was used, rather than platelet transfusion (25). Increasing the platelet count alone may improve prognosis, but platelet transfusion may not be the best method to correct reduced platelet counts. Some previous studies had contradictory results to ours (24, 26). They suggested that platelet transfusions did not improve

patients' clinical outcomes and rather increased the risk of death. Although it is suggested that platelet transfusions do not lead to overall clinical improvement, some scholars speculate that they may be beneficial to certain subgroups (23). Our study found that 28-day all-cause mortality rates in the PLT not increasing group were higher than those in the PLT increasing group. The adverse prognosis due to platelet transfusion must be interpreted with caution, as patients who receive transfusion often have severe disease, and this confounding cannot be eliminated. Possible mechanisms might involve excessive volume load, adult acute respiratory distress syndrome, and transfusion reactions. Additional potential hazards include an increased risk of infection or thrombosis, exacerbation of immune dysfunction, and platelet-monocyte aggregation (26–29).

Most previous studies have focused on pediatric patients, critically ill patients, surgical patients, patients with a hematological malignancy, or patients with sepsis (30, 31). Poor outcomes of platelet transfusion have been observed in these populations and their respective subgroups. Considering that thrombocytopenia is an independent risk factor for death in patients with sepsis, the prognoses of patients with different thresholds may differ—our study was based on this assumption. In a randomized trial by Curley et al., patients who received prophylactic platelet transfusion at higher thresholds (25,000/μL vs. 50,000/μL) had a higher mortality risk (31). In contrast, a retrospective study in China showed a greater extent of mortality reduction in patients with platelet counts between 30,000 and 49,000/μL than those with platelet counts <30,000/μL (23). Although the populations of these two studies did not focus on sepsis, they had contrary findings, which are very interesting and worth exploring. During sepsis, the coagulation system is activated, and the anticoagulation and fibrinolytic systems are inhibited, which promotes microthrombus formation and leads to microvascular dysfunction (32–34). In the lower-threshold group, where coagulation activation is more active, platelet transfusion may further exacerbate thrombosis and lead to microvascular occlusion of tissues and organs, resulting in organ damage. In the higher-threshold group, where we found a higher proportion of SCIU patients, platelet transfusion may have been used to replenish depleted platelets and prevent postoperative bleeding, which was associated with a better prognosis.

To assess the heterogeneity of our findings among subgroups, we performed a more detailed analysis based on a baseline risk-related multinomial logistics regression model, which is superior to conventional subgroup analyses. The results showed that patients with sepsis might not necessarily benefit from the lower threshold, as it was associated with absolute risk increase in all the risk groups. However, the absolute risk varied considerably, from 7.3% in the moderate-risk group to 40.0% in the low-risk group. Moreover, the difference in mortality between the two groups of patients in the low-risk group was significant. Regrettably, a small sample size of these subgroup result in nonsignificant associations between different platelet transfusion threshold and mortality rate in moderate- and high-risk group. On the other hand, our results are not consistent with the recommendations in some guidelines that suggest platelet transfusion when platelet

counts are <10,000/µL in the absence of apparent bleeding (i.e., in low-risk situations) (1). Following these findings, thrombocytopenia in patients with sepsis may need to be managed more conservatively. After all, the "less is more" concept can be applied here.

This study has several limitations. First, it was a single-center study with a retrospective design, and the data are not recent. Second, selection bias of prognostic determinants was introduced with the classification of patients into different threshold groups. However, even after adjustment for multivariate confounders and the use of *E*-values to assess the impact of potential unmeasured covariates, our conclusions remained robust. Third, the transfusion criteria and protocol were not uniform, due to the retrospective nature of the study. Similarly, the platelet threshold for each patient had to be estimated since there are no uniform platelet transfusion criteria—this may have reduced the accuracy in this study than it would in a prospective study. However, the combined mean value of all pretransfusion thresholds ensured precision in the constitution of the patient groups. Fourth, the specific causes of thrombocytopenia could not be measured in our study; however, the most eligible patients were included, given the strict inclusion and exclusion criteria that were considered. Fifth, the generalizability of our study results is limited because we could not determine whether the administered platelet transfusions were prophylactic or therapeutic. Finally, our findings are a post hoc analysis of a publicly available database and cannot be used to draw conclusions on causation. Further high-quality randomized controlled trials are needed to compare the effects of different transfusion thresholds on prognosis.

To conclude, patients with sepsis and thrombocytopenia who received lower-threshold platelet transfusions had higher all-cause mortality at 28 and 90 days than those who received higher-threshold platelet transfusions. Given these findings, a more conservative management of thrombocytopenia may be required in patients with sepsis. There is an urgent need for high-quality randomized controlled trials to explicitly address this vital knowledge gap.

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