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ORIGINAL RESEARCH

The Mediating Effect of Intracranial Hemorrhage Status on the Relationship between the INR and Mortality in Patients with Ischemic Stroke

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ABSTRACT

Introduction: The international normalized ratio (INR) is a biomarker of coagulopathy. The objective of this study was to assess the relationship between the INR and clinical outcomes in patients with large vessel occlusion (LVO) stroke who received endovascular therapy.

Methods: The RESCUE BT trial was a multicenter, randomized, double-blind, placebo-controlled clinical trial involving 948 stroke patients from 55 centers across China. We extracted INR data and related data from the BT database, with outcome measures comprising intracranial hemorrhage (ICH) and 90-day mortality. Logistic regression analysis was conducted to examine the associations between the INR and clinical outcomes in the entire patient cohort and across different stratified subgroups.

Results: A total of 885 patients met the study criteria, with 672 exhibiting a normal INR and 213 showing an elevated INR. Multivariable analysis indicated that an elevated INR was linked to an increased risk of ICH (OR 1.65, 95% confidence interval CI 1.17–2.33, P =0.005) and 90-day mortality (OR 1.78, 95% CI 1.17–2.70, P =0.007). Mediation analysis indicated that the association between the INR and 90-day mortality risk was partially mediated by ICH status, with the mediation effect contributing 11.4% to the overall relationship. Subgroup analyses revealed no significant differences between the different subgroups (P for interaction > 0.05). In patients receiving tirofiban, an elevated INR was more strongly associated with an increased 90-day mortality rate (OR 7.75, 95% CI 1.42–42.33, P =0.018).

Conclusion: Our findings underscore the critical importance of INR monitoring in patients with LVO stroke undergoing endovascular treatment (EVT). The association between the INR and 90-day mortality was mediated through

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ICH status. The use of tirofiban strengthened the associated between an elevated INR and a higher 90-day mortality rate. These insights offer valuable guidance for optimizing patient outcomes. ***Trial Registration***: URL: http://www.chictr.org.cn; ChiCTR-INR-17014167.

Keywords: International normalized ratio; Endovascular treatment; Stroke; Tirofiban

Key Summary Points

Why carry out this study?

Large vessel occlusion (LVO) stroke is a significant cause of disability and mortality, with coagulation function playing a crucial role in its progression and outcomes. As a key indicator of coagulation function, the international normalized ratio (INR) is particularly important in this context.

The hypothesis of this study is that an elevated INR is associated with an increased risk of intracranial hemorrhage (ICH) and 90-day mortality in patients who received endovascular treatment (EVT), with this relationship being more pronounced when tirofiban was used.

What was learned from the study?

The study suggested that an elevated INR is associated with increased 90-day mortality.

The impact of the INR on 90-day mortality is mediated through ICH status.

Further analysis suggests that the use of tirofiban, in conjunction with an elevated INR, is more likely to result in a higher 90-day mortality rate.

INTRODUCTION

Large vessel occlusion (LVO) stroke is a life-threatening illness with high mortality and disability rates. Endovascular treatment (EVT) is the standard treatment for LVO stroke because it provides safe and rapid reestablishment of blood flow, resulting in more favorable clinical outcomes [1–5]. However, even with improvement in blood flow, patients still experience poor outcomes, and identifying variables that influence therapeutic outcome is necessary to improve treatment and prognosis [6].

The international normalized ratio (INR) is an important biomarker that is widely used to assess patients' coagulation status and risk of bleeding, particularly in patients on anticoagulant therapy [7, 8]. An increase in the INR is associated with adverse events such as hemorrhagic events and mortality in several clinical settings, including aneurysms, trauma, and anticoagulant therapy [9–11]. Coagulation markers have been reported to affect the incidence and prognosis of ischemic stroke [12–15]. An elevated INR may occur in a hypercoagulable state or in anticoagulant therapy, as in the case of ischemic stroke. These factors not only influence thrombus formation and stability but also increase the risk of hemorrhagic transformation. However, the impact of the INR on clinical outcomes in ischemic stroke patients with EVT remains unclear. An elevated INR also results in impaired functional outcomes and an increased likelihood of death [16, 17]. Additionally, some studies have indicated that an elevated INR does not significantly impact the overall prognosis of patients after EVT [18, 19].

A multicenter, randomized, double-blind, placebo-controlled study conducted at 55 testing centers in China, the RESCUE BT trial [20], has yielded a detailed dataset addressing this question. The trial has 948 stroke patients and is the only one designed to evaluate the prognostic value of the INR in LVO ischemic stroke patients after receiving EVT. In addition, a separate cohort was used to evaluate whether the prognostic influence of the INR differed among patients receiving tirofiban and those who did not. Focusing on two essential outcomes, intracranial hemorrhage (ICH) and 90-day mortality, this study attempts to clarify the predictive role of INR values in adverse clinical outcomes.

The aim of this study was to determine whether the risk of poor outcomes in patients

with LVO undergoing EVT differs according to the INR and to determine whether a higher INR is associated with a greater risk of adverse events, including ICH, and mortality rates. Our focus was to investigate whether ICH status might mediate the association between the INR and 90-day mortality. Multivariable and subgroup analyses were conducted to enable the establishment of the extent to which these associations are consistent across various cohorts of patients and clinical settings, allowing for an exploration of the impact of the INR on relevant outcomes in patients who used tirofiban.

METHODS

Study Participants

From October 10, 2018, to October 31, 2021, investigators conducted the RESCUE BT trial, which was a randomized, double-blind, placebo-controlled, multicenter study. The aim of that trial was to assess the efficacy and safety of intravenous tirofiban in patients with acute ischemic stroke (AIS) due to anterior circulation LVO who were treated with EVT within 24 h of symptom onset. In a study involving 948 AIS patients with occlusions in the internal carotid artery (ICA) or the M1/M2 segment of the middle cerebral artery (MCA), participants were randomly allocated at a 1:1 ratio to receive either intravenous tirofiban or a placebo before undergoing EVT. The patient selection criteria and trial outcomes have been previously described [20]. As part of the present study, we excluded additional patients, including: (1) those lacking INR data upon admission; (2) those with an INR less than 0.8 upon admission; and (3) those who were not diagnosed with ICH within 48 h and did not have American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASTIN/SIR) data derived via digital subtraction angiography (Fig. 1).

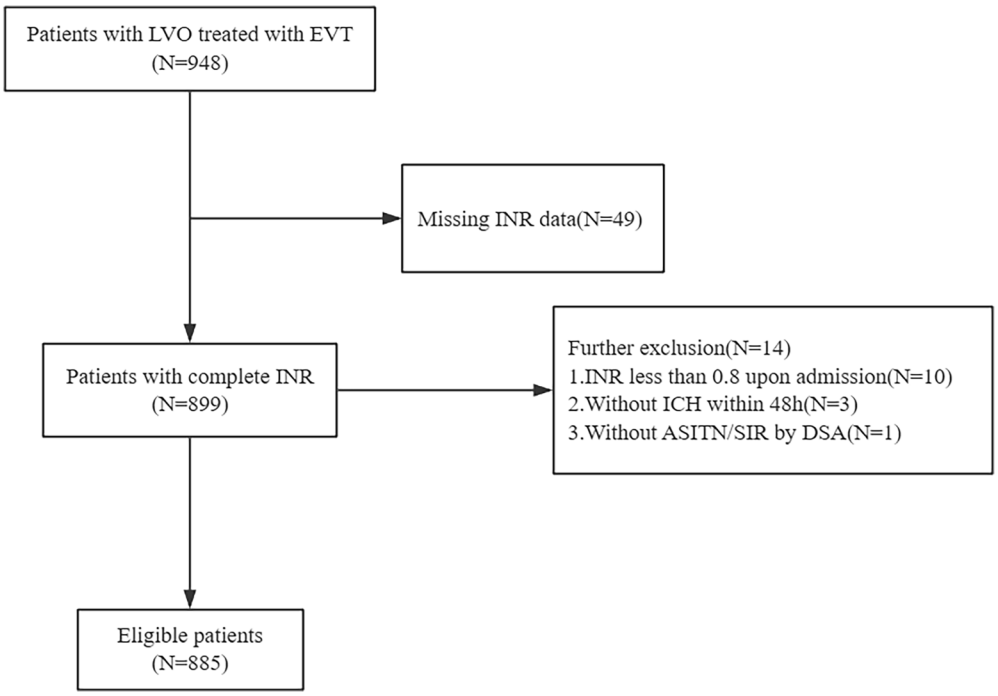

Fig. 1 Flow chart. *EVT* endovascular treatment, *ICH* intracranial hemorrhage, *INR* international normalized ratio, *LVO* large vessel occlusion

Ethical Approval

The Ethics Committee of Xinqiao Hospital, Army Medical University, along with ethics committees from all participating centers (See Supplementary Material), approved the study. Written informed consent was obtained from all patients or their authorized representatives. This study was conducted in accordance with the Declaration of Helsinki and local regulations. Informed consent was obtained from all the subjects or their legal representatives before the study.

Data Collection

During the enrolment phase, demographic data, vascular risk factors, baseline National Institutes of Health Stroke Scale (NIHSS) scores, workflow metrics, and treatment details were prospectively recorded. The RESCUE-BT imaging core laboratory conducted a centralized evaluation of all the imaging data. The target occlusion was located using admission CT or MR angiography and categorized as either the ICA or the M1 and M2 segments of the MCA. Ischemic damage was evaluated using the Alberta Stroke Program Early CT Score (ASPECTS). Ischemic strokes were classified into three subtypes on the basis of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria: large artery atherosclerosis (LAA), cardioembolism (CE), and other (strokes due to other specific causes or undetermined causes) [21]. The criteria used to grade collateral circulation were previously outlined by the ASTIN/SIR [22]. The Thrombolysis in Cerebral Infarction (TICI) scale was used to indicate substantial, near-complete, or complete reperfusion on the basis of the final angiogram [23].

The INR was recorded upon admission, with the normal range defined as 0.8–1.1. Elevated INR was defined as > 1.1, on the basis of standard laboratory cut-off values for abnormal elevation.

Definitions of Outcomes

The main focus was on all-cause mortality within 90 days. The secondary outcomes included ICH and symptomatic ICH (sICH), both of which were evaluated according to the Heidelberg criteria [24]. ICH was defined as any radiographically confirmed hemorrhage detected on follow-up imaging within 48 h post-EVT, including both symptomatic and asymptomatic hemorrhages, with sICH defined as the presence of ICH accompanied by a clinical deterioration of 4 or more points on the NIHSS score.

Statistical Analysis

Descriptive statistics, presented as counts (percentages) for categorical variables and medians with interquartile ranges (IQRs) for continuous variables, were used to summarize patient characteristics and clinical outcomes for both groups. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, whereas continuous variables were compared using the Student's t test or the Mann–Whitney U test, as appropriate.

To evaluate the relationships between an elevated INR and clinical outcomes, a multivariable mixed logistic regression model was used. Covariates for the multivariable analysis were chosen on the basis of published literature and established pathophysiological mechanisms, including sex, age, hypertension status, atrial fibrillation status, anticoagulant use history, baseline NIHSS score, baseline ASPECTS, expanded TICI (eTICI) grade, and onset-to-puncture time. Potential nonlinear relationships between the INR and adverse functional outcomes were examined using restricted cubic splines (RCSs). A mediation analysis was conducted to assess the extent to which ICH status influenced the link between the INR and 90-day mortality. Subgroup analyses were performed to assess potential variations among specific subgroups.

For all the statistical analyses, P values < 0.05 were considered to indicate statistical

significance. R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analyses.

RESULTS

Baseline Characteristics

Among the 885 randomized patients, 672 had normal INR values, whereas 213 had elevated INR values. Baseline characteristics stratified by INR elevation status are summarized in Table 1. The median (IQR) age was 67 (57–74) years, the median systolic blood pressure was 145 (130–160) mmHg, the median NIHSS score was 16 (12–19), and the median ASPECTS score was 8 (7–9). The baseline data revealed that patients in the elevated INR group were more likely to have a history of atrial fibrillation than were those in the normal INR group (49.8% vs. 28.0%, $P < 0.001$) and were more likely to be on anticoagulant therapy at home (17.8% vs. 4.3%, $P < 0.001$).

Associations with Outcomes

No differences were observed between the two groups in terms of functional independence at 90 days, whether measured by a modified Rankin score (mRS) score of 0–2 or 0–3 (44.6% vs. 48.7%, P =0.301) (60.1% vs. 64.3%, P =0.269; Table 1). Compared with patients with a normal INR, those with an elevated INR experienced higher rates of sICH (12.2% vs. 6.8%, P =0.013), increased all-cause mortality within 90 days (23.5% vs. 14.3%, P =0.002) (Table 2), and a greater incidence of ICH (41.3% vs. 28.3%, $P < 0.001$) (Table 3).

After adjusting for confounding factors, including sex, age, hypertension status, atrial fibrillation status, anticoagulant use history, baseline NIHSS score, baseline ASPECTS, eTICI grade, and onset-to-puncture time, both continuous and categorical variables were analyzed to assess the relationships between the INR and clinical outcomes. According to our results, when the INR was analyzed as a continuous variable, it remained significantly associated with 90-day all-cause mortality (OR 4.34, 95% confidence interval CI 1.79–11.77, P =0.003; Table 2) and the risk of developing ICH (OR 2.29, 95% CI 1.11–5.19, P =0.034; Table 3) after adjusting for the aforementioned confounding factors, but it was not associated with the risk of developing sICH (OR 1.42, 95% CI 0.39–3.59, P =0.513; Table S1). When the INR was analyzed as a categorical variable, after adjusting for confounding factors, patients with an elevated INR had significantly greater 90-day all-cause mortality risk (OR 1.78, 95% CI 1.17–2.70, P =0.007) and increased odds of developing ICH (OR 1.78, 95% CI 1.17–2.70, P =0.007). However, the association between the INR and sICH risk was not statistically significant (OR 0.61, 95% CI 0.35–1.06, P =0.071; Table S1). In the RCS regression, although the risk of 90-day mortality increased with increasing INR, no nonlinear relationship (P for nonlinearity = 0.521, P =0.012) was observed between an increased INR and mortality risk (Fig. 2).

Mediation Analysis

To investigate the mediating effect of ICH status on the relationship between the INR and 90-day all-cause mortality, we performed a mediation analysis adjusting for relevant confounding factors. After adjustment, we found that ICH status partially mediated the association between an elevated INR and 90-day mortality.

The total effect of the INR on 90-day mortality was statistically significant, with a coefficient of 0.114 (95% CI 0.073–0.142, P =0.008). The indirect effect mediated by ICH was also significant, with a coefficient of 0.013 (95% CI 0.001–0.035, P =0.040). The direct effect of the INR on 90-day mortality, after controlling for the mediator, was 0.101 (95% CI 0.055–0.131, P =0.012). The proportion of the total effect of the INR on 90-day mortality that was mediated by ICH was 11.4% (95% CI 0.1–33.8; Table 4).

Subgroup Analysis

In the subgroup analysis, we examined the potential differences in the associations between the INR and clinical outcomes across

Table 1 Patient characteristics

Characteristic	INR group			*p* value
	Overall, *n* = 885	≤ 1.1, *n* = 672	> 1.1, *n* = 213	
Age	67 (57, 74)	67 (57, 74)	67 (56, 75)	0.736
Sex				0.036
Men	524 (59.2%)	411 (61.2%)	113 (53.1%)	
Women	361 (40.8%)	261 (38.8%)	100 (46.9%)	
Baseline SBP	145 (130, 160)	146 (131, 160)	140 (121, 158)	0.001
Hypertension				0.025
No	394 (44.5%)	285 (42.4%)	109 (51.2%)	
Yes	491 (55.5%)	387 (57.6%)	104 (48.8%)	
Hyperlipidemia				0.009
No	758 (85.6%)	564 (83.9%)	194 (91.1%)	
Yes	127 (14.4%)	108 (16.1%)	19 (8.9%)	
Diabetes				0.342
No	694 (78.4%)	522 (77.7%)	172 (80.8%)	
Yes	191 (21.6%)	150 (22.3%)	41 (19.2%)	
Atrial fibrillation				< 0.001
No	591 (66.8%)	484 (72.0%)	107 (50.2%)	
Yes	294 (33.2%)	188 (28.0%)	106 (49.8%)	
Coronary heart disease				0.134
No	736 (83.2%)	566 (84.2%)	170 (79.8%)	
Yes	149 (16.8%)	106 (15.8%)	43 (20.2%)	
Ischemic stroke				0.624
No	734 (82.9%)	555 (82.6%)	179 (84.0%)	
Yes	151 (17.1%)	117 (17.4%)	34 (16.0%)	
Smoking				< 0.001
No	677 (76.5%)	494 (73.5%)	183 (85.9%)	
Yes	208 (23.5%)	178 (26.5%)	30 (14.1%)	
History antiplatelet use				0.376
No	803 (90.7%)	613 (91.2%)	190 (89.2%)	
Yes	82 (9.3%)	59 (8.8%)	23 (10.8%)	
History anticoagulation use				< 0.001
No	818 (92.4%)	643 (95.7%)	175 (82.2%)	

Table 1 continued

Characteristic	INR group			*p* value
	Overall, *n* = 885	≤ 1.1, *n* = 672	> 1.1, *n* = 213	
Yes	67 (7.6%)	29 (4.3%)	38 (17.8%)	
Prestroke mRS score 2 or more				0.469
No	862 (97.4%)	656 (97.6%)	206 (96.7%)	
Yes	23 (2.6%)	16 (2.4%)	7 (3.3%)	
Baseline NIHSS	16.0 (12.0, 19.0)	16.0 (11.0, 19.0)	16.0 (12.0, 20.0)	0.121
Baseline ASPECTS	8.00 (7.00, 9.00)	8.00 (7.00, 9.00)	8.00 (7.00, 9.00)	0.535
Onset to puncture	390 (256, 627)	388 (254, 636)	425 (264, 615)	0.507
Puncture to recanalization	69 (41, 105)	68 (41, 105)	74 (43, 105)	0.368
Group				0.966
Placebo	454 (51.3%)	345 (51.3%)	109 (51.2%)	
Tirofiban	431 (48.7%)	327 (48.7%)	104 (48.8%)	
Stroke etiology				< 0.001
LAA	403 (45.5%)	338 (50.3%)	65 (30.5%)	
CE	381 (43.1%)	253 (37.6%)	128 (60.1%)	
Other or unknown	101 (11.4%)	81 (12.1%)	20 (9.4%)	
Occlusion site				0.521
ICA	180 (20.3%)	134 (19.9%)	46 (21.6%)	
MCA-M1	572 (64.6%)	432 (64.3%)	140 (65.7%)	
MCA-M2	133 (15.0%)	106 (15.8%)	27 (12.7%)	
ASITN/SIR				0.062
ASITN/SIR 0–1	261 (29.5%)	202 (30.1%)	59 (27.7%)	
ASITN/SIR 2	365 (41.2%)	263 (39.1%)	102 (47.9%)	
ASITN/SIR 3–4	259 (29.3%)	207 (30.8%)	52 (24.4%)	
eTICI grade				0.531
eTICI 0-2a	70 (7.9%)	51 (7.6%)	19 (8.9%)	
eTICI 2b50-3	815 (92.1%)	621 (92.4%)	194 (91.1%)	
sICH				0.013
No	813 (91.9%)	626 (93.2%)	187 (87.8%)	
Yes	72 (8.1%)	46 (6.8%)	26 (12.2%)	
ICH				< 0.001
No	607 (68.6%)	482 (71.7%)	125 (58.7%)	

Table 1 continued

Characteristic	INR group			*p* value
	Overall, *n* = 885	≤ 1.1, *n* = 672	> 1.1, *n* = 213	
Yes	278 (31.4%)	190 (28.3%)	88 (41.3%)	
mRS score 0 to 2				0.301
No	463 (52.3%)	345 (51.3%)	118 (55.4%)	
Yes	422 (47.7%)	327 (48.7%)	95 (44.6%)	
mRS score 0 to 3				0.269
No	325 (36.7%)	240 (35.7%)	85 (39.9%)	
Yes	560 (63.3%)	432 (64.3%)	128 (60.1%)	
90-day mortality				0.002
No	739 (83.5%)	576 (85.7%)	163 (76.5%)	
Yes	146 (16.5%)	96 (14.3%)	50 (23.5%)	

ASITN/SIR American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology, *ASPECT* Alberta Stroke Program Early CT, *CE* cardioembolism, *eTICI* expanded thrombolysis in cerebral ischemia, *ICA* internal carotid artery, *ICH* intracranial hemorrhage, *INR* international normalized ratio, *LAA* large-artery atherosclerosis, *MCA* middle cerebral artery, *mRS* modified Rankin scale, *NIHSS* National Institutes of Health Stroke Scale, *SBP* systolic blood pressure, *sICH* symptomatic intracranial hemorrhage, *TOAST* Trial of ORG 10172 in Acute Stroke Treatment

Table 2 Association between the INR and 90-day mortality risk

Characteristic	*n*	Event *Nn*	OR	95% CI	*p* value
INR (unadjusted)	885	146	3.83	1.73, 9.29	0.002
INR (adjusted)	885	146	4.34	1.79, 11.77	0.003
Characteristic	***n***	**Event *n***	**OR**	**95% CI**	***p* value**
INR (unadjusted)					
≤ 1.1	672	96	–	–	
> 1.1	213	50	1.84	1.25, 2.69	0.002
INR (adjusted)					
≤ 1.1	672	96	–	–	
> 1.1	213	50	1.78	1.17, 2.70	0.007

The model was adjusted for sex, age, hypertension status, atrial fibrillation status, history of anticoagulant use, baseline NIHSS score, baseline ASPECTS, eTICI grade, and onset to puncture

CI confidence interval, *INR* international normalized ratio, *OR* odds ratio

various predefined subgroups. These subgroups were based on key variables such as sex, age, tirofiban or nontirofiban group, history of anticoagulant use, stroke etiology, baseline NIHSS score and baseline ASPECTS. No significant interactions were detected between the subgroups, indicating that the associations between the INR and clinical outcomes were

Table 3 Association between the INR and the risk of developing ICH

Characteristic	*n*	Event *n*	OR	95% CI	*p* value
INR (unadjusted)	885	278	2.39	1.20, 5.22	0.021
INR (adjusted)	885	278	2.29	1.11, 5.19	0.034
Characteristic	***n***	**Event *n***	**OR**	**95% CI**	***p* value**
INR (unadjusted)					
≤ 1.1	672	190	–	–	
> 1.1	213	88	1.79	1.29, 2.46	< 0.001
IINR (adjusted)					
≤ 1.1	672	190	–	–	
> 1.1	213	88	1.65	1.17, 2.33	0.005

The model was adjusted for sex, age, hypertension status, atrial fibrillation status, history of anticoagulant use, baseline NIHSS score, baseline ASPECTS, eTICI grade, and onset to puncture

CI confidence interval, *ICH* intracranial hemorrhage, *INR* international normalized ratio, *OR* odds ratio

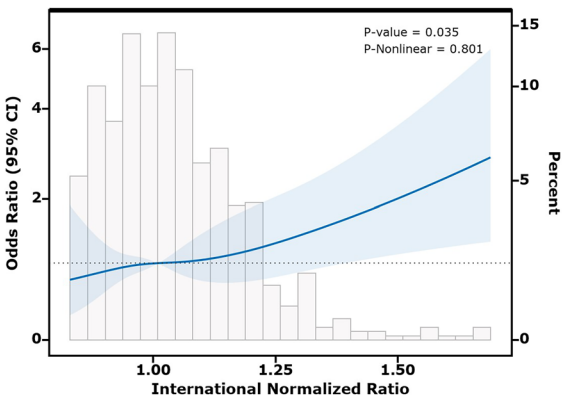

Fig. 2 Association between the INR and 90-day mortality risk visualized with the RCS function. Model with 4 knots located at the 5th, 35th, 65th and 95th percentiles. The *y*-axis represents the OR to present 90-day mortality for any value of the INR compared to individuals with a reference value (50th percentile) of the INR. The logistic regression model was adjusted for sex, age, hypertension status, atrial fibrillation status, history of anticoagulant use, baseline NIHSS score, baseline ASPECTS, eTICI grade, and onset to puncture. *INR* International Normalised Ratio, *OR* Odds Ratio, *NIHSS* National Institutes of Health Stroke Scale, *ASPECTS* Alberta Stroke Program Early CT Score, *eTICI* expanded Thrombolysis in Cerebral Infarction, *RCS* Restricted Cubic Splines

consistent across all groups (*P* for interaction > 0.05; Fig. 3).

DISCUSSION

In our study, an elevated INR was a significant predictor of both ICH and 90-day mortality. ICH status partially mediated the impact of elevated INR on 90-day mortality, suggesting that it contributed to the increased risk of death associated with a higher INR. Subgroup analysis confirmed that the link between an elevated INR and clinical outcomes was uniform across all subgroups, indicating a consistent relationship between an elevated INR and adverse outcomes across various patient populations. Our findings underscore the importance of careful INR monitoring in patients undergoing EVT to mitigate the risk of ICH and subsequent mortality.

Our study revealed that an elevated INR significantly increased the risk of developing ICH, which aligns with the findings of previous studies [25]. The association between an elevated INR and an increased risk of developing ICH can be explained by underlying pathophysiological mechanisms. The INR reflects coagulation status, and an elevated INR indicates a state

Table 4 Mediation analysis for the associations between the INR and 90-day mortality risk

Independent variable	Mediator	Total effect		Indirect effect		Direct effect		Proportion mediated, % (95% CI)
		95% CI	*P* value	95% CI	*P* value	95% CI	*P* value	
INR	ICH	0.114 (0.073, 0.142)	0.008	0.013 (0.001, 0.035)	0.040	0.101 (0.055, 0.131)	0.012	11.4 (0.1, 33.8)

The mediation analyses were adjusted for sex, age, hypertension status, atrial fibrillation status, history of anticoagulant use, baseline NIHSS score, baseline ASPECTS, eTICI grade, and onset to puncture

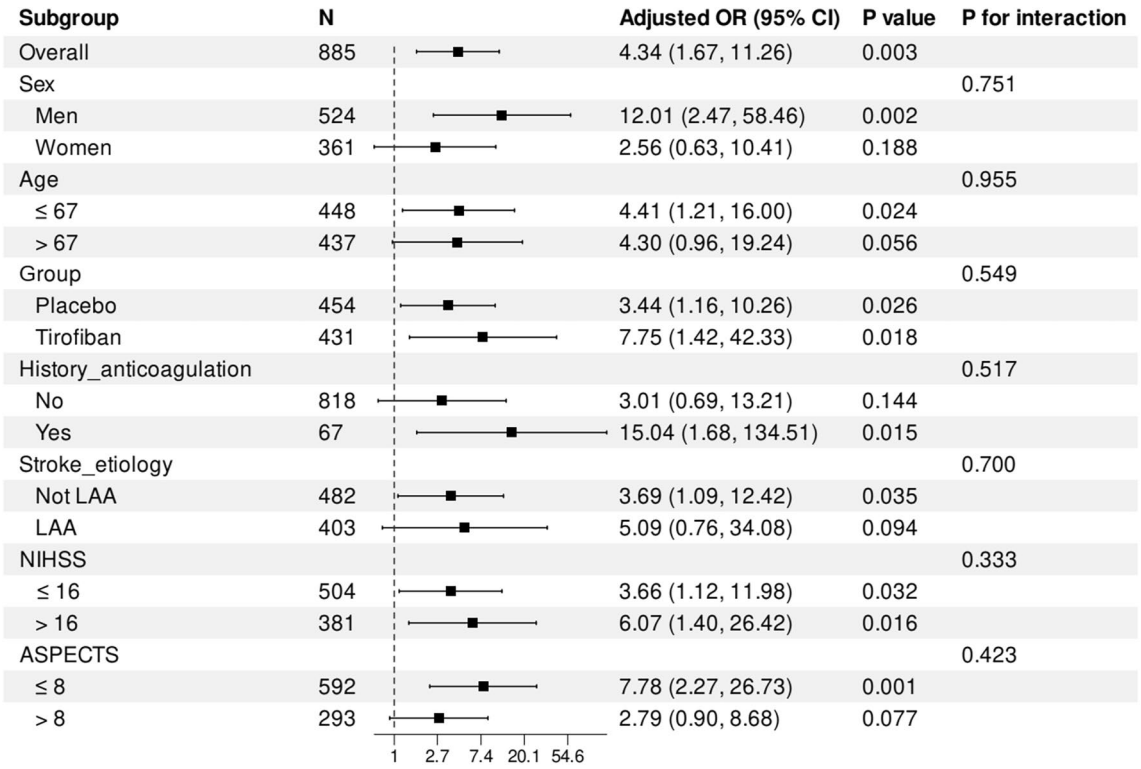

Fig. 3 Subgroup analyses of the association between the INR and 90-day mortality in patients who received EVT. *INR* International Normalized Ratio, *EVT* Endovascular Treatment, *LAA* Large Artery Atherosclerosis, *ASPECTS* Alberta Stroke Program Early CT Score, *NIHSS* National Institutes of Health Stroke Scale, *OR* Odds Ratio, *CI* Confidence Interval

of impaired hemostasis [26, 27]. More specifically, an elevated INR reflects impaired coagulation function, increasing the likelihood of hemorrhagic transformation, particularly in the fragile vascular environment of ischemic brain tissue undergoing reperfusion therapy [28]. An elevated INR impairs thrombin generation and reduces fibrin formation [29], which are critical for stabilizing blood clots and preventing hemorrhage. As a result, patients with a higher INR are more susceptible to any form of ICH, which directly contributes to poorer clinical outcomes. Previous studies have also revealed that INR elevations lead to the suppression of protein C activity [30], further exacerbating the risk of bleeding by weakening endothelial protection.

Therefore, the strong association between the INR and the risk of developing ICH in our findings emphasizes the need for tighter control of anticoagulant use status in stroke patients, particularly in the perioperative period of EVT.

Post-EVT ICH may be associated with both 90-day functional outcomes and 90-day mortality [31, 32]. The relationship between an elevated INR and 90-day mortality in our study was partially mediated by ICH status, with mediation analysis indicating that 11.4% of the overall effect of the INR on mortality was due to the occurrence of ICH. This finding is clinically significant, as it suggests that the INR not only directly influences mortality risk but also indirectly contributes to mortality through its role in promoting ICH. The mediating effect highlights the presence of any ICH as a key mechanism linking an elevated INR to poor outcomes, reaffirming the critical role of hemorrhagic complications in stroke prognosis. Previous studies have shown that anticoagulant use status can heavily influence post-EVT recovery, where even a mild elevation in the INR can exacerbate bleeding risk, leading to increased mortality [16]. Other potential reasons why an elevated INR may contribute to 90-day mortality include an increased risk of systemic hemorrhage and impaired blood clotting, leading to complications such as prolonged bleeding and increased susceptibility to recurrent strokes. Additionally, an elevated INR may reflect underlying health conditions, such as liver dysfunction or a history of anticoagulant use, which can further contribute to adverse clinical outcomes. An elevated INR has been associated with heightened inflammatory responses [33]. Inflammation can exacerbate vascular injury and contribute to complications such as atherosclerosis and thrombosis, further complicating the clinical picture [34].

As part of the subgroup analysis, we examined whether tirofiban use affects the association between the INR and clinical outcomes. Tirofiban, a platelet aggregation inhibitor, primarily exerts its antithrombotic effects by inhibiting the GPIIb/IIIa receptor [20], a mechanism distinct from that reflected by the INR, which assesses coagulation function. Compared with the placebo group, the tirofiban group had a more than twofold greater risk of 90-day mortality associated with an elevated INR. This may be attributed to the following factors: (1) tirofiban exerts its antiplatelet effect by inhibiting platelet aggregation, while an elevated INR reflects an anticoagulant state; this dual effect may compound, thereby increasing the 90-day mortality rate; (2) a high INR may indicate an imbalance in the patient's coagulation pathway. The additional use of tirofiban on this basis could further impair coagulation ability, thereby increasing the risk of mortality; and (3) the metabolism of tirofiban may be more unstable in patients with high INRs, potentially leading to unpredictable efficacy and an increased risk of bleeding. Additionally, an elevated INR may be associated with factors such as liver dysfunction, which can impair drug metabolism and further increase the risk of bleeding, ultimately impacting the 90-day mortality rate. Patients with high INRs constitute a high-risk group with a risk of bleeding, which makes treatment difficult. Patients demonstrate heterogeneity in both antiplatelet and anticoagulant therapies, and the interaction of tirofiban and a high INR highlight the need for individualized dose adjustment and careful bleeding risk monitoring to increase the safety and survival of these patients.

A higher INR was not independently associated with favorable functional outcomes (mRS score 0–2 or 0–3) in our study. One reason may be that the functional outcomes of patients are dependent on multiple aspects, such as the need for time, thrombolysis interventions, neurological recovery after a stroke, success of rehabilitation treatments, and control of complications. While the INR is associated with bleeding and bleeding-related mortality, it may be less relevant to long-term functional recovery than are other factors, e.g., age, collateral circulation status, and baseline NIHSS score [35–37], making the independent effect of the INR on the mRS score more difficult to discern.

This study has several limitations. First, its observational nature limits causal inferences between increased INR and poor outcomes, despite multivariable adjustments. Second, the multicenter design, though relatively large, involved 55 centers in China, potentially limiting generalizability due to regional differences in

demographics, medical practices, and lifestyles. Third, while tirofiban use was controlled for, its interaction with INR and bleeding risk was not explored in depth. Additionally, the 90-day follow-up period precluded the evaluation of long-term outcomes, such as 1-year survival or functional recovery, thereby restricting the clinician's global assessment of the effect of an elevated INR on a patient's prognosis. The study primarily focused on INR and did not consider other coagulation markers like activated partial thromboplastin time or fibrinogen, potentially limiting the assessment of coagulation status. Platelet function, especially in patients on inhibitors like tirofiban, was not directly evaluated, and interactions between platelet inhibition and coagulation abnormalities may affect prognosis. Furthermore, the absence of continuous or perioperative INR monitoring data limits insights into INR fluctuations and their relationship with clinical outcomes.

CONCLUSION

Our results imply that, given the strong relationship between the INR and clinical outcomes, INR monitoring and corresponding treatment should be part of the care pathway for stroke patients undergoing EVT. Strategies that are based on pre-EVT and post-EVT optimization of anticoagulant use levels might reduce the risk of developing ICH and increase overall survival in the long run. Measures could include more frequent evaluations of the INR, especially among patients with a known coagulation disorder or patients on anticoagulant therapy. The use or dosing adjustment of tirofiban in populations at risk, such as patients with an increased INR or coagulopathy, should be considered.

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Data Availability. Data related to this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest. Yapeng Guo, Lingshan Wu, Zhenxuan Tian, Xu Xu, Jinfu Ma, Changwei Guo, Linyu Li, Jie Yang, Wenjie Zi, Jiacheng Huang and Xianjun Huang declare that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval. Clinical trial registration for RESCUE BT was submitted to the Chinese Clinical Trial Registry (http://www.chictr.org.cn; ChiCTR-INR-17014167). The Ethics Committee of Xinqiao Hospital, Army Medical University (ID: 201900301), along with ethics committees from all participating centres (See Supplementary Material), approved the study. Written informed consent was obtained from all patients or their authorized representatives.

Consent to Participate. This study was conducted in accordance with the Declaration of Helsinki and local regulations. Informed consent

was obtained from all the subjects or their legal representatives before the study.

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