The rebound of platelet count could be a predictor of good prognosis of sepsis in the intensive care unit: a retrospective analysis of the large clinical database MIMIC-III

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Abstract

Background: The rise of platelets in sepsis patients with thrombocytopenia can lead to an improvement in clinical outcomes. We aimed to probe whether the rebound of platelet count could be a predictor of good prognosis in sepsis patients in a large, diverse population.

Methods: All sepsis patients were initially stratified according to nadir platelet counts (very low<50´10^9/L, intermediate-low 50 ´ 10^9 to 99 ´ 10^9/L, low 100 ´ 10^9 to 149 ´ 10^9/L, normal 150 ´ 10^9 to 399 ´ 10^9/L, or thrombocytosis > 400 ´ 10^9/L). The delta platelet count (DPC) was defined as the difference between the last platelet count prior to transfer or death and the nadir platelet count after ICU admission.

Results: A total of 3457 patients were enrolled in our study. The 28-day mortality in the very low (43.1%) and intermediate-low (36.9%) platelet count groups was higher than in the low (26.8%) and normal (23.2%) platelet count groups and thrombocytosis (18.2%) group (P <0.001). The patients in the ΔPC > 0 subgroup had lower 28-day morality (38.5% vs. 59.1%, P < 0.001, 33.3% vs. 44.7%, P = 0.015, 23.8% vs. 32.7% P = 0.01, 20.2 vs. 27.7, P = 0.001, respectively) except in the thrombocytosis group. The extended Cox proportional hazard regression model showed a decreased risk of death within 28 days in patients in the ΔPC > 0 subgroup (HR 0.570, 95% CI 0.498-0.651, P < 0.001).

Conclusions: The rebound platelet count could be a biomarker of good prognosis in patients with sepsis.

Background

Sepsis is a common clinical syndrome characterized by life-threatening organ dysfunction, which the hematologic system is frequently involved in and often shows a decrease in platelets[1]. Thrombocytopenia (TP) is a severe complication in the intensive care unit (ICU) defined as platelet counts < 150,000/mm^3[2]. It has been found that in sepsis patients with thrombocytopenia, the rise of platelets can lead to an improvement in clinical outcomes. In a prospective study of platelet changes and prognosis in 1449 ICU patients, Akca S[3] found that 30% of patients had decreased platelet counts, and the platelet levels of survivors were significantly higher than the levels among patients who died. Based on the dynamic observation of platelet levels in patients who died symptomatic supportive therapy was not always effective in improving platelet count.

Platelets play a vital role in the pathophysiological process of sepsis. One of the most important processes of platelets is immune function, which is complementary to cell-mediated immune cells. They can prevent the invasion of potential pathogens and act as the first defense mechanism when activated in injured sites and inflammatory tissues[4, 5]. In sepsis patients with thrombocytopenia, platelet rebound may enhance resistance to pathogens and improve clinical prognosis.

The use of platelet transfusions is common in patients with thrombocytopenia. However, platelet transfusion is not effective in all patients with thrombocytopenia, which is also one of the thorny problems that clinicians faced in the process of treating sepsis patients. A clinical trial with a large population confirmed that one in five transfusions was ineffectual and that sepsis was identified as a modifiable risk factor[6]. It is not clear whether the prognosis of patients with elevated platelets is better than that of patients without elevated platelets. Therefore, in our study, we sought to confirm the relationship between thrombocytopenia and the prognosis of patients with sepsis and, more importantly, to explore whether a rebound in platelet count can improve prognosis.

Patients And Methods

Database

The clinical data were derived from Medical Information Mart for Intensive Care III (MIMIC-III), which is a large-scale, single-center and freely available database[7–9]. The data contained more than forty thousand distinct adult patients who stayed in critical care units of Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, between 2001 and 2012 for whom vital signs, medications, laboratory tests, observations and other clinical variables had been recorded. The database was made available by data scientists at the Massachusetts Institute of Technology (MIT) Laboratory for Computational Physiology and collaborating research groups. The certification number for the database is 2093226.

Patient selection

Patients > 18 years of age who were diagnosed with “sepsis,” “severe sepsis,” or “sepsis shock” (ICD 9 codes 99591, 99592, or 78552, respectively) were selected for inclusion in the study, and we only retained those with at least one nadir platelet count available after ICU admission.

Data extraction and management

The extracted data include age, sex, admission type and location, first ICU service, date of ICU admission and discharge, date of death, Simplified Acute Physiology Score (SAPS), sequential organ failure assessment (SOFA) score, modified SOFA (which was calculated without the contribution of SOFA coagulation), heart rate, mean arterial pressure (MAP), weight, mechanical ventilation, amount of vasoactive drug applied, and dialysis demand. The SAPS and SOFA scores were both computed directly using the code provided by Johnson et al[10].

The nadir platelet count after ICU admission was used to stratify patients into various classes with very low platelet counts (< 50·10^9/L), intermediate-low platelet counts (50 · 10^9 to 99 · 10^9/L), low platelet counts (100 · 10^9 to 149 · 10^9/L), normal platelet counts (150 · 10^9 to 399 · 10^9/L), or thrombocytosis (400 · 10^9/L), and the thresholds were selected based on previous studies[11–13]. After stratification, we defined the delta platelet count (ΔPC) as the difference between the platelet count at the time prior to transfer or death and the nadir platelet count after ICU admission. The patients whose ΔPC was greater than

zero were categorized as the increased platelet count group (ΔPC > 0 group), while the remaining patients made up the decreased platelet count group (ΔPC = 0 group).

The primary endpoint of the study was 28-day mortality from the date of ICU admission. Secondary outcomes included hospital mortality, ICU and hospital length of stay, the percentage of dialysis and mechanical ventilation, total hours of mechanical ventilation, the total amount of dopamine, and norepinephrine.

We used PostgreSQL (version 9.6; PostgreSQL Global Development Group) for data extraction. We extracted data from the following tables: ADMISSION, ICUSTAYS, PATIENTS, CHARTEVNETS, DIAGNOSIS_ICD and LABITEMS.

Statistical analysis

SPSS (version 22.0; IBM, Armonk, NY) and R (version 3.5.2, www.r-project.org) were used for statistical analyses. The normally distributed continuous variables were described as the mean ± standard deviation (SD), and skewed distributed continuous variables were presented as the median and interquartile range (IQR; 25th and 75th percentiles). Student's *t* test or ANOVA was conducted to compare differences in the normally distributed continuous variables between groups. A Mann-Whitney *U* test or a Kruskal-Wallis test was used to compare differences in the skewed distributed continuous variables between groups. Categorical variables were described using percentages and frequencies, and they were analyzed by *chi-square* tests or Fisher's exact test.

Survival analysis was performed using the Kaplan-Meier test and the log-rank test to determine whether ΔPC affected 28-day mortality. Multivariate analysis was performed using the Cox hazard model to determine which variables were important for predicting the prognosis of the patients. Variables with $P < 0.1$ in the survival analysis were selected for the Cox proportional hazards regression model. A P value of < 0.05 was considered statistically significant.

Results

Patient characteristics

In total, 3457 patients were included in the current study (Table 1). A total of 510 patients (14.8%) had platelet counts of $< 50 \cdot 10^9$/L, 498 (14.4%) had counts of $50 \cdot 10^9$ to $99 \cdot 10^9$/L, 731 (21.1%) had counts of $100 \cdot 10^9$ to $149 \cdot 10^9$/L, 1548 (44.8%) had counts $150 \cdot 10^9$ to $399 \cdot 10^9$/L, and 170 (4.9%) had counts above the normal range. There were 1476 female and 1981 male patients, accounting for 42.7% and 57.3% of the total population, respectively. The median age of all patients was 68 years, while the patients with lower platelet counts had a lower age. Most of the patients were admitted with emergency status (95.3%), and most of them came from referrals (45.8%) from their admission location. The most common ICU type was a medical ICU (67.4%). The heart rate of patients with very low platelet counts and thrombocytosis was significantly higher ($P < 0.001$). Patients with very low, intermediate-low, or low platelet counts had higher modified SOFA scores and SASP ($P < 0.001$, respectively). Patients with very low or intermediate-low platelet counts received more transfused blood products, including platelets, plasma and red blood cells. ($P < 0.001$)

Table 1

Patients characteristics[1]

Parameter	All	Nadir Platelet Count					*P* value
		< 50 · 10^9/L	50–99· 10^9/L	100–149· 10^9/L	150–399· 10^9/L	≥ 400· 10^9/L	
Patients, n (%)	3457	510(14.8%)	498(14.4%)	731(21.1%)	1548(44.8%)	170(4.9%)	
Age (yrs.)	68.0(56.0 ~ 80.0)	61.0(53.0 ~ 69.3)[a]	66.0(56.0 ~ 79.0)[b]	69.0(57.0 ~ 81.0)[c]	71.0(59.0 ~ 82.0)[c,]	65.0(54.0 ~ 77.0)[a,b]	< 0.001
Gender, female, n (%)	1476	206(40.4%)[a,b]	199(40.0%)[a,b]	285(39.0%)[b]	715(46.2%)[a]	71(41.8%)[a,b]	0.006
Admission type, n (%)							< 0.001
Elective	117(3.4%)	33(6.5%)[a]	21(4.2%)[a,b]	10(1.4%)[c]	47(3.0%)[b,c]	6(3.5%)[a,b,c]	
Urgent	46(1.3%)	7(1.4%)[a]	10(2.0%)[a]	9(1.2%)[a]	19(1.2%)[a]	1(0.6%)[a]	
Emergency	3294(95.3%)	470(92.2%)[a]	467(93.8%)[a,b]	712(97.4%)[c]	1482(95.7%)[b,c]	163(95.9%)[a,b,c]	
Admission location, n (%)							< 0.001
Referral	1582(45.8%)	252(49.4%)	247(49.6%)	340(46.5%)	673(43.5%)	70(41.2%)	
Emergency	1263(36.5%)	142(27.8%)[a]	148(29.7%)[a]	255(34.9%)[a,b]	647(41.8%)[c]	71(41.8%)[b,c]	
Transfer	612(17.7%)	116(22.7%)[a]	103(20.7%)[a]	136(18.6%)[a,b]	228(14.7%)[b]	29(17.7%)[a,b]	
First ICU type, n (%)							0.001
MICU	2331(67.4%)	368(72.2%)	323(64.9%)	493(67.4%)	1041(67.2%)	106(62.4%)	
CCU	254(7.3%)	23(4.5%)[a]	32(6.4%)[a,b]	68(9.3%)[b]	124(8.0%)[a,b]	7(4.1%)[a,b]	
SICU	492(14.2%)	79(15.5%)	79(15.9%)	94(12.9%)	206(13.3%)	34(20.0%)	
CSRU	120(3.5%)	16(3.1%)	25(5.0%)	25(3.4%)	51(3.3%)	3(1.8%)	
TSICU	260(7.5%)	24(4.7%)[a]	39(7.8%)[a,b]	51(7.0%)[a,b]	126(8.1%)[a,b]	20(11.8%)[b]	
Heart rate	91.2(78.6 ~ 104.2)	95.8(83.9 ~ 108.9)[a]	90.6(79.7 ~ 104.0)[b,c]	90.6(70.8 ~ 102.8)[b]	89.4(77.4 ~ 102.7)[b]	96.0(84.4 ~ 108.6)[a,c]	< 0.001
MAP	71.0(65.7 ~ 77.3)	70.7(66.9 ~ 77.7)	71.0(65.9 ~ 77.2)	70.6(65.6 ~ 76.8)	71.0(65.7 ~ 77.4)	71.8(65.3 ~ 78.8)	0.623
Modified SOFA[2]	6(3–8)	8(5–11)[a]	7(4-9.5)[a]	6(3–8)[b]	5(3–7)[c]	4(2–6)[d]	< 0.001
SOFA[2]	6(4 ~ 9)	10(7 ~ 13)[a]	8(6 ~ 11)[b]	6(4 ~ 9)[c]	5(3 ~ 7)[d]	4(2 ~ 6)[e]	< 0.001
SASP II[2]	43.0(34 ~ 55)	52(41 ~ 61)[a]	46(36 ~ 58)[b]	43(34 ~ 53)[c]	41(32 ~ 51)[c]	36(28 ~ 48)[d]	< 0.001
Transfusion of blood product, n (%)	1532(44.3%)	426(83.5%)[a]	294(59.0%)[b]	256(35.0)%[c]	512(33.1%)[c]	44(25.9%)[c]	< 0.001
Platelet transfusion, n (%)	387(11.2%)	310(60.8%)[a]	52(10.4%)[b]	11(1.5%)[c]	13(0.8%)[c]	1(0.6%)[c]	< 0.001
Plasma transfusion, n (%)	585(16.9%)	210(41.2%)[a]	138(27.7%)[b]	97(13.3%)[c]	134(8.7%)[d]	6(3.5%)[d]	< 0.001
Red blood cell transfusion, n (%)	1352(39.1%)	373(73.1%)[a]	260(52.2%)[b]	215(29.4%)[c]	463(29.9%)[c]	41(24.1%)[c]	< 0.001

[1]Values are given as the median (IQR), number (%), or mean ± SD, unless otherwise indicated.

[a,b,c,d,e,]: each subscript letter denotes a subset of platelet categories whose column proportions do not differ significantly from each other at the 0.05 level.

[2]Mod-SOFA: Modified SOFA, which was calculated without the contribution of SOFA coagulation. The score was calculated within 24 h of entering the ICU; SOFA: the sequential organ failure score; SAPS: the simplified acute physiology score

ICU indicates intensive care unit; MICU, medical intensive care unit; CCU, coronary care unit; SICU, surgical intensive care unit; CSRU, cardiac surgery recovery unit; TSICU, trauma surgical intensive care unit.

Outcome analysis

As shown by the mortality rate s and the length of hospital and ICU stay in Table 2, the 28-day mortality in patients in the very low (43.1%) and intermediate-low (36.9%) platelet count groups were higher than those in the low (26.8%) and normal (23.2%) platelet count groups and thrombocytosis (18.2%) group (P < 0.001), while there was no significant difference among the low platelet count, normal platelet count and thrombocytosis groups. Furthermore, the hospital mortality of patients in the very low platelet count group was 56.7%, which was significantly higher than in the other groups ($P < 0.001$). Platelet transfusion did not improve 28-day mortality ($P > 0.05$) (Fig. 1a). However, the 28-day mortality of patients who received transfusion of plasma was higher (49.0% vs. 39.0%, $P = 0.024$, 51.4% vs. 31.4%, $P < 0.001$, 38.1% vs. 25.1% $P = 0.007$, 32.8% vs. 22.3%, $P = 0.06$, respectively) except in the thrombocytosis group (Fig. 1b). Red blood cell transfusion did not improve 28-day mortality ($P > 0.05$) (Fig. 1c). Meanwhile, in the subgroup (Table 3), the patients in each ΔPC > 0 subgroup, except in the thrombocytosis group, had lower 28-day morality (38.5% vs. 59.1%, $P < 0.001$, 33.3% vs. 44.7%, $P = 0.015$, 23.8% vs. 32.7% $P = 0.01$, 20.2 vs. 27.7, $P = 0.001$, respectively) and, except in the intermediate-low platelet count and thrombocytosis groups, had lower hospital morality (53.7% vs. 67%, $P = 0.011$, 24.2% vs. 32.3%, $P = 0.019$, 18.8% vs. 24.3%, $P = 0.009$). The median lengths of ICU and hospital stay for all patients were 3.4 days and 11.0 days, respectively; however, the lengths of ICU and hospital stay for the very low platelet count (15.8 days) group were longer than those for the other groups. In each subgroup, the patients in the ΔPC > 0 group had longer ICU durations (19.6 days vs. 8.0 days, $P < 0.001$, 6.6 days vs. 2.0 days, $P < 0.001$, 5.5 days vs. 1.8 days, $P < 0.001$, 4.3 days vs. 1.7 days, $P < 0.001$, 3.1 days vs. 1.5 days, $P < 0.001$, respectively) and hospital durations (19.6 days vs. 8.0 days, $P < 0.001$, 15.3 days vs. 7.2 days, $P < 0.001$, 12.3 days vs. 6.6 days, $P < 0.001$, 12.0 days vs. 6.9 days, $P < 0.001$, 13.7 days vs. 9.8 days, $P = 0.028$, respectively). The ratio of patients in the very low (70.0%) or intermediate-low platelet count (57.6%) group who required mechanical ventilation was higher ($P < 0.001$). The duration of mechanical ventilation in patients who developed thrombocytopenia was longer than in those who did not ($P < 0.001$). Meanwhile, the patients in the ΔPC > 0 subgroup were more likely to need mechanical ventilation (75.2% vs. 52.2%, $P < 0.001$, 66.4% vs. 39.0%, $P < 0.001$, 59.2% vs. 35.5%, $P < 0.001$, 56.6% vs. 30.2%, $P < 0.001$, 46.4% vs. 26.7%, $P = 0.008$, respectively), and the duration of mechanical ventilation was longer (173.2 h vs. 53.9 h, $P < 0.001$, 144.0 h vs. 23.0 h, $P < 0.001$, 149.5 h vs. 25.4 h, $P < 0.001$, 104.1 h vs. 25.0 h $P < 0.001$, 69.8 h vs. 16.3 h, $P = 0.001$, respectively). There was a significant difference in the requirement for a vasopressor among the groups, reaching 69.6% in the very low platelet count group ($P < 0.001$). Patients with lower platelet counts needed more doses of norepinephrine per kilogram of weight after ICU admission ($P < 0.001$), especially patients with very low platelet counts (0.48 mg/kg). The patients in each ΔPC > 0 subgroup had higher rates of request for a vasopressor (71.9% vs. 61.7%, $P = 0.037$, 67.0% vs. 47.8%, $P < 0.001$, 59.2% vs. 44.6%, $P < 0.001$, 49.9% vs. 37.0%, $P < 0.001$), except for patients in the thrombocytosis group, and higher rates of request for norepinephrine in the intermediate-low platelet count and normal platelet count groups (0.29 vs. 0.19, $P = 0.008$, 0.10 vs. 0.07, $P = 0.022$, respectively).

Table 2
Comparison of clinical outcome data of sepsis patients

Parameter	All	Nadir Platelet Count					*P* value
		< 50 · 10^9/L	50–99· 10^9/L	100–149· 10^9/L	150–399· 10^9/L	≥ 400· 10^9/L	
28-day mortality, n (%)	990(28.6%)	220(43.1%)[a]	184(36.9%)[a]	196(26.8%)[b]	359(23.2%)[b]	31(18.2%)[b]	< 0.001
Hospital mortality, n (%)	1036(30.0%)	289(56.7%)[a]	194(39.0%)[b]	197(26.9)[c]	325(21.0%)[d]	31(18.2%)[c,d]	< 0.001
Length of ICU stay (d)	3.4(1.8 ~ 8.0)	6.2(2.6 ~ 13.2)[a]	4.5(2.1 ~ 9.6)[b]	3.5(1.9 ~ 8.1)[b]	2.9(1.7 ~ 6.0)[c]	2.2(1.3 ~ 4.0)[d]	< 0.001
Length of hospital stay (d)	11.0(5.9 ~ 21.2)	15.8(7.9 ~ 33.7)[a]	13.0(6.8 ~ 22.8)[b]	9.7(5.8 ~ 18.2)[c]	9.8(5.5 ~ 18.9)[c]	11.9(5.9 ~ 23.3)[b,c]	< 0.001
Vasopressor, n (%)	1790(51.8%)	355(69.6%)[a]	303(60.8%)[a]	396(54.2%)[b]	692(44.7%)[c]	44(25.9%)[d]	< 0.001
Norepinephrine (mg/kg)	0.17(0.05–0.54)	0.48(0.14 ~ 1.04)[a]	0.26(0.08 ~ 0.69)[b]	0.16(0.05 ~ 0.48)[c]	0.09(0.03 ~ 0.29)[d]	0.11(0.04 ~ 0.46)[b,c,d]	< 0.001

[1]From the beginning of mechanical ventilation to the start of oxygen therapy.

[2]The total amount of vasoactive drugs required per kilogram of weight.

Table 3
Comparison of baseline characteristics and outcome between the ΔPC > 0 subgroup and the ΔPC = 0 subgroup in different c

Parameter	very low platelet count		*P*	intermediate-low platelet count		*P*	low platelet count		*P*	normal platelet count	
	ΔPC = 0	ΔPC > 0		ΔPC = 0	ΔPC > 0		ΔPC = 0	ΔPC > 0		ΔPC = 0	ΔPC >
Patients, n (%)	115(22.5%)	395(77.5%)		159(31.9%)	339(68.1%)		251(34.3%)	480(65.7%)		622(40.2%)	926(5
Age (yrs.)	63.0(54.0 ~ 74.0)	60.0(52.0 ~ 69.0)	0.013	66.0(56.0 ~ 80)	66.0(55.0 ~ 79.0)	0.451	70.0(58.0 ~ 81.0)	69.0(56.0 ~ 81.0)	0.557	73.0(60.0 ~ 82.)	70.0(5 ~ 81.0
Gender, female, n (%)	44(38.3%)	162(41.0%)	0.597	61(38.4%)	138(40.7%)	0.619	107(42.6%)	178(37.1%)	0.144	277(44.5%)	438(4
Heart rate	96.2 ± 18.5	96.2 ± 18.8	0.991	91.6(78.9 ~ 103.2)	90.4(80.2 ~ 104.6)	0.683	90.0(77.0 ~ 103.5)	90.9(76.5 ~ 102.6)	0.650	87.9(76.3 ~ 99.8)	91.2(7 ~ 104
MAP	68.4(64.1 ~ 75.7)	71.1(66.3 ~ 78.0)	0.009	70.0(65.3 ~ 78.1)	71.1(66.0 ~ 77.1)	0.557	70.3(65.2 ~ 75.6)	71.0(66.1 ~ 77.1)	0.068	70.3(65.0 ~ 77.3)	71.4(6 ~ 77.5
SOFA	10(7 ~ 14)	10(7 ~ 13)	0.968	7.0(5.0 ~ 11.0)	9.0(6.0 ~ 11.0)	0.005	6.0(4.0 ~ 9.0)	6.0(4.0 ~ 9.0)	0.321	5.0(3.0 ~ 7.0)	5.0(3.(7.25)
Modified sofa	8(4 ~ 11)	8(5 ~ 11)	0.973	6.0(4.0 ~ 9.0)	7.0(5.0 ~ 10.0)	0.003	5.5(3.0 ~ 8.0)	6.0(4.0 ~ 8.0)	0.205	5.1 ± 3.1	5.5 ± 3
SASP II	52(41 ~ 66)	51(41 ~ 61)	0.417	45.0(34.0 ~ 58.0)	46.0(37.0 ~ 58.0)	0.464	41.0(33.0 ~ 53.0)	43.0(34.0 ~ 53.0)	0.643	40.5(31.0 ~ 52.0)	42.0(3 ~ 51.0
28-day mortality, n (%)	68(59.1%)	152(38.5%)	< 0.001	71(44.7%)	113(33.3%)	0.015	82(32.7%)	114(23.8%)	0.010	172(27.7%)	187(2
Hospital mortality, n (%)	77(67.0%)	212(53.7%)	0.011	69(43.4%)	125(36.9%)	0.164	81(32.3%)	116(24.2%)	0.019	151(24.3%)	174(1
Length of ICU stay(d)	2.5(1.4 ~ 4.6)	8.1(3.6 ~ 16.5)	< 0.001	2.0(1.1 ~ 3.9)	6.6(3.4 ~ 12.1)	< 0.001	1.8(1.1 ~ 2.9)	5.5(3.0 ~ 12.1)	< 0.001	1.7(1.1 ~ 2.6)	4.3(2.4 8.9)
Length of hospital stay(d)	8.0(4.2 ~ 16.6)	19.6(10.1 ~ 36.0)	< 0.001	7.2(4.1 ~ 15.9)	15.3(9.0 ~ 25.9)	< 0.001	6.6(3.6 ~ 11.0)	12.3(7.5 ~ 21.1)	< 0.001	6.9(4.1 ~ 14.0)	12.0(6 21.1)
Dialysis, n (%)	51(44.3%)	188(47.6%)	0.539	86(54.1%)	171(50.4%)	0.448	115(45.8%)	240(50.0%)	0.283	314(50.5%)	472(5
Ventilation, n (%)	60(52.2%)	297(75.2%)	< 0.001	62(39.0%)	225(66.4%)	< 0.001	89(35.5%)	284(59.2%)	< 0.001	188(30.2%)	524(5
Vasopressor, n (%)	71(61.7%)	284(71.9%)	0.037	76(47.8%)	227(67.0%)	< 0.001	112(44.6%)	284(59.2%)	< 0.001	230(37.0%)	462(4
Ventilation time (h)	53.9(14.7 ~ 122.5)	173.2(74.0 ~ 330.8)	< 0.001	23.0(10.5 ~ 84.8)	144.0(74.3 ~ 258.9)	< 0.001	25.4(10.7 ~ 58.5)	149.5(57.6 ~ 302.6)	< 0.001	25.0(9.0 ~ 57.1)	104.1(~ 216
Norepinephrine (mg/kg)	0.38(0.13 ~ 0.89)	0.49(0.15 ~ 1.01)	0.222	0.19(0.04 ~ 0.50)	0.29(0.10 ~ 0.75)	0.008	0.11(0.04 ~ 0.43)	0.17(0.06 ~ 0.50)	0.053	0.07(0.03 ~ 0.21)	0.10((~ 0.36

Table 4
Univariate analysis of 28-day outcome according to demographics and hospital characteristics

	Survival[1]	Nonsurvival[2]	*P*
Age (yrs.)	66.0(55.0 ~ 78.0)	74.0(61.0 ~ 83.0)	< 0.001
Gender, female, n (%)	1410(57.2%)	571(57.7%)	0.779
Admission type, n (%)			0.014
Elective	97(3.9%)	20(2.0%)	
Urgent	35(1.4%)	11(1.1%)	
Emergency	2335(94.6%)	959(96.9%)	
Admission location, n (%)			0.067
Referral	1149(46.6%)	433(43.7%)	
Emergency	904(36.6%)	359(36.3%)	
Transfer	414(16.8%)	198(20.0%)	
First ICU type, n (%)			0.076
MICU	1646(66.7%)	685(69.2%)	
CCU	171(6.9%)	83(8.4%)	
SICU	370(15.0%)	122(12.3%)	
CSRU	93(3.8%)	27(2.7%)	
TSICU	187(7.6%)	73(7.4%)	
Heart rate	90.3(77.9 ~ 103.0)	93.9(80.4 ~ 106.2)	< 0.001
MAP	71.6(66.5 ~ 78.1)	69.1(64.0 ~ 75.6)	< 0.001
Modified SOFA[3]	5.0(3.0 ~ 7.0)	8.0(5.0 ~ 10.0)	< 0.001
SOFA	5.0(3.0 ~ 8.0)	8.0(6.0 ~ 12.0)	< 0.001
SASP II	40.0(31.0 ~ 50.0)	53.0(43.0 ~ 65.0)	< 0.001
Transfusion of platelets, n (%)	227(9.2%)	160(16.2%)	< 0.001
Total transfusion of platelets, ml	526.0(259.0 ~ 1337.0)	556.0(293.3 ~ 1070)	0.985
Transfusion of plasma, n (%)	328(13.3%)	257(26.0%)	< 0.001
Total transfusion of plasma, ml	833.9(538.0 ~ 1581.5)	1106.0(563.5 ~ 1801.0)	0.048
Transfusion of red blood cells, n (%)	910(36.9%)	442(44.6%)	< 0.001
Total transfusion of red blood cells, ml	750.0(375.0 ~ 1750.0)	752.1(375.0 ~ 1691.0)	0.949
ΔPC > 0, n (%)	1646(66.7%)	578(58.4%)	< 0.001
Nadir platelet count, n (%)			< 0.001
Very low platelet count	290(11.8%)	220(22.2%)	
Intermediate-low platelet count	314(12.7%)	184(18.6%)	
Low platelet count	535(21.7%)	196(19.8%)	
Normal platelet count	1189(48.2%)	359(36.3%)	
Thrombocytosis	139(5.6%)	31(3.1%)	

[1]The patient was still alive 28 days after ICU admission.

[2] The patient died within 28 days of ICU admission.

[3] Mod-SOFA: Modified SOFA, which was calculated without the contribution of SOFA coagulation.

ICU indicates intensive care unit; MICU, medical intensive care unit; CCU, coronary care unit; SICU, surgical intensive care unit; CSRU, cardiac surgery recovery unit; TSICU, trauma surgical intensive care unit.

Cox proportional hazards analyses of 28-day mortality

In the comparison 28-day outcomes by demographic and hospital characteristics (supplementary), we chose to input age, gender, admission location, modified SOFA, SOFA, SASP II, platelet transfusion, plasma transfusion, red blood cell transfusion, ΔPC and nadir platelet count into the Cox proportional hazards regression model (Fig. 2a). In the regression model, the risk of death within 28 days in patients in the ΔPC > 0 group was 0.570 times that in patients in the ΔPC = 0 group (HR 0.570, 95% CI 0.498–0.651, $P < 0.001$). The survival curve showed (see Fig. 2b) that the survival probability in the ΔPC > 0 group was higher than that in the ΔPC = 0 group. However, higher admission SASP II, plasma transfusion, intermediate-low platelet count or low platelet count were correlated with increased mortality risk in both Cox proportional hazard regression analyses (HR 1.035 95% CI 1.029–1.041, $P < 0.001$; HR 1.435 95% CI 1.210–1.703 $P < 0.001$; HR 1.751 95% CI 1.098–2.792, $P = 0.019$; HR 1.538 95% CI 1.018–2.325 $P = 0.041$).

Discussion

Of the 3457 patients who were enrolled in the study, 1739 had a platelet nadir of less than 150,000/mm^3. The occurrence of thrombocytopenia was 50.3%, which is consistent with previous reports[14, 15]. Sepsis-related thrombocytopenia may be affected by a variety of factors, including infection, disseminated intravascular coagulation (DIC), myelosuppression, drug factors, fluid replacement, and surgery[16]. Our study shows that patient mortality rate is correlated with the degree of thrombocytopenia. With a reduction in the nadir platelet count, the 28-day mortality drastically increases, peaking at 43.1%. It can be easily seen that the prognosis of septic patients with thrombocytopenia is poor. Platelets, which are nonnuclear cells differentiated from megakaryocytes, play a vital role in the coagulation process and immune response and serve as a bridge between endogenous and acquired immune responses[17]. In sepsis, many inflammatory mediators, cytokines, endotoxins and metabolites can be released to promote platelet activation by direct or indirect action on platelet surface receptors and cause damage to the vascular endothelium system. The activated platelets gather around inflammatory cells and induce endothelial cells, smooth muscle cells and macrophages to secrete a large number of cytokines, regulate neutrophil aggregation and exudation to inflammatory sites, and promote the activation of coagulation factor by means of signal transduction and other mechanisms, resulting in the coagulation system being overactivated and the body exhibiting a high coagulation state. Activated platelets also release many inflammatory chemokines (such as IL-6, IL-8, etc.) and procoagulant substances (ADP, P-selectin, thrombin sensitive protein, fibrinogen, etc.), further aggravating the inflammatory response. This release leads to an uncontrolled inflammatory response and excessive activation of the coagulation system, eventually leading to multiple organ dysfunctions syndrome (MODS) and directly affecting the patient's prognosis[18].

Furthermore, we noted that a relative improvement in platelet count would lead to a decline in hospital mortality, even for those patients whose platelets are within the normal range. One platelet transfusion generally increases platelet count by 23×10^9/L, although not for all patients. No matter what treatment is used, such as blood transfusion, anti-infection or others, platelet elevation cannot be guaranteed in every patient with thrombocytopenia. This may be related to the aggravation of infection, bone marrow suppression and other factors[6]. If there is no rise in a patient's platelet count, careful attention should be paid, the patient should be treated carefully, and family members should be informed of the possibility of poor prognosis. In our study, platelet transfusion had no effect on 28-day mortality regardless of the platelet count of the patient. Platelet transfusion does not necessarily improve clinical outcomes, but platelet elevation does. This finding reminds us that there is no obvious direct relationship between the amount of platelet infusion and the prognosis of sepsis patients, but the recovery of platelet count indicates the improvement of the condition. Even after platelet transfusion in many patients, platelet still cannot recover is a thorny problem faced by many clinicians in the course of sepsis treatment. The rebound of platelet count can be considered a predictor of good prognosis. Platelets have been shown to limit the growth and spread of bacteria in experimental sepsis[19]. Platelets affect leukocyte recruitment and function[20], cytokine response[21], the activation of vascular endothelial cells[22] and the coagulation system[22]. In addition, platelets maintain vascular integrity, especially in a strong inflammatory environment[23]. More critically, in septic patients, the number of platelets declines while their function is also damaged. The mean platelet volume (MPV) and the platelet distribution width (PDW) are important indicators reflecting platelet function. In severe inflammatory reactions, bone marrow is stimulated by bone marrow compensatory response or pathogenic factors, causing megakaryocytes to proliferate and resulting in elevated MPV, which produces immature, disparate, and disparate platelets. At this time, the platelet volume dispersion increases, but the newly produced larger platelets contain more active dense particles; the adhesion, aggregation, and release functions of platelets become stronger, and the inflammatory reaction of the body is amplified, directly affecting the prognosis of patients[24]. Therefore, it is easy to explain why patients who are not diagnosed with thrombocytopenia still benefit from the increase in platelets.

Many scholars believe that platelets should be regarded as a new therapeutic target[25]. The SCCM guideline in 2016 suggested "prophylactic platelet transfusion when counts are < 10,000/mm^3 (10 × 10^9/L) in the absence of apparent bleeding and when counts are < 20,000/mm^3 (20 × 10^9/L) if the patient has a significant risk of bleeding." However, this guideline is a weak recommendation, and the quality of evidence supporting this guideline is extremely low because it is based on clinical trials of thrombocytopenia, which is usually caused by leukemia and stem cell transplantation. Our study proves that an increase in platelets in septic patients, regardless of the approaches that have been applied, will improve the prognosis.

We must admit that there are some limitations of our study. Although the study population was large, this study was unfortunately based on a single center, which may limit the extension of these results to other cohorts of patients. In addition, we did not analyze MPV, PDW or other indicators to study changes in platelet function during sepsis. Like many other studies[26–28], this study does not include a repeat platelet count to confirm TP, thereby limiting the accuracy of TP diagnosis.

Conclusion

In conclusion, our study shows that there is no obvious direct relationship between the amount of platelet infusion and the prognosis of sepsis patients, but the recovery of platelet count indicates the improvement of the condition.

Abbreviations

MIMIC-Medical Information Mart for Intensive Care; BIDMC-Beth Israel Deaconess Medical Center; MIT-Massachusetts Institute of Technology; TP-Thrombocytopenia; ICU-intensive care unit; MICU-medical intensive care unit; CCU-coronary care unit; SICU-surgical intensive care unit; CSRU-cardiac surgery recovery unit; TSICU-trauma surgical intensive care unit; LOS-length of stay; HR-hazard ratio; CI-confidence interval; SOFA-Sequential Organ Failure Score; SAPS-Simplified Acute Physiology Score

Declarations

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Ethics approval and consent to participate:

The database was supported by Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology, and consent was obtained for the original data collection. Hence, ethics approval and consent were waived for this study.

Declaration of Conflicting of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The datasets generated and analyzed during the current study are available in the MIMIC III database. https://physionet.org/works/MIMICIIIClinicalDatabase/.

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Figures

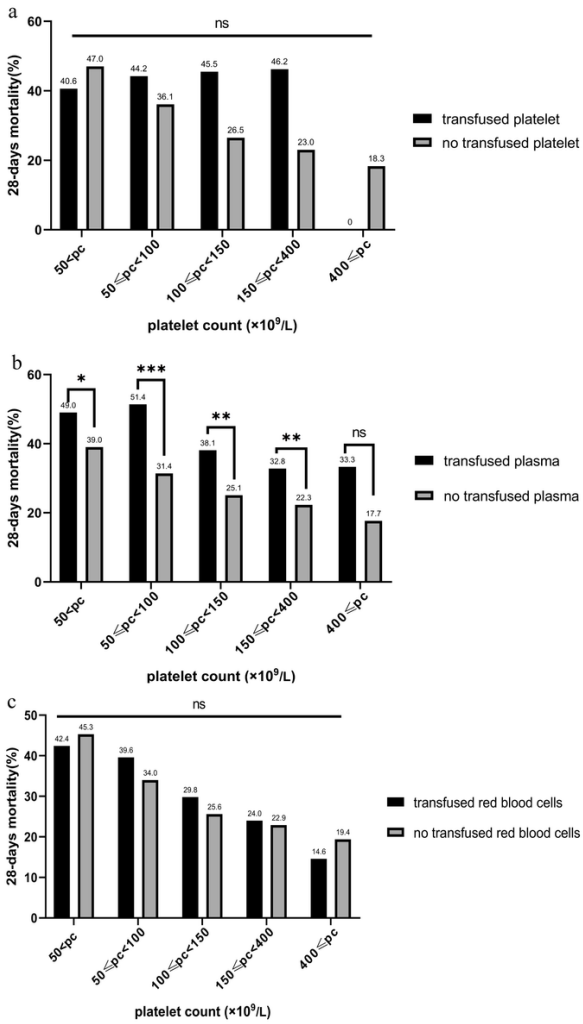

Figure 1

28-day mortality according to transfused blood product, including platelets (1a), plasma (1b) and red blood cells (1c).

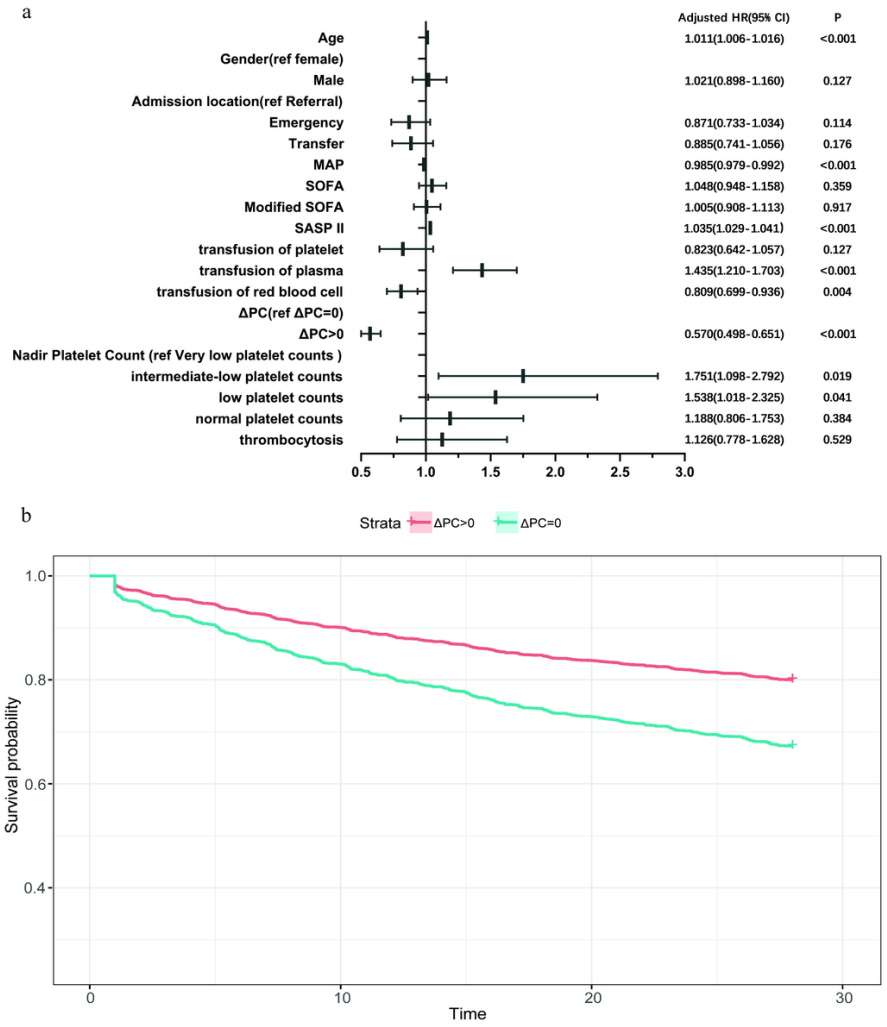

Figure 2

Results of the Cox proportional hazard regression analysis for 28-day survival (2a) and adjusted survival curve from the Cox proportional hazard regression model for 28-day survival stratified by ΔPC (2b). Each horizontal line represents the 95% CI range, and the small black spots in the middle of the crosses represent the HR value. The survival probability in the increased platelet group was higher than in the decreased platelet group (P value < 0.001 by the log-rank test).