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ARTICLE

Mediating Role of Platelet Count Increase in Unfractionated Heparin Treatment for Sepsis Patients: A Retrospective Cohort Analysis

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Abstract

Aims/Background The role of heparin in sepsis therapy has been widely debated. The controversy surrounding heparin's use as an anticoagulant in sepsis may stem from differences in sepsis definitions, study designs, timing and dosage of drug administration, treatment duration, complications, and patient severity. In this study, we aimed to determine the optimal timing and dosage of heparin in patients with sepsis, identify specific subgroups that could benefit from heparin therapy, and explore laboratory markers to assess its efficacy.

Methods This retrospective cohort study was conducted using the Medical Information Mart for Intensive Care-IV dataset. Data from patients with sepsis were extracted based on the Sepsis 3.0 criteria. Patients were categorized according to heparin use. The effectiveness of early and appropriate heparin administration was assessed, and a subgroup analysis was performed to identify patients most likely to benefit from heparin therapy. Additionally, factors mediating the improvement in sepsis prognosis following heparin treatment were analyzed.

Results We recruited 4149 participants who met the inclusion criteria, with an overall 28-day mortality rate of 19.5%. There were 2192 individuals in the heparin group and 1957 in the non-heparin group. After propensity score matching, heparin therapy demonstrated a significantly greater effect on reducing both 28-day and 90-day mortality compared to the non-heparin treatment (18.1% vs. 10.7%, $p < 0.001$; 18.8% vs. 12.6%, $p < 0.001$). However, the heparin group had a higher incidence of major bleeding (10.9% vs. 6.3%, $p = 0.001$), increased use of mechanical ventilation (54.3% vs. 45.1%, $p < 0.001$), and a longer intensive care unit stay (3.6 vs. 2.5 days, $p < 0.001$) compared to the non-heparin group. Early administration of high-dose heparin improved 28-day survival. Early and adequate heparin administration was more effective than late and insufficient dosing ($p < 0.01$), except in patients with sepsis who had low white blood cell counts, alkalosis, or reduced platelet counts. The increase in platelet count had a significant mediating effect on the entire cohort ($p < 0.001$ for the causal mediation effect), with a mediation proportion of 14%.

Conclusion Early and adequate heparin administration can significantly improve the prognosis of sepsis. An increase in platelet count may serve as a potential indicator of the effectiveness of heparin therapy in sepsis.

Key words: sepsis; platelet count; mediation analysis; organ dysfunction; heparin

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Introduction

Sepsis is characterized by life-threatening immune dysregulation and organ dysfunction triggered by infection, representing a major global health challenge (Evans et al, 2021). The incidence of sepsis has reached 48.9 million cases, contributing to 11.0 million fatalities worldwide, accounting for 19.7% of global deaths (Rudd et al, 2020). However, the prevalence and mortality rates of sepsis vary across studies. Despite advances in therapy, sepsis continues to exhibit high morbidity and mortality rates, and current therapeutic options remain limited (Lin et al, 2018). Current management strategies for sepsis include interventions such as antibiotic therapy, fluid resuscitation, and the use of vasopressors.

The role of heparin in sepsis therapy has been widely debated (Iba et al, 2024). Several studies have suggested that heparin plays a crucial therapeutic role in sepsis management, offering substantial benefits (Huang et al, 2023; Zhou et al, 2024). Heparin has emerged as a promising candidate for developing treatment strategies that combine anticoagulant and anti-inflammatory properties (Hogwood et al, 2023). However, conflicting findings indicate that heparin therapy may not be effective in certain cases (Iba et al, 2012). It is essential to consider the potential risk of major bleeding when using anticoagulants like heparin. The controversy surrounding heparin's use in sepsis may stem from variations in sepsis definitions, study designs, the timing and dosage of administration, the duration of treatment, complications, and patient severity. Further research and well-designed studies are needed to provide more conclusive evidence regarding the role of heparin in sepsis management.

The primary objectives of this study were to conduct a comprehensive analysis of publicly available databases to determine the optimal timing and dosage of heparin in sepsis patients, to identify individuals most likely to benefit from this treatment, and to explore laboratory markers for assessing heparin's efficacy. The findings of this study may contribute to developing new strategies for the effective treatment of sepsis.

Methods

Data Source and Study Subjects

A retrospective analysis was conducted using the Medical Information Mart for Intensive Care-IV (MIMIC-IV) dataset, which includes intensive care unit (ICU) stay data for 73,181 patients recorded between 2008 and 2019 in Boston. Access to the database is granted to individuals who have completed the Collaborative Training Program exam (certification number: 46304508, author: CH). Patient consent and ethical approval were not required, as the data were de-identified and patient identifiers were removed. All studies within the MIMIC-IV database were conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki, which governs medical research involving human subjects. The database primarily focuses on critical care (Johnson et al, 2023). Due to the de-identified nature of the data, the need for informed consent was waived. This study specifically focused on a cohort of 6600 adult patients who met the Sepsis-3 criteria within 24

hours of admission (Singer et al, 2016). Sepsis was defined as a suspected infection accompanied by evidence of organ dysfunction, as determined by a sequential organ failure assessment (SOFA) score ≥2 within the first 24 hours of admission (Singer et al, 2016).

For better research, we assumed that all patients had a baseline SOFA score of 0 (Lat et al, 2021). Consequently, the inclusion criteria encompassed cases in which antibiotics were administered, microbiological cultures were obtained, and the SOFA score was ≥2 within the first 24 hours of ICU admission. The exclusion criteria included incomplete data, hematological disorders, ICU stays of less than 24 hours, and durations of heparin usage of less than 24 hours. In cases of multiple ICU admissions, only the initial admission was considered in the analysis (Chen et al, 2020).

Variable and Clinical Outcomes

The following variables were assessed: (1) demographic characteristics, including sex, age, body mass index (BMI), and ethnicity; (2) severity at admission, including the SOFA score and the Elixhauser comorbidity index; (3) chronic comorbidities, such as hypertension, diabetes, heart failure, chronic kidney disease (CKD), cancer, and chronic obstructive pulmonary disease (COPD); and (4) laboratory tests, including white blood cell count, platelet count, hemoglobin, alanine aminotransferase (ALT), total bilirubin, creatinine, blood glucose, potassium, sodium, calcium, chloride, pH, oxygenation index (PaO_2/FiO_2), lactate levels, prothrombin time (PT), and activated partial thromboplastin time (APTT). To assess the effectiveness of heparin in sepsis, the term △Platelet Count (referring to the difference between the count at ICU discharge and the count at admission, △PLT) was used to denote the change in a patient's platelet count over 7 days.

The primary endpoint of the study was the 28-day mortality rate. Secondary endpoints included the incidence of mechanical ventilation, use of continuous renal replacement therapy (CRRT), major bleeding (defined as a decrease in hemoglobin of ≥20 g/L within 24 hours), length of ICU stay, and 90-day mortality rate.

To optimize heparin treatment, the heparin group was divided into three subgroups based on the timing of heparin initiation: 24 hours before admission to the ICU (pre-early), within 24 hours of admission (normal-early), and after 24 hours (late). Additionally, the heparin group was further divided into two subgroups based on whether the dose exceeded 10,000 units: low-dose and high-dose groups.

The optimal heparin group was identified based on criteria for both early initiation (within 24 hours before admission to the ICU and within the first 24 hours after admission) and dosage (a minimum of 10,000 units within the 24 hours preceding ICU admission) of unfractionated heparin. In contrast, the non-optimal heparin group consisted of individuals who received heparin but did not meet these established criteria. Furthermore, patients were categorized using Cox proportional hazards models based on various indices of sepsis severity, including white blood cell count, pH, lactate, prothrombin time, platelet count, total bilirubin, creatinine, and PaO_2/FiO_2. Logistic regression analysis was employed to examine the relationship between bleeding complications and 28-day mortality.

Propensity Score Matching (PSM) Analysis

Patients were categorized into non-heparin and heparin groups. The non-heparin group comprised patients who did not receive unfractionated heparin during hospitalization. The heparin group included individuals administered unfractionated heparin 24 hours prior to ICU admission and at the time of transfer out of the ICU, with a duration exceeding 24 hours. The variables used in the derivation of the propensity score are outlined in Table 1 and included sex, age, body mass index (BMI), ethnicity, SOFA score, Elixhauser comorbidity index, and chronic comorbidities. Clinical outcomes were compared between the two groups using PSM to ensure the independence of the correlations from baseline characteristics (Table 1). A caliper width of 0.02 and a 1:1 ratio were used in PSM sampling without replacement. Before and after PSM, standardized mean differences (SMD) were calculated to compare patient characteristics involved in the generation and distribution of propensity scores, with SMD values below 0.2 considered satisfactory. Subsequently, 792 matched patient pairs were generated and further analyzed. The relationship between heparin use and clinical outcomes was analyzed following the establishment of a propensity score-matched cohort. The survival status of the groups was determined using the Kaplan-Meier method to generate survival curves.

Causal Mediation Analysis

Causal mediation analysis (CMA) was employed to differentiate between the direct and indirect effects of events. Indirect effects are mediated by specific mediators (Zhang et al, 2016). This study aimed to investigate the role of increased platelet count over 7 days as a mediating variable and to assess the potential impact of heparin therapy on the primary outcome through these changes. The mediation proportion was estimated using the R package "mediation" (R Foundation, version 3.4.3, Vienna, Austria), and bootstrapping methods were applied to calculate 95% confidence intervals (CIs) around this estimate.

Statistical Analysis

Categorical variables were represented as frequencies, while continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]). For continuous variables, appropriate statistical tests, such as Student's *t*-test, analysis of variance, or the Mann-Whitney U test, were employed. The χ^2 test or Fisher's exact test was used to determine statistical significance for comparing categorical variables. Cox proportional hazards regression models were utilized to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between different groups and 28-day survival. All statistical analyses were conducted using R Statistical Software (Version 4.2.2, The R Foundation, Vienna, Austria), with a significance level set at $p < 0.05$.

Table 1. Comparisons of baseline characteristics between the original and matched cohorts.

Variable	Original cohort						Matched cohort				
	Total	Non-heparin	Heparin	*p*-value	Statistics	SMD	Non-heparin	Heparin	*p*-value	Statistics	SMD
	(*n* = 4149)	(*n* = 1957)	(*n* = 2192)				(*n* = 792)	(*n* = 792)			
Demographics											
Male, *n* (%)	2262 (54.5)	1063 (54.3)	1199 (54.7)	0.806	0.061	0.0077	435 (54.9)	442 (55.8)	0.723	0.125	0.0178
Age, median (IQR)	67.0 (55.0, 78.0)	68.0 (55.0, 79.0)	66.0 (54.0, 77.0)	0.002	9.77	0.0939	67.0 (56.0, 76.0)	66.0 (55.0, 76.0)	0.700	0.149	0.0187
BMI, median (IQR)	29.6 (25.2, 35.3)	29.4 (25.1, 34.3)	30.0 (25.4, 36.3)	0.013	5.541	0.1537	29.6 (25.4, 34.6)	29.3 (25.1, 35.0)	0.724	0.124	0.0128
Ethnicity, *n* (%)				0.020	11.651	0.1066			0.976	0.475	0.0347
White	2749 (66.3)	1341 (68.5)	1408 (64.2)				560 (70.7)	557 (70.3)			
Black	407 (9.8)	190 (9.7)	217 (9.9)				96 (12.1)	97 (12.2)			
Asian	114 (2.7)	43 (2.2)	71 (3.2)				23 (2.9)	24 (3)			
Hispanic	143 (3.4)	64 (3.3)	79 (3.6)				29 (3.7)	25 (3.2)			
Other	736 (17.7)	319 (16.3)	417 (19.0)				84 (10.6)	89 (11.2)			
SOFA score, median (IQR)	6.0 (4.0, 10.0)	6.0 (4.0, 9.0)	7.0 (4.0, 10.0)	<0.001	21.673	0.1141	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)	0.800	0.064	0.0070
Elixhauser comorbidity index, median (IQR)	19.0 (8.0, 30.0)	17.0 (7.0, 29.0)	19.0 (9.0, 30.0)	0.005	7.925	0.0534	18.0 (7.0, 31.0)	19.0 (8.0, 30.0)	0.520	0.414	0.0076
Chronic comorbidity, *n* (%)											
Hypertension, *n* (%)	1564 (37.7)	727 (37.1)	837 (38.2)	0.492	0.472	0.0214	302 (38.1)	298 (37.6)	0.836	0.043	0.0104
Diabetes, *n* (%)	680 (16.4)	263 (13.4)	417 (19.0)	<0.001	23.533	0.1519	152 (19.2)	133 (16.8)	0.214	1.545	0.0625
Heart failure, *n* (%)	1370 (33.0)	613 (31.3)	757 (34.5)	0.028	4.821	0.0684	267 (33.7)	262 (33.1)	0.790	0.071	0.0134
CKD, *n* (%)	1095 (26.4)	500 (25.5)	595 (27.1)	0.245	1.354	0.0362	226 (28.5)	223 (28.2)	0.867	0.028	0.0084
Cancer, *n* (%)	42 (1.0)	13 (0.7)	29 (1.3)	0.034	4.477	0.0664	10 (1.3)	11 (1.4)	0.826	0.048	0.0110
COPD, *n* (%)	249 (6.0)	105 (5.4)	144 (6.6)	0.103	2.657	0.0508	55 (6.9)	61 (7.7)	0.563	0.335	0.0291

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SOFA, sequential organ failure assessment; SMD, standardized mean differences.

Results

Baseline Characteristics and Clinical Outcomes

After initial database retrieval, a cohort of 6600 patients diagnosed with sepsis based on the Sepsis 3.0 criteria was identified. Of these, 4149 patients who met the inclusion criteria were analyzed (Fig. 1). The median age was 67 years (IQR: 55–78), with male patients comprising 54.5% of the cohort. The majority of patients were Caucasian (2749), followed by African American (407). The median SOFA score was 6 (IQR: 4–10), the Elixhauser comorbidity index was 19 (IQR: 8–30), and the BMI was 29.6 (IQR: 25.2–35.3) kg/m^2. Hypertension and heart failure were present in 37.7% and 33.0% of the included patients, respectively. The cohort included 2192 patients (52.8%) who received heparin therapy and 1957 patients (47.2%) who did not receive heparin during hospitalization. The overall 28-day mortality rate was 19.5%. The demographic and clinical characteristics of both the unmatched and propensity score-matched cohorts are presented in Table 1. The heparin group exhibited significantly higher SOFA scores [7 (4–10) vs. 6 (4–9), $p < 0.001$] and Elixhauser comorbidity indices [19 (IQR: 9–30) vs. 17 (IQR: 7–29), $p = 0.005$] compared to the non-heparin group. After applying PSM, all discernible differences between the two cohorts were eliminated.

All clinical outcomes, including the incidence of mechanical ventilation, use of CRRT, major bleeding, length of ICU stay, 28-day mortality, and 90-day mortality, were significantly different between the heparin and non-heparin groups. After PSM, the heparin group had a higher likelihood of experiencing major bleeding (10.9% vs. 6.3%), requiring mechanical ventilation (54.3% vs. 45.1%), and having a longer ICU stay (3.6 days vs. 2.5 days) compared to the non-heparin group. However, data on 28-day and 90-day mortalities before and after PSM matching indicated that heparin had favorable treatment outcomes for sepsis (Table 2). Univariate Cox regression analysis revealed a significant reduction in 28-day mortality associated with heparin therapy (HR: 0.73, 95% CI: 0.57–0.94, $p = 0.014$). All laboratory variables are shown in **Supplementary Table 1**. Fig. 2 presents the Kaplan-Meier curves, demonstrating a significantly better prognosis ($p < 0.001$) when stratified by heparin therapy.

Associations between Different Heparin Treatment Groups and Sepsis Prognoses

The clinical effect of heparin was systematically investigated by considering the timing and dose of administration (**Supplementary Tables 2,3**). A multifactorial Cox regression analysis was employed to assess the primary outcomes, revealing that different initiation times and doses of heparin exerted distinct effects on 28-day mortality rates (Fig. 3). The most favorable intervention time frames were identified as pre-early (HR: 0.23, 95% CI: 0.11–0.48, $p < 0.001$) and normal-early (HR: 0.49, 95% CI: 0.37–0.64, $p < 0.001$). Adequate heparin administration was associated with a notable reduction in mortality rates (HR: 0.45, 95% CI: 0.35–0.59, $p < 0.001$). Conversely, low-dose heparin administration at later stages did not significantly reduce mortality rates ($p > 0.05$).

Table 2. Comparisons of clinical outcomes between the original and matched cohorts.

Variable	Original cohort					Matched cohort			
	Total (n = 4149)	Non-heparin (n = 1957)	Heparin (n = 2192)	p-value	Statistics	Non-heparin (n = 792)	Heparin (n = 792)	p-value	Statistics
Mechanical ventilation, n (%)	2356 (56.8)	997 (50.9)	1359 (62.0)	<0.001	51.472	357 (45.1)	430 (54.3)	<0.001	13.458
CRRT, n (%)	257 (6.2)	93 (4.8)	164 (7.5)	<0.001	13.257	34 (4.3)	41 (5.2)	0.408	0.686
Major bleeding	392 (9.4)	141 (7.2)	251 (11.5)	<0.001	21.786	50 (6.3)	86 (10.9)	0.001	10.424
ICU stay days, Median (IQR)	3.3 (2.0, 6.8)	2.7 (1.7, 4.8)	4.3 (2.3, 9.0)	<0.001	274.904	2.5 (1.6, 4.1)	3.6 (2.1, 7.2)	<0.001	77.785
28-day mortality, n (%)	807 (19.5)	476 (24.3)	331 (15.1)	<0.001	56.131	143 (18.1)	85 (10.7)	<0.001	17.235
90-day mortality, n (%)	876 (21.1)	490 (25.0)	386 (17.6)	<0.001	34.258	149 (18.8)	100 (12.6)	<0.001	11.441

Abbreviations: CRRT, continuous renal replacement therapy; ICU, intensive care unit; IQR, interquartile range.

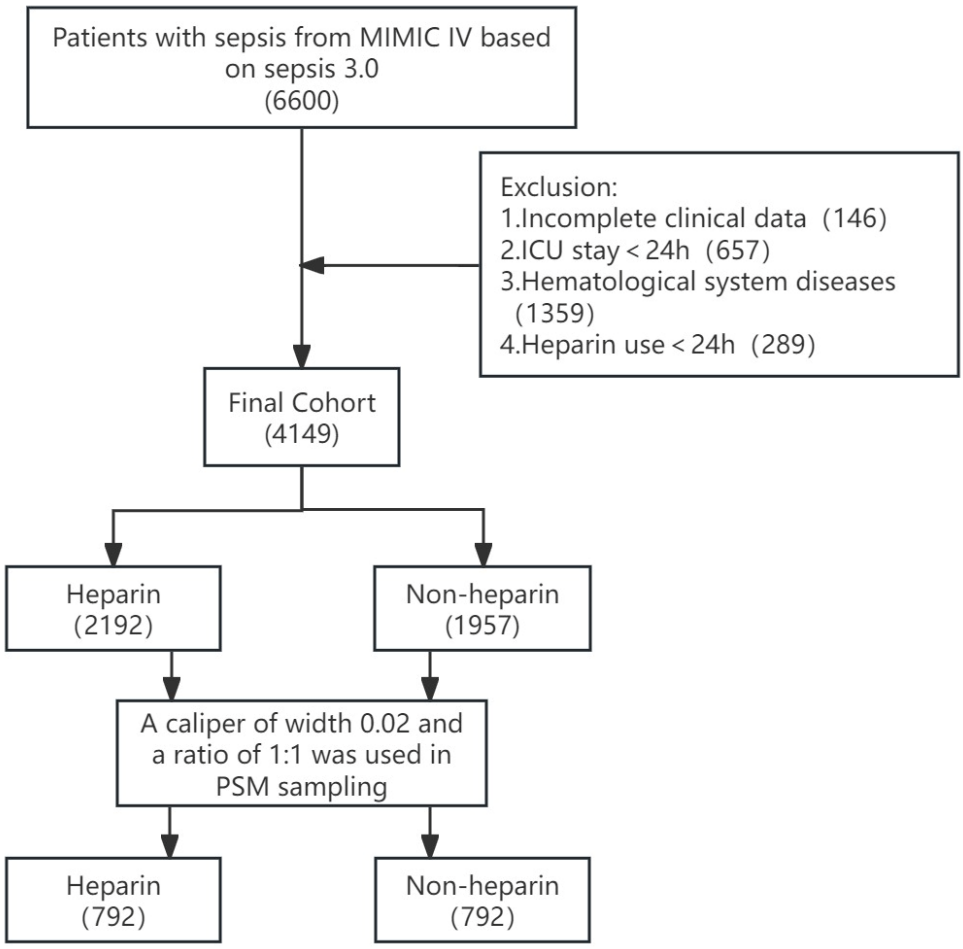

Fig. 1. Flow chart of the study design. Abbreviations: MIMIC-IV, Medical Information Mart for Intensive Care-IV; ICU, intensive care unit; PSM, propensity score matching.

We further compared prognosis among three groups: optimal heparin, non-optimal heparin, and no heparin. Comparisons regarding heparin use, including demographic data, laboratory parameters, and clinical outcomes, are presented in **Supplementary Table 4**. The Kaplan-Meier survival curves indicated that the 28-day mortality rate was significantly lower in the optimal heparin group (HR: 0.42, 95% CI: 0.31–0.56, $p < 0.001$) compared to the other two groups (Fig. 4). However, logistic regression analysis showed no significant relationship between major bleeding and 28-day mortality among the optimal heparin (odds ratio [OR]: 1.64, 95% CI: 0.72–3.7, $p = 0.238$), non-optimal heparin (OR: 0.54, 95% CI: 0.09–3.22, $p = 0.498$), and no-heparin groups (OR: 0.55, 95% CI: 0.21–1.44, $p = 0.224$) (**Supplementary Table 5**).

Subgroup Analyses of Beneficial Patients from Heparin Use

Cox hazard analyses indicated that heparin therapy was associated with improved primary outcomes in patients with normal or elevated white blood cell counts (HR: 0.49, 95% CI: 0.25–0.94, $p = 0.032$; HR: 0.38, 95% CI: 0.27–0.54,

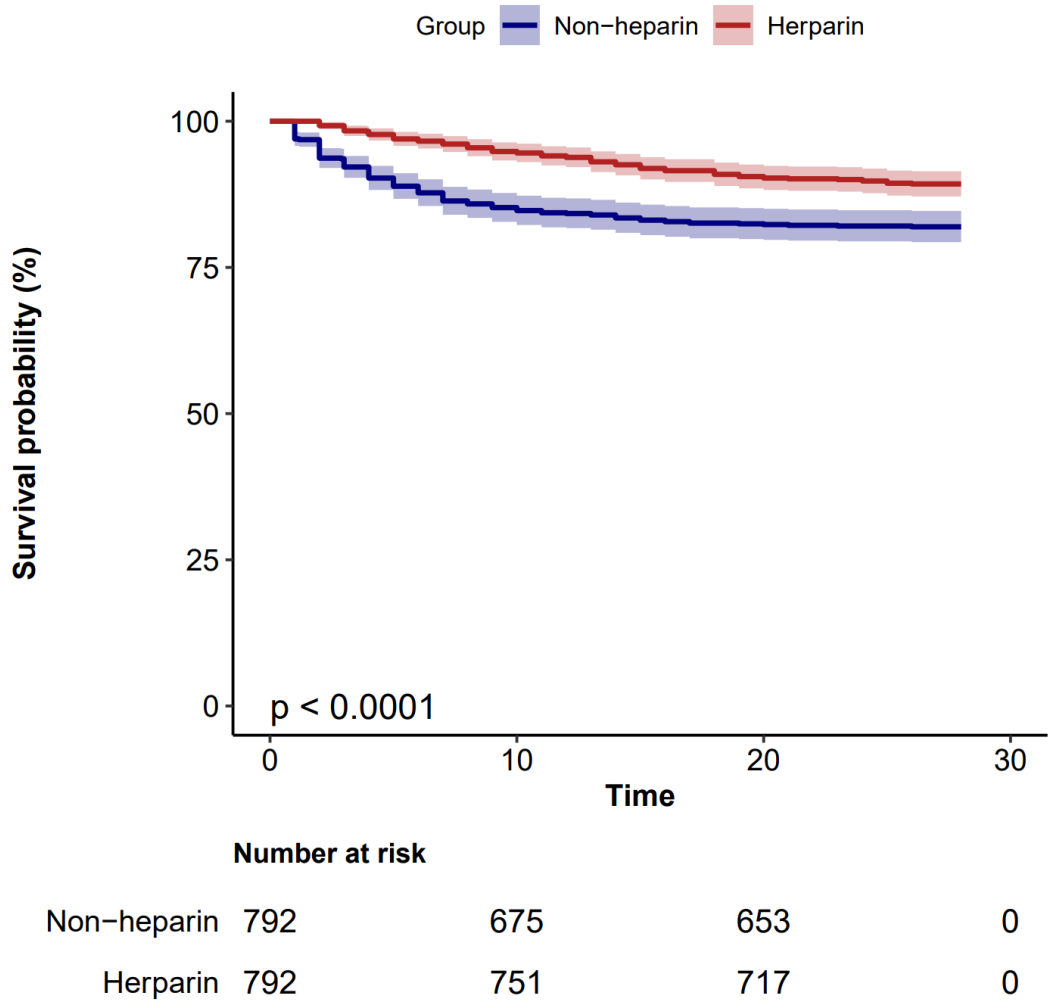

Fig. 2. Kaplan-Meier survival curves for patients with sepsis. Kaplan-Meier survival curves for patients with sepsis, stratified by various heparin groups, were analyzed. After propensity score matching, the Kaplan-Meier survival curves showed differences in outcomes between the heparin and non-heparin groups.

$p < 0.001$). Similar results were observed for those with normal pH (HR: 0.52, 95% CI: 0.29–0.92, $p = 0.026$) and acidosis (HR: 0.38, 95% CI: 0.23–0.62, $p < 0.001$; HR: 0.24, 95% CI: 0.1–0.56, $p = 0.001$). Heparin therapy appeared to enhance patient prognosis when platelet counts were at or above 100×10^9 (HR: 0.28, 95% CI: 0.18–0.43, $p < 0.001$; HR: 0.35, 95% CI: 0.18–0.68, $p = 0.002$). A significant relationship between heparin therapy and 28-day mortality was consistently observed, irrespective of liver function, renal function, coagulation status, oxygenation level, or lactic acid concentration. No significant interactions were found among the subgroups, and additional results are illustrated in Fig. 5.

CMA

CMA was performed to assess the influence of increased platelet count on the association between heparin administration and 28-day mortality. The total effect was estimated to be –0.0755 (95% CI: –0.099 to –0.0491), the direct effect was –

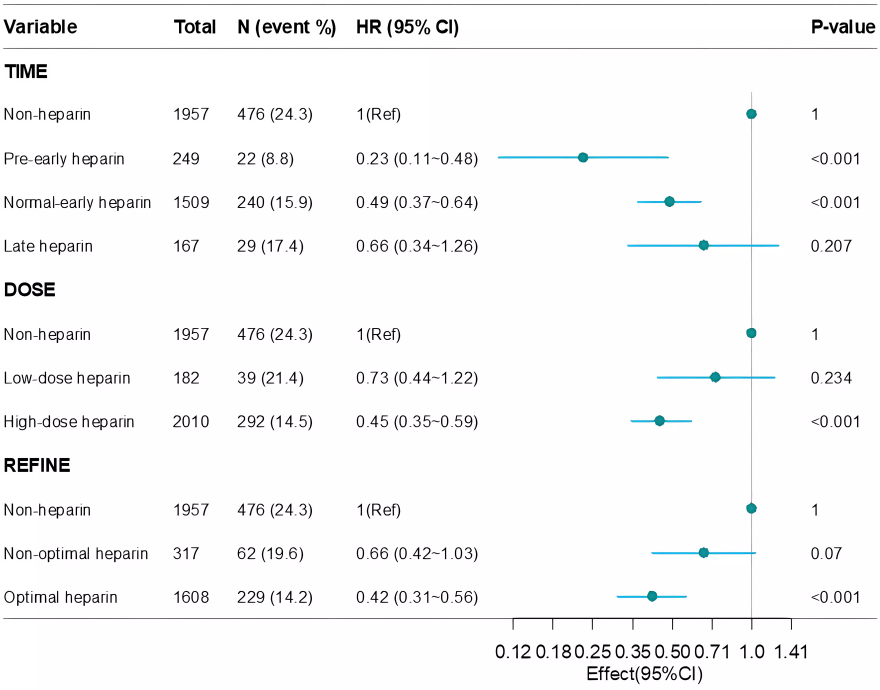

Fig. 3. Forest plot of 28-day mortality in groups with different heparin-treatment initiation times and doses. The Cox proportional hazards model was adjusted for different variables, including sex, age, BMI, ethnicity, SOFA score, Elixhauser comorbidity index, hypertension, diabetes, CHD, CKD, COPD, and cancer. Abbreviations: BMI, body mass index; CHD, chronic heart disease; 95% CI, 95% confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; SOFA, sequential organ failure assessment.

0.0648 (95% CI: –0.0881 to –0.0397), and the indirect effect was –0.0106 (95% CI: –0.0177 to –0.0039). The mediating effect of platelet count increase was significant for the whole cohort ($p < 0.001$ for the causal mediation effect) and showed a mediation proportion of 14% (Fig. 6).

Discussion

In this retrospective cohort study, heparin therapy significantly reduced the sepsis-related 28-day mortality rate. PSM was employed to ensure that the correlations were independent of baseline characteristics. Following various dimensional analyses, such as evaluating initiation time and daily heparin dose, administering high doses within the initial 24 hours of admission to the ICU appeared to enhance treatment outcomes. Subsequent subgroup analyses consistently revealed a significant association between heparin therapy and 28-day mortality, irrespective of variations in liver function, renal function, coagulation status, oxygenation levels, or lactic acid concentration. Our study indicated that the effect of heparin on mortality during hospitalization was influenced, at least in part, by varying platelet counts. This finding supports the theory that one of the main effects of heparin therapy is to increase platelet counts, thereby improving treatment outcomes in patients with sepsis.

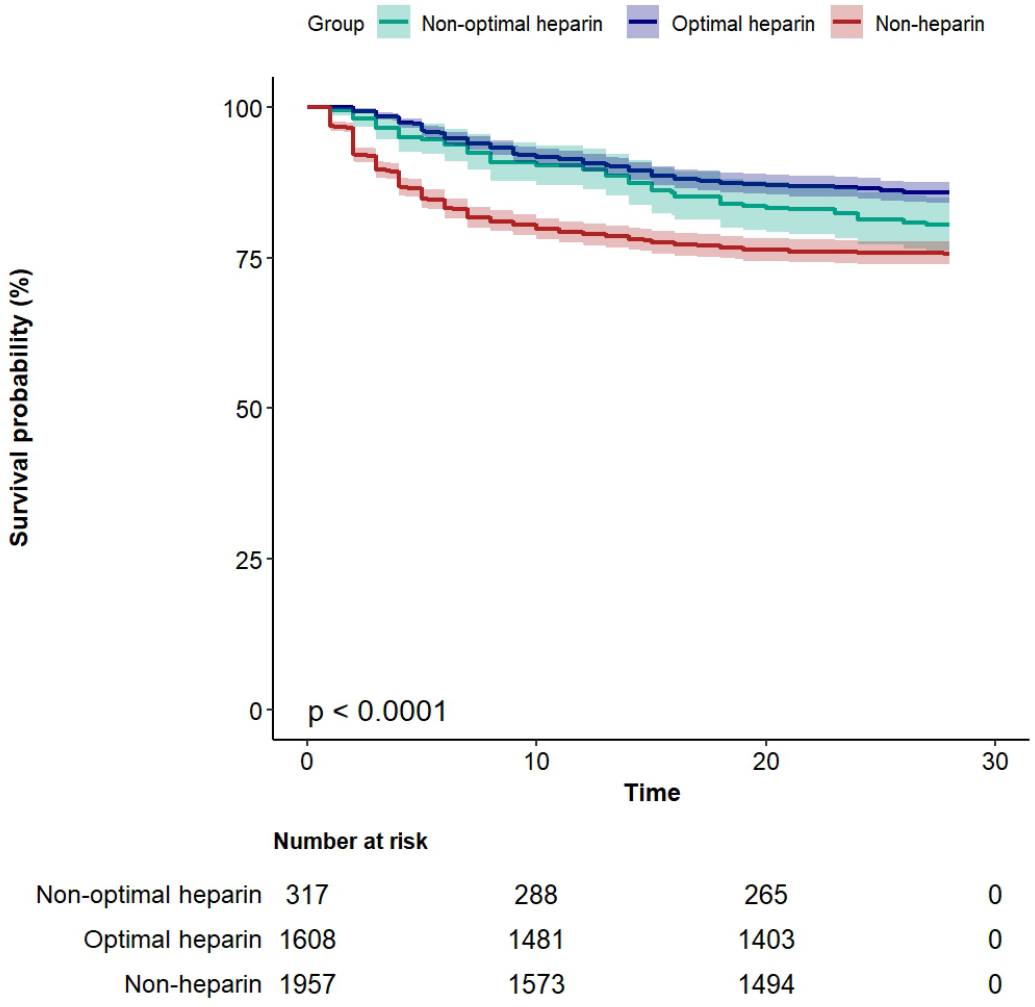

Fig. 4. Kaplan-Meier survival curves for patients with sepsis were stratified by various heparin groups, including non-heparin, optimal heparin, and non-optimal heparin groups.

Basic research and clinical practice studies have demonstrated the potential benefits of heparin in patients with sepsis (Li et al, 2011; Li and Ma, 2017; Wang et al, 2014). Patients with sepsis, septic shock, or disseminated intravascular coagulation linked to infections may experience substantial advantages from heparin therapy, potentially reducing 28-day mortality in individuals with sepsis (Levi et al, 2007; Zhao et al, 2009). However, the use of heparin as an anticoagulant therapy for sepsis remains controversial. Our study confirmed that the prognosis of sepsis is influenced by the initiation time and dose of heparin. Heparin therapy was not associated with improved primary outcomes in patients with leukopenia, thrombocytopenia, or alkalosis. Several studies on the treatment of sepsis have indicated that the effect of heparin is not statistically significant (Iba et al, 2012; Jaimes et al, 2009), and our findings may offer an explanation for this phenomenon. The primary concern regarding heparin use is the potential risk of major bleeding; however, an analysis has demonstrated that heparin does not substantially increase the risk of major bleeding (Wang et al, 2014). We found that patients with thrombo-

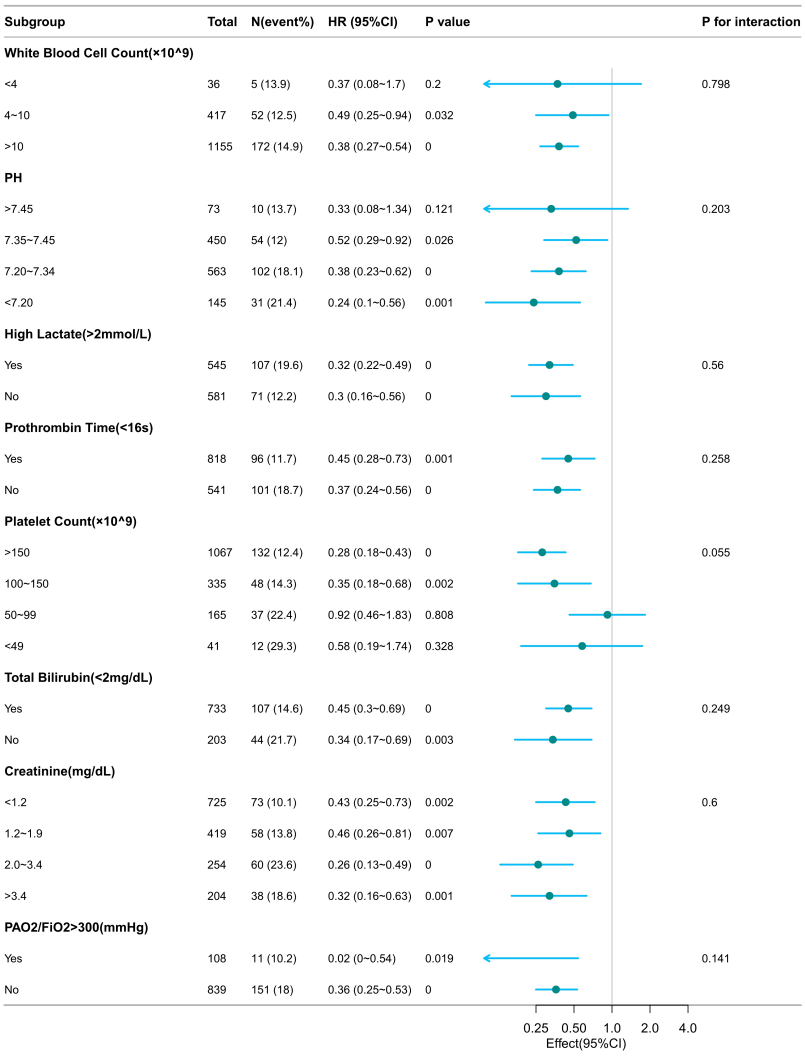

Fig. 5. Forest plot of 28-day mortality in different subgroups defined according to several baseline characteristics. The Cox proportional hazard model was adjusted for different variables, including sex, age, BMI, ethnicity, SOFA score, Elixhauser comorbidity index, hypertension, diabetes, CHD, CKD, COPD, and cancer. Abbreviations: BMI, body mass index; CHD, chronic heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment.

cytopenia did not benefit from heparin therapy, suggesting that low platelet counts may increase the risk of bleeding.

Through mediation analysis, our study revealed that an increase in platelet count was a significant indicator of heparin treatment efficacy in reducing mortality rates among patients with sepsis. Sepsis induces systemic organ tissue damage through inflammation, with key processes involving endothelial damage, microthrombus formation, and disruption of peripheral circulation (Ren et al, 2022; Zhang and Li, 2019). Heparin is a primary anticoagulant that efficiently inhibits microthrombus formation and exerts anti-inflammatory and immunomodulatory effects beyond its anticoagulant properties (Wildhagen et al, 2014). The potential

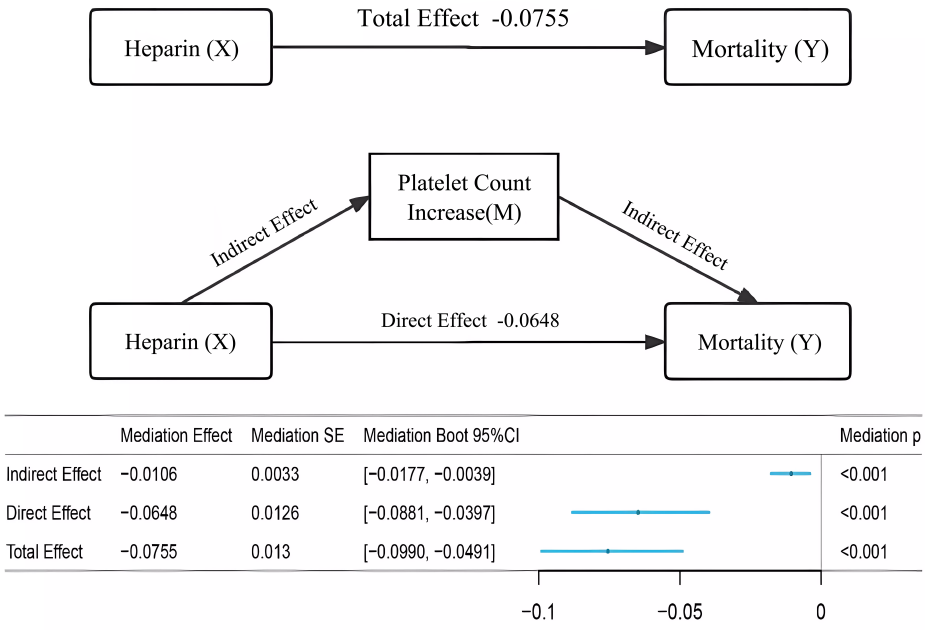

Fig. 6. Causal mediation analysis assessing how platelet count increase influences the association between heparin administration and 28-day mortality.

mechanism through which heparin protects endothelial cells may involve its ability to inhibit heparanase and enhance syndecan mRNA expression (Han and Hiebert, 2013). Recent research has highlighted the role of heparin in mitigating caspase-11-dependent immune responses and sepsis lethality by inhibiting caspase-11 activation through blocking lipopolysaccharide cytosolic delivery, supported by the fact that heparin prevents glycocalyx degradation (Li et al, 2011). Heparin prevents further deterioration by providing anticoagulation and protecting the endothelium. Therefore, an elevated platelet count is a key indicator of heparin efficacy. For clinicians, a profound understanding of the increase in platelet count among patients with sepsis undergoing heparin therapy is essential for accurately assessing its effectiveness. This approach facilitates the identification of effective heparin utilization and helps to diminish potential complications, including bleeding, by averting prolonged use of ineffective heparin.

One of the strengths of this study was the incorporation of a substantial and representative patient cohort with septic shock, enabling us to derive clinically significant inferences. First, we employed rigorous statistical analyses and PSM to minimize bias and enhance the credibility of the data. Second, we deliberately excluded patients with hematological diseases and adhered to strict criteria, allowing the use of heparin only when administered for more than 24 hours. Third, a comprehensive evaluation was conducted across various dimensions and subgroups to assess stability and effectiveness. Finally, our study described changes in platelet count in patients with sepsis undergoing heparin therapy, which can assist clini-

cians in distinguishing the effectiveness of heparin treatment, thereby avoiding its ineffective use and associated complications.

Our study has some limitations. First, the definition of sepsis was based on Sepsis 3.0, which primarily focuses on organ failure; however, the specific diagnosis of infection remained unspecified (IDSA Sepsis Task Force, 2018). Second, this study used a retrospective cohort design, relying on past data that was not collected with a predefined research purpose, which may lead to issues with data accuracy and completeness. Thus, the present study was prone to selection and information biases, making it challenging to establish causality between exposure and outcomes. However, we addressed these biases using PSM and Cox regression for correction. Third, this retrospective analysis did not collect relevant indicators, such as antithrombin levels, and further analysis is needed through prospective studies (Sun et al, 2024). Fourth, we only analyzed the initial heparin dosage administered on the first day, without accounting for any subsequent changes. Finally, the present findings were derived from a retrospective statistical analysis of clinical data; therefore, further validation through prospective studies or randomized controlled trials is necessary.

Conclusion

Early and sufficient administration of heparin can significantly improve the prognosis of sepsis, except in cases where patients have low white blood cell counts, alkalosis, or reduced platelet counts. An increase in platelet count may serve as a potential indicator of the effectiveness of heparin therapy in sepsis. Our findings may guide improved administration of heparin in the treatment of sepsis.

Key Points

- Sepsis has a high mortality rate and currently lacks effective treatment options.
- Heparin administration has been shown to significantly improve sepsis prognosis.
- Early and adequate heparin dosing enhances treatment outcomes.
- An increase in platelet count may serve as an indicator of the effectiveness of heparin therapy in sepsis patients.

Abbreviations

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; BMI, body mass index; CIs, confidence intervals; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CMA, causal mediation analysis; CRRT, continuous renal replacement therapy; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; MIMIC-IV, Medical Information Mart for Intensive Care-IV; PLT, Platelet Count; PT, prothrombin time; PSM, propensity score

matching; SMD, standardized mean differences; SOFA, sequential organ failure assessment; CHD, chronic heart disease; OR, odds ratio.

Availability of Data and Materials

The data that support the findings of this study are available from Medical Information Mart for Intensive Care (MIMIC)-IV but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of MIMIC-IV.

Author Contributions

GW conceptualized and designed the study, performed statistical analyses, interpreted the results, and authored the manuscript. XZ contributed to the study's design and manuscript revision. JS was involved in designing the study and revising the manuscript. CH and GC assisted in the analysis, interpretation of data, and drafting of the manuscript. YS and YZ participated in collecting data. YA and HZ designed, coordinated, and revised the study manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Patient consent and ethical approval were not required, as the data were de-identified and patient identifiers were removed. All studies within the MIMIC-IV database were conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki, which governs medical research involving human subjects.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0434.

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