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Optimizing outcomes in acute pancreatitis: the impact of of heparin therapy duration on mortality in a multi-center retrospective study

Linlin Fu[1], Hanyang Li[2], Qian Ni[3], Qiaoling Zhu[4*] and Baoyan Wang[4*]

Abstract

Objective Acute pancreatitis is a critical condition in the intensive care unit (ICU), often complicated by systemic issues, which may benefit from heparin therapy due to its anti-inflammatory and anticoagulant properties. However, the optimal duration of heparin therapy remained unclear. This retrospective study aimed to evaluate the association between heparin therapy duration and mortality outcomes in patients diagnosed with acute pancreatitis.

Method This retrospective study utilized data from the Medical Information Mart for Intensive Care (MIMIC-IV) and eICU Collaborative Research Database (eICU-CRD), including 1705 patients diagnosed with acute pancreatitis between 2008 and 2019. Restricted cubic splines (RCS) were employed to analyze the non-linear relationship between heparin therapy duration and 30-day and 90-day mortality. Patients were categorized into four groups based on quartiles: < 4 days, 4–7 days, 8–14 days, and > 14 days, using characteristics identified in the RCS curves, with 4–7 days as the reference. Cox multivariate regression and Kaplan-Meier analysis assessed the association between these groups and mortality, with 30-day mortality as the primary outcome and 90-day mortality as the secondary outcome.

Result The relationship between heparin therapy duration and mortality at 30 and 90 days in patients with acute pancreatitis exhibited a J-shaped curve, with the lowest mortality observed around 7 days for both 30-day and 90-day mortality. Heparin therapy durations less than 4 days were significantly associated with higher 30-day mortality (HR: 2.57, 95% CI: 1.53–4.30) and increased 90-day mortality (HR: 1.57, 95% CI: 1.07–2.32), with mortality stabilizing beyond 7 days of therapy. Subgroup analysis stratified by severity consistently supported these findings.

Conclusion In critically ill patients with acute pancreatitis, heparin therapy lasting less than 4 days was associated with increased 30-day and 90-day mortality, whereas the lowest mortality was observed among patients receiving heparin therapy for approximately 7 days.

Keywords Acute pancreatitis, Heparin, MIMIC-IV database, eICU-CRD

*Correspondence:
Qiaoling Zhu
z.qlu@163.com
Baoyan Wang
wby6261275@163.com

Full list of author information is available at the end of the article

Highlights

Knowledge gap Despite the theoretical advantages of heparin therapy, the optimal duration of treatment in acute pancreatitis remains uncertain and controversial, necessitating further research to inform clinical practice.

Key findings The study revealed a J-shaped curve relationship between heparin therapy duration and mortality, with the lowest mortality observed around 7 days of treatment. Shorter durations were significantly associated with increased mortality, while mortality stabilized beyond 7 days. These findings were consistent across disease severity subgroups.

Clinical implications This information has the potential to inform clinical decision-making and improve patient outcomes, while also guiding future research directions in the management of this challenging disease.

Introduction

Acute pancreatitis represents a potentially life-threatening disease characterized by rapid progression and systemic complications, presenting substantial clinical challenges [1]. Epidemiological studies indicated a global rise in hospital admissions due to acute pancreatitis, with hundreds of thousands of cases occurring annually [2]. Despite advances in intensive care and supportive therapies, severe acute pancreatitis leaded to critical complications in up to 25% of patients, including multi-organ dysfunction syndrome and pancreatic necrosis, with a mortality rate as high as 20% [3]. The management of this disease often involves various therapeutic strategies, including the use of anticoagulants [4].

Heparin, a widely utilized anticoagulant with additional anti-inflammatory properties, has garnered attention as a potential therapeutic agent in acute pancreatitis. Experimental and clinical studies have suggested that the capacity of heparin to inhibit inflammatory mediators may mitigate the systemic inflammatory response observed in acute pancreatitis [5]. Furthermore, the anticoagulant properties could play a pivotal role in preventing microvascular thrombosis [6]. These mechanism of action renders heparin an appealing candidate for adjunctive therapy in acute pancreatitis, potentially reducing disease severity and enhancing patient outcomes. Despite these theoretical advantages, determining the optimal duration of heparin therapy in acute pancreatitis remains controversial and warrants further investigation.

This retrospective study aimed to examine the impact of heparin duration on mortality outcomes in acute pancreatitis patients. This investigation utilized data from the Medical Information Mart for Intensive Care (MIMIC-IV) and the eICU Collaborative Research Database (eICU-CRD) to bridge existing knowledge gaps and provide insights that may guide clinical practices and future research directions in managing acute pancreatitis.

Methods

Study design and patients

This study utilized two key databases in critical care medicine: MIMIC-IV and eICU-CRD. MIMIC-IV, managed by MIT CSAIL, includes data from ICU patients at Beth Israel Deaconess Medical Center in Boston. eICU-CRD, a collaboration with Philips and U.S. medical centers, aggregates ICU patient data nationwide. These databases provided extensive clinical information essential for evaluating heparin therapy duration in acute pancreatitis patients and its impact on clinical outcomes. This retrospective study included patients diagnosed with acute pancreatitis based on the International Classification of Diseases, 9th and 10th revisions, admitted to ICU between 2008 and 2019 for management of the condition. Exclusion criteria were as follows: (1) Patients under 18 years old at admission; (2) Patients with multiple ICU admissions due to acute pancreatitis, with only data from their first admission being analyzed; (3) patients with severe comorbidities such as end-stage renal failure who need to use heparin for dialysis purposes (e.g., active bleeding disorders); (4) Heparin therapy lasting less than 2 days; (5) Patients lacking sufficient clinical data during hospitalization. The patient extraction process for acute pancreatitis study showed in Fig. 1.

Data collection

Data extraction for this study utilized Postgres SQL (version 8.2) and Navicat Premium (version 16) via Structured Query Language (SQL). A comprehensive set of variables was extracted from the MIMIC-IV and eICU-CRD databases. For each patient, data included the duration of heparin therapy, with both initiation and cessation times documented to calculate the total duration of use. Key demographic information comprised patient age and gender. Medical history captured potential etiologies, such as gallstones, alcohol consumption, hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound (EUS), pancreatic tumors or cystic lesions, and

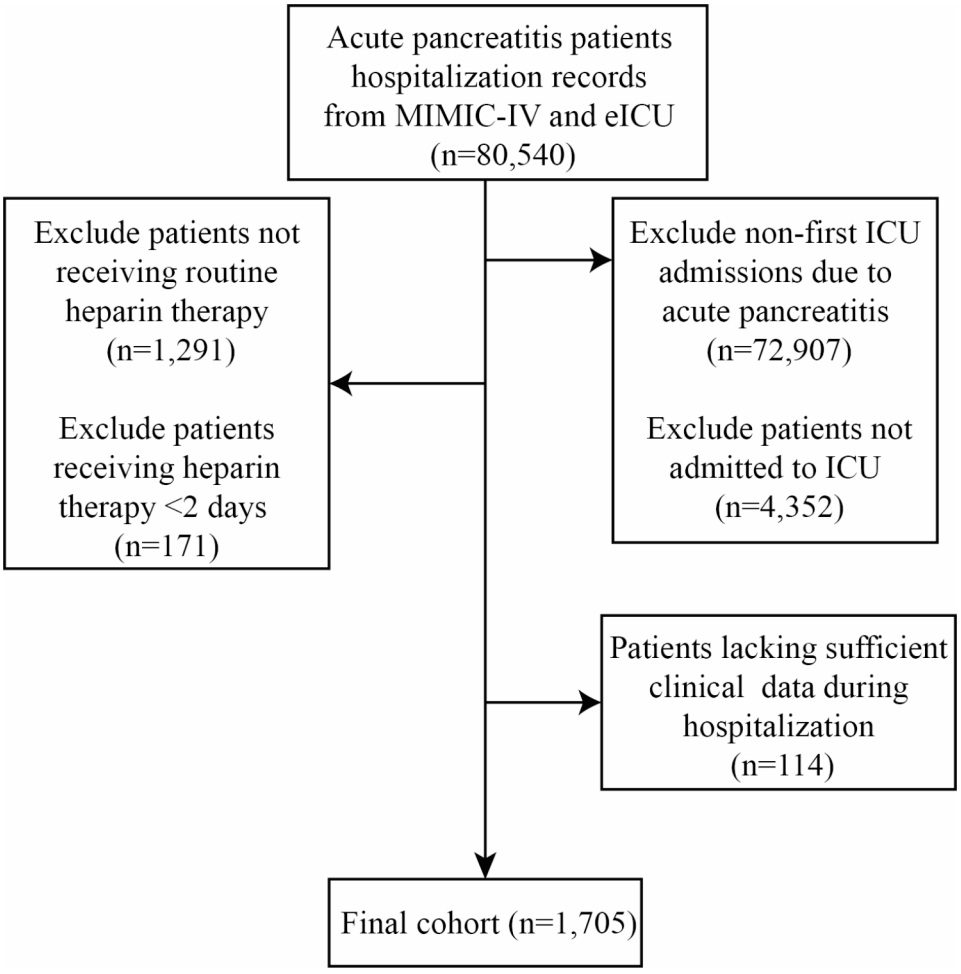

Fig. 1 patient extraction process for acute pancreatitis study

medication-induced causes. Vital signs recorded during the therapy period included heart rate, respiratory rate, temperature and body mass index (BMI). Laboratory parameters encompassed white blood cell count (WBC), blood urea nitrogen (BUN), hemoglobin (Hb), creatinine (Cr), hematocrit (Hct), and red cell distribution width (RDW).

Additionally, the study extracted relevant indicators including the systemic inflammatory response syndrome (SIRS) criteria and Charlson Comorbidity Index (CCI) data [7]. The CCI classification categorized patients based on predefined criteria: 0 points indicated the absence of specific comorbidities and a low risk with higher survival rates; 1–2 points indicated one to two mild comorbidities, representing moderate risk; 3–4 points indicated a moderate comorbidity burden, associated with moderate to high risk; 5–6 points indicated significant comorbidities requiring close monitoring, representing high risk; and 7 points or more indicated severe comorbidities, associated with lower survival rates and higher treatment risks. Furthermore, the severity of acute pancreatitis was assessed using the Bedside Index for Severity in Acute Pancreatitis (BISAP) score, which categorized scores into three groups: scores of 0 or1 indicated mild severity, scores of 2 indicated moderate severity, and scores of 3 or above indicated severe severity [8, 9]. The BISAP score included parameters such as elevated BUN levels (>25 mg/dL), impaired mental status, SIRS criteria, age over 60 years, and the presence of pleural effusion.

Treatment protocol

The treatment protocol in this study was based on patient data extracted from the MIMIC-IV and eICU-CRD databases. Anticoagulation therapy in this study primarily utilized heparin, with the treatment regimen derived from clinical data recorded in the databases. The duration of heparin therapy was defined as the continuous period from the initiation of treatment to its cessation. The treatment initiation time refers to the first administration of heparin during the patient's hospital stay, typically occurring within 24 h of admission for patients meeting the criteria for anticoagulation therapy. The

treatment cessation time is defined as the moment when the treatment ends or when the clinician decides to discontinue heparin. During treatment, heparin dosages were adjusted based on clinical monitoring and laboratory test results. As this study relies on patient records from the databases, all treatment decisions and adjustments to the regimen were made by clinicians based on the patient's specific condition, ensuring the clinical representativeness of the treatment protocol.

Study outcome

The primary outcome was the 30-day mortality, while the secondary outcome was the 90-day mortality in patients diagnosed with acute pancreatitis.

Statistical analysis

To explore the potential non-linear relationship between heparin therapy duration and mortality, restricted cubic spline (RCS) curves were employed within Cox proportional hazards models on a continuous scale. Knots ranging from 3 to 7 were tested, and the model with the lowest Akaike Information Criterion value was selected for the RCS. The categorization of heparin therapy duration into quartiles (< 4 days, 4–7 days, 8–14 days, > 14 days) was informed by observed inflection points in these curves. The 4–7 days duration was chosen as the reference category to enable meaningful clinical and statistical interpretation aligned with the trends observed in the RCS curves.

Cox proportional hazards models were employed to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the association between the heparin therapy duration and mortality. The models were adjusted as follows: Model 1 was adjusted for age, gender, and BMI. Model 2 included additional adjustments for the etiologies of acute pancreatitis and laboratory parameters such as Hb, Cr, Hct, and RDW. Model 3 further incorporated adjustments for CCI and BISAP score.

To compare clinical outcomes between the groups, the stabilized inverse probability of treatment weights (IPTW) was utilized to balance covariates and ensure comparability of results in Kaplan-Meier analysis. Propensity scores for each treatment group were computed using multivariate logistic regression of all covariates. Subsequently, stabilized IPTW based on these propensity scores was applied to adjust for measured covariates, effectively creating a pseudo dataset that preserved the original sample size. Kaplan-Meier analysis was subsequently used to assess differences in clinical outcomes between groups, with the Log-Rank test used to compare survival curves. P-value < 0.05 was considered significant.

To avoid possible bias, variables were excluded if they had more than 20% missing values. In the dataset of 1,705 patients, 2.5% had missing vital signs and laboratory parameters, which were imputed using the mean. Subgroup analysis was conducted to evaluate clinical outcomes within specific BISAP score and etiology subgroups using multivariate Cox proportional hazards regression models adjusted for the variables in Model 3. Interaction significance between treatment group and subgroup was set at *P*-for-interaction < 0.1. Statistical analysis was performed using R software (version 4.4.1).

Results

This study enrolled a total of 1705 critically ill patients diagnosed with acute pancreatitis. RCS analysis revealed a pronounced non-linear J-shaped relationship between the heparin therapy duration and clinical outcomes in patients with acute pancreatitis (Fig. 2). Shorter durations of heparin therapy were closely associated with significantly increased risks of 30-day and 90-day mortality, with mortality stabilizing beyond certain thresholds of therapy duration. Specifically, in models 1, 2, and 3, the analysis identified the lowest points in 30-day mortality at therapy durations of 6.8 days, 7.1 days, and 7.1 days, respectively. Similarly, the lowest points in 90-day mortality rates were observed at 6.5 days, 6.8 days, and 7.1 days, demonstrating consistent trends across all three models. These findings underscored that the optimal heparin therapy duration for improving outcomes in acute pancreatitis patients was approximately around 7 days.

These observed inflection points were used to define the boundaries for grouping therapy durations. This study categorized heparin therapy duration into four predefined groups based on quartiles: 1st-25th (< 4 days), 26th-50th (4–7 days), 51th-75th (8–14 days), and 75th-100th (> 14 days). Selecting the 4–7 days group as the reference category was driven by its relatively stable effect observed in the spline analysis. Furthermore, employing quartile-based grouping provided each category with adequate statistical robustness and clinical interpretability.

Patient characteristics

The baseline characteristics of the patients were detailed in Table1. Significant differences in age were observed among the groups, with patients in the <4 days group having a higher average age (63.04 ± 16.80) and patients in the >14 days group showing a lower average age (57.57 ± 16.21). Common etiologies of acute pancreatitis included gallstones (34.5%) and alcohol (27.6%). Gallstone-induced acute pancreatitis was most prevalent in the < 4 days and 8–14 days groups. Patients with pancreatic tumors or cystic lesions, as well as those with infections, were primarily found in the > 14 days group. Additionally, cases of acute pancreatitis attributed to post-ERCP/EUS and medications were significantly more frequent in the 8–14

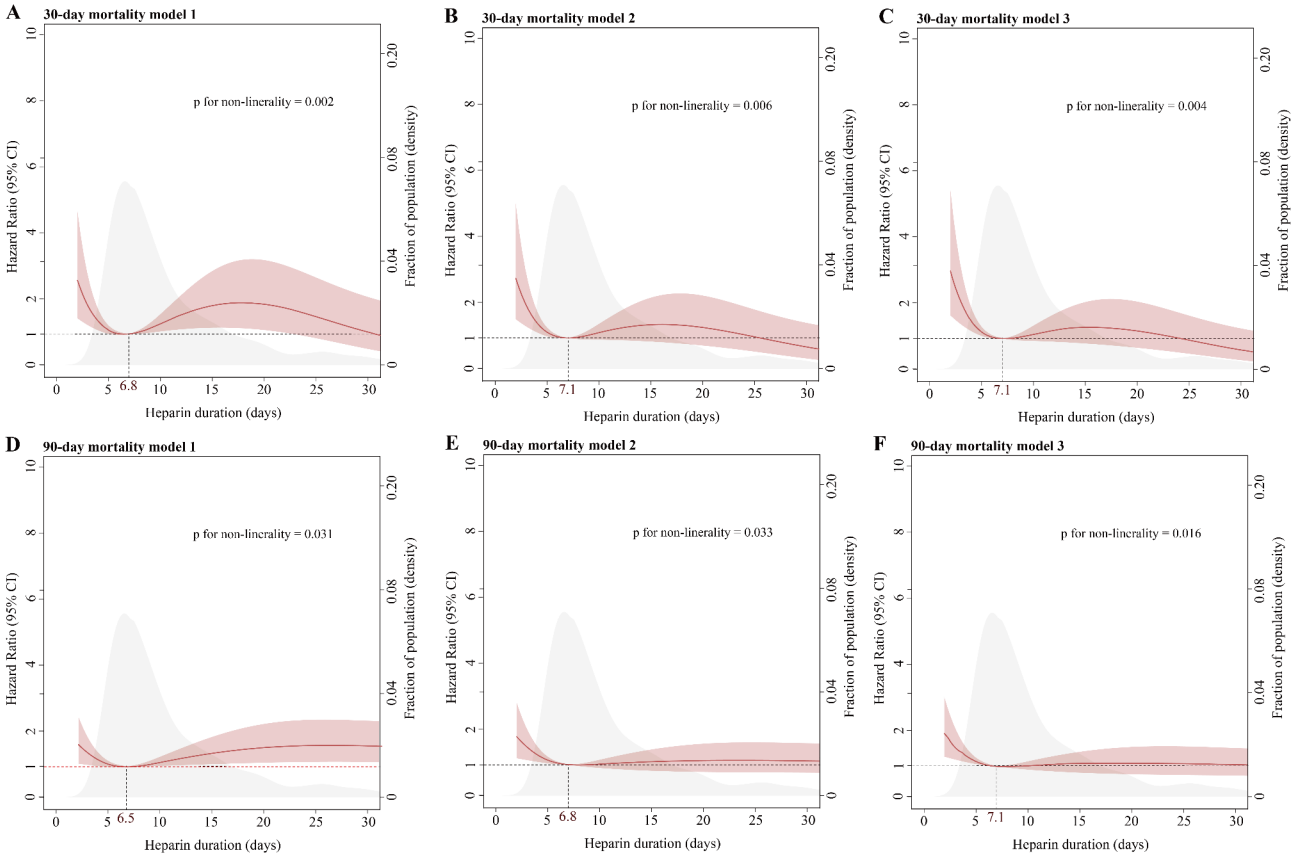

Fig. 2 (**A**), (**B**), and (**C**) restricted cubic spline for 30-day mortality after adjustment for Model 1, Model 2, and Model 3, respectively. (**D**), (**E**), and (**F**) restricted cubic spline for 90-day mortality after adjustment for Model 1, Model 2, and Model 3, respectively. The solid red line represents the adjusted HR with the 95%CI shaded in red. The dashed line at HR = 1.0 denotes no association. The gray shaded area indicates the proportion of the population at different heparin therapy duration. HR, hazard ratio; CI, confidence interval

The range of heparin therapy duration was restricted to 0 to 40 days because predictions greater than 40 days (97th percentile) are based on too few data points. Model 1: adjusted for age, gender, and BMI

Model 2: included additional adjustments for the etiologies of acute pancreatitis, encompassing gallstones, alcohol, hypertriglyceridemia, ERCP/EUS, pancreatic tumors or cystic lesions, medications, infection, and laboratory parameters such as Hb, Cr, Hct, and RDW

Model 3: further incorporated adjustments for CCI and BISAP score

days and > 14 days groups. CCI scores showed relatively consistent distributions across different treatment durations. For the BISAP scores, patients with scores of 0 or 1 were most prevalent in the <4 days group, while those with a score of 2 or ≥ 3 were most commonly observed in the >14 days group. Laboratory tests including BUN, WBC, Cr, Hct, and RDW exhibited significant differences among groups ($P < 0.001$), reflecting physiological and pathological changes during the early phase of acute pancreatitis.

Clinical outcomes

The Kaplan-Meier survival analysis (Fig. 3) indicated a statistically significant difference in 30-day mortality among the groups (log-rank $P = 0.0032$), although no significant difference was observed in 90-day mortality (log-rank $P = 0.082$).

Further analysis using Cox proportional hazards models across Models 1, 2, and 3 (Fig. 3). Model 3 showed that the < 4 days group had higher 30-day mortality compared to the 4–7 days group (HR: 2.57, 95% CI: 1.53–4.30). In contrast, the 8–14 days and > 14 days groups exhibited similar 30-day mortality to the 4–7 days group (HR: 1.10, 95% CI: 0.64–1.87; HR: 0.86, 95% CI: 0.49–1.51). For 90-day mortality, Models 3 indicated higher 90-day mortality in the < 4 days group compared to the 4–7 days group (HR: 1.57, 95% CI: 1.07–2.32), with the 8–14 days and > 14 days groups showing similar 90-day mortality to the 4–7 days group (HR: 0.84, 95% CI: 0.57–1.23; HR: 0.91, 95% CI: 0.63–1.34). Heparin therapy duration less than 4 days was consistently associated with increased mortality in critically ill patients, irrespective of baseline characteristics. Cox proportional hazard regression models identified an inflection point within the 4–7 group,

Table 1 Baseline characteristics of the included patients

	Groups					
	All	**1st-25th (< 4 days)**	**26th-50th (4–7 days)**	**51th-75th (8–14 days)**	**75th-100th (> 14 days)**	***P***
No of patients	1705	280	596	424	405	
Gender						0.282
Male	990(58.06)	160(57.14)	339(56.88)	239(56.37)	252(62.22)	
Female	715(41.94)	120(42.86)	257(43.12)	185(43.63)	153(37.78)	
Age	60.88±16.98	63.04±16.80	62.39±17.42	60.50±16.78	57.57±16.21	< 0.001
BMI	28.46±7.61	28.49±6.38	27.83±9.00	29.09±7.22	28.70±6.41	0.060
Etiologies						
Gallstones	588(34.49)	108(38.57)	205(34.40)	168(39.62)	107(26.42)	< 0.001
Alcohol	471(27.62)	71(25.36)	164(27.52)	125(29.48)	111(27.41)	0.691
Hypertriglyceridemia	172(10.09)	26(9.29)	72(12.08)	31(7.31)	43(10.62)	0.088
Post-ERCP/EUS	113(6.63)	13(4.64)	30(5.03)	36(8.49)	34(8.40)	0.034
Pancreatic tumors or cystic lesions	259(15.19)	27(9.64)	69(11.58)	65(15.33)	98(24.20)	< 0.001
Medications	114(6.69)	15(5.36)	20(3.36)	42(9.91)	37(9.14)	< 0.001
Infection	165(9.68)	23(8.21)	31(5.20)	36(8.49)	75(18.52)	< 0.001
CCI score						0.905
1 (CCI = 0)	172(10.09)	28(10.00)	52(8.72)	44(10.38)	48(11.85)	
2 (CCI = 1 or 2)	448(26.28)	67(23.93)	163(27.32)	113(26.65)	105(25.94)	
3 (CCI = 3 or 4)	433(25.40)	79(28.21)	147(24.66)	101(23.82)	106(26.17)	
4 (CCI = 5 or 6)	329(19.30)	50(17.86)	121(20.30)	85(20.05)	73(18.02)	
5 (CCI ≥ 7)	323(18.93)	56(20.00)	113(19.00)	81(19.10)	73(18.02)	
BISAP score						< 0.001
1 (BISAP = 0 or 1)	542(31.79)	108 (38.57)	225 (37.75)	132 (31.13)	77 (19.01)	
2 (BISAP = 2)	608 (35.66)	94 (33.57)	215 (36.08)	138 (32.55)	161 (39.75)	
3 (BISAP ≥ 3)	555 (32.55)	78 (27.86)	156 (26.17)	154 (36.32)	167 (41.24)	
Laboratory Examinations						
BUN (mg/dL)	26.84±23.31	24.13±20.23	24.33±20.39	28.29±25.09	30.88±26.55	< 0.001
WBC ($\times 10^9$/L)	12.51±7.46	10.80±6.41	11.86±7.21	13.00±7.64	14.12±7.93	< 0.001
Hb (g/dL)	11.27±2.29	11.47±2.18	11.35±2.19	11.21±2.23	11.08±2.53	0.100
Cr (mg/dL)	1.71±1.91	1.59±1.55	1.48±1.41	1.91±2.24	1.94±2.33	< 0.001
Hct (%)	31.92±6.02	33.32±5.65	32.87±5.72	31.60±6.11	29.91±6.06	< 0.001
RDW (%)	15.35±2.28	15.11±2.24	15.10±2.10	15.48±2.45	15.75±2.32	< 0.001

where mortality risk was minimized, validating the robustness of these findings across analysis.

Subgroup analysis

Subgroup analysis using model 3 further examined the impact of heparin duration on mortality across different patient subgroups, including BISAP score (Fig. 4) and etiology (Fig. 5). Among patients with BISAP scores ≥ 3, heparin duration < 4 days significantly increased 30-day mortality (HR: 2.47, 95% CI: 1.26–4.88). However, no significant interactions were observed between BISAP score subgroups and treatment duration for both 30-day and 90-day mortality. In the etiology subgroup analysis for 30-day mortality, heparin therapy < 4 days increased mortality across all groups except in patients with hypertriglyceridemia. Regarding 90-day mortality in the etiology subgroup, heparin duration < 4 days significantly increased mortality in patients with gallstones (HR: 2.84, 95% CI: 1.47–5.48), alcohol consumption (HR: 2.75, 95% CI: 1.26-6.00), and those without hypertriglyceridemia (HR: 1.60, 95% CI: 1.07–2.38), with no significant interactions observed between subgroups and treatment duration.

Discussion

In this study of 1705 individuals from the MIMIC-IV and eICU-CRD databases, a pronounced J-shaped relationship was identified between heparin duration and, both 30-day mortality and 90-day mortality. Specifically, heparin duration less than 4 days was significantly associated with elevated 30-day mortality and 90-day mortality among critically ill patients with acute pancreatitis. This analysis pinpointed that the heparin therapy duration associated with the lowest risk of 30-day mortality and 90-day mortality was approximately 7 days, with mortality rates stabilizing beyond 7 days of therapy. These findings retained statistical significance even after rigorous adjustment for various confounding risk factors.

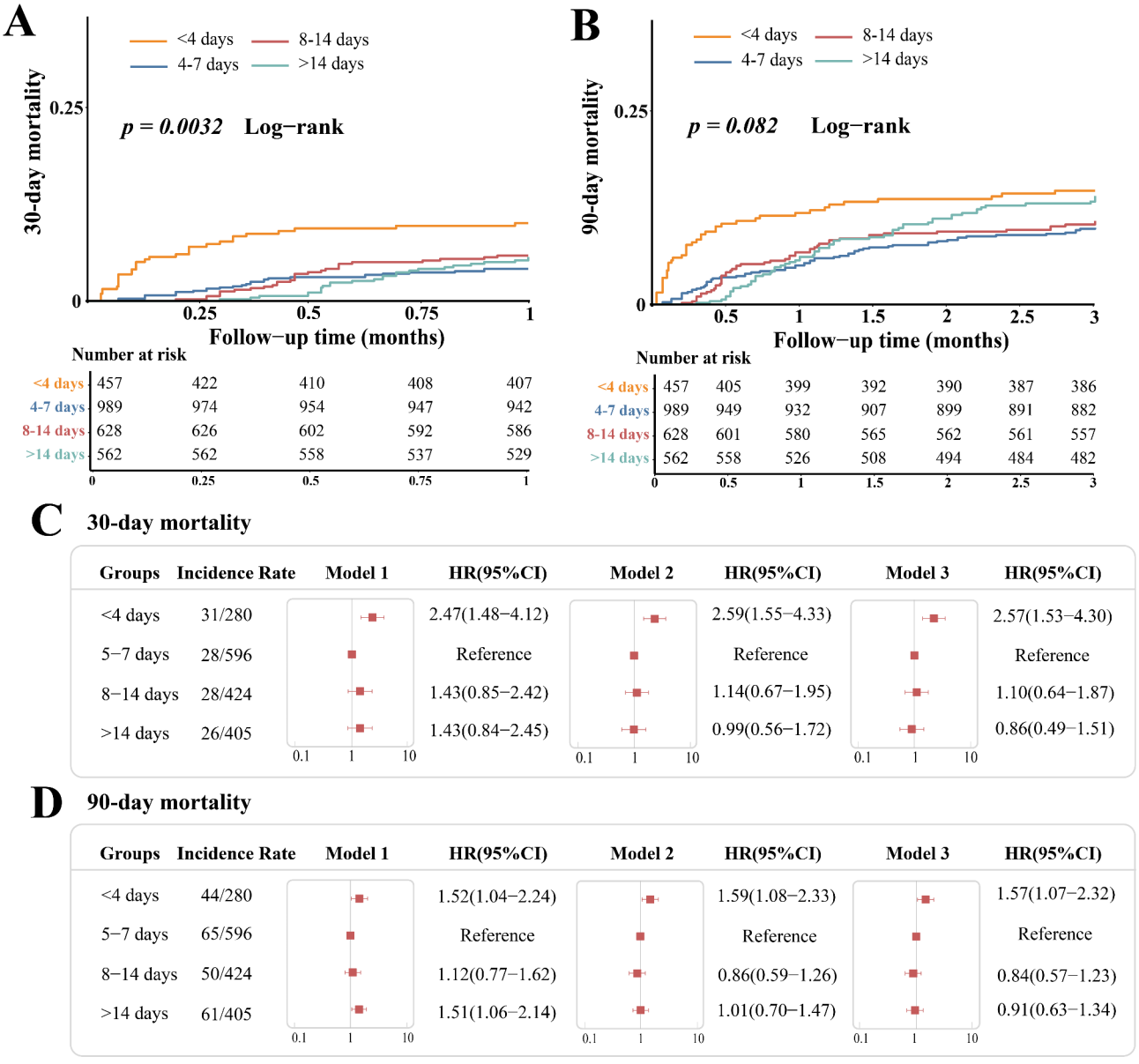

Fig. 3 The weighted cumulative incidence curves of 30-day mortality (**A**), and 90-day mortality (**B**); Cox proportional hazard ratios (HRs) and incidence rates (IRs) for 30-day mortality (**C**), and 90-day mortality (**D**). CI, Confidence interval

Possible explanations for our findings

To explain these findings, it is crucial to consider the complex interplay between inflammation, coagulation abnormalities, and endothelial dysfunction in acute pancreatitis [10]. Pancreatic enzyme autodigestion and the release of inflammatory mediators directly induce inflammation and necrosis in pancreatic tissue, while also triggering the coagulation cascade, leading to thrombus formation in blood vessels, particularly within the pancreatic microcirculation [6, 10]. This process exacerbates local hypoperfusion and tissue ischemia [11]. Additionally, inflammatory cytokines and activated leukocytes exert detrimental effects on endothelial cells, compromising their barrier function and promoting pathological vascular dilation and thrombus formation [5].

Heparin, recognized for its anticoagulant properties, exerts multifaceted effects in managing acute pancreatitis. It inhibits thrombin, reduces fibrin clot formation, and thereby prevents microvascular thrombosis, improves tissue perfusion, and reduces ischemic damage [12, 13]. Furthermore, the anti-inflammatory of heparin mitigates the release of inflammatory mediators, attenuating systemic inflammation and the progression of organ damage [14]. Heparin also preserves endothelial integrity, critical for preventing vascular leakage and

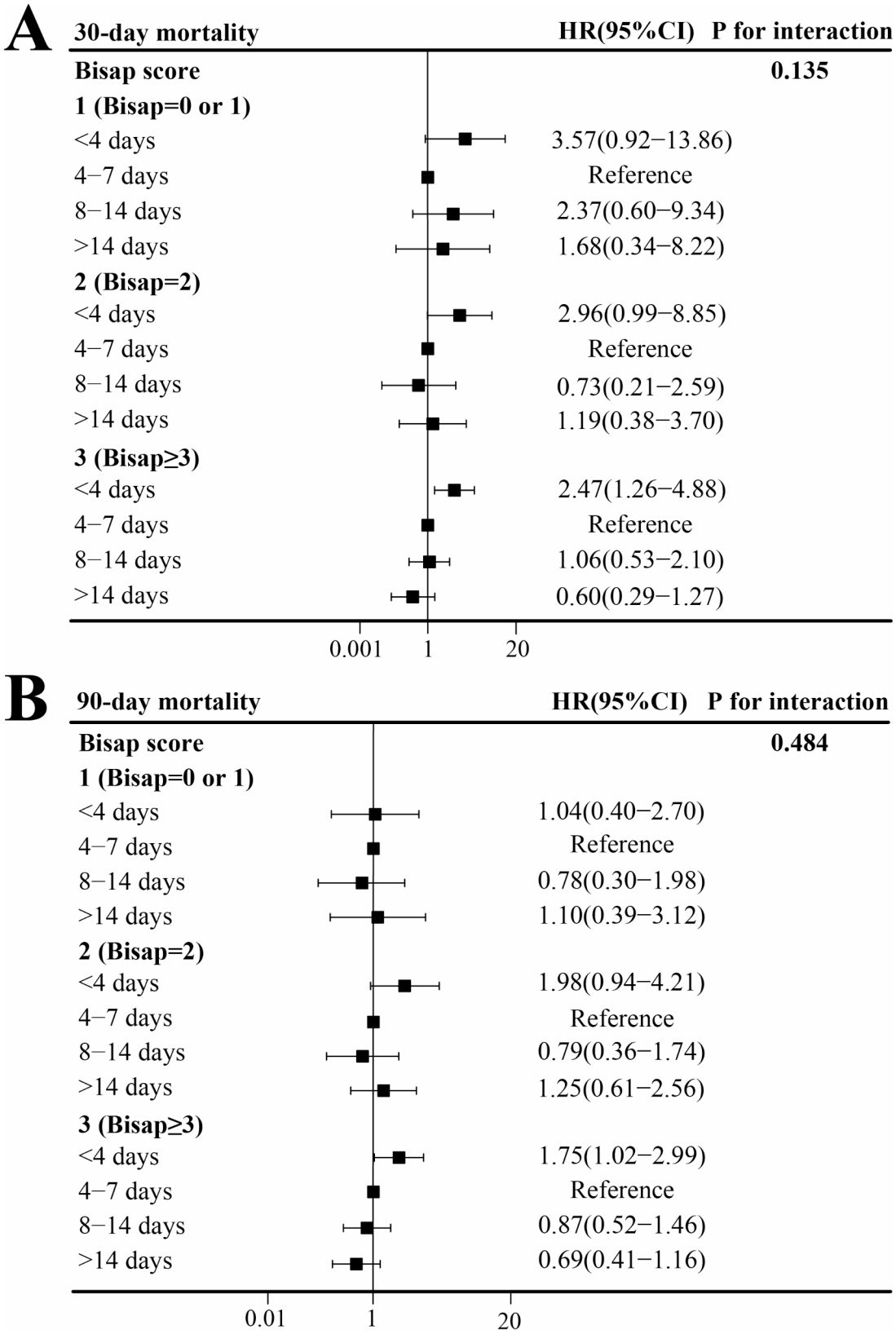

Fig. 4 Forest plots of hazard ratios for the 30-day mortality (**A**) and 90-day mortality (**B**) in BISAP score subgroups. HR, hazard ratio; CI, confidence interval; BISAP, Bedside Index for Severity in Acute Pancreatitis

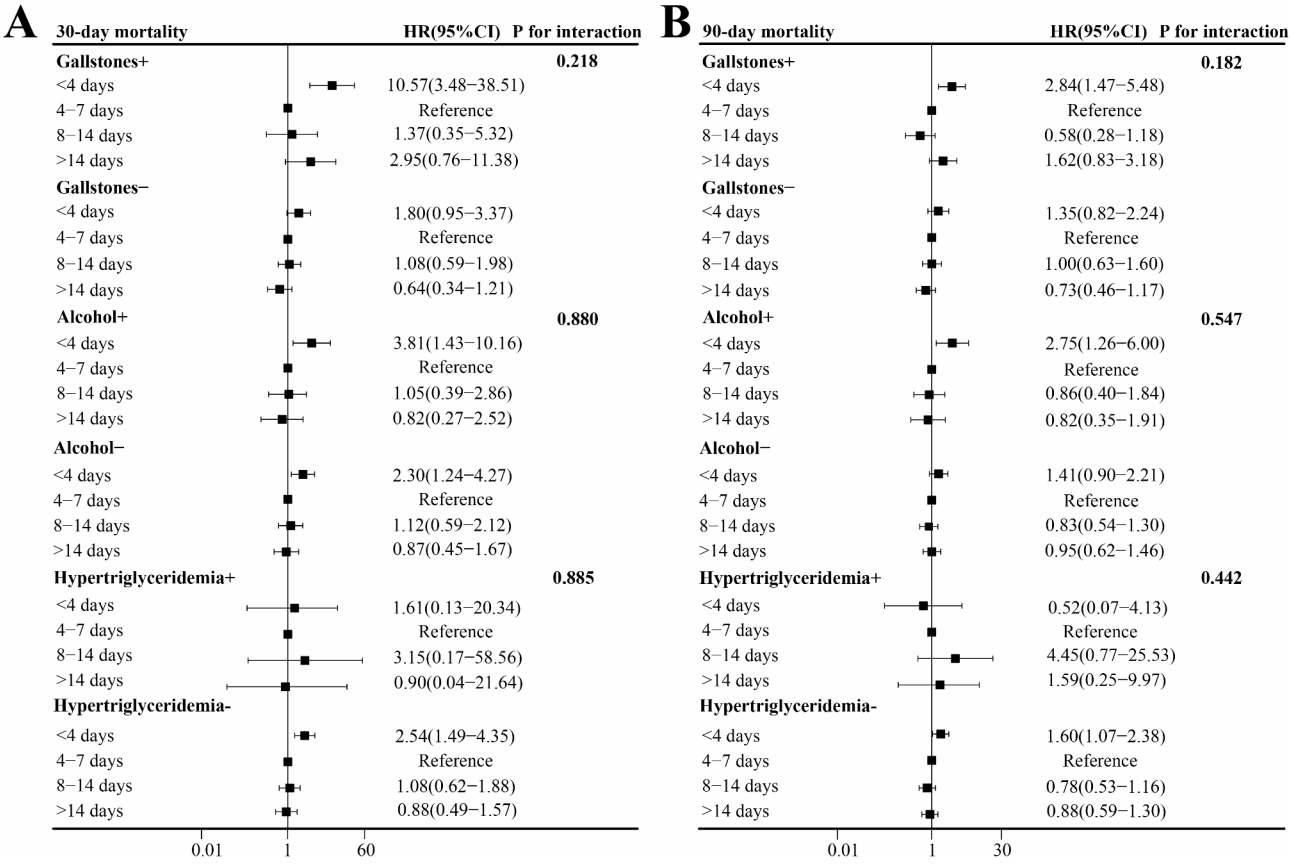

Fig. 5 Forest plots of hazard ratios for the 30-day mortality (**A**) and 90-day mortality (**B**) in etiologies subgroups. HR, hazard ratio; CI, confidence interval

maintaining microvascular function [12]. Additionally, by inhibiting pancreatic digestive enzymes such as trypsin, heparin attenuates autodigestive processes, thereby reducing pancreatic injury [15].

However, the duration of heparin therapy is crucial for these effects. An inadequate duration of heparin therapy may fail to fully suppress initiated coagulation processes, allowing continuous thrombus formation and exacerbating pancreatic microcirculatory disturbances, thereby promoting tissue injury and organ dysfunction. In such cases, the continued presence of thrombus formation can further intensify the inflammatory response, complicating the patient's condition.Considering prolonged heparin use in acute pancreatitis treatment, several critical factors also merit discussion. Extended heparin duration may impact platelet function, increase the risk of bleeding,andeven contribute to osteoporosis and a higher likelihood of fractures [16, 17]. Extended therapy beyond optimal window may not significantly enhance clinical outcomes in acute pancreatitis, while potentially escalating healthcare costs and exposing patients to unnecessary risks. A moderate duration of heparin therapy can effectively avoid the risks of excessive anticoagulation while maintaining its crucial roles in anti-inflammation and preventing thrombus formation.

Subgroup analysis revealed further insights into the variability of treatment effects across different patient populations. We stratified patients according to BISAP score due to its clinical utility and predictive accuracy, aiming to assess treatment effects across varying severity levels, thereby enhancing the precision and relevance of our findings. The etiology of acute pancreatitis varies significantly, with gallstones (21-33%), alcohol consumption (16-27%), and hypertriglyceridemia (2-5%) being the predominant causes [18]. These three etiologies were selected not only for their clinical prevalence but also for their representativeness of the diverse mechanisms underlying acute pancreatitis. Notably, the association between short durations of heparin therapy and increased mortality was consistent across subgroups defined by BISAP score and etiology, except for patients with hypertriglyceridemia. This observation suggested that patients with hypertriglyceridemia may have distinct underlying mechanisms affecting their response to heparin therapy compared to those with other etiologies. Nevertheless, the absence of significant interactions between subgroups and treatment duration underscores the robustness of our findings across the broader patient population.

Previous studies

Previous clinical and laboratory studies have explored the potential role of heparin in the management of acute pancreatitis, but controversy remains regarding the optimal timing and duration of heparin therapy. A retrospective cohort study investigated the impact of systemic anticoagulation on 90-day readmission rates among patients with acute necrotizing pancreatitis [19]. Their findings revealed that anticoagulation therapy was independently linked to a reduced risk of 90-day readmission, potentially influenced by a decreased occurrence of splanchnic vein thrombosis. Furthermore, patients receiving anticoagulation showed enhanced vitality scores, highlighting its potential long-term benefits. Similarly, a nationwide retrospective case-control study analyzed data from hospitalized acute pancreatitis patients to evaluate the effects of systemic anticoagulation on hospital outcomes [20]. They reported that anticoagulation therapy was associated with lower risks of ICU admission, acute kidney injury, organ failure, and in-hospital mortality. These insights, combined with our research, emphasized the multifaceted benefits of anticoagulation in acute pancreatitis management. By identifying the optimal duration of heparin therapy linked to reduced mortality risks in critically ill patients, our study offered valuable guidance for treatment optimization. Future prospective studies are essential to validate these findings and further refine clinical guidelines, potentially improving outcomes for acute pancreatitis patients.

Clinical importance

This study meticulously examined the intricate relationship between the duration of heparin therapy and mortality in severely ill patients with acute pancreatitis, providing robust empirical evidence for tailoring clinical treatment strategies precisely. The results highlighted a potential optimal treatment duration of approximately 7 days, aiming to enhance anticoagulation and anti-inflammation benefits of heparin, while mitigating risks such as bleeding complications from excessive treatment. Although this study did not specifically address the optimization of heparin dosing, it suggests that future research should explore the optimal dosing strategies, considering patient-specific factors, to further improve therapeutic outcomes and minimize risks. Future research will further elucidate the mechanisms of heparin therapy in acute pancreatitis, supporting ongoing refinement of treatment protocols.

Strengths and limitations

The strengths of the study lied in its rigorous adjustment for numerous confounding factors influencing mortality, ensuring robust control of biases. Advanced analytical methods, including restricted cubic spline analysis and Cox proportional hazards modeling, were employed to explore the impact of heparin duration in acute pancreatitis. The findings highlight the importance of limiting heparin therapy to around 7 days to mitigate mortality risks and reduce complications, thereby optimizing treatment strategies for patients.

However, several limitations should be considered. Firstly, despite efforts to enhance result stability through various methods, the retrospective design of this study introduced the possibility of unmeasured variables that could potentially confound our findings. Secondly, due to data source limitations, we lacked detailed information on the specific causes of patient mortality, relying solely on mortality rates as an outcome measure, which may provide a limited perspective. Thirdly, accurately capturing all adverse events following heparin administration posed a significant challenge. Future research should prioritize prospective studies to validate our findings across diverse patient populations and clinical settings. Nevertheless, this study represented the most definitive evidence to date regarding the impact of heparin duration on prognosis in acute pancreatitis patients, offering critical insights for guiding drug treatment strategies in ICU settings.

Conclusions

In critically ill patients with acute pancreatitis, heparin therapy lasting less than 4 days was associated with increased 30-day and 90-day mortality. Based on a comprehensive analysis indicating reduced mortality, the optimal duration is suggested to be around 7 days. These findings underscore the importance of precise control over heparin therapy duration to maximize therapeutic benefits and minimize potential risks in the management of acute pancreatitis in the ICU.

Abbreviations

ICU	intensive care unit
MIMIC-IV	Medical Information Mart for Intensive Care
eICU-CRD	eICU Collaborative Research Database
SQL	Structured Query Language
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
BMI	body mass index
WBC	white blood cell count
BUN	blood urea nitrogen
Hb	hemoglobin
Cr	creatinine
Hct	hematocrit
RDW	red cell distribution width
SIRS	systemic inflammatory response syndrome
CCI	criteria and Charlson Comorbidity Index
BISAP	Bedside Index for Severity in Acute Pancreatitis
RCS	restricted cubic spline
HR	hazard ratio
CI	confidence interval
IPTW	inverse probability of treatment weights

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Author contributions
LLF and BYW generated the research concept. LLF and HYL conducted the investigation and managed the data. LLF performed data analysis, visualization, and drafted the initial manuscript. QN and QLZ provided key feedback, while BYW handled the review and revisions. All authors approved the final manuscript.

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Data availability
The data that support the fundings of this study are available from the MIMIC-IV database, but restrictions apply to the availability of these data, which were used under license for the current research and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the holder of the database.

Declarations

Ethics approval and consent to participate
The study was performed according to the guidelines of the Helsinki Declaration. The use of the MIMIC-IV database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The eICU-CRD is provided through the work of researchers at the MIT Laboratory for Computational Physiology, Philips Healthcare, and their collaborators. One author (Linlin Fu) who has passed the "Protecting Human Research Participants" examination, could access the database and was responsible for data extraction (Record ID: 62316096), therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pharmacy, Nanjing Drum Tower Hospital, Basic Medicine and Clinical Pharmacy College, China Pharmaceutical University, 210008 Nanjing, China
[2]Department of Biochemistry and Molecular Biology, Nanjing Medical University, 211166 Nanjing, China
[3]Department of Vascular Surgery, Nanjing Drum Tower Hospital, Nanjing Drum Tower Hospital Clinical College, Nanjing University of Chinese Medicine, Nanjing, China
[4]Department of Pharmacy, Affiliated Hospital of Medical School, Nanjing Drum Tower Hospital, Nanjing University, 210008 Nanjing, China

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