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Association between minimal decrease in platelet counts and outcomes in septic patients: a retrospective observational study

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ABSTRACT

Objectives Although platelets have been linked to inflammatory development in sepsis, knowledge on their role as an indicator in sepsis treatment is scarce. Here, we investigated the association between time-dependent changes in platelet counts with mortality rates to reveal the role of platelets in sepsis therapy.

Design A retrospective cohort study.

Setting We screened the Medical Information Mart for Intensive Care (MIMIC-IV), a public database comprising data from critical care subjects at the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, USA.

Participants A total of 7981 patients, who were admitted to the BIDMC between 2008 and 2019, were analysed based on Sepsis-3 criteria from MIMIC-IV.

Primary and secondary outcome measures Primary and secondary outcomes included 30-day mortality after admission and length of intensive care unit (ICU) stay and hospitalisation, respectively.

Results Patients with ≤10% reduction in proportion of platelet counts were associated with significantly lower 30-day mortality (14.1% vs 23.5%, p<0.001, Kaplan-Meier analysis, p<0.0001). Multivariable analysis revealed that decreased platelet-count percentage ≤10% on day 4 after ICU admission was associated with lower probability of 30-day non-survival (OR=0.73, 95% CI 0.64 to 0.82, p < 0.001). Patients in the ≤10% group had significantly shorter ICU stays than those in the >10% group (6.8 vs 7.5, p < 0.001). Restricted cubic spline curves revealed that mortality rates decreased with increase in proportion of platelet counts.

Conclusions A ≤10% decrease in platelet-count percentage among sepsis patients after treatments is independently associated with decreased 30-day mortality, suggesting that changes in proportion of platelet counts after treatments could be an indicator for assessing the therapeutic effects of sepsis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This retrospective study employed a large sample size, from the high-quality Medical Information Mart for Intensive Care database, which increases the credibility of the findings.
⇒ We employed the restricted cubic spline curve model to reveal the association between rates of platelet count change and 30-day mortality in septic patients.
⇒ There was a small amount of missing data, which was handled by multiple imputation using classification and regression trees.
⇒ We did not evaluate differences in long-term outcomes between groups due to a lack of long-term follow-up data in the targeted database.

INTRODUCTION

Sepsis is a life-threatening condition that requires acute treatment. The associated high incidence and mortality as well as poor patient prognosis have made it a primary global health concern. In America, sepsis does not only comprise one of the highest expenses but also causes numerous deaths among hospitalised patients.[1 2] Estimates from some high-income nations indicate that about 50.9 million patients develop sepsis every year, of which 5.3 million die annually due to the associated complications.[3]

Studies have shown that sepsis is characterised by multiple organ failure, which subsequently endanger life due to dysregulated host response to infections.[4] Sepsis is a complicated pathophysiological process in which a pathogen triggers a person's inflammatory-immune response, thereby leading to activation or repression of various facets, including endothelium, coagulopathy, immunological and hormonal functions. Endothelial damage, inflammatory pathways and coagulation synergise to activate platelets in sepsis, which are crucial for pathogenic defence. Platelets not only possess unambiguous structures but also play crucial functions in host defence, including regulating expression of toll-like receptors that detect hallmark signals of bacterial infection, an array of microbicidal peptides, as well as other host defence molecules and functions.[5–7] Some studies have shown that platelets can exert a bactericidal

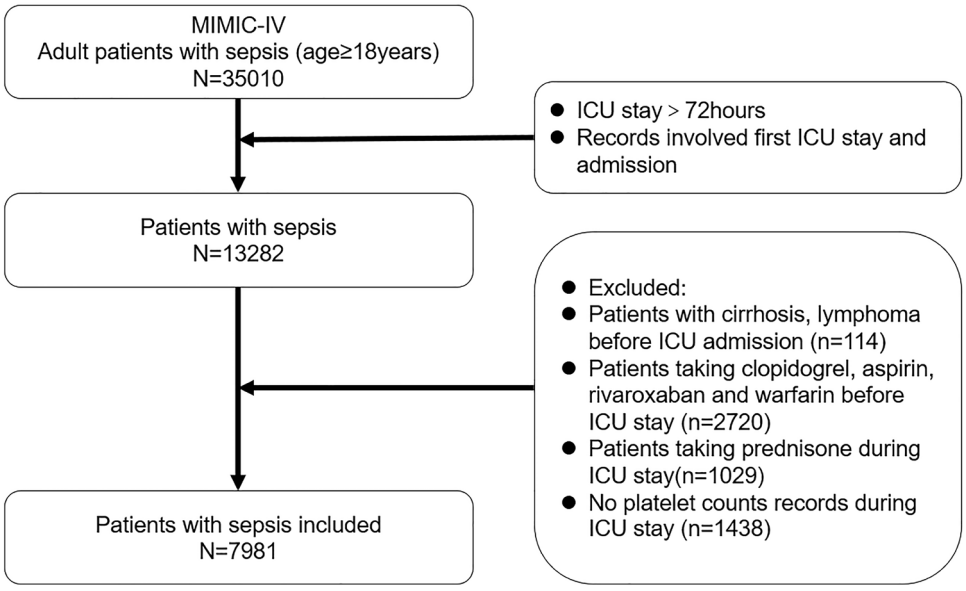

Figure 1 Flowchart showing step-by-step selection on patients included in the study. ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care.

effect by releasing platelet antimicrobial peptides,[8] while others have demonstrated that platelet hyperreactivity could contribute to sepsis complications, such as acute respiratory distress syndrome, disseminated intravascular coagulation, acute kidney injury and septic cardiomyopathy.[9] Moreover, a recent study revealed that sepsis induces platelet transcription and translation, while circulating platelets exhibited higher levels of integrin subunit αIIb (ITGA2B), which is linked to higher mortality.[10]

Platelet counts have been used as critical markers for sequential organ failure assessment (ie, Sofa Score) in patients with sepsis, and effectively reflect patient prognosis.[11] Numerous studies have demonstrated that thrombocytopenia is correlated with poor prognosis.[12–14] Moreover, Mavrommatis *et al* [15] found that a lower platelet count was associated with more severe sepsis incidence. Consequently, researchers have hypothesised that thrombocytopenia patients could benefit from platelet-elevating medications to improve sepsis prognosis.[16] One study targeted recombinant human thrombopoietin and found that sepsis with thrombocytopenia could effectively promote platelet counts in patients, thereby resulting in shorter stays in the intensive care unit (ICU).[17] Other trials investigating the efficacy of antiplatelet drugs in sepsis subjects showed that they reduce undesirable thrombosis, inflammatory host responses and organ damage.[18 19] To date, however, the potential for platelets as an indicator in evaluation of the effects of sepsis treatments remains unknown. Therefore, this study aimed to retrospectively analyse the relationship between changes in proportion of platelet counts after treatments with clinical outcomes of patients with sepsis.

MATERIALS AND METHODS

Data sources

This study was conducted in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology guidelines.[20] Data were retrieved from the Medical Information Mart for Intensive Care (MIMIC-IV V.1.0),[21] which comprises clinical data from a custom hospital-wide electronic health record and an ICU-specific clinical information system for more than 380 000 patients who were admitted to the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, USA, between 2008 and 2019. The database includes detailed information on patient demographics, laboratory tests, medication use, vital signs and disease diagnosis, among others. It also contains records for patients admitted to the BIDMC emergency department or the ICUs, with clearly defined data standards. Patient records were fully anonymised, and data collection was following approval by the BIDMC and Massachusetts Institute of Technology Institutional Review Board. We first underwent training on the programme and passed the Collaborative Institutional Training Initiative test, before we were eligible to receive free access to the database. Thereafter, we conducted the related research in accordance with the rules. The author (XL) passed certification for the Collaborative Institutional Training Initiative (Certification Number 48605954).

Patient and public involvement

Neither patients nor members of the public were involved in any part of this study.

Selection criteria

Data were included in the study if the patients met the following criteria: (1) were diagnosed with sepsis, according to Sepsis-3 standard;[4] (2) were adults, aged 18 years and above and (3) their ICU stay was >72 hours. For patients with records showing multiple ICU stays and admissions, only data involving the first ICU stay and admission were included. We excluded data for patients diagnosed with cirrhosis, lymphoma and taking

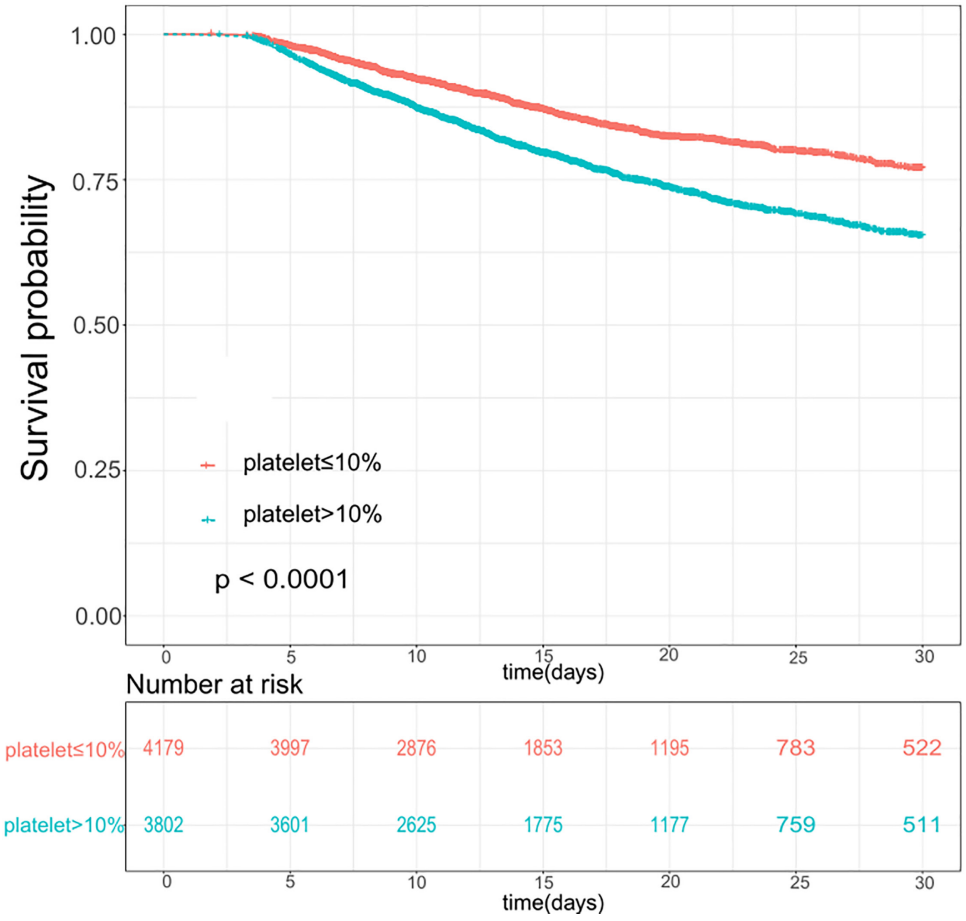

Figure 2 Kaplan-Meier survival curves for the mortality within 30 days.

clopidogrel, aspirin, rivaroxaban and warfarin. In addition, we did not consider patients with prednisone while they were transferred to the ICU and also excluded data sets with missing data for day 1 and day 4 platelet counts.

Data extraction

Data extraction from the MIMIC-IV database was achieved using PostgreSQL. Platelet counts, recorded on the first and fourth day after admission to the ICU, were extracted from MIMIC-IV. Differences in platelet counts were calculated using the formula: (platelet $counts_{day4}$−platelet $counts_{day1}$)/platelet $counts_{day1}$×100%. The variables at day 1 of ICU admission included age, gender, weight, ethnicity, chronic diseases, sofa score, acute physiology score (aps iii), simplified acute physiology score (saps ii), prothrombin time (pt), activated partial thromboplastin time (aptt) and white cell counts. These characteristics served as possible confounders in this study.

Outcomes

The primary endpoint was 30-day mortality after admission, whereas length of hospitalisation and ICU stay were considered secondary outcomes.

Missing values

All variables in this study had less than 11% missing values (online supplemental table S1). We employed classification and regression trees[22 23] for multiple imputation of the missing values for variables, including weight, pt, aptt and white cell counts.

Statistical analysis

The percentage change in platelet counts was recorded on day 4 following ICU admission. We generated receiver operating characteristic curve (ROC) to calculate the cut-off of the platelet-count percentage, which was subsequently employed to categorise patients in the baseline characteristics table. For computational simplicity, the threshold for the ROC was −9.5% (almost equivalent to −10%). Statistical significance was defined as two-sided p values <0.05. Furthermore, we used a multivariate logistic regression analysis to assess the relationship between the proportion of platelet counts and 30-day mortality.

Next, we applied the variables listed in online supplemental table S2 to identify potential confounding variables for logistic regression. These factors were incorporated into the multivariate regression model, as adjusting variables, at a p value of less than 0.05. We generated Kaplan-Meier (KM) curves to visualise the survival curves and compare changes in proportion of platelet counts over 30 days, while the log-rank test was used for survival analysis. Restricted cubic spline curves were generated using logistic models and used to evaluate the relationship

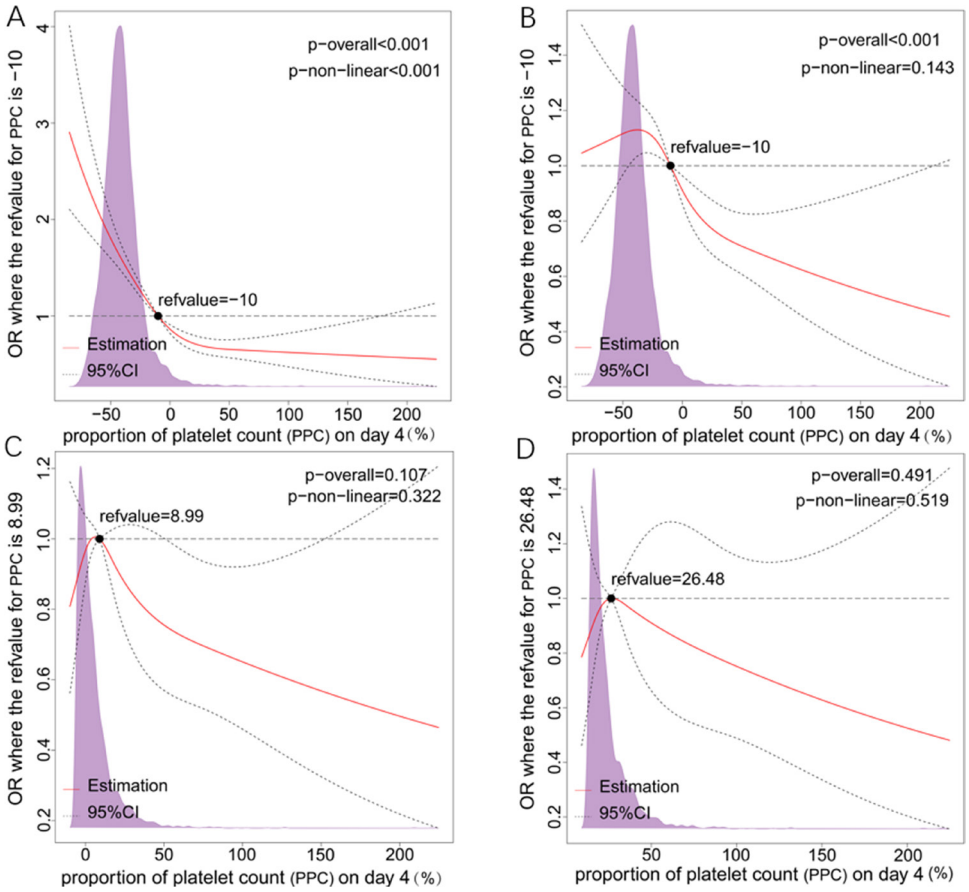

Figure 3 The association between proportion of platelet counts (PPC) and mortality within 30 days was shown in restricted cubic spline curves (RCS) based on logistic models in the whole population and different subsets. Solid red lines are OR, with dashed black lines showing 95% CIs derived from restricted cubic spline regressions with four knots. Reference lines for no association are indicated by the dashed grey lines at an OR of 1.0. Violet density curves show the fraction of the population with different levels of the proportion of platelet counts. Refvalue indicates PPC improves mortality within 30 days. (A, B) The proportion of platelet counts was modelled as a continuous variable and fitted in an unadjusted and adjusted model using restricted cubic spline analysis in the whole population. (C, D) The proportion of platelet counts was modelled as a continuous variable and fitted in the adjusted models in the patients, with a decline of the proportion of platelet counts >10% excluded and an increasing proportion of platelet counts ≥8.99% included. Analysis was adjusted for age, cardiovascular disease, liver disease, renal disease, vascular disease, cancer, sofa, saps ii, aps iii, pt, aptt and white cell counts at baseline.

between proportion of platelet counts and the principal endpoint.

Data with normal distribution were presented as means and respective SD, whereas non-normally distributed variables were presented as medians and IQRs. Normally and non-normally distributed continuous variables were compared between groups using analysis of variance and Kruskal-Wallis test, respectively. For subgroup analysis, variables were subclassified into age, gender, sofa score, pt, aptt and white cell count categories, then forest plots generated to depict the relationship between proportion of platelet counts and mortality rates. All statistical analyses were performed using packages implemented in R software, V.4.2.1.

RESULTS

The MIMIC-IV database contains data for 35 010 adult sepsis patients. A total of 7981 adult patients diagnosed with sepsis using Sepsis-3 criteria met our inclusion criteria and were included in the study (figure 1). All participants were classified into two groups, and basic characteristics are outlined in online supplemental table S2. Analysis of platelet-count percentages on day 4 showed that 3802 and 4179 sepsis patients had reduced platelet-count percentage of >10%, and ≤10%, respectively. Patients in the >10% group were significantly older (age 66.2 vs 65.3, p=0.012) and displayed markedly severe coagulation dysfunction (pt 14.6 vs 14.1, p<0.001 and aptt 33.0 vs 30.8, p<0.001) than their counterparts in the ≤10% group. Similarly, patients with >10% reduction in platelet-count percentage displayed significantly higher white cell counts (13.0 vs 11.3, p<0.001) and a markedly higher sofa score (8 vs 6, p<0.001) than those with ≤10%. The higher score in patients with >10% reduction in proportion of platelet counts might also be indicated in other organ dysfunction rating systems, such as aps iii and saps ii.

Patients with ≤10% reduced proportion of platelet counts had significantly lower mortality rates within 30

subgroups	patients (n)	platelet>10% n(%)	platelet≤10% n(%)	OR(95%CI)
overall	**7981**	**892(23.5)**	**591(14.1)**	**0.73(0.64 0.82)**
Age				
<65 yr	3851	335(18.7)	211(10.2)	0.70(0.57 0.85)
≥65 yr	4130	557(27.7)	380(18)	0.74(0.63 0.87)
Gender				
male	4594	503(23.1)	349(14.5)	0.73(0.62 0.86)
female	3387	389(24)	242(13.7)	0.73(0.60 0.89)
Sofa score				
<7	3471	199(14.9)	186(8.7)	0.61(0.49 0.76)
≥7	4510	693(28.1)	405(19.8)	0.79(0.68 0.92)
Baseline pt above median				
No	3628	321(19.6)	231(11.6)	0.66(0.54 0.80)
Yes	4353	571(26.4)	360(16.5)	0.78(0.66 0.92)
Baseline aptt above median				
No	3678	307(19.7)	232(10.9)	0.61(0.50 0.75)
Yes	4303	585(26.1)	359(17.4)	0.82(0.70 0.97)
Baseline WBC above median				
No	3964	369(22.1)	321(14)	0.76(0.63 0.90)
Yes	4017	523(24.5)	270(14.4)	0.70(0.59 0.84)

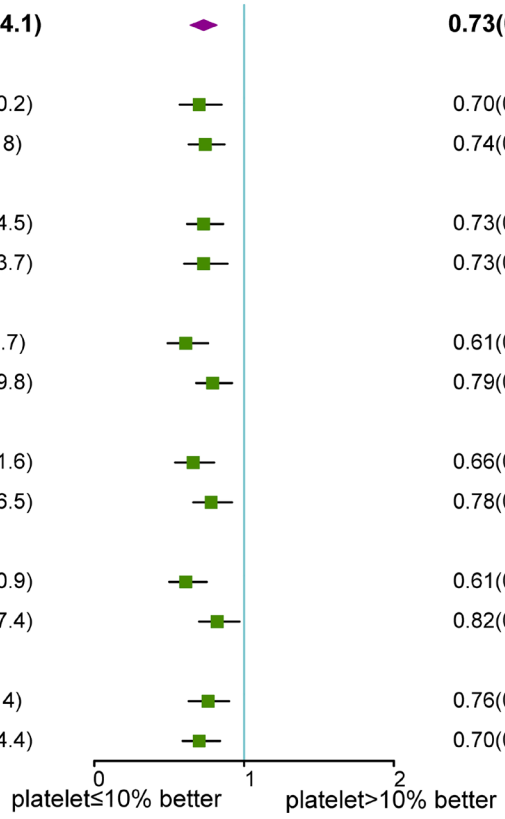

Figure 4 Forest plot of subgroups. In different subgroups, the continuity variables including age, sofa score, pt, aptt and white cell counts (WBC) were stratified by the median.

days (14.1% (591) vs 23.5% (892), p<0.001) and significantly shorter ICU stays (6.8 vs 7.5, p<0.001) than their counterparts in the >10% group. However, we found no statistically significant differences between the groups with regards to the length of hospital stays (13.7 vs 14.1, p=0.122). KM curves showed that patients in the ≤10% group had significantly longer survival times within 30 days than those in the >10% group (mean survival time 26.4 vs 24.4 days; p<0.0001) (figure 2). Multivariable logistic regression model showed that reduced platelet-count percentage ≤10% was an independent predictor of reduction in mortality rates within 30 days (OR 0.73; 95% CI 0.64 to 0.82; p<0.001). In the modified analysis, we adjusted for confounders such as, age, saps ii score, sofa score, aps iii score and white cell counts (online supplemental table S3). Restricted cubic spline model showed that lower reduction in proportion of platelet counts on day 4 were associated with lower mortality rates within 30 days. Additionally, the model indicated that a greater proportion of platelet counts could predict a reduction in 30-day mortality for septic patients with one subset excluding reduction in the proportion of platelet counts >10% on day 4 after ICU admission, while the other having elevated proportion of platelet counts on day 4 after ICU admission (figure 3). Our findings were supported by different subanalysis in which one subset excluded no decline or even an increase in platelet counts on day 4 compared with day 1 after ICU admission, while the other subset excluded platelet count <100 k/µl on day 1 after ICU admission (online supplemental tables S4, S5 and figure S1, S2). Subgroup analysis revealed that age, gender, organ dysfunction status, infection level and coagulation functional condition were all stratified, a trend that was mirrored by a reduction in mortality within 30 days among patients in the ≤10% group (figure 4).

DISCUSSION

In the present study, we analysed data for 7981 patients with sepsis and found that a ≤10% decrease in proportion of platelet count on day 4 after ICU admission was associated with low mortality rates within 30 days. Subgroup analysis results corroborated these findings. Moreover, restricted cubic spline curves revealed that increased proportion of platelet counts was associated with reduced mortality rates within 30 days. These findings showed that change in proportion of platelet counts would be used as a reference to evaluate the effect of sepsis treatments.

Platelets, anucleate cells, originate from mature megakaryocytes in the bone marrow. Previous studies have shown that platelets not only play a role in haemostasis but also in various other tasks, such as host defence against infection, including phagocytosis of bacteria and viruses, superoxide production and platelet-derived

microbactericidal proteins.[24] Notably, platelets have a series of surface receptors and adhesion molecules that allow them to interact with leucocytes and pathogens in the bloodstream, which is critical for the proinflammatory and chemotactic processes.[6] When sepsis occurs, due to conditions such as infections, platelets are activated and directly interact with leucocytes in the blood.[25–27] Through the interaction, circulating leucocytes can effectively exert anti-infection effects. Neutrophils may locate infection sites because of their interaction with platelets,[28] while activated neutrophils produce and release neutrophil extracellular traps that subsequently capture and destroy infections.[29]

Recent research has revealed that thrombocytopenia is associated with a poor patient prognosis. For example, Moreau *et al* [12] showed that a 30% fall in platelet counts was an independent predictor of mortality in both medical and surgical ICUs, while Nijsten *et al*[30] demonstrated that a slow or lack of increase in platelet counts among surgical ICU patients was associated with higher mortality rates. The authors calculated platelet proportions 10 days after ICU admission and found that the value was more than five times higher in survivors compared with non-survivors ($30\pm46\times10^3/mm^3$/day vs $6\pm28\times10^3/mm^3$/day, p<0.001). However, results from a retrospective analysis of sepsis patients with leucocytosis revealed a 6.9% increase in hospital mortality rates among patients in the thrombocytosis group, which was classified as having >500 000 platelets/L.[31] To date, a handful of studies have evaluated the correlation between platelet counts and sepsis outcomes while the role of platelets as an indicator of therapeutic efficacy remains unknown.

Platelets are not only often applied as clinical monitoring indices but also play a role in anti-infective responses.[26] Nevertheless, few studies have employed platelets as a new inflammatory cell for clinical evaluation of inflammatory response in sepsis. Host response is the core pathomechanism of sepsis, and different pathogens causing sepsis may require various monitoring of the inflammatory response, such as procalcitonin and 1,3-β-d-glucan testing. Currently, platelets, as an inflammatory mediator, essentially respond to the sepsis host response process.[8] Results of the present study showed that septic patients with minimal decrease of platelet counts on day 4 compared with day 1 had improved 30-day mortality. Day 4 is considered the ideal timeframe to evaluate the efficacy of sepsis treatment, and thus, changes in proportion of platelet counts on this day can serve as a reference for future evaluation of clinical efficacy and optimisation of treatment protocols. Additionally, thrombocytosis has potential as a standalone indicator of a favourable prognosis in ICU patients. A previous study found that patients with general and trauma ICU platelet counts of more than 450×10^9/L on at least one occasion were associated with lower ICU mortality (p=0.003).[32] This outcome was consistent with our findings of research.

This study had several limitations. First, considering that this was an observational study, we did not elucidate the underlying mechanism by which changes in platelet counts might affect sepsis outcomes, thus further studies are needed to clarify this. Second, our findings may not generalise to all critical care patients in the ICU because the eligible population was limited to septic patients. Third, our results lack a causal association because we only examined data from an extensive public retrospective database. In future, larger clinical trials are needed to compare changes in proportion of platelet counts and their effect in evaluating the therapeutic effect of sepsis. Finally, we did not explore the association between treatments and platelet levels owing to the observational nature of the study. However, by taking advantage of the large sample size of the public database, this study provides a reference for further prospective studies in sepsis.

Conclusions

In summary, reduction in proportion of platelet counts of ≤10% in sepsis patients after treatments is an independent predictor of improved mortality rates within 30 days. Meanwhile, this study found a downward trend in mortality within 30 days in sepsis patients as the platelet counts increased. Collectively, these findings provide new insights regarding the role of platelets in evaluating efficacy of sepsis treatments.

Contributors WHY and XL designed this study. YWQ and XL conducted data collection and data analysis. XL wrote the manuscript. WHY, YL and TJZ analysed and interpreted the results. WHY designed and supervised this study, and is responsible for the overall content as guarantor. All authors have reviewed and approved this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was in accordance with the ethical standards of the Declaration of Helsinki and was approved by the ethics review boards of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center (researcher certification number 48605954). MIMIC-IV was retrospective with lack of patient intervention, and all patients' data were de-identified; thus individual patient informed consent was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data used in this study can be obtained by the corresponding author upon request.

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Table S1. All Missing values of data from MIMIC-IV

variables	Missing number n (%)
age	
gender	
weight	38 (0.47)
ethnicity	
myocardial_infarct	
congestive_heart_failure	
peripheral_vascular_disease	
cerebrovascular_disease	
dementia	
chronic_pulmonary_disease	
rheumatic_disease	
peptic_ulcer_disease	
mild_liver_disease	
diabetes_without_cc	
diabetes_with_cc	
paraplegia	
renal_disease	
malignant_cancer	
severe_liver_disease	
metastatic_solid_tumor	
aids	
sofa score	
apsiii	
sapsii	
pt	760 (9.52)
aptt	805 (10.08)
white_blood_cell_counts	3 (0.03)
platelet_counts0[a]	
platelet_counts3[b]	
LOS_hospital	
hospital_expire_flag[c]	
LOS_ICU	

LOS=length of stay

[a]platelete_counts0 are regarded as platelet counts on day 1 of ICU admission

[b]platelete_counts3 are regarded as platelet counts on day 4 of ICU admission

[c]hospital_expire_flag is regarded as in-hospital death

Liu X, *et al. BMJ Open* 2023; 13:e069027. doi: 10.1136/bmjopen-2022-069027

Table S2: Baseline of patient characteristics stratified by proportion of platelet counts on day four of ICU admission

Characteristic	Overall	declining proportion of platelet counts		*p* value
		platelet>10%	platelet≤10%	
Number	7981	3802	4179	
Gender, M (%)	4594 (57.6)	2180 (57.3)	2414 (57.8)	0.717
Median age (IQR), yr	65.8 [53.6 77.3]	66.2 [54.6 77.4]	65.3 [52.6 77.3]	0.012
Median weight (IQR), kg	80.0 [67.0 96.5]	79.8 [66.8 96.5]	80.0 [67.0 96.4]	0.586
Ethnicity, n (%)				0.671
American Indian	20 (0.3)	8 (0.2)	12 (0.3)	
Asian	205 (2.6)	100 (2.6)	105 (2.5)	
Black	707 (8.9)	325 (8.5)	382 (9.1)	
White	5025 (63.0)	2382 (62.7)	2643 (63.2)	
Hispanic	258 (3.2)	132 (3.5)	126 (3.0)	
Others	1766 (22.1)	855 (22.5)	911 (21.8)	
Select comorbidities[a], n (%)				
Cardiovascular disease	2826 (35.4)	1473 (38.7)	1353 (32.4)	<0.001
Chronic pulmonary disease	1945 (24.4)	941 (24.8)	1004 (24.0)	0.467
Liver disease	1466 (18.4)	816 (21.5)	650 (15.6)	<0.001
Renal disease	1582 (19.8)	796 (20.9)	786 (18.8)	0.019
diabetes	2256 (28.3)	1109 (29.2)	1147 (27.4)	0.093
Vascular disease	2359 (29.6)	1082 (28.5)	1277 (30.6)	0.043
Cancer[b]	1189 (14.9)	620 (16.3)	569 (13.6)	0.001
Aids	56 (0.7)	19 (0.5)	37 (0.9)	0.054
Others[c]	1507 (18.9)	705 (18.5)	802 (19.2)	0.477
Status at admission (median [IQR])				
Sofa score	7.0 [5.0 11.0]	8.0 [5.0 12.0]	6.0 [4.0 9.0]	<0.001
Apsiii	61.0 [44.0 81.0]	66.0 [49.0 88.8]	56.0 [42.0 74.0]	<0.001
Sapsii	40.0 [32.0 51.0]	44.0 [35.0 54.0]	38.0 [30.0 47.0]	<0.001
Laboratory test (median [IQR])				
White blood cell counts, k/ul	12.0 [8.6 16.3]	13.0 [9.3 17.8]	11.3 [8.3 15.1]	<0.001
Pt (s)	14.3 [12.7 17.3]	14.6 [12.8 18.2]	14.1 [12.6 16.5]	<0.001
Aptt (s)	31.7 [27.5 40.7]	33.0 [28.1 44.6]	30.8 [27.2 37.7]	<0.001
ICU outcome				
30-day mortality, n (%)	1483 (18.6)	892 (23.5)	591 (14.1)	<0.001
Median hospital LOS (IQR), d	13.9 [9.0 22.0]	14.1 [9.0 22.3]	13.7 [9.0 21.8]	0.122
Median ICU LOS (IQR), d	7.1 [4.8 12.1]	7.5 [4.9 12.9]	6.8 [4.7 11.3]	<0.001

IQR, interquartile range; Sofa, sequential organ failure assessment; Apsiii, acute physiology score; Sapsii, simplified acute physiology score; Pt, prothrombin time; Aptt, activated partial thromboplastin time; LOS, length of stay.

[a]Comorbidities are defined by the Charlson comorbidity index.

[b]Cancer includes malignant cancer and metastatic solid tumor.

[c]Others includes dementia, rheumatic disease, peptic ulcer disease and paraplegia.

Table S3: Univariate and multivariate analysis for assessing the mortality within 30 days

	Univariate analysis			Multivariate analysis		
Variables	OR	CI 95%	*p*	OR	CI 95%	*p*
Age	1.02	1.02-1.03	<0.001	1.03	1.03-1.04	<0.001
Cardiovascular disease	1.41	1.26-1.58	<0.001	1.07	0.94-1.23	0.307
Liver disease	1.94	1.70-2.21	<0.001	1.61	1.37-1.89	<0.001
Renal disease	1.48	1.30-1.69	<0.001	0.97	0.83-1.12	0.646
Vascular disease	1.31	1.16-1.48	<0.001	1.56	1.36-1.78	<0.001
Cancer	1.75	1.52-2.02	<0.001	1.91	1.62-2.25	<0.001
Sapsii	1.04	1.03-1.04	<0.001	0.99	0.98-0.99	<0.001
Sofa score	1.15	1.13-1.16	<0.001	1.01	0.99-1.03	0.469
Apsiii	1.03	1.03-1.03	<0.001	1.03	1.03-1.03	<0.001
WBC (k/ul)	1.01	1.01-1.02	<0.001	1.01	1.00-1.01	0.080
Pt (s)	1.03	1.02-1.04	<0.001	1.01	1.01-1.02	<0.001
Aptt (s)	1.01	1.01-1.01	<0.001	1.00	1.00-1.01	0.051
[a]platelet≤10%	0.54	0.48-0.60	<0.001	0.73	0.64-0.82	<0.001

CI, confidence interval; OR, odds ratio; Sapsii, simplified acute physiology score; Sofa, sequential organ failure assessment; Apsiii, acute physiology score; WBC, white blood cell counts; Pt, prothrombin time; Aptt, activated partial thromboplastin time.

[a]platelet≤10% is regarded as declining proportion of platelet counts on day 4 of ICU admission.

Table S4. Univariate and multivariate analyses were performed to assess mortality within 30 days, excluding patients who had no decline or even an increase in platelet counts on day four at the time of study inclusion

Variables	Univariate analysis			Multivariate analysis		
	OR	CI 95%	*p*	OR	CI 95%	*p*
Age	1.02	1.01-1.02	<0.001	1.03	1.02-1.03	<0.001
Cardiovascular disease	1.32	1.15-1.52	<0.001	1.09	0.93-1.28	0.294
Liver disease	1.94	1.66-2.26	<0.001	1.57	1.30-1.89	<0.001
Renal disease	1.33	1.13-1.56	0.001	0.92	0.76-1.10	0.347
Vascular disease	1.22	1.06-1.41	0.007	1.56	1.32-1.83	<0.001
Cancer	1.69	1.42-2.00	<0.001	1.83	1.50-2.22	<0.001
Sapsii	1.04	1.03-1.04	<0.001	0.99	0.98-1.00	0.003
Sofa	1.14	1.12-1.16	<0.001	1.00	0.97-1.03	0.885
Apsiii	1.03	1.02-1.03	<0.001	1.03	1.03-1.03	<0.001
WBC (k/ul)	1.01	1.01-1.02	<0.001	1.01	1.00-1.01	0.166
Pt (s)	1.03	1.03-1.04	<0.001	1.02	1.01-1.03	<0.001
Aptt (s)	1.01	1.01-1.01	<0.001	1.00	1.00-1.01	0.139
[a]platelet≤10%	0.55	0.46-0.65	<0.001	0.69	0.57-0.84	0.001

CI, confidence interval; OR, odds ratio; Sapsii, simplified acute physiology score; Sofa, sequential organ failure assessment; Apsiii, acute physiology score; WBC, white blood cell counts; Pt, prothrombin time; Aptt, activated partial thromboplastin time.

[a]platelet≤10% is regarded as declining proportion of platelet counts on day 4 of ICU admission.

Figure S1. Kaplan-Meier survival curves

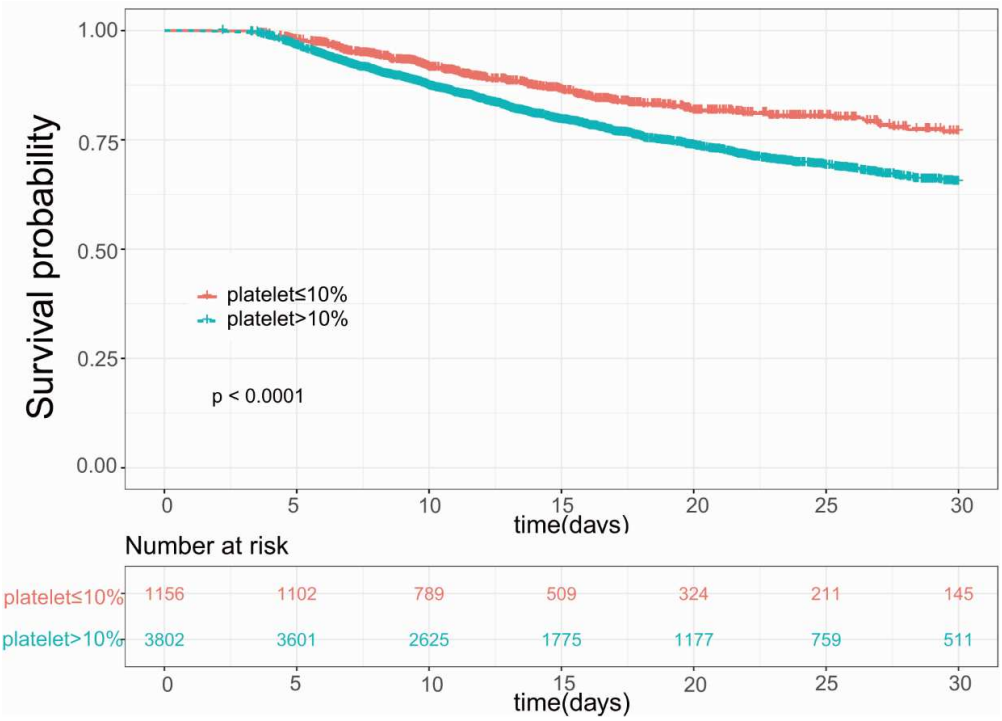

Figure S1. Kaplan-Meier survival curves were used to analyse the association between the percentage change in platelet count on day four compared to day one and the mortality within 30 days, excluding patients with no decline or even an increase in platelet counts on day four at the time of inclusion into the study

Table S5. Univariate and multivariate analyses were performed to assess mortality within 30 days, excluding patients with platelet counts < 100 K/ul on day one at the time of inclusion

Variables	Univariate analysis			Multivariate analysis		
	OR	CI 95%	*p*	OR	CI 95%	*p*
Age	1.03	1.02-1.03	<0.001	1.03	1.03-1.04	<0.001
Cardiovascular disease	1.49	1.31-1.69	<0.001	1.10	0.95-1.28	0.210
Liver disease	1.63	1.37-1.92	<0.001	1.40	1.15-1.70	0.001
Renal disease	1.50	1.30-1.74	<0.001	0.94	0.80-1.11	0.484
Vascular disease	1.40	1.22-1.59	<0.001	1.59	1.37-1.83	<0.001
Cancer	1.70	1.44-2.00	<0.001	1.90	1.57-2.29	<0.001
Sapsii	1.04	1.03-1.04	<0.001	0.99	0.98-1.00	0.001
Sofa	1.14	1.12-1.16	<0.001	0.99	0.97-1.02	0.576
Apsiii	1.03	1.03-1.03	<0.001	1.03	1.03-1.04	<0.001
WBC (k/ul)	1.02	1.01-1.03	<0.001	1.01	1.00-1.01	0.143
Pt (s)	1.02	1.02-1.03	<0.001	1.01	1.00-1.02	0.016
Aptt (s)	1.01	1.01-1.01	<0.001	1.00	1.00-1.01	0.125
[a]platelet≤10%	0.54	0.47-0.61	<0.001	0.72	0.63-0.83	<0.001

CI, confidence interval; OR, odds ratio; Sapsii, simplified acute physiology score; Sofa, sequential organ failure assessment; Apsiii, acute physiology score; WBC, white blood cell counts; Pt, prothrombin time; Aptt, activated partial thromboplastin time.
[a]platelet≤10% is regarded as declining proportion of platelet counts on day 4 of ICU admission.

Figure S2. Kaplan-Meier survival curves

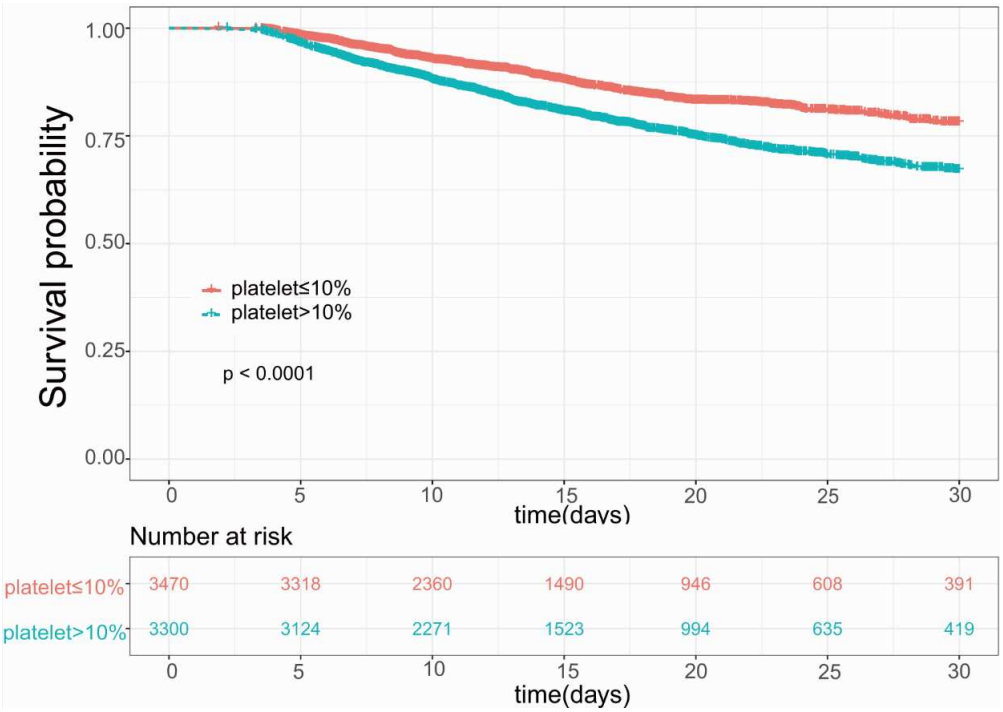

Figure S2. Kaplan-Meier survival curves were used to analyse the association between the percentage change in platelet count on day four compared to day one and the mortality within 30 days, excluding patients with platelet counts < 100 K/ul on day one at the time of inclusion into the study.