Association of prophylactic heparin therapy and outcomes in critically ill patients with sepsis-induced coagulopathy: A marginal structural Cox model cohort study

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Research Article

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Abstract

Background

Sepsis-induced coagulopathy (SIC) is defined as infection-induced organ dysfunction and coagulopathy. Although anticoagulation with heparin has been widely used in practice, its effectiveness for treating SIC remains controversial. This study aimed to investigate whether prophylactic heparin administration would provide a survival advantage for patients with SIC.

Methods Patients with SIC were identified from the Medical Information Mart for Intensive Care (MIMIC)-IV database. The primary endpoint was ICU mortality, and the secondary outcomes were 7-day, 14-day, and 28-day mortality as well as hospital mortality. A Cox proportional hazards model and propensity score matching (PSM) were used to account for baseline differences in the probability of using prophylactic heparin. The marginal structural Cox model (MSCM) was employed to adjust for both baseline and time-varying confounding factors. E-value analysis was used for unmeasured confounding.

Results A total of 6498 septic patients with SIC were enrolled in the study, with 1284 in the heparin group and 5124 in the nonheparin group. There was no significant effect on ICU mortality in the overall population (prematched, hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.77-1.14, *P*=0.517, postmatched, HR 0.89, 95% CI 0.70-1.12, *P*=0.323). Interestingly, the MSCM identified a significant effect on ICU mortality in the overall population (HR 0.77, 95% CI 0.60-0.98, *P*=0.032). Stratification analysis with the MSCM showed that prophylactic heparin administration was associated with decreased ICU mortality only among patients with a SIC score of 4 (HR 0.63, 95% CI 0.45-0.89, *P*=0.009). Similar results were replicated with PSM only for patients with a SIC score of 4 (ICU mortality HR 0.68, 95% CI 0.49-0.95, *P*=0.025; 7-day mortality HR 0.59, 95% CI 0.36-0.98, *P*=0.040; 14-day mortality HR 0.66, 95% CI 0.44-0.98, *P*=0.040; Hospital mortality HR 0.77, 95% CI 0.58-1.03, *P*=0.074; 28-day mortality HR 0.77, 95% CI 0.54-1.10, *P*=0.147). E-value analysis indicated robustness to unmeasured confounding.

Conclusions: Prophylactic heparin administration to patients with a SIC score of 4 appears to be associated with improved survival outcomes, including ICU mortality and 7-day and 14-day mortality, but not with improvement in hospital or 28-day mortality. These results need to be verified in prospective randomized controlled trials.

Introduction

Nearly 50 million patients suffer from sepsis worldwide each year, and sepsis-associated mortality (more than 11 million cases) was higher than mortality associated with ischaemic heart disease (9 million cases) or tumours (10 million cases) in 2019 [1, 2]. The mortality of sepsis increases significantly when combined with coagulopathy, which represents a mounting clinical challenge for healthcare professionals. Previous studies have shown that the incidence of disseminated intravascular coagulation (DIC) is as high as 35% in septic patients [3]. Sepsis-induced coagulopathy (SIC) is regarded as an earlier phase of DIC because SIC includes most cases of International Society of Thrombosis & Haemostasis (ISTH) overt DIC [4, 5], which provides the possibility for early clinical intervention of sepsis.

However, DIC can also be classified as hyperfibrinolytic, hypofibrinolytic, and balanced types, and both SIC and coronavirus disease 2019 (COVID-19)-associated coagulopathy demonstrate hypofibrinolytic properties [6]. Low molecular weight heparin (LMWH) not only have anticoagulant effect, but also promote the release of tissue plasminogen activator(T-PA). Heparin has been widely used as a coagulant in clinical practice, although a recent report showed that survival of critically ill patients with COVID-19 was not significantly increased by heparin compared with that of controls [7]. A randomized, double-blind, placebo-controlled, multicentre, phase 3 clinical trial demonstrated that heparin did not improve 28-day mortality in a subgroup of septic patients (OR 1.07 [0.83–1.38], P = 0.62) [8]. Nevertheless, systematic reviews have documented that treatment with a low dose of heparin is associated with a significant reduction in 28-day mortality among patients with sepsis [9, 10]. Our previous study found an association between early prophylactic heparin administration to septic patients and decreased risk-adjusted mortality (HR 0.70, 95% CI 0.56–0.87, $P < 0.001$) [11]. Therefore, the indications for and timing and dosage of heparin administration to patients with sepsis are still unclear.

Emerging evidence has indicated that heparin modulates lipopolysaccharide (LPS)-induced cytokine production via different signalling pathways [12, 13]. Recently, a study suggested a novel role of heparin in inhibiting the caspase-11 pathway to prevent septic coagulation and lethality [14]. In addition to anticoagulation, heparin exerts anti-inflammatory effects, anticomplement activity, and protease regulation [15, 16]. An initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge among noncritically ill patients with COVID-19 in comparison to controls [17]. Since SIC is an early stage of septic DIC and SIC and COVID-19-associated coagulopathy demonstrate hypofibrinolysis, whether prophylactic anticoagulation treatment would benefit patients with SIC remains largely unknown. In the present retrospective cohort study, we used data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) to evaluate the effectiveness of prophylactic heparin in patients with SIC.

Materials And Methods

Data source and study design

We performed a retrospective cohort study using data from the MIMIC-IV (version 1.0), which included two in-hospital database systems—a custom hospital-wide electronic health record (EHR) and ICU-specific clinical information—that contain the deidentified, comprehensive clinical data of patients admitted to the ICUs of Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2019. An individual who has finished the collaborative institutional training initiative examination (certification number 38995627 for author Huang) can access the database.

Participants

There were 382278 individuals and 51150 patients admitted to the ICUs during the study period. Patients were eligible if they (1) were ≥18 years old, (2) met the definition of Sepsis 3.0 criteria, which was defined as a suspected infection combined with an acute increase in the Sequential Organ Failure Assessment (SOFA) score ≥2 [18], and (3) had a SIC score ≥4 (Table S1) within the first 24 h (h) after ICU admission.

The exclusion criteria were (1) multiple ICU admissions; (2) age<18 years, ICU stay < 24 h; (3) usage of heparin for dialysis or treatment, rather than for prophylactic use, or LMWH administration or warfarin treatment during the ICU stay; (4) pregnancy; (5) a history of embolism and thrombosis; (6) a history of heparin-induced thrombocytopaenia; (7) hepatic failure; (8) chronic kidney disease stage 5; and (9) malignant cancer.

Research procedures and definitions

Data were extracted from the MIMIC-IV database through Structured Query Language [19]. We used the methods described in previous studies to search this database (sepsis) and analyse the extracted patient data [11, 20]. For patients with multiple hospitalizations, only the first hospitalization was included. The initial baseline characteristics and laboratory results for the first day of ICU admission were collected, including age at the time of hospital admission, sex, weight, laboratory results (white blood cell [WBC] count, platelet count, haemoglobin, international normalized ratio [INR], partial thromboplastin time [PTT], and prothrombin time [PT]), vital signs (mean arterial pressure [MAP], heart rate, temperature, respiratory rate, and partial pressure of oxygen [PO_2]), comorbidities (hypertension, diabetes, chronic heart disease, and chronic pulmonary disease), urine output, use of vasopressors, mechanical ventilation, renal replacement therapy (RRT), acute kidney injury (AKI) stage, SIC score, length of hospital stay, and length of ICU stay. Clinical severity scales, including the SOFA score and Simplified Acute Physiology Score II (SAPS II), were also extracted. The SOFA score was calculated within the first 24 h after ICU admission. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [21]. Both urine output and creatinine levels during the first 24 h after ICU entry were used to define AKI stages.

The laboratory variables platelet count and INR were measured throughout the entire ICU stay. The chart time of measurement and physiological values were extracted from the database. For patients with multiple measurements, the lowest daily platelet count value and highest daily INR value were included in the analysis. None of the screening variables had more than 10% of the values missing (Table S2). Single imputation was performed for variables with fewer than 10% of the values missing [22].

Exposure and outcomes

Participants were categorized into two groups: the heparin group, comprising patients who received heparin subcutaneously at preventive doses within 24 h after ICU entry, and the control group, comprising patients who received no heparin on the first day. The primary endpoint was ICU mortality, which was defined as patient survival at the time of ICU discharge. The secondary endpoints were 7-day mortality, 14-day mortality, 28-day mortality, and hospital mortality.

Statistical analysis

Categorical variables are expressed as numbers or percentages. They were compared between the heparin and nonheparin groups with the Chi-square test or Fisher's exact test as appropriate. Continuous variables are expressed as the mean (standard deviation) or median (interquartile range [IQR]) as appropriate.

Propensity score matching (PSM) was used to account for the baseline differences in the probability of receiving heparin [23]. The PSM measures the probability of a patient being treated with heparin. In PSM analysis, the heparin group received prophylactic heparin within 24 h after ICU entry. Patients in the treatment group were matched to untreated patients by nearest neighbour matching. The standardized mean difference (SMD) was calculated before and after matching to examine whether PSM reduced the differences in pretreatment covariates between the treatment and control groups. Finally, a Cox proportional hazards model was used to adjust for residual imbalance by including parameters with P<0.05 and potential confounding judged by clinical expertise.

Heparin treatment during the ICU stay was considered a time-dependent variable in the marginal structural Cox model (MSCM). Potential baseline confounders, such as age, sex, use of mechanical ventilation, RRT, vasopressor, and the SOFA and SAPS II scores, were obtained on day 1 after ICU admission. Platelet count and INR throughout the entire ICU stay were included in the model as time-varying confounding factors. The parameters of the MSCM could be estimated using inverse probability weighting (IPW) to correct for both confounding and forms of selection bias such as informative censoring [24]. Weighting each patient by IPW allowed the creation of two pseudopopulations that were similar with regard to baseline and time-dependent confounding factors and different in heparin exposure. Details of IPW and the R code for performing the MSCM can be found in the electronic supplemental material (ESM) S1. The IPW package was used for estimating inverse probability weights [25].

Stratification analysis was conducted to explore whether heparin administration and ICU mortality differed across the subgroups classified by SIC, AKI, mechanical ventilation, and use of vasopressors. Subgroup analysis also used a Cox model adjusted for all variables in the patient baseline information. We explored the potential for unmeasured confounding between heparin and ICU mortality by calculating E-values [26]. The E-values quantify the required magnitude of an unmeasured confounder to negate the observed association between heparin and ICU mortality. Several prespecified subgroup analyses were performed with the MSCM. Two-tailed P values less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the R package (version 4.1.1).

Results

Characteristics of patients

The initial search identified 382,278 ICU admissions in the MIMIC-IV database. A total of 32,404 patients fulfilled the definition of sepsis, and 6498 had a diagnosis of SIC within 24 h after ICU admission. Of the study cohort, 1284 patients were administered heparin in the first 24 h after ICU entry, and the remaining 5214 patients did not receive heparin (Fig. 1).

As shown in Table 1, except for weight, age, and RRT, most of the variables showed significant differences between the two groups. Of note, there were more critically ill patients in the heparin group than in the nonheparin group (SOFA score of 7 [5, 10] *vs.* 6 [4, 9], P < 0.001). Patients in the nonheparin group were more

likely to use vasopressors (59.7% *vs.* 46.4%; $P < 0.001$) and require mechanical ventilation (54.2% *vs.* 43.4%, $P < 0.001$) than those in the heparin group.

Table 1
Baseline characteristics of patients with sepsis-induced coagulopathy before and after propensity score matching

	Propensity score matching							
	Before				After			
Characteristics of patients	No heparin (n = 5124)	Heparin (n = 1284)	P value	SMD	No heparin (n = 1264)	Heparin (n = 1264)	P value	SMD
Demographics, clinical characteristics								
Gender, male (%)	3304 (63.4)	732 (57.0)	< 0.001	0.13	713 (56.4)	720 (57.0)	0.81	0.011
Age (yr)	67.10 (15.50)	66.73 (17.60)	0.462	0.022	66.47 (16.46)	66.80 (17.60)	0.629	0.019
Weight (kg)	81.35 (21.03)	81.53 (24.42)	0.784	0.008	80.93 (22.64)	81.40 (24.35)	0.621	0.02
Hypertension, n(%)	2389 (45.8)	515 (40.1)	< 0.001	0.116	505 (40.0)	503 (39.8)	0.968	0.003
Diabetes, n(%)	989 (19.0)	347 (27.0)	< 0.001	0.192	339 (26.8)	334 (26.4)	0.857	0.009
Chronic heart disease, n(%)	1505 (28.9)	231 (18.0)	< 0.001	0.259	213 (16.9)	230 (18.2)	0.403	0.035
Chronic pulmonary disease, n(%)	1169 (22.4)	346 (26.9)	0.001	0.105	322 (25.5)	337 (26.7)	0.526	0.027
Heart rate (bpm)	85.93 (14.66)	89.34 (17.34)	< 0.001	0.212	89.12 (16.17)	89.10 (17.24)	0.973	0.001
MAP (mmHg)	75.24 (8.77)	74.40 (10.33)	0.003	0.087	74.72 (9.36)	74.45 (10.28)	0.497	0.027
Respiratory rate (bpm)	18.90 (3.76)	20.40 (4.42)	< 0.001	0.366	20.34 (4.29)	20.35 (4.40)	0.923	0.004
Temperature (°C)	36.92 (0.60)	36.98 (0.67)	< 0.001	0.105	36.97 (0.65)	36.98 (0.67)	0.548	0.024
SpO_2 (%)	91.91 (6.38)	91.18 (6.77)	< 0.001	0.112	91.16 (6.60)	91.18 (6.79)	0.931	0.003

Abbreviations: MAP, mean arterial pressure; AKI, acute kidney injury; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; RRT, renal replacement therapy; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II. Values were expressed as mean (SD) unless otherwise indicated.

	Propensity score matching							
Urine output (ml)	1858.70 (1172.70)	1717.08 (1296.26)	< 0.001	0.115	1729.29 (1319.78)	1724.26 (1295.60)	0.923	0.004
Laboratory findings, median (IQR)								
WBC (10^3/μl)	14.99 (7.77)	15.69 (11.03)	0.009	0.073	15.38 (8.62)	15.62 (10.68)	0.536	0.025
Hemoglobin (g/l)	9.23 (1.96)	9.91 (2.06)	< 0.001	0.336	9.96 (2.14)	9.89 (2.05)	0.393	0.034
Minimum platelet (10^3/μl)	127.67 (79.09)	153.17 (107.28)	< 0.001	0.271	148.34 (109.18)	149.44 (97.51)	0.79	0.011
PT (s)	21.37 (14.57)	19.37 (8.41)	< 0.001	0.168	19.87 (8.98)	19.38 (8.47)	0.158	0.056
APTT (s)	42.04 (22.16)	43.78 (23.66)	0.013	0.076	43.58 (25.55)	43.51 (23.16)	0.939	0.003
Maximum INR	2.03 (1.47)	1.87 (0.91)	< 0.001	0.134	1.91 (1.00)	1.87 (0.92)	0.256	0.045
AKI stage, n (%)			< 0.001	0.286			0.815	0.039
0	2250 (43.2)	519 (40.4)			520 (41.1)	515 (40.7)		
1	1040 (19.9)	157 (12.2)			170 (13.4)	157 (12.4)		
2	1411 (27.1)	391 (30.5)			376 (29.7)	382 (30.2)		
3	513 (9.8)	217 (16.9)			198 (15.7)	210 (16.6)		
RRT, n (%)	242 (4.6)	77 (6.0)	0.052	0.06	69 (5.5)	74 (5.9)	0.731	0.017
Vasopressor, n (%)	3112 (59.7)	596 (46.4)	< 0.001	0.268	571 (45.2)	590 (46.7)	0.473	0.03
Ventilation, n (%)	2825 (54.2)	557 (43.4)	< 0.001	0.217	525 (41.5)	551 (43.6)	0.315	0.042
SIC score, n (%)			< 0.001	0.229			0.556	0.043

Abbreviations: MAP, mean arterial pressure; AKI, acute kidney injury; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; RRT, renal replacement therapy; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II. Values were expressed as mean (SD) unless otherwise indicated.

	Propensity score matching							
4	2506 (48.1)	762 (59.3)			724 (57.3)	746 (59.0)		
5	1543 (29.6)	306 (23.8)			326 (25.8)	303 (24.0)		
6	1165 (22.3)	216 (16.8)			214 (16.9)	215 (17.0)		
SOFA score, median (IQR)	6[4, 9]	7 [5, 10]	< 0.001	0.184	7[5, 10]	7[5, 10]	0.758	0.012
SAPS II score, median (IQR)	37[30,46]	41[31,50]	< 0.001	0.18	39[32,49]	40[31,50]	0.504	0.027
Hospital stays (d), median (IQR)	7[5, 12]	9[5, 15]	< 0.001	0.125	8[5, 14]	8[5, 15]	0.826	0.009
ICU stays (d), median (IQR)	2[1, 4]	3[2, 5]	< 0.001	0.197	3[2, 5]	3[2, 5]	0.866	0.007

Abbreviations: MAP, mean arterial pressure; AKI, acute kidney injury; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; RRT, renal replacement therapy; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II. Values were expressed as mean (SD) unless otherwise indicated.

Outcomes

Propensity score analysis

The 1264 patients who received heparin were matched to 1264 patients who did not receive heparin by PSM. The imbalances between the heparin and nonheparin groups were significantly reduced after PSM (Fig S1, Table 1). Since there were still residual imbalances between the heparin and nonheparin groups, a Cox proportional hazards model was used. The results revealed that treatment with heparin was not associated with reduced mortality in the overall population (ICU mortality: hazard ratio [HR]: 0.89; 95% CI 0.70–1.12; *P* = 0.323). Similar results were noted for the secondary endpoints except for 7-day mortality (HR: 0.67; 95% CI 0.46–0.96; *P* = 0.028) (Table 2).

Table 2
Association between heparin use and clinic outcomes in patients with SIC

Pre-matched cohort	**Control group (n = 5124)**	**Heparin group (n = 1284)**	**HR (95%CI)**	***P* value**
Primary outcome				
ICU mortality[a]	431(8.4%)	142(11.1%)	0.94(0.77,1.14)	0.517
Secondary outcomes				
7-day mortality[b]	384(7.5%)	120(9.3%)	0.91(0.67,1.24)	0.554
14-day mortality[b]	522(10.2%)	166(12.9%)	0.93(0.72,1.19)	0.554
Hospital mortality[a]	616(12.0%)	202(15.7%)	1.03(0.88,1.21)	0.712
28-day mortality[b]	617(12.0%)	201(15.7%)	0.98(0.79,1.21)	0.841
Post-matched cohort	**Control group (n = 1264)**	**Heparin group (n = 1264)**		
Primary outcome				
ICU mortality[a]	154(12.2%)	138(10.9%)	0.89(0.70,1.12)	0.323
Secondary outcomes				
7-day mortality[b]	139(11.0%)	117(9.3%)	0.67(0.46,0.96)	0.028
14-day mortality[b]	185(14.6%)	162(12.8%)	0.77(0.57,1.03)	0.082
Hospital mortality[a]	213(16.9%)	198(15.7%)	0.97(0.79,1.18)	0.747
28-day mortality[b]	213(16.9%)	197(15.6%)	0.89(0.69,1.14)	0.358
a. adjust for age, weight, MAP, respiratory rate, SpO_2, WBC, PT, APTT, urine output, AKI, SOFA, SAPS II, and vasopressor.				
b. adjust for age, weight, MAP, respiratory rate, SpO_2, WBC, PT, APTT, urine output, AKI, SOFA, SAPS II, vasopressor, gender, ventilation, hospital stays, and ICU stays.				
CI, confidence interval.				

Marginal structural Cox model and stratification analysis

Time-varying confounders and heparin treatment were included in the MSCM. The distribution of IPW is shown in Fig S2. The MSCM results showed that heparin administration was associated with significantly decreased ICU mortality (HR 0.77; 95% CI 0.60–0.98; $P = 0.032$) in the overall septic population with SIC. Stratification analysis revealed that heparin treatment was associated with reduced ICU mortality risk

among patients with a SIC score of 4 (HR 0.63; 95% CI 0.45–0.89; $P = 0.009$). Different effects were observed in patients with SIC scores of 5 or 6, and treatment with heparin did not have a significant impact on ICU mortality. Stratification analysis also showed that the use of heparin was significantly associated with reduced ICU mortality among patients who did not receive mechanical ventilation, did not use vasopressors, and had a SOFA score ≤ 6, with HRs of 0.59, 0.59, and 0.36, respectively ($P < 0.05$) (Fig. 2).

Subgroup analysis

In the subgroup analysis, heparin was observed to be beneficial for septic patients with SIC scores of 4, with improved survival outcomes including ICU mortality (HR: 0.68; 95% CI 0.49–0.95; $P = 0.025$), 7-day mortality (HR: 0.59; 95% CI 0.36–0.98; $P = 0.040$), and 14-day mortality (HR: 0.66; 95% CI 0.44–0.98; $P = 0.040$), but there was no reduction in hospital mortality (HR: 0.77, 95% CI 0.58–1.03, $P = 0.074$) or 28-day mortality (HR: 0.77, 95% CI 0.54–1.10, $P = 0.147$) (Table 3). It was also found that in patients with SIC scores of 4, treatment with 8000–12000 IU of heparin was associated with a decreased risk of ICU mortality compared with no heparin treatment (HR 0.34; 95% CI 0.18–0.63; $P < 0.001$) (Table 4).

Table 3
Association of heparin use and mortality outcome in the patients with SIC score 4 with propensity score analysis

SIC score 4 (n = 1470)	HR (95% CI)	*P* value
Primary outcome		
ICU mortality[a]	0.68(0.49,0.95)	0.025
Secondary outcomes		
7-day mortality[b]	0.59(0.36,0.98)	0.040
14-day mortality[b]	0.66(0.44,0.98)	0.040
Hospital mortality[a]	0.77(0.58,1.03)	0.074
28-day mortality[b]	0.77(0.54,1.10)	0.147
a. adjust for age, weight, MAP, respiratory rate, SpO_2, WBC, PT, APTT, urine output, AKI, SOFA, SAPS II, and vasopressor.		
b. adjust for age, weight, MAP, respiratory rate, SpO_2, WBC, PT, APTT, urine output, AKI, SOFA, SAPS II, vasopressor, gender, ventilation, hospital stays, and ICU stays.		

Table 4
Dose-response relationship between heparin and ICU mortality in patients with SIC score 4

Daily heparin usage (non-heparin group as reference)	No. of patients*	HR (95%CI)	*P* value
0-4000 IU	161	1.49(0.81,2.75)	0.199
4000–8000 IU	347	0.96(0.59,1.57)	0.873
8000–12000 IU	250	0.34(0.18,0.63)	< 0.001
> 12000 IU	24	0.22(0.04,1.26)	0.090
*The number of patients with prophylactic heparin administration			

Sensitivity analysis

The significant known and measured risk factors for ICU mortality after PSM within the multivariable Cox proportional hazards model included age (HR, 1.03, 95% CI, 1.02–1.05), WBC (HR, 1.02, 95% CI, 1.01–1.03), INR (HR, 1.19, 95% CI, 1.1–1.03), PT (HR, 1.02, 95% CI, 1.01–1.03), AKI (HR, 1.82, 95% CI, 1.23–2.68), maximum SOFA score on day 1 (HR, 1.11, 95% CI 1.06–1.16), maximum SAPS II on day 1 (HR, 1.05, 95% CI 1.04–1.06), and use of vasopressors (HR, 1.61, 95% CI 1.12–2.31) (Table 5).

Table 5
Cox regression model after propensity score matching in patients with SIC score 4

Variables	HR (95%CI)	*P* value
Gender	0.86 (0.68,1.08)	0.202
Age	1.02 (1.01, 1.02)	< 0.001
Weight	0.99 (0.98-1)	0.003
Heart rate	1.01 (1.00, 1.01)	0.079
MAP	0.97 (0.96, 0.99)	< 0.001
Respiratory rate	1.07 (1.05, 1.10)	< 0.001
SPO2	0.96 (0.94–0.97)	< 0.001
Minimum platelet	1.00 (1.00, 1.00)	0.874
WBC	1.02 (1.01–1.03)	< 0.001
PT	1.02 (1.01–1.03)	< 0.001
APTT	1.01 (1.00, 1.01)	0.002
AKI	1.82 (1.23–2.68)	0.003
RRT	1.26 (0.85, 1.87)	0.245
Ventilation	1.16 (0.90, 1.49)	0.257
SOFA	1.11 (1.06–1.16)	< 0.001
SAPS II	1.05 (1.04–1.06)	< 0.001
Vasopressor	1.93 (1.50, 2.50)	< 0.001

Abbreviations: MAP, mean arterial pressure; WBC, white blood cell; PT, prothrombin time; APTT, activated partial thromboplastin time; AKI, acute kidney injury; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II .

We performed an E-value analysis to assess the sensitivity to unmeasured confounding (https://www.evalue-calculator.com/evalue/). The primary findings were robust, unless there were unmeasured confounders, a low relative risk of ICU mortality, and an HR higher than 2.55 (upper limit 4.05), meaning that residual confounding could explain the observed association if there was an unmeasured covariate having a relative risk association > 2.55 with both ICU mortality and prophylactic heparin administration. Thus, it was unlikely that an unmeasured or unknown confounder would have a substantially greater impact on ICU mortality (relative risk exceeding 2.55) than these known risk factors.

Discussion

The emerging role of heparin in COVID-19-associated coagulopathy has attracted increasing attention. Increasing evidence has indicated that heparin might improve outcomes in noncritical septic patients with COVID-19. Early prophylactic heparin administration was associated with a decreased risk of 30-day mortality, and therapeutic doses of LMWH reduced death among patients with COVID-19 [17, 27, 28]. Although the pathogenesis of COVID-19 has not been fully explained, the currently available data on hospitalized patients have revealed that serum cytokine and chemokine levels are high in patients with severe COVID-19, similar to patients with sepsis. However, sepsis is a highly heterogeneous syndrome, and more research is required to determine the timing, dose, and efficacy of heparin in the management of septic complications. Our results from the MIMIC-IV data suggested that prophylactic heparin administration to patients with a SIC score of 4 was associated with improved survival parameters, including ICU mortality, 7-day mortality and 14-day mortality, but was not associated with reduced hospital mortality or 28-day mortality. Stratification and subgroup analysis further indicated that patients with a SIC score of 4 who did not receive mechanical ventilation, did not use vasopressors, had a SOFA score ≤ 6, and were administered 8000–12000 IU/day heparin had a reduced risk of ICU mortality.

It is known that heparin acts as an anticoagulant, mainly by binding antithrombin III (AT III), but AT III levels are significantly decreased with the aggravation of sepsis. When AT III levels are lower than 60%, heparin usually does not have anticoagulant activity. Many DIC patients have AT depletion secondary to accelerated thrombin generation; thus, AT depletion is one reason for the lack of response to heparin therapy [29–32]. Heparin chains of any length that contain a unique pentasaccharide sequence can facilitate an interaction between AT and thrombin (factor IIa and Xa), which is responsible for most of the other anticoagulant activity of heparin [33, 34].

Several animal studies and clinical trials have demonstrated that heparin possesses properties in addition to anticoagulation, including anti-inflammatory activity, anticomplement activity, immune modulation, and antihistone effects [14, 35, 36, 37]. Nonanticoagulant heparin has been implicated as a viable and effective alternative antihistone reagent in histone infusion models [36] and has the potential to attenuate multiple organ dysfunction syndrome and improve the survival of critically ill patients. A report described a novel and interesting immune-modulating mechanism of heparin *in vitro* and showed that in septic mouse models, nonanticoagulant heparin might exert a protective effect by blocking circulating histones [38]. Herein, our data showed that in patients with SIC, receiving 8000–12000 IU heparin was beneficial for reducing ICU mortality, and this might be associated with the nonanticoagulant effect of the underlying mechanisms. A recent report implied that heparin prevented caspase-11-dependent immune responses and lethality in sepsis independent of its anticoagulant properties [39]. Heparin inhibited the high mobility group box-1 protein (HMGB1)-LPS interaction and prevented macrophage glycocalyx degradation by heparanase. These events blocked the cytosolic delivery of LPS in macrophages and the activation of caspase-11, a cytosolic LPS receptor that mediates lethality in sepsis, and ultimately ameliorated organ injury and improved the survival rate [14]. These observations raise the possibility that treatment with heparin might be effective in the management of septic patients, and it is of urgent importance to elucidate the mode of action and appropriate timing and dosage.

In septic patients with a SIC score of 4, not receiving mechanical ventilation, not using vasopressors and having a SOFA score ≤ 6 were associated with a reduced risk of ICU mortality. This is in contrast to a previous study of a post hoc subgroup analysis of a nationwide multicentre retrospective registry in Japan, which demonstrated that anticoagulant therapy may be associated with a survival benefit only among patients with SIC in the high-risk subset (SOFA score 13–17) but not in the subsets of patients with sepsis with a low to moderate risk [40]. Another retrospective study in septic patients with SIC showed that unfractionated heparin (UFH) administration was significantly associated with reduced 28-day mortality (HR, 0.323, 95% CI, 0.258–0.406; $P < 0.001$) and hospital mortality (HR, 0.380, 95% CI, 0.307–0.472; $P < 0.001$) without increasing the risk of intracranial haemorrhage or gastrointestinal bleeding [36], but other study reported no marked effect on 28-day mortality [8]. The effectiveness of heparin in treating SIC remains unclear. In the current study, there was no significant effect of heparin on ICU mortality in the overall population before or after PSM, while stratification analysis revealed that heparin treatment was associated with a reduced ICU mortality risk among patients with a SIC score of 4. What is the underlying reason? The previous study may have used only Cox regression analysis stratified by propensity scores, rather than MSCM, to account for time-varying confounding. The strength of the current study was the use of MSCM to account for both baseline and time-varying confounding. The clinical use of heparin is time-varying and depends on prior measurements of platelet count and INR, and heparin influences the subsequent platelet count and INR. Thus, there may be complex and dynamic relationships among heparin usage, platelet count, INR, and mortality. With the MSCM method, Dupuis C and colleagues evaluated the impact of red blood cell (RBC) transfusion on mortality in critically ill septic patients. The clinical scenario was quite similar to our study in which RBC transfusion was determined by previous haemoglobulin levels and could influence the subsequent haemoglobulin levels [41]. The MSCM model has also been successfully employed in other situations of time-dependent interventions [42, 43]. For the unmeasured confounding, we used risk factor analysis with a multivariable Cox proportional hazards model and E-value analysis to coassess the data. The result indicated that it was unlikely that an unmeasured confounder would have a substantially greater effect on ICU mortality than these known risk factors.

Of note, our results must be interpreted in the context of some limitations of our study. First, the study was based on an EHR whose data were generated during routine clinical practice. Thus, it is possible that the cohort selection was not exactly consistent with the definition of sepsis from the guidelines. Nonetheless, we tried to identify patients with sepsis that was consistent with the third definition of sepsis (e.g., infection plus an acute change in the total SOFA score ≥ 2 points). Second, the retrospective design of the study made it subject to confounding by indication, so we used PSM and MSCM to balance important confounding factors. Third, some variables of the patients were not extracted from the database, leading to some confounding or bias. We used the E-value sensitivity analysis to quantify the potential implications of unextracted confounders and found that an unextracted confounder was unlikely to explain the entirety of the treatment effect. Fourth, the database spanned more than 10 years, and clinical practice for the management of sepsis changed during the study period. The results may not be generalizable to current practice. Fifth, multiple subgroup analyses were performed, which might result in false positive findings. Both PSM analysis and MSCM showed consistent results, which confirmed the robustness of the findings.

Conclusions

The present study suggests that prophylactic heparin administration to patients who have a SIC score of 4 appears to be associated with improved survival outcomes, including ICU mortality, 7-day mortality, and 14-day mortality, especially in patients without mechanical ventilation, without vasopressor use, and with a SOFA score ≤ 6. Moreover, patients with a SIC score of 4 who received 8000–12000 IU had a reduced risk of ICU mortality compared with those in the nonheparin group. However, prophylactic heparin usage does not decrease hospital mortality or 28-day mortality in patients suffering from septic complications. Therefore, the indications for and timing and dosage of heparin in patients with SIC need to be verified in prospective randomized controlled trials.

Declarations

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Not applicable.

Author contributions

MW and JJH conceived and designed the study. JJH contributed in data management. JJH, ZYZ and YL contributed in data analysis. ZPZ, ZJY and JJZ were responsible for literature retrieval. JJH, YYL and MW contributed in interpretation of the data and drafting the manuscript . YMY supervised the project and critically reviewed the final version of the paper. All authors read and approved the final manuscript, being fully accountable for ensuring its integrity and accuracy.

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Availability of data and materials

Publicly available datasets were analyzed in this study. This data could be found: https://mimic-iv.mit.edu/

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Shenzhen Second People's Hospital (20220519001-MC01). The need for informed consent from individual patients was waived owing to the retrospective and observational nature of the study

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

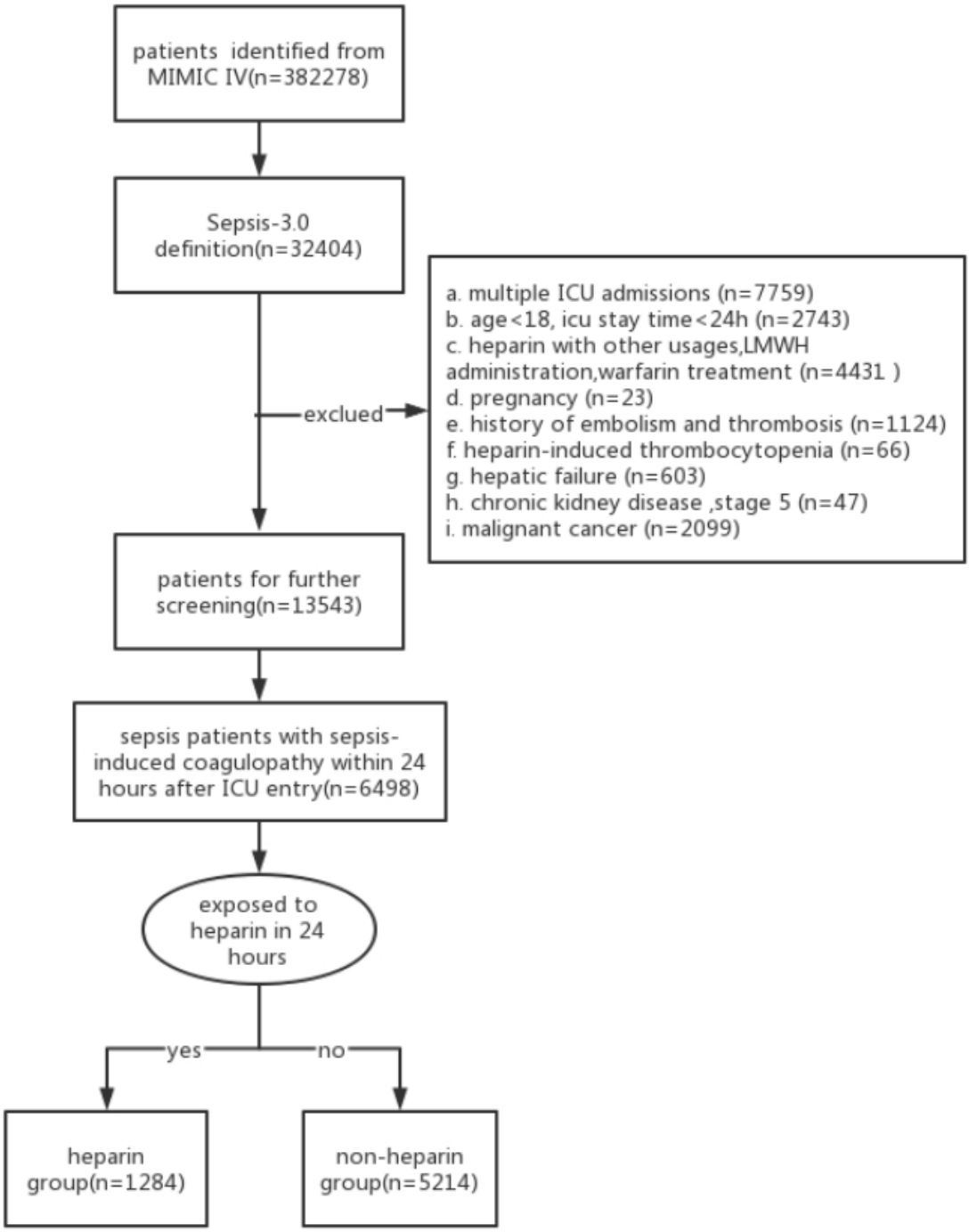

Figure 1

Flowchart of patient selection

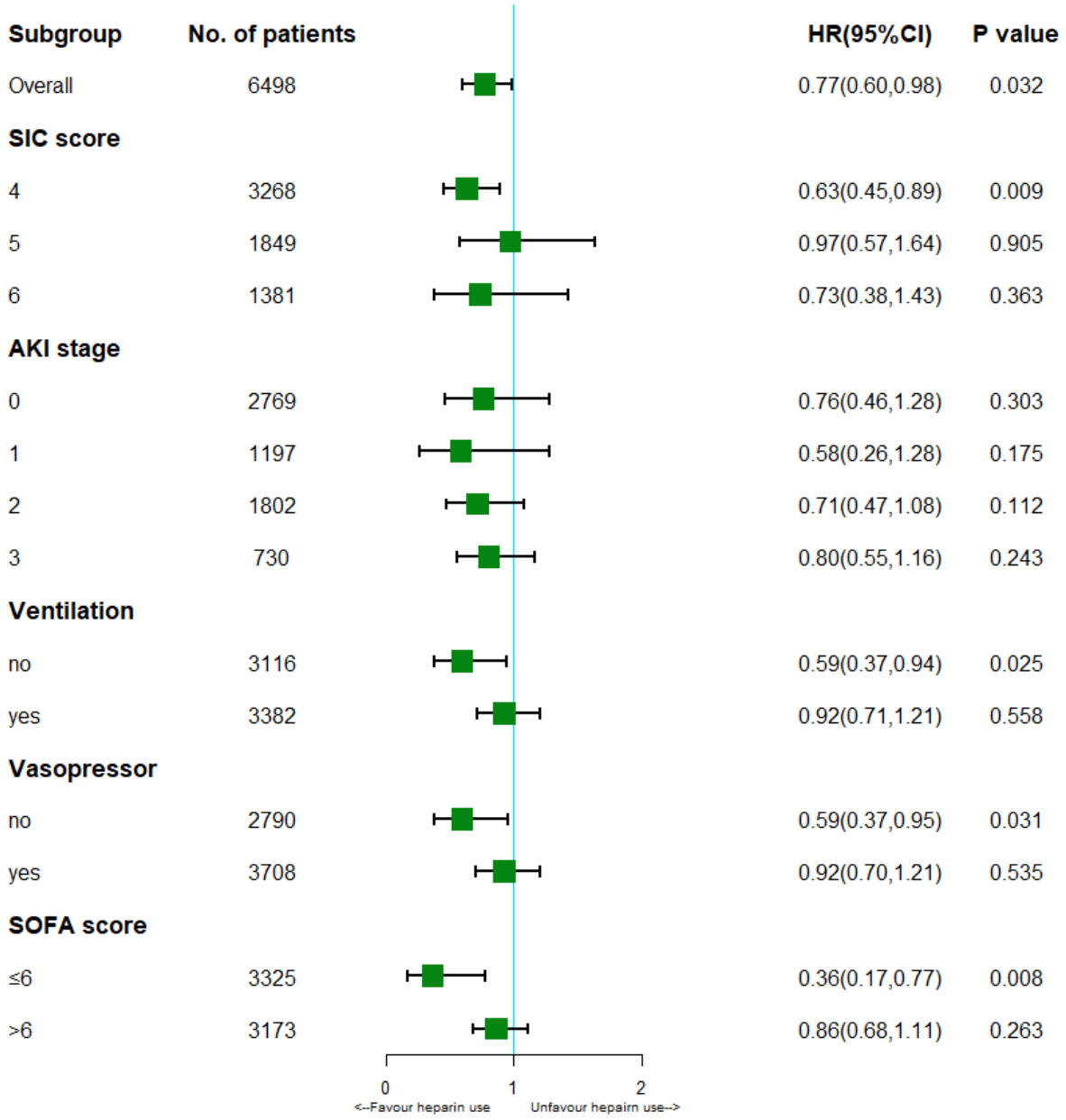

Figure 2

Results of ICU mortality in overall population with marginal structural Cox model and stratification analysis

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