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ORIGINAL RESEARCH

Early Prophylactic Anticoagulation and In-Hospital Mortality in Patients with Severe Acute Pancreatitis: A Retrospective Cohort Study

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Purpose: To investigate the association between early prophylactic anticoagulation and in-hospital mortality in ICU patients with severe acute pancreatitis.

Patients and Methods: This retrospective cohort study used data from the MIMIC-IV database (v3.1), including adult ICU patients diagnosed with SAP between 2008 and 2019. Patients receiving therapeutic anticoagulation were excluded. Early prophylactic anticoagulation was defined as subcutaneous heparin or enoxaparin administered within 24 hours of ICU admission. The primary outcome was in-hospital mortality. Multivariable Cox regression models with multiple imputation and propensity score matching were used to adjust for confounding.

Results: Among 1341 eligible patients, 286 (21.3%) received early prophylactic anticoagulation. While crude in-hospital mortality was not significantly different between groups, patients receiving early anticoagulation had significantly lower in-hospital mortality (Log-rank P = 0.015). Multivariable Cox models confirmed a consistent protective association across imputed datasets (HRs ranging from 0.60 to 0.62; all P < 0.05). Subgroup analysis showed no significant interaction across age, gender, or comorbidity status. After 1:1 propensity score matching (n = 284 pairs), the mortality benefit persisted (HR = 0.51; 95% CI: 0.32–0.82; P = 0.005). Additional sensitivity analyses yielded similar results.

Conclusion: Early prophylactic anticoagulation within 24 hours of ICU admission was associated with reduced in-hospital mortality in patients with severe acute pancreatitis. These findings suggest potential benefits of early anticoagulation in this high-risk population and warrant further prospective validation.

Keywords: severe acute pancreatitis, early prophylactic anticoagulation, in-hospital mortality, critical care

Introduction

Severe acute pancreatitis (SAP) is a common and life-threatening condition of the digestive system, characterized by high morbidity, high complication rates, and considerable mortality.[1] Despite advancements in fluid resuscitation, infection control, and organ support, the prognosis of SAP remains poor—particularly in patients who develop sepsis or multiple organ dysfunction syndrome (MODS).[2,3] Thus, identifying effective therapeutic strategies to alter the disease trajectory of SAP remains a critical clinical need.

The pathophysiology of SAP involves complex interactions between systemic inflammation and coagulation abnormalities.[4] It has been demonstrated that the inflammatory response can cause endothelial injury, trigger tissue factor expression, and activate the coagulation cascade, leading to the formation of microthrombi.[5,6] These microvascular thrombi contribute to impaired perfusion and tissue hypoxia, which can in turn accelerate the onset of organ

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dysfunction.[7,8] This interplay between inflammation and coagulation is particularly pronounced in cases of SAP complicated by secondary infection or sepsis.[9,10] Consequently, there is growing interest in whether anticoagulation therapy might interrupt this vicious cycle by improving microcirculation and reducing thrombotic burden.

However, the role of anticoagulant therapy in SAP remains controversial. While some studies suggest that heparin and its derivatives may exert beneficial effects through anticoagulant, anti-inflammatory, and endothelial-protective mechanisms,[11,12] others caution against increased bleeding risk and point to inconsistent findings,[13,14] most of which stem from observational data. Indeed, several meta-analyses have yielded mixed results regarding the efficacy and safety of anticoagulants in acute pancreatitis, with some suggesting a benefit in preventing complications like splanchnic vein thrombosis, while effects on overall mortality remain debated.[15,16] Importantly, major international guidelines, including those from the United States[17] and Europe,[18] as well as the the 2019 International Guidelines for the Management of Pancreatitis[19] and the 2021 Guidelines from the Chinese Society of acute pancreatitis[20]—do not recommend prophylactic anticoagulation as a standard treatment for SAP, highlighting the lack of consensus and evidence in this area.

In light of this clinical uncertainty, the present study aimed to evaluate the impact of early prophylactic anticoagulation, administered within 24 hours of ICU admission, on clinical outcomes in patients with SAP. By focusing on early intervention rather than therapeutic anticoagulation, this study seeks to provide real-world evidence that may inform future strategies for the management of coagulation dysfunction in SAP.

Materials and Methods

Study Population

This study employed a retrospective cohort design utilizing data from the Medical Information Mart for Intensive Care IV (MIMIC-IV), version 3.1. The database contains de-identified health records from over 70,000 intensive care unit admissions at Beth Israel Deaconess Medical Center in Boston, Massachusetts, collected between 2008 and 2019.[21] Access to the dataset was granted through completion of the required data use agreement (Certification ID: 62432248, Zhao). Given the nature of the dataset—publicly accessible and anonymized—this study was exempt from informed consent requirements. The study protocol was submitted to the Institutional Review Board of The First Affiliated Hospital of Anhui Medical University, which waived the need for formal ethical approval. All procedures were carried out in accordance with established ethical standards.

Individuals included in this study were adults (aged 18 years or older) diagnosed with acute pancreatitis (AP), identified using relevant diagnostic codes from the International Classification of Diseases: ICD-9 code 577.0 and ICD-10 codes K85.90, K85.91, K85.92, and K85. From an initial cohort of 7509 patients with AP, several exclusion criteria were applied to ensure data completeness and consistency: (1) lack of ICU admission records (n = 5823); (2) multiple ICU admissions, with only the first admission considered (n = 253); (3) use anticoagulant agents for dialysis or treatment, not for prophylactic (n=58); (4) ICU length of stay under 48 hours (n = 34). After applying these criteria, 1341 patients remained for final analysis. The patient selection workflow is summarized in Figure 1. Follow-up began at the time of ICU admission and continued until hospital discharge, in-hospital death, or the last available record in the database. This study adheres to the reporting standards outlined in the STROBE statement.[22]

Expose and Outcomes

The primary exposure in this study was defined as the administration of prophylactic anticoagulation within 24 hours following ICU admission. Anticoagulant agents considered in this analysis included subcutaneous unfractionated heparin and enoxaparin, both used explicitly for prophylactic purposes. Warfarin was excluded due to its oral formulation, which is generally contraindicated in patients with severe acute pancreatitis who were often not allowed oral intake during early ICU care.

For heparin, only subcutaneous administration at a dose of 5000 units per injection was included, with verification based on medical orders issued within the first 24 hours of ICU entry. Any heparin use associated with dialysis or therapeutic intent was excluded from analysis. Enoxaparin usage was classified according to documentation available in the database, which clearly distinguished between prophylactic and therapeutic indications. Other anticoagulants such as

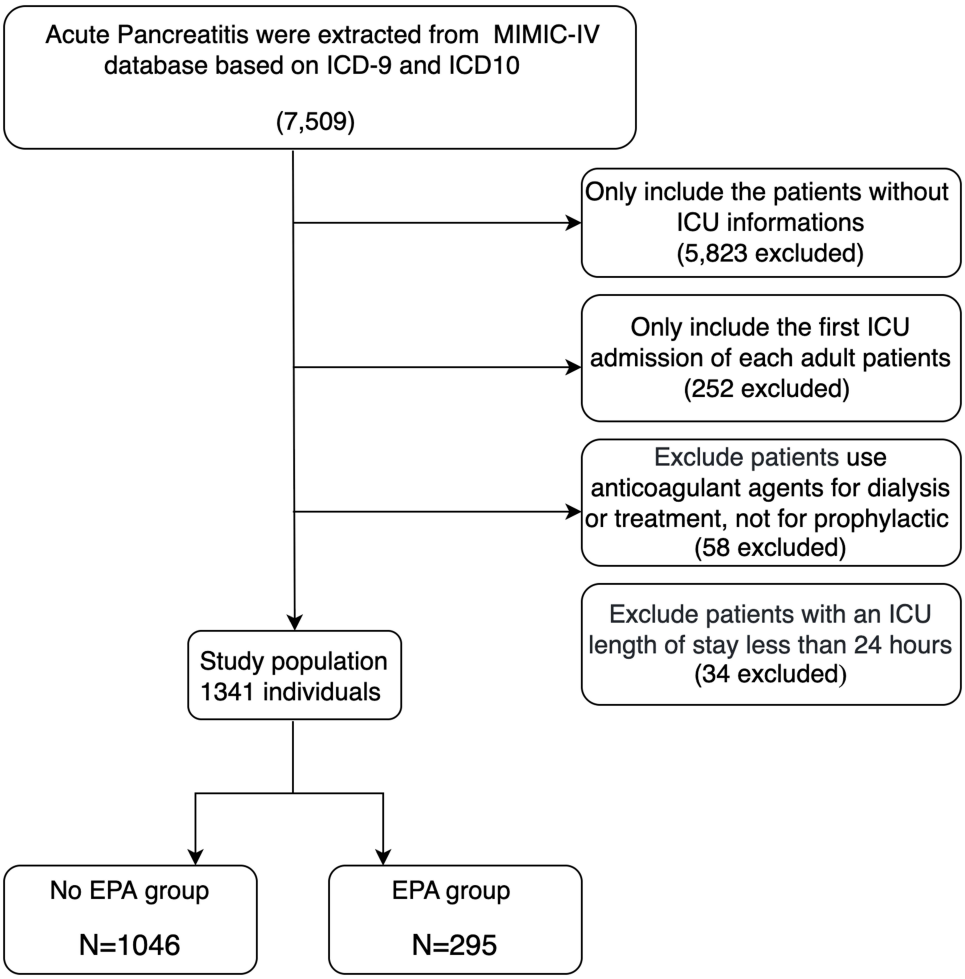

Figure 1 Flowchart of study population.

low molecular weight heparins (eg, dalteparin, tinzaparin) and thrombomodulin were not observed in the dataset and thus were not considered in the exposure definition.

The outcome was in-hospital mortality defined as death occurring during the hospital stay following ICU admission.

Data Extraction and Processing

Relevant clinical information was extracted from the MIMIC-IV database (version 3.1) through Structured Query Language (SQL) queries. Data management and processing were conducted using PostgreSQL and Navicat Premium to maintain data consistency and accuracy. Baseline variables were defined as those recorded within the first 24 hours following ICU admission. These included demographic data, vital signs, laboratory results, pre-existing comorbidities, severity scores, and therapeutic interventions. For vital signs and laboratory parameters, both the initial measurements upon ICU entry and the most extreme values within the first 24 hours were captured for analysis. This structured approach ensured that all variables relevant to evaluating the association between early prophylactic anticoagulation and in-hospital mortality among patients with severe acute pancreatitis were systematically collected.

Statistical Analysis

To address missing data and reduce bias without sacrificing statistical power, multiple imputation using chained equations (MICE) was performed under the assumption that data were missing at random (MAR).[23] All variables included in the main analysis, along with supplementary auxiliary variables, were utilized to construct five imputed

datasets. The imputed results were subsequently combined according to Rubin's rules to incorporate the uncertainty arising from the imputation process.[24]

Continuous variables were described as mean (standard deviation, SD) if normally distributed or median (interquartile range, IQR) when skewed. Categorical variables were presented as counts and percentages. Comparisons between groups were conducted using either the Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, depending on distribution normality, and chi-square or Fisher's exact tests for categorical variables.

The relationship between early prophylactic anticoagulation and in-hospital mortality was further evaluated using Cox proportional hazards regression models. Baseline covariates were chosen for inclusion in the multivariable models based on their clinical importance and demonstrated association with outcomes, as indicated by a change greater than 10% in effect estimates. To prevent multicollinearity among predictors, variance inflation factors (VIFs) were calculated, and variables with VIFs exceeding 10 were excluded to preserve model stability.[25] Four models were developed for analysis: Model 1 included no adjustments; Model 2 adjusted for demographic variables; Model 3 adjusted for clinically relevant covariates, including vital signs, laboratory results, pre-existing comorbidities, and severity scores, all selected based on the pre-specified criteria and Model 4 further included therapeutic interventions, all selected based on the pre-specified criteria. The specific variables incorporated in each model are detailed within the respective result tables. Kaplan-Meier survival curves were generated for the groups, and differences between the curves were assessed using the Log rank test.

To reduce potential confounding and selection bias, propensity score matching (PSM) was applied. For the matching procedure, the first imputed dataset obtained from multiple imputation was used for analysis. Propensity scores were estimated using a logistic regression model with early prophylactic anticoagulation as the exposure variable and baseline covariates as predictors. The covariates selected for the model were chosen for their established association with both treatment allocation and mortality in SAP, and included the variables used in our final multivariable model (Model 4), such as demographics, comorbidities, and the APACHE II score. Patients were matched in a 1:1 ratio using a nearest-neighbor algorithm without replacement, with a caliper width set at 0.2 standard deviations of the logit of the propensity score. Covariate balance between the matched groups was evaluated by calculating standardized mean differences (SMDs), with an SMD of less than 0.1 considered indicative of acceptable balance (Supplementary Figure 1). In addition to PSM, sensitivity analyses were performed using alternative propensity score-based approaches, including inverse probability of treatment weighting (IPTW), standardized mortality ratio weighting (SMRW), pairwise algorithmic (PA), and overlap weighting (OW) methods, to further validate the robustness of the findings.

Subgroup analyses were performed to evaluate the consistency of the association across various demographic and clinical strata. Additionally, sensitivity analyses were conducted using the unimputed dataset to assess the robustness of the findings against missing data handling. These analyses aimed to determine whether the results were consistent when missing values were excluded from the analysis.

A two-tailed *P*-value of less than 0.05 was regarded as statistically significant. Statistical analyses were carried out using R software (version 4.3.2; https://www.r-project.org) and the Free Statistics platform (version 2.1.1; Beijing, China; http://www.clinicalscientists.cn/freestatistics).

Result

Baseline Characteristics

Table 1 summarizes the baseline characteristics of the study population. Compared to the none early prophylactic anticoagulation group, patients in the early prophylactic anticoagulation group were significantly younger (mean age 56.0 vs 59.7 years, P < 0.001) and had higher heart rates (116.3 vs 110.8 bpm, *P* < 0.001) and respiratory rates (30.4 vs 28.6 bpm, P < 0.001). Additionally, patients in the early prophylactic anticoagulation group had significantly higher levels of creatinine (1.2 vs 1.0 μmol/L, *P* = 0.016) and total bilirubin (1.4 vs 1.0 μmol/L, *P* = 0.001). Comorbidity scores, such as the APACHE II and SOFA, were also higher in the early prophylactic anticoagulation group, with differences reaching statistical significance (*P* = 0.001 and *P* = 0.04, respectively). No significant differences were observed between the two groups in terms of gender, race, and several other clinical parameters.

Table 1 Baseline Characteristics of Study Population

Variables	No EPA (N = 1046)	EPA (N = 295)	*P*
Demographics			
Age, years	59.7 ± 16.3	56.0 ± 7.8	< 0.001
Gender, n (%)			0.871
Female	420 (40.2)	120 (40.7)	
Male	626 (59.8)	175 (59.3)	
Race, n (%)			0.329
White	679 (64.9)	178 (60.3)	
Black	113 (10.8)	34 (11.5)	
Others	254 (24.3)	83 (28.1)	
Vital signs			
HR, bpm	110.8 ± 22.4	116.3 ± 22.8	< 0.001
MAP, mmHg	62.6 ± 16.1	64.4 ± 18.4	0.093
RR, bpm	28.6 ± 6.9	30.4 ± 7.2	< 0.001
T, °C	37.5 ± 0.8	37.6 ± 0.8	0.022
Comorbidities			
CHF, n (%)	193 (18.5)	48 (16.3)	0.389
COPD, n (%)	234 (22.4)	51 (17.3)	0.059
DM, n (%)	345 (33)	94 (31.9)	0.718
Renal Disease, n (%)	182 (17.4)	52 (17.6)	0.928
Treatments, n (%)			
Mechanical ventilation	429 (41)	119 (40.3)	0.835
Vasopressors	280 (26.8)	86 (29.2)	0.417
RRT	117 (11.2)	56 (19)	< 0.001
Laboratory measurements			
HGB, g/dL	10.0 (8.5, 11.8)	10.7 (9.0, 12.4)	0.002
WBC, 10^9/L	13.1 (9.3, 19.4)	14.1 (10.5, 19.6)	0.022
PLT, 10^9/L	173.0 (120.0, 248.0)	154.0 (109.0, 217.0)	0.005
ALB g/dL	3.0 (2.5, 3.5)	2.9 (2.4, 3.5)	0.307
AG mmol/L	16.0 (13.2, 19.0)	17.0 (15.0, 21.0)	< 0.001
HCO_3^-, mmol/L	21.0 (18.0, 24.0)	19.0 (15.0, 22.0)	< 0.001
BUN, mmol/L	20.0 (13.0, 34.0)	19.0 (11.0, 38.2)	0.809
Cre, μmol/L	1.0 (0.7, 1.8)	1.2 (0.8, 2.3)	0.016
INR	1.3 (1.1, 1.6)	1.3 (1.2, 1.6)	0.437
PTT, s	31.4 (27.5, 40.0)	31.8 (27.7, 38.5)	0.872
TBL, μmol/L	1.0 (0.5, 2.8)	1.4 (0.7, 3.7)	0.001
Lac, mmol/L	2.0 (1.4, 3.7)	2.3 (1.5, 3.9)	0.223
Scoring systems			
CCI	4.0 (2.0, 6.0)	3.0 (2.0, 5.0)	0.046
APACHEII	43.0 (32.0, 59.0)	48.0 (36.0, 65.0)	0.001
SOFA	3.0 (2.0, 5.0)	4.0 (3.0, 5.0)	0.04
Outcomes			
In-hospital mortality, n (%)	115 (11)	28 (9.5)	0.46
Los_hospital, days	10.6 (5.8, 19.8)	12.9 (6.6, 25.0)	0.002

Abbreviations: EPA, early prophylactic anticoagulation; HR, Heart rate; MAP, mean arterial pressure; RR, Respiratory rate; T, Temperature; HGB, Hemoglobin; WBC, White blood count; PLT, Platelet count; ALB, albumin; AG, Anion gap; HCO_3^-, bicarbonate; BUN, Blood urea nitrogen; Cre, Creatinine; INR, International Normalized Ratio; PTT, Partial Thromboplastin Time; TBL, Total bilirubin; Lac, Lactate; RRT, renal replacement therapy; Vasopressors, including norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, dobutamine, and isoprenaline; CCI, Charlson Comorbidity Index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; Los, length of stay.

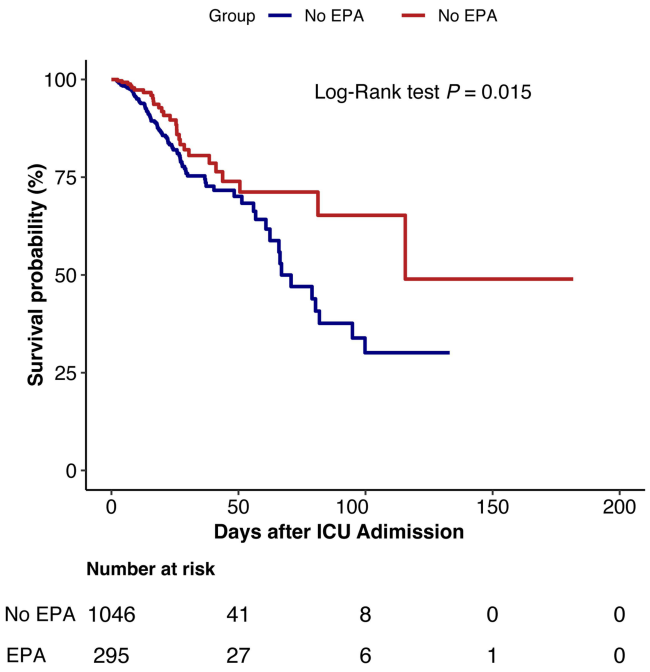

Figure 2 Kaplan–Meier survival curve of in-hospital mortality in AP patients across the early prophylactic anticoagulation admission or not.

Relationship Between Early Prophylactic Anticoagulation and In-Hospital Mortality

The Kaplan-Meier analysis indicated a significantly lower in-hospital mortality in patients who had used early prophylactic anticoagulation (Log rank test: P =0.015, Figure 2).

Multivariable Cox proportional hazards regression models (Table 2) consistently showed the protective effect of early prophylactic anticoagulation on in-hospital mortality. In Model 1, early anticoagulation was associated with a significant reduction in mortality (HR: 0.60, 95% CI: 0.40–0.91, P = 0.016). In Model 2 the HR was 0.61 (95% CI: 0.40–0.93, P = 0.022), maintaining the significant association. Model 3 and Model 4, both based on multiple imputed datasets, further adjusted for additional clinical and therapeutic factors. In Model 3, the HR was 0.64 (95% CI: 0.41–0.99, P = 0.048), and in Model 4, the HR remained 0.62 (95% CI: 0.40–0.96, P = 0.036), confirming that the protective effect of early prophylactic anticoagulation persisted even after comprehensive adjustments.

Subgroup analyses were conducted based on the confounders in model 4 (Figure 3). No significant interaction was observed in any of the subgroups (*P* for interaction > 0.05 for all). Specifically, in the subgroups defined by age and

Table 2 Association Between Early Prophylactic Anticoagulation and in-Hospital Mortality

	N	HR	95% CI	*P*
Model 1	1341	0.60	(0.4~0.91)	0.016
Model 2	1341	0.61	(0.4~0.93)	0.022
Model 3	1341	0.64	(0.41~0.99)	0.048
Model 4	1341	0.62	(0.4~0.96)	0.036

Notes: Model1: unadjusted. Model2: adjusted for Age, Gender, Race. Model3: adjusted for Age, Gender, Race, HGB, Lac, AG, HCO_3^-, INR, PTT, TBL, CHF, APACHEII. Model 4: adjusted for Age, Gender, Race, Hgb, Lac, AG, HCO_3^-, INR, PTT, TBL, CHF, APACHEII, Ventilation, Vasopressors, RRT.

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval.

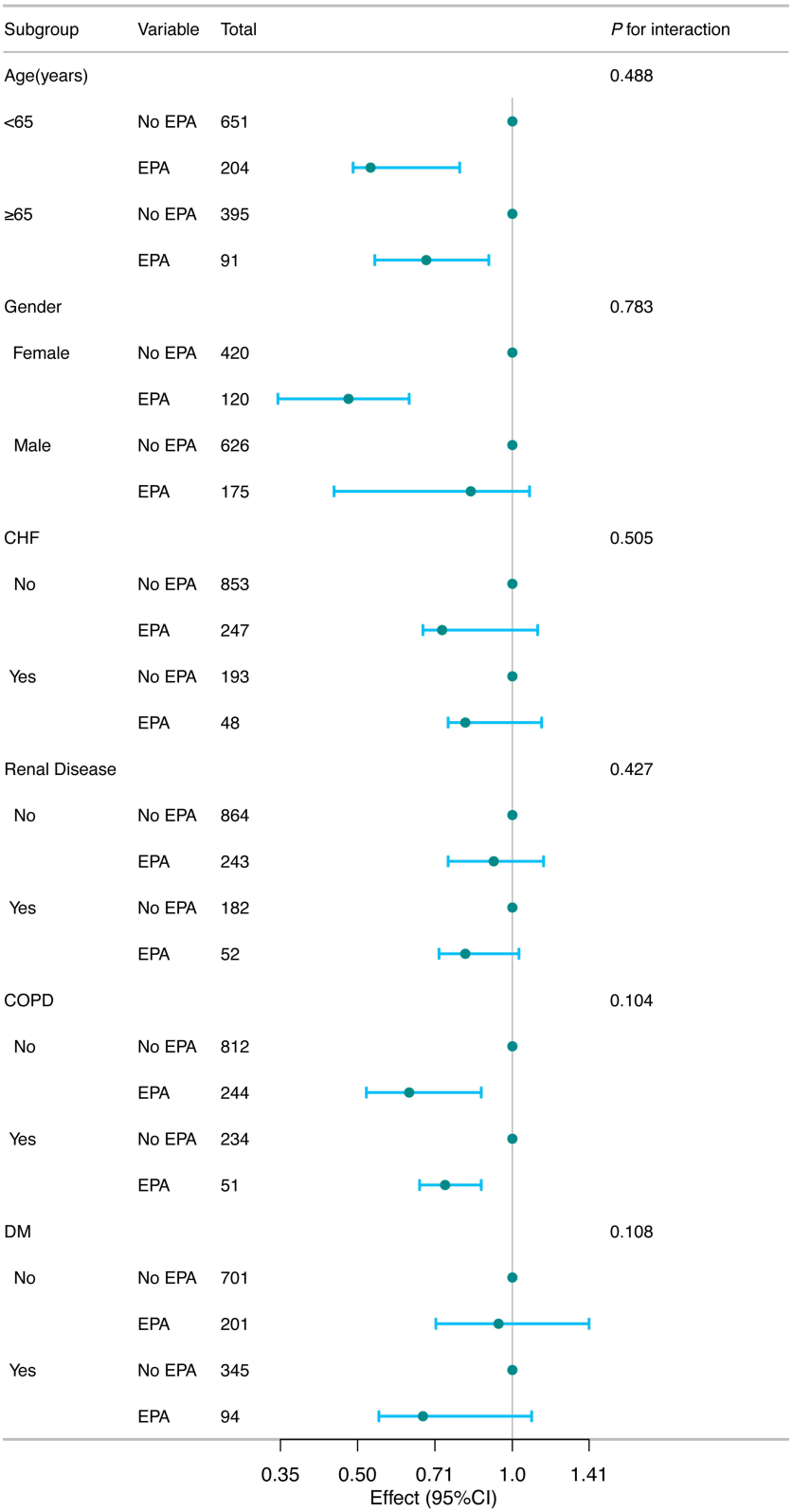

Figure 3 Forest plot illustrating the hazard ratios (HR) for in-hospital mortality in AP patients across subgroups of early prophylactic anticoagulation admission. Each stratification was adjusted for all covariates as model 4. Circles indicate OR, with horizontal lines indicating 95% CI. Hazard ratios were calculated for categories, with the no EPA admission as the reference.

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Table 3 In-Hospital Mortality Analysis with Different Models

Models	HR	95% CI	*P*
Propensity score matching	0.51	0.32~0.82	0.005
Propensity score adjusted	0.54	0.35~0.84	0.006
Propensity score IPTW	0.59	0.39~0.91	0.041
Propensity score SMRW	0.54	0.36~0.81	0.005
Propensity score PA	0.54	0.33~0.88	0.005
Propensity score Ow	0.55	0.31~1	0.007

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; IPTW, Inverse probability of treatment weighting; SMRW, Standardized mortality ratio weighting; PA, Pairwise algorithmic; OW, Overlap weight.

COPD status, the effect sizes remained consistent across these groups, suggesting no difference in the treatment effect between the subgroups.

Analysis with PSM Cohorts

After matching the patients based on propensity scores, 284 pairs were successfully paired, resulting in balanced baseline characteristics across both groups, as detailed in Supplementary Table 1. The standardized mean differences (SMD) were predominantly below 0.1, indicating that the groups were well-matched (Supplementary Figure 1). In the propensity score-adjusted model, the HR for in-hospital mortality was 0.54 (95% CI: 0.35–0.84, P = 0.006), which showed a clear protective effect of early prophylactic anticoagulation. Following propensity score matching as detailed in Table 3, the HR further improved to 0.51 (95% CI: 0.32–0.82, P = 0.005), reinforcing the robustness of these results after adjusting for baseline covariates. Additionally, sensitivity analyses using various weighted models, such as IPTW, SMRW, and other approaches (PA and OW), all showed consistent findings, with HRs ranging from 0.51 to 0.59, confirming a significant reduction in in-hospital mortality in the anticoagulation group.

Sensitivity Analysis

To evaluate the robustness of the association between prophylactic anticoagulation and in-hospital mortality, sensitivity analyses were performed using unimputed data (Supplementary Table 2) and by adjusting the caliper values for PSM at 0.1 and 0.3 (Supplementary Tables 3 & 4). This approach was undertaken to assess the impact of different matching thresholds and the handling of missing data on the overall findings. The results from these sensitivity analyses were consistent with the primary findings, suggesting the robustness of the association.

Discussion

This study highlights that early prophylactic anticoagulation significantly reduces in-hospital mortality in critically ill patients with SAP admitted to the ICU. Notably, patients in the early prophylactic anticoagulation group presented with more severe clinical conditions at baseline, as evidenced by higher APACHE II and SOFA scores. This created a confounding-by-indication bias, where the treatment's protective effect was masked in the unadjusted analysis because sicker patients were preferentially selected to receive anticoagulation. It was only after adjusting for these baseline covariates that a clear mortality benefit became apparent. After propensity score matching, the early prophylactic anticoagulation group showed a marked reduction in mortality (HR = 0.51, 95% CI: 0.32–0.82, P = 0.005), suggesting a significant benefit in this high-risk population. Sensitivity analyses further reinforced the consistency and robustness of these findings.

The findings of this study indicate that early administration of prophylactic anticoagulation therapy, including heparin and enoxaparin, was associated with a significant reduction in in-hospital mortality among patients with SAP, suggesting important clinical implications for the management of this high-risk population. SAP is often characterized by a profound systemic inflammatory response that may progress to sepsis and multiorgan failure.[26] The pathophysiology involves

a vicious cycle of inflammation and coagulation, often termed thrombo-inflammation. A key initiating event is endothelial injury, which leads to coagulation system activation, platelet aggregation, and microthrombus formation, ultimately resulting in microcirculatory dysfunction and organ hypoxia.[27–29] Our findings may be explained by the dual role of agents like heparin and enoxaparin, which act on both pathways of this cycle. Beyond their well-known anticoagulant properties, both agents possess significant non-anticoagulant effects that are highly relevant in SAP. These include potent anti-inflammatory actions, such as neutralizing pro-inflammatory cytokines like TNF-α and IL-6,[30,31] and inhibiting the activation of the complement system, a key driver of systemic inflammation.[32] Furthermore, heparins can protect the endothelial glycocalyx, preserving vascular barrier function and reducing further endothelial injury.[33] By simultaneously targeting the coagulation cascade to limit microthrombi and attenuating the systemic inflammatory response, early prophylactic anticoagulation may interrupt the cycle of thrombo-inflammation that leads to organ failure. These multifaceted mechanisms provide a plausible physiological explanation for the observed reduction in mortality and support the potential role of early prophylactic anticoagulation in the management of critically ill patients with severe pancreatitis.

A large body of research has examined the potential benefits of anticoagulation therapy in sepsis and critically ill patients, particularly the use of heparin in improving outcomes. Several observational studies and systematic reviews have suggested that heparin use may be associated with reduced mortality in sepsis, possibly through its anticoagulant, anti-inflammatory, and microcirculatory improvement effects. For example, a systematic review by Zarychanski et al[34] suggested that low-dose heparin was associated with a significant reduction in mortality in sepsis patients, attributed to its ability to inhibit coagulation and modulate immune responses.[35] Similarly, a meta-analysis by Fu et al found that heparin use was linked to a decrease in organ dysfunction and mortality in patients with severe sepsis and septic shock, potentially by reducing thrombin formation and alleviating endothelial damage.[36] These findings suggest that the benefits of heparin are not solely confined to thrombosis prevention but also involve complex immunomodulatory effects.

However, Allen et al have yielded inconsistent results, especially regarding anticoagulant therapy has not been shown to improve mortality or morbidity in severe sepsis, despite the link between inflammation and coagulation.[37] Furthermore, a randomized Phase III trial found that while low-dose heparin was beneficial in reducing venous thromboembolism in sepsis, it did not significantly improve survival rates or other clinical outcomes in patients with lung cancer, suggesting that the timing, dose, and patient population play a critical role in determining the success of anticoagulation therapy.[38]

Unlike previous studies that have evaluated therapeutic anticoagulation, which typically begins later in the disease course, our study specifically focused on early prophylactic anticoagulation administered within 24 hours of ICU admission. We excluded patients receiving anticoagulation for therapeutic purposes, making our approach distinct from studies that investigated anticoagulation initiated during later stages of SAP. By focusing on early, prophylactic anticoagulation, we emphasize the critical importance of timely intervention, aiming to prevent thrombosis and modulate systemic inflammation before disease progression increases the risks associated with therapeutic anticoagulation. This strategy not only aligns more closely with real-world clinical decision-making but also addresses the pressing need for early management in high-risk patients.[3,39] Our findings offer preliminary evidence supporting the potential clinical value of early, prophylactic anticoagulation in SAP patients, which contrasts with current guidelines that do not explicitly recommend anticoagulation for this population. By emphasizing the feasibility and safety of early intervention, we provide a novel perspective on expanding anticoagulation therapy in non-infectious severe inflammatory states, with the potential to significantly improve patient outcomes.

This study provides preliminary evidence supporting early prophylactic anticoagulation in patients with acute severe pancreatitis (SAP), but several limitations should be considered. First, the retrospective design limits the ability to establish causality and introduces potential selection and information biases, as the decision to administer anticoagulation was likely influenced by the severity of the disease and physician judgment. Second, our study relied on in-hospital mortality as the primary outcome, which, while clinically important, is an indirect measure of the treatment's effect on the pathophysiology of pancreatitis itself. We were unable to analyze dynamic changes in biomarkers that would provide more direct evidence of benefit. Additionally, the relatively small sample size may reduce the statistical power of the study, particularly in detecting differences in subgroups. The study also did not assess the long-term effects of

anticoagulation therapy, such as post-discharge survival rates or quality of life. Furthermore, the optimal anticoagulation regimen, including drug dosage, timing, and monitoring methods, was not explored in this study. Specifically, due to the limitations of the database, we could not reliably analyze the total duration or cumulative number of anticoagulant doses for each patient. Additionally, the scope of our subgroup analyses did not extend to specific stratification by the severity of renal impairment or other organ failure scores, which could help identify populations that benefit most from early anticoagulation. This remains an important area for future prospective investigation. While multiple imputation was applied to handle missing data in the Cox regression analysis, the PSM was performed using only a single imputed dataset. This decision was made due to the methodological and computational complexity associated with implementing and combining PSM across multiple imputed datasets, as standardized approaches for pooling matched results remain limited. As such, this may affect the robustness and generalizability of the matched analysis findings. Finally, the results are specific to ICU patients with acute severe pancreatitis, limiting the generalizability of the findings to broader populations. Future prospective studies are needed to validate these findings and optimize treatment strategies. Future prospective studies are needed to validate these findings and optimize treatment strategies.

Conclusion

Based on the findings of this retrospective analysis, early prophylactic anticoagulation within 24 hours of ICU admission was associated with a lower risk of in-hospital mortality in patients with SAP after adjusting for baseline confounders. While this study suggests a potential clinical benefit, it is important to note that this conclusion is based on an observational, clinical endpoint and does not constitute direct evidence of a change in the underlying disease process. The potential mechanisms, such as preventing micro thrombosis and modulating inflammation, require further exploration in future prospective studies, which are needed to confirm these findings and refine treatment strategies.

Data Sharing Statement

Data in the article can be obtained from mimic-IV database. (https://mimic.physionet.org/).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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