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# The influence of International Normalized Ratio on the prognosis of acute coronary syndrome patients in intensive care units: A retrospective analysis based on MIMIC-Ⅳ database

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## ABSTRACT

**Objective:** To investigate the infulence of the International Normalized Ratio (INR) on the prognosis of patients with acute coronary syndrome (ACS) admitted to intensive care units (ICUs).

**Methods:** A retrospective analysis was conducted on ACS patients from the MIMIC-Ⅳ 2.0 database, who were admitted to ICUs for the first time between 2008 and 2019 and met the study criteria. The association between the initial INR upon admission and the prognosis of ACS patients was assessed using a restricted cubic spline model at a continuous level. Based on the restricted cubic spline (RCS) curve, patients were stratified into three groups, and a multivariate Cox regression model was applied to analyze the effect of INR on the prognosis of ACS patients.

**Results:** When INR was ⩽1.0, the mortality risk gradually decreased with increasing INR levels; when INR ranged between 1.0 and 1.5, the mortality risk rose significantly with further elevation of INR; when INR exceeded 1.5, the mortality risk stabilized at a persistently high level, with minimal fluctuations observed despite substantial changes in INR values. Multivariate Cox regression analysis also demonstrated that patients in the medium (1.0-1.5) and high (>1.5) INR groups exhibited significantly higher mortality risks compared to those in the low (⩽1.0) INR group.

**Conclusions:** Fluctuations in the INR among patients with ACS admitted to the ICU are associated with an increased risk of mortality and adversely affect patient prognosis.

**KEYWORDS:** International Normalized Ratio; Acute coronary syndrome; Prognosis

**Summary**

**Question:** Is there an association between the International Normalized Ratio (INR) level and the prognosis of patients with acute coronary syndrome (ACS) in intensive care units ?

**Findings:** In patients with ACS admitted to the intensive care units, INR levels show a nonlinear association with mortality risk: lowest near INR 1.0, significantly increased between 1.0–1.5, and plateauing above 1.5. Maintaining INR close to 1.0 may improve short-term survival.

**Meaning:** This study comprehensively evaluates the complex relationship between admission INR values and the prognosis of ACS patients. It provides a more accurate and scientific basis for the management of anticoagulation therapy in ACS patients, while also offering new approaches for prognostic assessment in clinical practice.

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## 1. Introduction

Acute coronary syndrome (ACS), encompassing acute myocardial infarction and unstable angina, represents a severe cardiovascular emergency that poses significant global public health challenges due to its high incidence and mortality rates[1]. Despite advancements in medical technology and improvements in diagnostic and therapeutic protocols in recent years, the prognosis of ACS patients has shown improvements yet remains a primary cause of premature adult death[2,3]. Anticoagulation therapy, a vital component of the comprehensive management of ACS, aims to reduce thrombus formation and prevent cardiovascular adverse events[4]. The International Normalized Ratio (INR) plays a pivotal role in assessing coagulation function, guiding anticoagulant therapy, preventing thrombus development, and evaluating disease risks[5].

In previous studies, the relationship between INR levels and the prognosis of ACS patients remains controversial. Some studies have demonstrated that, compared with aspirin monotherapy, moderate- to high-intensity anticoagulant therapy (INR$\geqslant$2.0) can more effectively reduce the occurrence of cardiovascular events in patients with coronary artery disease[6]. Another study also pointed out that maintaining an INR within the range of 2-3 is more beneficial for the prognosis of ACS patients[7]. However, there are also studies suggesting that in post-myocardial infarction patients, maintaining an INR of 1.8 (1.4-2.2) with warfarin combined with low-dose aspirin did not provide clinical benefits beyond aspirin monotherapy[8]. Therefore, exploring the relationship between INR and survival rates among ACS patients is of great significance for optimizing treatment strategies for these patients.

The initial INR value upon admission for ACS patients not only reflects their coagulation-anticoagulation balance but also exerts profound impacts on subsequent treatment planning, drug dosage adjustments, and prognosis assessment. An INR value within the target range typically indicates that the patient has received appropriate anticoagulant therapy, whereas deviations from this range may increase the risks of bleeding or thromboembolism. Therefore, this study aims to comprehensively evaluate the intricate relationship between the INR value upon admission and the prognosis of ACS patients through a large-sample retrospective analysis, employing the restricted cubic spline (RCS) model. We aspire to provide more precise and scientific evidence for the management of anticoagulant therapy in ACS patients, while also introducing novel perspectives and methods for assessing their prognosis in clinical practice.

## 2. Methods

### *2.1. Data source*

This study utilized data from the MIMIC-Ⅳ 2.0 database, a publicly accessible resource that contains comprehensive clinical information on intensive care unit (ICU) patients from Beth Israel Deaconess Medical Center between 2008 and 2019[9,10]. The authors obtained access to the database after completing the required data research training provided by the associated institution. The data were sourced from the official Physionet website (https://

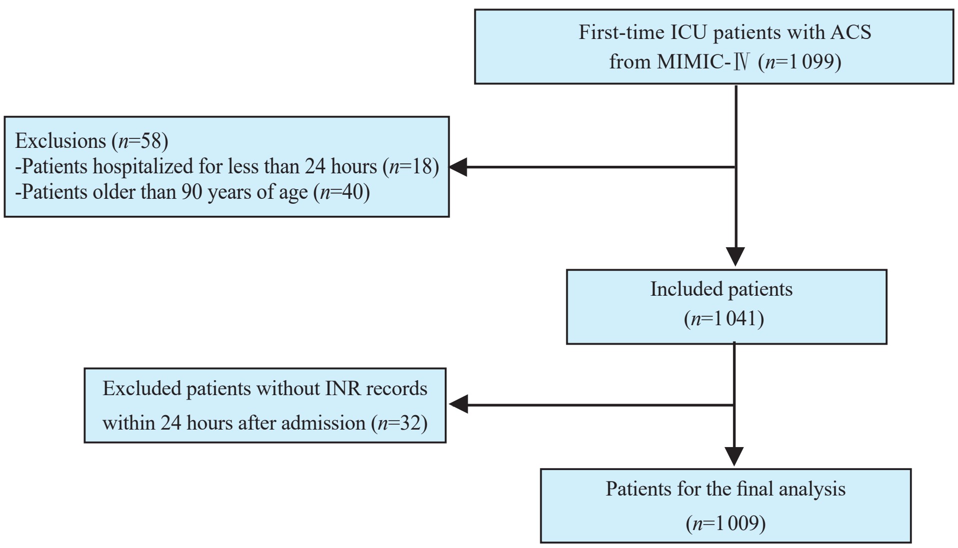


**Figure 1.** Patient disposition chart. ICU: intensive care unit; ACS: acute coronary syndrome; INR: International Normalized Ratio.

**Table 1.** Baseline variables and outcomes of patients with ACS.

| Variable | INR⩽1.0, *n*=321 | 1.0<INR⩽1.5, *n*=610 | INR>1.5, *n*=78 | *P* |
|---|---|---|---|---|
| Gender | | | | |
| Male | 237 (73.8%) | 446 (73.1%) | 55 (70.5%) | 0.838 |
| Female | 84 (26.2%) | 164 (26.9%) | 23 (29.5%) | |
| Admission type | | | | |
| Elective | 158 (49.2%) | 210 (34.4%) | 31 (39.7%) | <0.001 |
| Emergence | 93 (29.0%) | 312 (51.1%) | 41 (52.6%) | |
| Urgent | 70 (21.8%) | 88 (14.4%) | 6 (7.7%) | |
| Age, year | 65.0 (57.0, 71.0) | 67.0 (58.0, 76.0) | 69.5 (60.5, 81.0) | 0.002 |
| Weight, kg | 84.0 (72.5, 98.3) | 84.0 (73.0, 95.5) | 86.5 (75.3, 102.0) | 0.315 |
| White blood cell count, $\times10^9$/L | 8.8 (7.1, 11.0) | 9.4 (7.4, 12.8) | 11.0 (8.1, 15.5) | <0.001 |
| Hemoglobin, g/dL | 14.1 (12.6, 15.1) | 13.3 (11.6, 14.3) | 12.6 (10.7, 14.6) | <0.001 |
| Platelet count, $\times10^9$/L | 224.0 (188.0, 274.0) | 219.0 (182.0, 272.0) | 226.5 (176.5, 287.0) | 0.471 |
| Prothrombin time, sec | 11.1 (10.6, 11.3) | 12.9 (12.1, 13.9) | 22.3 (18.8, 32.7) | <0.001 |
| International Normalized Ratio | 1.0 (1.0, 1.0) | 1.2 (1.1, 1.2) | 2.1 (1.7, 3.0) | <0.001 |
| Potassium, mmol/L | 4.2 (3.9, 4.5) | 4.1 (3.8, 4.4) | 4.3 (3.8, 4.7) | 0.004 |
| Blood glucose, mg/dL | 124.0 (101.0, 165.0) | 131.0 (107.0, 176.0) | 151.0 (118.0, 190.8) | 0.002 |
| Heart rate, bpm | 76.5 (69.0, 85.0) | 79.0 (71.0, 88.0) | 83.0 (74.0, 94.8) | <0.001 |
| Systolic blood pressure, mmHg | 115.0 (108.0, 124.0) | 112.0 (105.0, 121.0) | 109.0 (99.0, 118.0) | <0.001 |
| Diastolic blood pressure, mmHg | 63.0 (55.8, 72.0) | 62.0 (56.0, 70.0) | 60.0 (56.0, 68.0) | 0.191 |
| Mean arterial pressure, mmHg | 78.0 (72.0, 85.0) | 77.0 (72.0, 83.0) | 75.0 (69.0, 80.8) | 0.027 |
| Respiratory rate, bpm | 18.0 (16.0, 20.0) | 18.0 (17.0, 21.0) | 19.5 (17.0, 23.0) | <0.001 |
| Temperature, ℃ | 36.7 (36.6, 36.9) | 36.7 (36.5, 37.0) | 36.7 (36.3, 37.0) | 0.147 |
| Oxygen saturation, % | 97.0 (96.0, 98.0) | 97.0 (96.0, 98.0) | 97.0 (96.0, 98.0) | 0.038 |
| Pulmonary disease | 50 (15.6%) | 117 (19.2%) | 18 (23.1%) | 0.213 |
| Liver disease | 11 (3.4%) | 36 (5.9%) | 11 (14.1%) | 0.001 |
| Renal disease | 47 (14.6%) | 80 (13.1%) | 17 (21.8%) | 0.116 |
| Hyperlipemia | 223 (69.5%) | 332 (54.4%) | 31 (39.7%) | <0.001 |
| Diabetes | 108 (33.6%) | 198 (32.5%) | 23 (29.5%) | 0.775 |
| Hypertension | 179 (55.8%) | 331 (54.3%) | 35 (44.9%) | 0.219 |
| Hospital length of stay, day | 5.0 (3.0, 8.0) | 6.0 (3.0, 10.0) | 6.5 (3.0, 12.0) | 0.004 |
| 30-day mortality | 11 (3.4%) | 64 (10.5%) | 26 (33.3%) | <0.001 |
| 90-day mortality | 17 (5.3%) | 84 (13.8%) | 28 (35.9%) | <0.001 |

mimic.physionet.org/). Therefore, ethical approval and the demand for informed consent were waived for our research.

## 2.2. Patient cohort

Figure 1 presents a flowchart detailing the selection process of the study population. From the MIMIC-Ⅳ 2.0 database, an initial cohort of 1 099 patients with a first-time admission to the ICU for ACS was identified. Patients were excluded based on the following criteria: hospital stay shorter than 24 hours, age exceeding 90 years or below 18 years, and the absence of INR data within the first 24 hours of admission. Consequently, a total of 1 009 patients were included in the final study cohort.

## 2.3. Data extraction

Data was extracted using structured query language. The extracted information encompassed patient demographics (gender, admission type, age, weight), admission and discharge timestamps, time of death, comorbidities (including lung disease, liver disease, kidney disease, hyperlipidemia, diabetes, and hypertension), as well as initial clinical biochemical measurements upon admission, specifically: white blood cell count, hemoglobin, platelet count, prothrombin time, INR, serum potassium, and blood glucose. Additionally, mean values of vital signs on the first day of admission were retrieved, including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate, temperature, and oxygen saturation.

## 2.4. Outcomes

The primary endpoints of this study were 30-day and 90-day all-cause mortality, while the secondary endpoint was the length of hospital stay.

## 2.5. Statistical analysis

A summary of the detailed information regarding missing data is provided in Supplementary Table 1, with all variables exhibiting less than 5% missingness. Given the compatibility of the R packages employed with missing values, we opted to retain the missingness in the data without imputation, thus preserving the authenticity of the dataset for practical applications.

During data analysis, we employed a diverse range of statistical methods tailored to the unique characteristics of various variables. For continuous variables that deviated from normal distribution, the Kruskal-Wallis test was utilized to assess intergroup differences, with medians and interquartile ranges serving as the primary statistics to accurately describe and report their distributions. Conversely, for continuous variables adhering to normal distribution, means and standard deviations were employed to encapsulate their central tendencies and dispersions, with analysis of Variance conducted for differential analysis. As for categorical variables, their distribution characteristics were directly presented in terms of counts and percentages, and the *Chi*-square test was applied to examine statistically significant differences among different categories.

Our study constructed a RCS model with 5 knots (corresponding to the 5th, 27.5th, 50th, 72.5th, and 95th percentiles) to evaluate the potential non-linear relationship between INR levels and patient outcomes, including length of hospital stay, 30-day mortality, and 90-day mortality. To adjust for potential confounders, multiple variables were included in the model, such as gender, age, admission type, blood glucose, hemoglobin, liver disease, lung disease, diabetes, renal disease, hyperlipidemia, and hypertension. Subsequently, we employed analysis of variance to perform non-linearity tests. The parameter on the spline curve corresponding to the INR value associated with the highest mortality risk is the one with the highest hazard ratio (HR). Additionally, we conducted stratified analyses to explore the non-linear relationship between INR values and 90-day mortality based on gender and age, with adjustments made using the same set of covariates.

Based on the graphical results of the RCS analysis, INR was categorized into three groups: low INR group (⩽1.0), medium INR group (1.1-1.5), and high INR group (>1.5). The associations between these INR groups and 30-day and 90-day mortality were analyzed using Kaplan-Meier survival analysis and Cox proportional hazards regression models, with HRs and 95% confidence intervals (*CIs*) calculated. To more precisely elucidate the independent effect of INR groups on outcomes, a multivariable-adjusted Cox regression model was also employed, controlling for the same set of covariates as in the RCS model, to account for potential confounders.

All statistical analyses were conducted using R software. Specifically, the "survival" package was utilized for Kaplan-Meier survival analysis and Cox proportional hazards regression modeling, while the "rms" package was employed for constructing RCS. A two-sided $P$ value of <0.05 was considered statistically significant.

## 3. Results

### *3.1. Baseline characteristics of ACS patients*

Among the 1 009 patients, 321, 610, and 78 patients were categorized into the low INR group, medium INR group, and high INR group, respectively. The baseline characteristics of the patients are presented in Table 1. Significant differences were observed across the three groups of patients in terms of age, white blood cell count, hemoglobin, prothrombin time, INR, potassium, blood glucose, heart rate, systolic blood pressure, mean arterial pressure, respiratory rate, oxygen saturation, prevalence of liver disease, prevalence of hyperlipidemia, length of hospital stay, 30-day mortality, and 90-day mortality. With increasing INR levels, there was a trend of increased age, white blood cell count, prothrombin time, blood glucose, heart rate, respiratory rate, prevalence of liver disease, length of hospital stay, and mortality rates, while hemoglobin, systolic blood pressure, mean arterial pressure, and prevalence of hyperlipidemia decreased. Detailed characteristics of the overall patient cohort are provided in Supplementary Table 2.

### *3.2. Correlation between INR and hospital stay in ACS patients*

An RCS model was constructed to estimate the association between INR and hospital stay at a continuous level. The results indicated that both the overall $P$-value and the nonlinear $P$-value of the model were >0.05, suggesting no significant correlation between INR and hospital stay in patients (Figure 2A).

### *3.3. Correlation between INR and mortality in ACS patients*

Our analysis using the RCS model revealed a significant nonlinear relationship between INR and 30-day as well as 90-day mortality rates among ACS patients (nonlinear $P<0.05$). Specifically, this nonlinear relationship manifested as follows: When INR levels were below or equal to 1.0, the mortality risk gradually decreased with increasing INR. However, within the range of 1.0 to 1.5, the mortality risk increased with further elevation of INR. Beyond an INR of 1.5, the mortality risk stabilized, no longer fluctuating significantly with marked changes in INR (Figures 2B and 2C).

Based on the characteristics of the RCS curve, patients were stratified into three groups: low INR group (⩽1.0), medium INR group (1.0-1.5), and high INR group (>1.5). The survival rates of patients in each group were presented in Kaplan-Meier curves (Figures 3A and 4A). Compared to the low INR group, both the medium and high INR groups exhibited higher mortality rates. Specifically, the 30-day mortality rates were 3.4% versus 10.5% ($P<0.001$) and 3.4% versus 33.3% ($P<0.001$), respectively, while

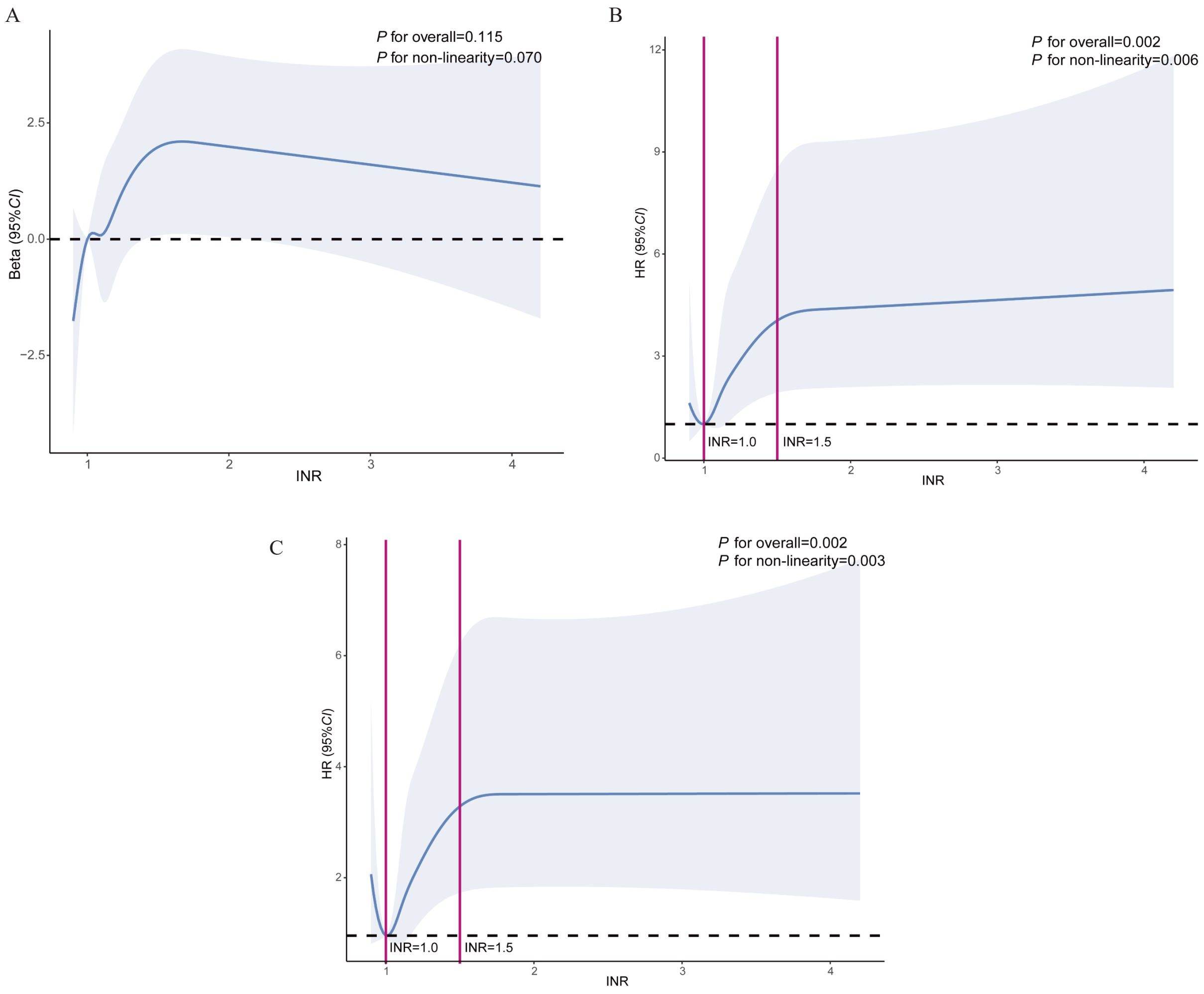


**Figure 2.** Nonlinear relationships between INR levels and clinical outcomes in patients with ACS, analyzed using RCS with five knots. (A) Association between INR and hospital length of stay; (B) Association between INR and 30-day all-cause mortality; (C) Association between INR and 90-day all-cause mortality. The blue solid curve represents predicted values, with the shaded area indicating 95% confidence intervals. The reference point is set at the nadir of the solid curve. Models were adjusted for: gender, age, admission type, blood glucose, hemoglobin, liver disease, pulmonary disease, diabetes, renal disease, hyperlipidemia, and hypertension. RCS: restricted cubic splines.

the 90-day mortality rates were 5.3% versus 13.8% ($P$<0.001) and 5.3% versus 35.9% ($P$<0.001).

A multivariate Cox proportional hazards regression model was employed to further analyze the relationship between INR groups and mortality rates. Using the low INR group as the reference, the HRs for the medium INR group at 30 days and 90 days were 2.25 (95% *CI* 1.16-4.36, $P$<0.05) and 1.83 (95% *CI* 1.06-3.15, $P$<0.05), respectively (Figure 3B and 4B). This indicates that compared to the low INR group, the medium INR group experienced a 125% and 83% increase in the risk of 30-day and 90-day mortality, respectively. Notably, the high INR group exhibited even higher mortality risks, with HRs of 4.92 (95% *CI* 2.30-10.50, $P$<0.001) and 3.36 (95% *CI* 1.75-6.45, $P$<0.001) for 30-day and 90-day mortality, respectively (Figure 3B and 4B). This translates to a 392% and 236% increase in the risk of 30-day and 90-day mortality, respectively, compared to the low INR group.

We conducted stratified analyses to evaluate the impact of gender and age on potential variations in the observed effects. A nonlinear relationship between INR and 90-day mortality was consistently identified across different gender and age subgroups (Figure 5a and 5b). Notably, this association was more pronounced among female patients and elderly patients with ACS.

## 4. Discussion

INR, as a crucial indicator of coagulation function, directly reflects the balance between coagulation and anticoagulation within the body[11]. In patients with atrial fibrillation, maintaining a higher INR level can more effectively prevent the occurrence of

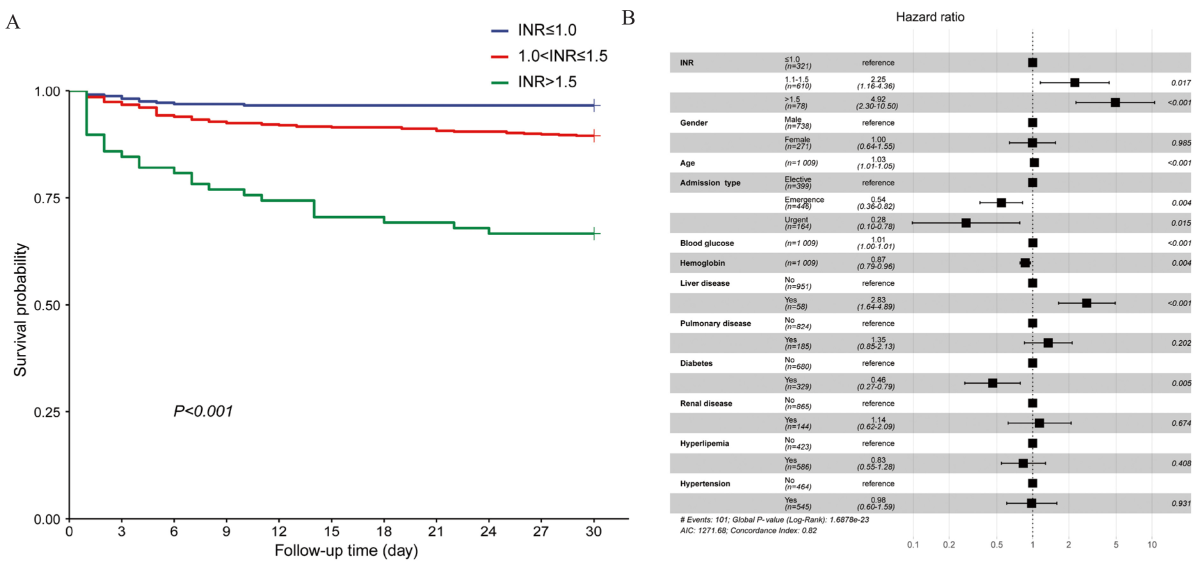


**Figure 3.** (A) The Kaplan-Meier curve shows the adjusted 30-day all-cause mortality of the three INR groups. (B) The adjusted Cox hazard regression model shows the relationship between each INR group and the 30-day all-cause mortality.

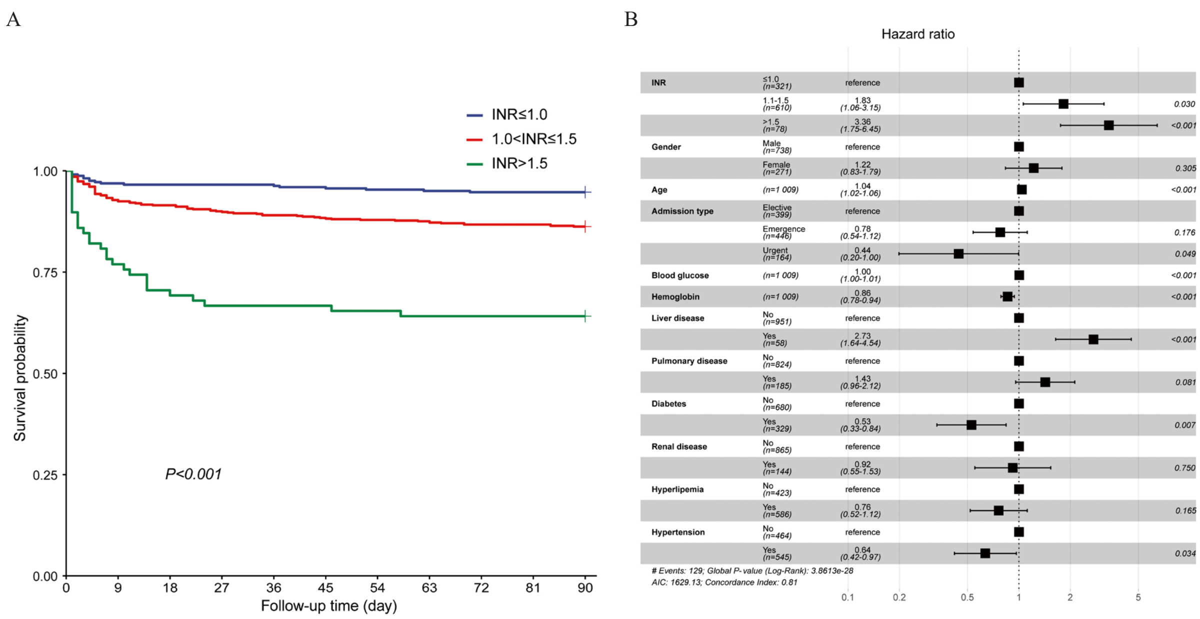


**Figure 4.** (A) The Kaplan-Meier curve shows the adjusted 90-day all-cause mortality of the three INR groups. (B) The adjusted Cox hazard regression model shows the relationship between each INR group and the 90-day all-cause mortality.

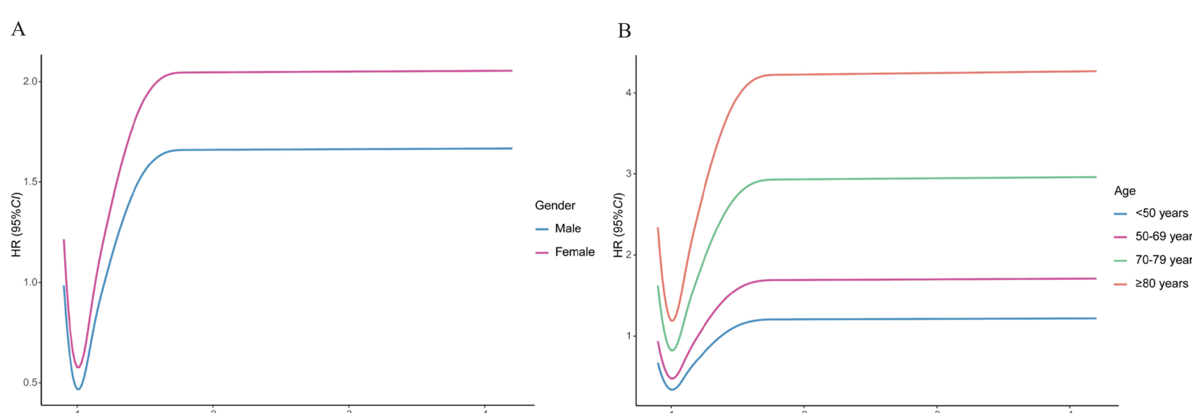


**Figure 5.** The restricted cubic spline analysis with five knots was performed to explore the nonlinear relationship between INR levels and 90-day all-cause mortality among patients with ACS on a continuous scale. (A) gender; (B) age.

thromboembolic events[12]. Similarly, patients who have undergone mechanical valve replacement require long-term anticoagulation therapy and maintenance of a higher INR level due to the potential for thrombosis associated with mechanical valves[13,14]. However, there remains some controversy regarding anticoagulation therapy in ACS patients. A randomized study has shown that aspirin combined with warfarin can improve the overall outcomes of ACS patients compared to aspirin alone[15]. Nevertheless, other studies have found that anticoagulation therapy after acute myocardial infarction does not reduce mortality or the incidence of reinfarction[16,17].

The restricted cubic spline model serves as a flexible and powerful statistical tool that demonstrates complex nonlinear relationships between continuous variables by partitioning data into multiple intervals and applying a smooth fit using cubic polynomials within each interval[18,19]. In this study, we explored the relationship between INR and all-cause mortality in ACS patients. Through a retrospective analysis of 1 009 ACS patients, we identified a significant nonlinear association between INR and survival rates among these patients. Specifically, when INR levels were below or equal to 1.0, the risk of mortality decreased as INR increased. At excessively low INR levels, ACS patients exhibit a hypercoagulable state and an increased risk of thrombosis, which may contribute to their relatively higher mortality risk[20]. As INR rose to between 1.0 and 1.5, the risk of mortality significantly increased, whereas further elevations in INR above 1.5 led to a stabilization in mortality risk, albeit at a persistently high level.

Studies have indicated that for myocardial infarction patients, the clinical benefits achieved through a fixed low-dose combination of warfarin and low-dose aspirin are not superior to those of aspirin monotherapy[21]. Among patients after cardiac arrest, the risk increases when the INR exceeds 1.2. Studies have demonstrated a positive correlation between elevated INR and 30-day, 90-day, 1-year, and in-hospital all-cause mortality (with hazard ratios ranging from 1.44 to 1.46), indicating that high INR values independently predict mortality events[22]. These findings align with our research outcomes. The subgroup analysis based on the RCS curve suggests that the mortality risk in the intermediate INR group, with a median INR of 1.2 (IQR: 1.1, 1.2), was significantly higher than that in the low INR group, which had a median INR of 1.0 (IQR: 1.0, 1.0). The results of the multivariate Cox regression analysis also indicate that compared to the low INR group, the 30-day and 90-day mortality risks in the intermediate INR group increased by 125% and 83%, respectively. Another study has indicated that adjusting the dose of anticoagulants to achieve an INR greater than 2 helps prevent reocclusion after fibrinolysis and recurrent ischemic events in patients with ST-segment elevation myocardial infarction[23–25]. However, our study reveals that in the high INR group, with a median INR of 2.1 (IQR: 1.7-3.0), patients experienced a higher mortality risk compared to both the low and intermediate INR groups. This discrepancy may stem from the fact that excessively high INR levels can increase the incidence of major bleeding events, thereby adversely affecting patient prognosis[17,18].

The stratified analysis revealed the presence of a nonlinear relationship between INR and 90-day survival rates among both male and female ACS patients across different gender groups, albeit this relationship was more pronounced in female patients. The anticoagulant effect of estrogen contributes to reducing the incidence of cardiovascular diseases, particularly atherosclerotic cardiovascular diseases[26]. However, post-menopause, when estrogen levels decline in female patients, the risk of ACS rapidly increases[27,28]. Variations in estrogen levels within females may influence the balance between coagulation and anticoagulation systems, thereby accounting for the more significant nonlinear relationship observed between INR and mortality in ACS patients of this gender. Regarding age-based subgroups, the nonlinear relationship between INR and short-term survival rates was more evident in ACS patients aged 70 and above. With advancing age, particularly among elderly ACS patients, there is a general decline in physiological functions, including reduced hepatic and renal function as well as impaired drug metabolism[29]. This physiological decline complicates and renders unpredictable the patients' response to anticoagulant medications. Consequently, even subtle variations in INR levels may have more pronounced effects on elderly patients, directly impacting their survival rates. These findings underscore the importance of considering gender and age factors when devising treatment strategies, aiming for more individualized INR management and optimized treatment outcomes.

Several limitations of this study should be acknowledged. Firstly, the data utilized in this study is confined to a single medical center's database, limiting its ability to comprehensively capture the diversity and complexity of ACS patients globally. Due to the selective nature of the sample, the generalizability and applicability of the findings may be impacted when extrapolating them to broader patient populations with varying geographical regions, racial compositions, socioeconomic conditions, or healthcare service levels. Secondly, despite controlling for multiple potential confounding factors through a multivariate Cox regression model, there may still be unrecognized or inadequately controlled confounding variables that could influence the results. Lastly, INR is a dynamic indicator, subject to fluctuations based on patients' treatment responses, disease progression, and medication adjustments. This study primarily grouped patients based on their INR levels at admission, failing to comprehensively reflect the impact of INR's dynamic changes throughout the disease course on mortality. Future research could consider incorporating continuous monitoring data of INR to more accurately assess its relationship with mortality.

In conclusion, this study has uncovered a nonlinear relationship between the INR level at admission and prognosis in patients with ACS admitted to the ICU. Specifically, when INR⩽1.0, the risk of death decreases with increasing INR; within the range of 1.0-1.5, the risk of death significantly rises; and beyond 1.5, the risk of death plateaus. Multivariable Cox regression analysis reveals that compared to the low INR group (⩽1.0), patients in the medium INR group (1.0-1.5) and high INR group (>1.5) exhibit significantly elevated risks of 30-day and 90-day mortality. These findings suggest that maintaining INR levels close to 1.0 in ACS patients may help reduce the risk of death. INR can serve as an important indicator for predicting short-term prognosis, providing a reference for setting anticoagulation therapy targets.

## Conflict of interest statement

The authors report no conflict of interest.

## Funding

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## Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The data were available on the MIMIC-Ⅳ website at https://mimic-iv.mit.edu/.

## Authors' contributions

YXX and JYS were responsible for formulating the research plan, collecting data, and writing the first draft of the paper. YG and YS assisted with the research design and data collection. JX, YFZ, and HML conducted the statistical analysis. XLM assisted in the revision of the paper and data confirmation. MYZ participated in data interpretation and paper revision. All authors have read and approved the final version of the paper.

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