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Association between admission D-dimer level and post-stroke epilepsy in patients with acute ischemic stroke: a retrospective cohort study

Running title: D-dimer and post-stroke epilepsy

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Abstract

Background: D-dimer reflects thrombus formation and fibrinolysis and is associated with stroke severity and outcome, but whether it predicts post-stroke epilepsy (PSE) is unclear. We examined whether admission D-dimer predicts PSE and assessed its diagnostic and incremental predictive value in acute ischemic stroke (AIS).

Methods: A total of 21,459 patients with AIS were analyzed. Admission D-dimer was divided into quartiles; the two lowest were merged as the reference. Multivariable logistic regression with three adjustment models, restricted cubic spline and subgroup analyses were performed. Discrimination (ROC/AUC), decision curve analysis, and the net reclassification index (NRI) and integrated discrimination improvement (IDI) assessed predictive value.

Results: Within one year, 936 (4.4%) patients developed PSE. Each 1 mg/L increase in D-dimer was associated with higher PSE risk (fully adjusted OR 1.46, 95% CI 1.37-1.57); compared with the merged Q1+Q2 reference, fully adjusted ORs were 9.13 (Q3) and 15.23 (Q4) (P for trend < 0.001). The association was non-linear (P < 0.001), with a threshold at 0.867 mg/L, and was stronger in men, younger patients, and those without hypertension (P for interaction < 0.001). D-dimer discriminated PSE with an AUC of 0.822 (95% CI 0.810-0.835), higher than ALT, uric acid, creatinine and urea; adding it to a baseline model (age, gender, NIHSS, hypertension) raised the AUC from 0.866 to 0.920 (P < 0.001; NRI 0.8438, IDI 0.2031).

Conclusions: Admission D-dimer was independently and non-linearly associated with PSE and improved discrimination and reclassification beyond conventional factors. It may aid early identification of AIS patients at high PSE risk.

Keywords

D-dimer; post-stroke epilepsy; acute ischemic stroke; biomarker; prognosis

Background

Stroke is a leading cause of death and long-term disability worldwide [1-3], and acute ischemic stroke (AIS) accounts for the majority of cases. Among survivors, post-stroke epilepsy (PSE) is one of the most disabling neurological complications, with cumulative incidence estimates of approximately 4-6% [4,5] and substantial impacts on mortality, quality of life, and health-care burden. PSE refers to recurrent unprovoked seizures occurring after a stroke, usually beyond the acute symptomatic period [4,5]. Early recognition of patients at risk is therefore clinically important.

Several clinical prediction tools have been developed, of which the SeLECT score based on infarct location, cortical involvement, middle cerebral artery territory, aphasia, and early seizures showed good performance in external settings [6]. Nevertheless, risk prediction remains imperfect, and machine-learning models incorporating laboratory biomarkers have been proposed to improve accuracy [7]. In particular, a recent large cohort study from Chongqing, China, developed interpretable machine-learning models for secondary epilepsy after AIS and identified the National Institutes of Health Stroke Scale (NIHSS) score, white blood cell count, and D-dimer as the most important predictors [8]. These findings raise the question of whether D-dimer, a routine coagulation parameter, can be used as a simple biomarker for PSE risk stratification.

D-dimer is a fibrin degradation product that reflects ongoing thrombosis and fibrinolysis [9]. Elevated D-dimer levels in AIS have been consistently associated with stroke severity, cardioembolic etiology, early neurological deterioration, and poor short- and long-term functional outcomes [9-14]. A recent secondary analysis of the same multicenter cohort reported that admission D-dimer was independently associated with one-year PSE [18]. However, that study modeled D-dimer on a logarithmic scale and did not define a clinically interpretable threshold or quantify the incremental predictive value of D-dimer beyond conventional risk factors. Previous studies of blood biomarkers for PSE focused mainly on markers of inflammation and neuronal injury [15-17], and D-dimer has been evaluated largely as one of many features within machine-learning frameworks [8] rather than through dedicated threshold and incremental-value analyses.

Therefore, using a large multicenter cohort of 21,459 patients with AIS, and building on this prior report [18], we aimed to characterize the dose-response and threshold relationship between admission D-dimer and PSE, to examine the consistency of the association across clinically relevant subgroups, and to quantify the incremental

predictive value of D-dimer beyond conventional clinical risk factors, including decision-curve and reclassification metrics.

Methods

Study design and data source

This retrospective cohort study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [19]. We analyzed the publicly available dataset "Predictive models for secondary epilepsy in patients with acute ischemic stroke within one year" (doi:10.5061/dryad.w0vt4b92c), deposited in the Dryad Digital Repository by Deng et al. [20]. The dataset contains de-identified medical records, radiology reports, and laboratory results of 21,459 adult patients (aged 18-90 years) with a diagnosis of ischemic stroke recruited from four hospitals in Chongqing, China. Because the data were fully de-identified and publicly available for research use, no additional ethics approval or informed consent was required.

Outcome and exposure

The outcome of interest was post-stroke epilepsy (PSE), defined as secondary epilepsy occurring within one year after the index stroke, as recorded by the variable "second_epilepsy" in the dataset [20]. Admission D-dimer (mg/L) was the exposure of interest. For categorical analyses, patients were divided into quartiles (Q1, Q2, Q3, Q4) of D-dimer. Because the incidence of PSE in Q1 (0.3%) and Q2 (1.1%) was very low, Q1 and Q2 were merged into a single reference category to ensure a stable odds ratio (OR) estimate.

Covariates

The following covariates were used for adjusted analyses: (i) demographics and stroke severity: age, gender, and NIHSS score; (ii) complications: deep vein thrombosis (DVT), fatty liver, diabetes mellitus, hypertension, cerebral hernia, and atrial fibrillation; and (iii) laboratory indicators: white blood cell count (WBC), platelet count (PLT), C-reactive protein (CRP), triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin, urea, creatinine, and blood uric acid (BUA).

Statistical analyses

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) according to their distribution, and categorical variables as numbers (percentages). Group differences were evaluated by analysis of variance or Kruskal-Wallis test for continuous variables and by chi-square test for categorical variables. The association between D-dimer and PSE was examined using multivariable logistic regression with three sequential adjustment models: Model I adjusted for age,

gender, and NIHSS; Model II further adjusted for DVT, fatty liver, diabetes, hypertension, cerebral hernia, and atrial fibrillation; Model III further adjusted for WBC, PLT, CRP, TG, AST, ALT, bilirubin, albumin, urea, creatinine, and BUA. D-dimer was modeled both as a continuous variable (effect sizes expressed per 1 mg/L increment) and as a quartile-based categorical variable using the merged Q1+Q2 as reference.

To characterize the dose-response shape, D-dimer was modeled with a restricted cubic spline (RCS) with 4 knots, with the reference fixed at a D-dimer level of approximately the cohort median (0.91 mg/L). Non-linearity was tested by a likelihood ratio test comparing the spline model with a linear model. A two-piecewise (threshold) logistic regression model was then fitted, in which the cut-off value of D-dimer was selected by an iterative scan that maximized the model likelihood. Below the breakpoint, PSE events were extremely rare; the effect estimate was unstable owing to sparse events (near-complete separation) and is therefore reported descriptively rather than as an effect size.

Subgroup analyses were performed according to age (< 65 and ≥ 65 years), gender, NIHSS (< 12 and ≥ 12), fatty liver, diabetes, and hypertension, using the fully adjusted model (Model III). Differences across strata were tested by likelihood ratio tests for interaction.

The discriminative ability of D-dimer was assessed using ROC curves and the area under the curve (AUC), and pairwise comparisons were made with the DeLong test [21]. Decision curve analysis (DCA) was performed to further evaluate the discriminative ability [22]. A baseline clinical model including age, gender, NIHSS, and hypertension was compared with an extended model additionally including D-dimer; differences in AUC were tested by the DeLong method, and the incremental value was further quantified by the continuous NRI and IDI [23].

All analyses were performed using R software (version 4.2.2) and the Free Statistics platform (Beijing, China) [24]. All tests were two-sided, and P values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 21,459 patients by D-dimer quartiles. The mean age was 66.4 ± 12.4 years, 50.5% were male, the median D-dimer was 0.9 (IQR 0.7-1.5) mg/L, and the mean NIHSS score was 8.0 ± 2.9. During follow-up, 936 (4.4%) patients developed PSE, with a clear gradient across quartiles: 16 (0.3%) in Q1, 60 (1.1%) in Q2, 213 (4.0%) in Q3, and 647 (12.0%) in Q4. Patients with higher D-dimer were older, had higher NIHSS scores, and more often had DVT, atrial fibrillation, and cerebral hernia, whereas fatty liver and diabetes were less frequent in the highest

quartile. Higher D-dimer was also accompanied by higher CRP, AST, ALT, bilirubin, and LDH, and by lower albumin (all $P < 0.05$).

Association between D-dimer and PSE

To explore the relationship between D-dimer and incidence of post-stroke epilepsy, logistic regression analysis was performed. Three adjusted models were established to further validate this relationship. Model I was adjusted for gender, age and NIHSS scores; Model II was further adjusted for deep vein thrombosis (DVT), fatty liver, diabetes, hypertension, cerebral hernia and atrial fibrillation. Model III was further adjusted for WBC, PLT, CRP, TG, AST, ALT, bilirubin, albumin, urea, creatinine and serum uric acid. As shown in Table 2, each 1 mg/L increase in D-dimer was associated with higher odds of PSE in all models (non-adjusted OR 1.74, 95% CI 1.68-1.80; Model I OR 1.61, 95% CI 1.55-1.67; Model II OR 1.98, 95% CI 1.88-2.08; Model III OR 1.46, 95% CI 1.37-1.57; all $P < 0.001$). In categorical analyses using merged Q1+Q2 as reference, the fully adjusted OR of PSE increased monotonically from 9.13 (95% CI 6.49-12.85) in Q3 to 15.23 (95% CI 10.70-21.67) in Q4, with a significant trend across the models (all P for trend < 0.001).

Dose-response relationship and threshold analysis

Multivariable-adjusted restricted cubic spline analysis was used to investigate whether there was a linear relationship between D-dimer and PSE. Restricted cubic spline analysis revealed a non-linear relationship between D-dimer and PSE (P for overall association < 0.001; P for non-linearity < 0.001): the OR rose steeply from the reference point, became more gradual at intermediate values, and increased again at high D-dimer concentrations (Figure 1). The two-piecewise threshold model identified a breakpoint at 0.867 mg/L, which closely approximated the cohort median. D-dimer showed a clear threshold relationship with PSE. Below the breakpoint (0.867 mg/L), events were too rare to allow reliable estimation. Above the breakpoint, the OR was 1.254 (95% CI 1.113-1.413). Among patients with D-dimer ≥ 0.867 mg/L, PSE occurred in 871 (7.45%), compared with 65 (0.67%) below the threshold (likelihood ratio test $P < 0.001$) (Table 3).

Subgroup analyses

The forest plot in Figure 2 displays the fully adjusted ORs per 1 mg/L increase in D-dimer across prespecified subgroups. The association was present in all strata, but its magnitude differed by age, gender, and hypertension. Specifically, adjusted ORs were higher in patients younger than 65 years (2.65, 95% CI 2.09-3.35) than in older patients (1.30, 95% CI 1.19-1.42; P for interaction < 0.001), higher in men (2.07, 95% CI 1.81-2.37) than in women (1.20, 95% CI 1.09-1.33; P for interaction < 0.001), and higher in patients without hypertension (2.48, 95% CI 1.91-3.24) than in those with hypertension (1.14, 95% CI 1.03-1.26; P for interaction < 0.001). The association was also modified by

NIHSS group (adjusted OR 1.59, 95% CI 1.36-1.86 for NIHSS ≥ 12 vs. 1.32, 95% CI 1.18-1.46 for NIHSS < 12; P for interaction < 0.001), whereas no significant interaction was found with fatty liver (P = 0.799) or diabetes (P = 0.832).

Predictive value of D-dimer

The AUC of D-dimer for PSE was 0.822 (95% CI 0.810-0.835), which was significantly higher than that of ALT (0.617), uric acid (0.538), creatinine (0.571), and urea (0.527) (all P < 0.001), and comparable to that of AST (0.810; P = 0.123) (Table 4, Figure 3A). On decision curve analysis (Figure 3B), D-dimer yielded a higher net benefit than AST, ALT, uric acid, creatinine and urea across the clinically relevant threshold range. Furthermore, adding D-dimer to a baseline clinical model (age, gender, NIHSS, hypertension) significantly improved the AUC from 0.866 (95% CI 0.855-0.878) to 0.920 (95% CI 0.912-0.928; P < 0.001) (Figure 4). The continuous NRI and IDI were 0.8438 (95% CI 0.7829-0.9047) and 0.2031 (95% CI 0.1826-0.2236), respectively (both P < 0.001) (Table 5).

Discussion

In this large multicenter cohort of 21,459 patients with AIS, we found a strong, independent, and non-linear association between admission D-dimer and one-year PSE risk. The association followed a threshold pattern, became stronger with increasing D-dimer above the median, and was modified by age, gender, and hypertension. Importantly, D-dimer markedly improved discrimination and reclassification over a conventional clinical model, suggesting a clinically useful role for this routine coagulation marker in PSE risk stratification.

Our finding concurs with and extends earlier observations. In previous studies, elevated D-dimer in AIS predicted stroke severity, infarct growth, and functional outcomes [9-14], and blood biomarker studies identified inflammatory and neuronal markers as correlates of post-stroke seizures [15-17]. Machine-learning analyses of the same cohort found D-dimer among the top predictors of secondary epilepsy [8,20]. Most directly, a recent secondary analysis of the same cohort also reported an independent, non-linear D-dimer-PSE association, modeling D-dimer on a logarithmic scale [18]. Our study adds to and refines this evidence by focusing on the diagnostic and incremental predictive value of D-dimer rather than on the association alone. First, we characterized the dose-response relationship and identified a clinically interpretable threshold (0.867 mg/L) that separates a very-low-risk group from a higher-risk group and is straightforward to apply at the bedside. Second, we evaluated the standalone discriminative ability of D-dimer (AUC 0.822) and its incremental predictive value using decision-curve analysis and the NRI and IDI, whereas the previous report provided only a single C-statistic for the fully adjusted model. Third, we benchmarked D-dimer against other routinely available laboratory

indicators, showing that it outperformed ALT, uric acid, creatinine, and urea. Notably, the effect was particularly pronounced in younger patients, men, and patients without hypertension, while remaining significant in the complementary strata. These interactions, although biologically plausible, should be viewed as hypothesis-generating pending external confirmation.

Several mechanisms may underlie the D-dimer-PSE association. D-dimer is a product of fibrin degradation and a surrogate of thrombus burden and systemic hypercoagulability; in AIS it correlates with infarct volume, embolic burden, and microvascular occlusion [9,14]. Larger infarcts and extensive microvascular thrombosis compromise the blood-brain barrier and promote the proinflammatory and metabolic cascades that lead to epileptogenesis and cortical hyperexcitability [4,5]. D-dimer also reflects homeostasis-related pathways, such as atrial fibrillation and DVT, both of which were strongly associated with higher quartiles in our data and are risk factors for PSE. Importantly, D-dimer levels reflect stroke severity, thrombus burden and systemic hypercoagulability, all of which are independently associated with post-stroke seizures. The identified threshold may therefore partly reflect disease severity rather than a direct pathophysiological link, and residual confounding cannot be excluded.

From a clinical perspective, D-dimer is inexpensive, measured routinely at admission, and widely available. Combining it with age, sex, NIHSS, and hypertension yielded an AUC of 0.920 and large NRI/IDI improvements, indicating both improved rank ordering and reclassification compared with the existing prediction tools [6-8]. The non-linear relationship further suggests that a simple dichotomous rule around the median (approximately 0.9 mg/L) may capture most of the prognostic information, which is practical for early risk screening in busy stroke units.

This study has several limitations. First, its retrospective design prevents causal inference, and only a single admission D-dimer measurement was available, so dynamic changes could not be evaluated. Second, PSE was ascertained from medical records rather than structured epilepsy interviews or long-term EEG, which may introduce misclassification; the follow-up was limited to one year. Third, although we adjusted for a wide range of covariates, unmeasured confounders such as antithrombotic and antiseizure treatment, cardioembolic source quantification, and infarct volume cannot be excluded. Fourth, the two-piecewise model below the breakpoint is limited by sparse events; we therefore did not report an effect size there. Finally, the patients primarily came from the Chongqing region, and generalization to other populations requires external validation. In addition, this publicly available dataset has already been used in prior prediction-model and biomarker studies, including a recent D-dimer-PSE analysis [8,18,20]; our findings should therefore be regarded as an extension and refinement of that work rather than a first-in-field report.

Conclusions

Admission D-dimer was independently and non-linearly associated with the one-year risk of post-stroke epilepsy in patients with acute ischemic stroke, with a threshold around the population median and stronger effects in men, younger patients, and patients without hypertension. D-dimer substantially improved risk discrimination and reclassification beyond established clinical factors. D-dimer may become an effective indicator for early risk assessment of PSE, guiding monitoring and individualized follow-up.

List of abbreviations

AIS: acute ischemic stroke; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the curve; BUA: blood uric acid; CI: confidence interval; CRP: C-reactive protein; DCA: decision curve analysis; DVT: deep vein thrombosis; IDI: integrated discrimination improvement; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; NRI: net reclassification index; OR: odds ratio; PLT: platelet count; PSE: post-stroke epilepsy; RCS: restricted cubic spline; ROC: receiver operating characteristic; SD: standard deviation; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TG: triglycerides; WBC: white blood cell count.

Declarations

Ethics approval and consent to participate

Not applicable. This study used a fully de-identified, publicly available dataset (Dryad Digital Repository, doi:10.5061/dryad.w0vt4b92c); therefore no additional ethical approval or informed consent was required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available in the Dryad Digital Repository, doi:10.5061/dryad.w0vt4b92c.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Ziying Li: Conceptualization, Data curation, Methodology, Software, Writing - original draft.
Dongming Liang: Conceptualization, Methodology, Validation, Writing - original draft.
Yulin Wang: Project administration, Conceptualization, Supervision, Methodology, Writing - review & editing.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used FreeCode AI to improve language and readability and to format the manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Figure legends

Figure 1. Dose-response relationship between admission D-dimer and post-stroke epilepsy. Restricted cubic spline logistic regression with four knots was used, with the reference fixed at a D-dimer level of 0.91 mg/L (approximately the cohort median). The solid line represents the adjusted odds ratio and the shaded area represents the 95% confidence interval. P values for overall association and non-linearity were both < 0.001.

Figure 2. Subgroup analysis of the association between D-dimer and post-stroke epilepsy. Forest plot showing fully adjusted odds ratios (95% confidence intervals) per 1 mg/L increase in D-dimer across strata of age (< 65 vs. ≥ 65 years), gender, NIHSS scores (< 12 vs. ≥ 12), fatty liver, diabetes, and hypertension, with P values for interaction derived from likelihood ratio tests.

Figure 3. (A) Receiver operating characteristic (ROC) curves comparing the discriminative ability of D-dimer with other laboratory indicators (AST, ALT, uric acid [BUA], creatinine, urea) for post-stroke epilepsy. (B) Decision curve analysis comparing the clinical net benefit of decision strategies based on D-dimer versus those based on other laboratory indicators (AST, ALT, uric acid [BUA], creatinine and urea) across threshold probabilities, with the treat-all and treat-none strategies as references.

Figure 4. Receiver operating characteristic (ROC) curves of the baseline clinical model (Model 1: age, gender, NIHSS, hypertension) and the extended model (Model 2: Model 1 + D-dimer) for post-stroke epilepsy. The area under the curve (AUC) increased from 0.866 (95% CI 0.855-0.878) to 0.920 (95% CI 0.912-0.928; P < 0.001).

Tables

Table 1. Demographic and clinical baseline characteristics of the study population by D-dimer quartiles.

Table 2. Association between D-dimer and post-stroke epilepsy in multivariable logistic regression models.

Table 3. Threshold effect analysis of the relationship between D-dimer and incidence of post-stroke epilepsy.

Table 4. Comparison of D-dimer with other laboratory indicators for predicting post-stroke epilepsy using AUC.

Table 5. Incremental predictive value of D-dimer (NRI and IDI).

Fgure 1

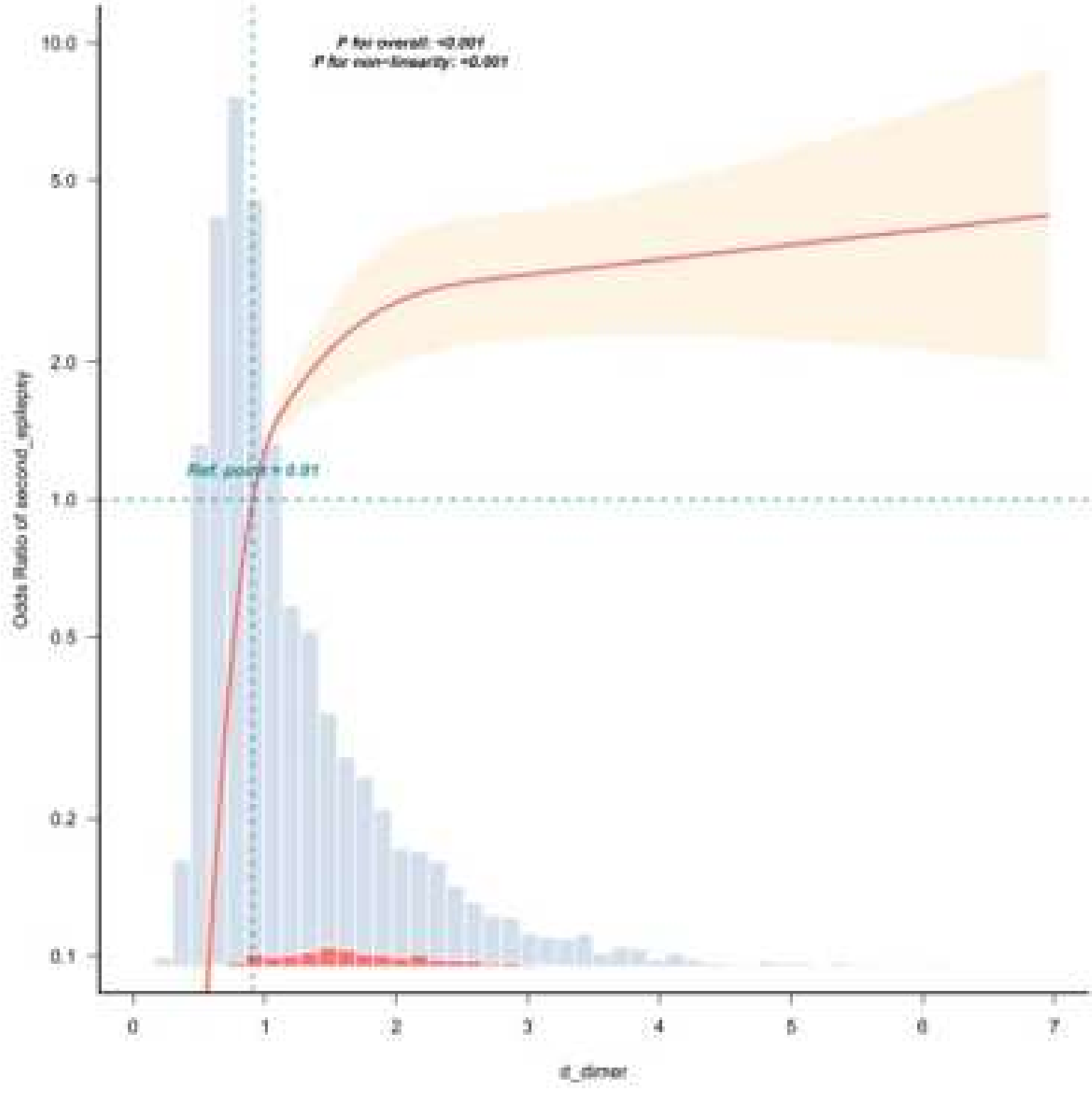

P for overall: <0.001
P for non-linearity: <0.001
Ref. point = 0.91
Odds Ratio of second_epilepsy
10.0
5.0
2.0
1.0
0.5
0.2
0.1
0
1
2
3
4
5
6
7
d_dimer

Figure 2

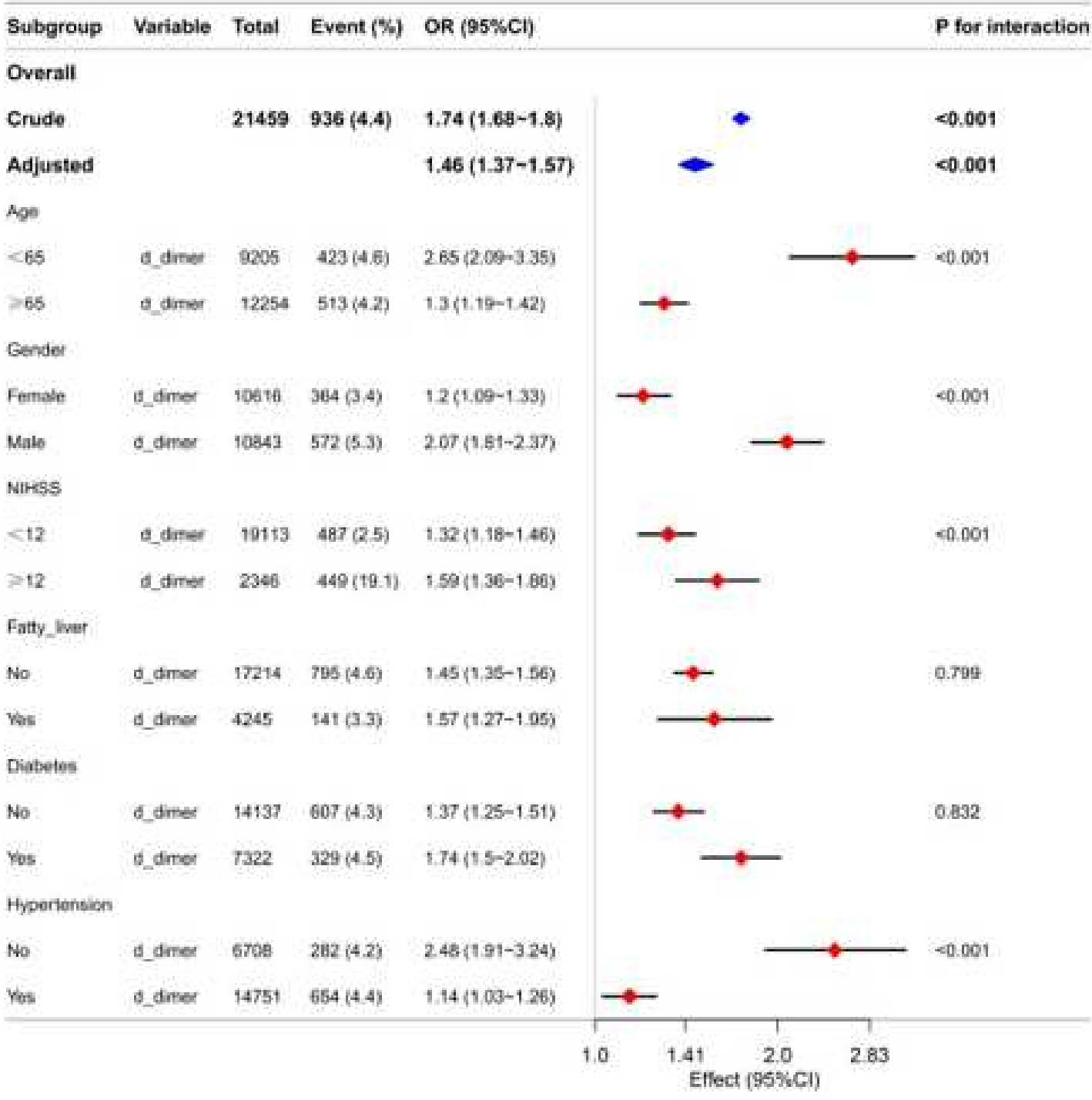
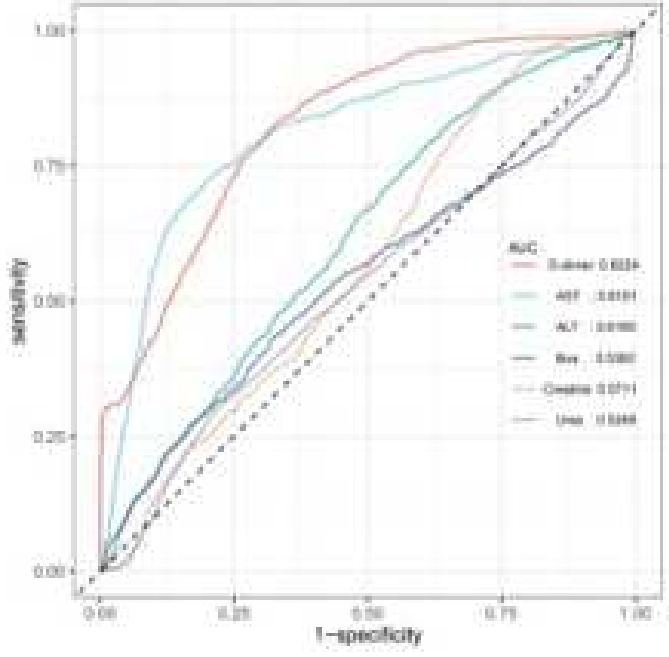

Subgroup
Variable
Total
Event (%)
OR (95%CI)
P for interaction
Overall
Crude
21459
936 (4.4)
1.74 (1.68~1.8)
<0.001
Adjusted
1.46 (1.37~1.57)
<0.001
Age
<65
d_dimer
9205
423 (4.6)
2.65 (2.09~3.35)
<0.001
≥65
d_dimer
12254
513 (4.2)
1.3 (1.19~1.42)
Gender
Female
d_dimer
10616
364 (3.4)
1.2 (1.09~1.33)
<0.001
Male
d_dimer
10843
572 (5.3)
2.07 (1.81~2.37)
NIHSS
<12
d_dimer
19113
487 (2.5)
1.32 (1.18~1.46)
<0.001
≥12
d_dimer
2346
449 (19.1)
1.59 (1.36~1.86)
Fatty_liver
No
d_dimer
17214
795 (4.6)
1.45 (1.35~1.56)
0.799
Yes
d_dimer
4245
141 (3.3)
1.57 (1.27~1.95)
Diabetes
No
d_dimer
14137
607 (4.3)
1.37 (1.25~1.51)
0.832
Yes
d_dimer
7322
329 (4.5)
1.74 (1.5~2.02)
Hypertension
No
d_dimer
6708
282 (4.2)
2.48 (1.91~3.24)
<0.001
Yes
d_dimer
14751
654 (4.4)
1.14 (1.03~1.26)
1.0
1.41
2.0
2.83
Effect (95%CI)

Figure 3

A


sensitivity
1−specificity
AUC

B

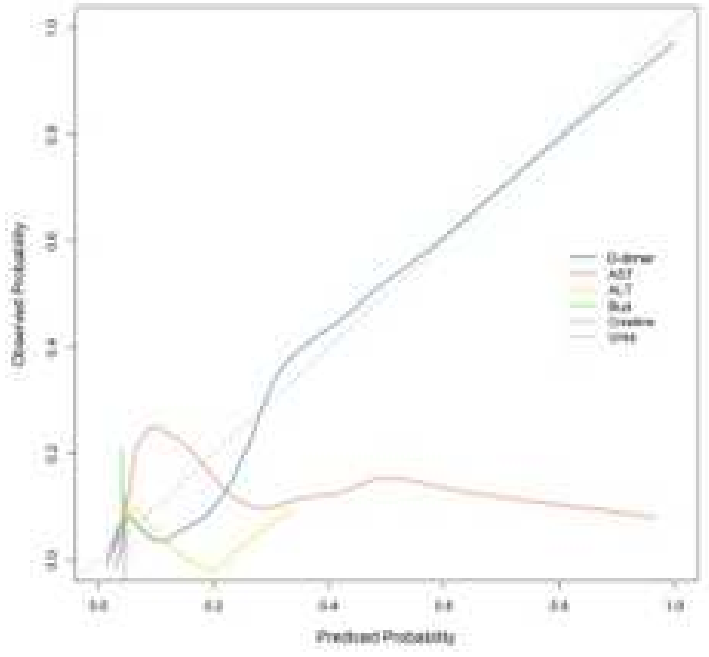

Observed Probability
Predicted Probability

Figure 4

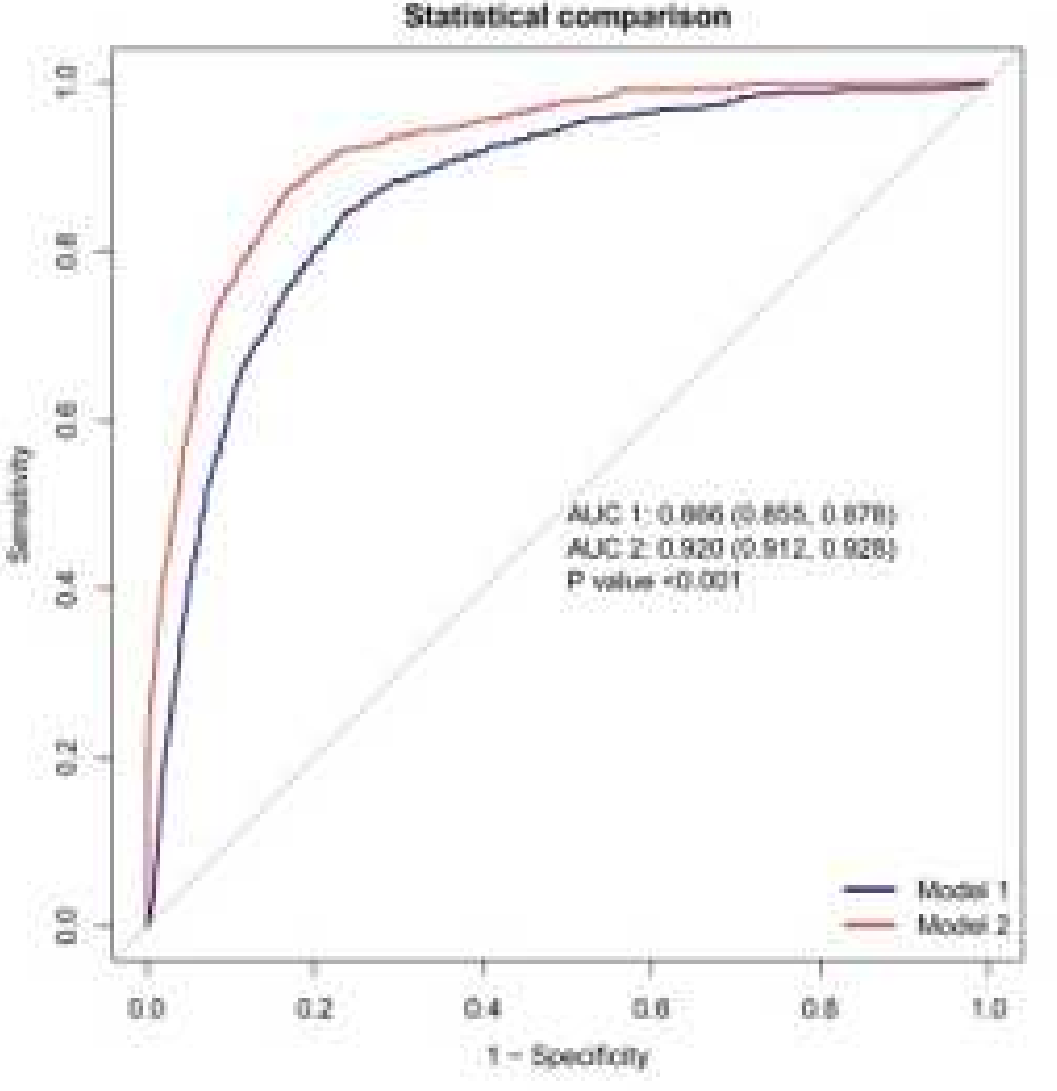

Statistical comparison
Sensitivity
1 − Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUC 1: 0.866 (0.855, 0.878)
AUC 2: 0.920 (0.912, 0.928)
P value <0.001
Model 1
Model 2

Table 1. Demographic and clinical baseline characteristics of the study population by D-dimer quartiles.

Variables	D-dimer					*p*
	Total (n = 21459)	Q1 (n = 5130)	Q2 (n = 5542)	Q3 (n = 5391)	Q4 (n = 5396)	
Post-stroke epilepsy, n (%)						< 0.001
No	20523 (95.6)	5114 (99.7)	5482 (98.9)	5178 (96)	4749 (88)	
Yes	936 (4.4)	16 (0.3)	60 (1.1)	213 (4)	647 (12)	
Uremia, n (%)						0.12
No	21269 (99.1)	5083 (99.1)	5506 (99.4)	5333 (98.9)	5347 (99.1)	
Yes	190 (0.9)	47 (0.9)	36 (0.6)	58 (1.1)	49 (0.9)	
DVT, n (%)						< 0.001
No	20135 (93.8)	5116 (99.7)	5490 (99.1)	5150 (95.5)	4379 (81.2)	
Yes	1324 (6.2)	14 (0.3)	52 (0.9)	241 (4.5)	1017 (18.8)	
Fatty liver, n (%)						< 0.001
No	17214 (80.2)	3731 (72.7)	4458 (80.4)	4309 (79.9)	4716 (87.4)	
Yes	4245 (19.8)	1399 (27.3)	1084 (19.6)	1082 (20.1)	680 (12.6)	
Diabetes, n (%)						< 0.001
No	14137 (65.9)	3194 (62.3)	4138 (74.7)	3345 (62)	3460 (64.1)	
Yes	7322 (34.1)	1936 (37.7)	1404 (25.3)	2046 (38)	1936 (35.9)	
Hypertension, n (%)						< 0.001
No	6708 (31.3)	1105 (21.5)	2097 (37.8)	1674 (31.1)	1832 (34)	
Yes	14751 (68.7)	4025 (78.5)	3445 (62.2)	3717 (68.9)	3564 (66)	
Coronary disease, n (%)						< 0.001
No	11787 (54.9)	2997 (58.4)	3116 (56.2)	2684 (49.8)	2990 (55.4)	
Yes	9672 (45.1)	2133 (41.6)	2426 (43.8)	2707 (50.2)	2406 (44.6)	
Atrial fibrillation, n (%)						< 0.001
No	19416 (90.5)	5068 (98.8)	5189 (93.6)	4613 (85.6)	4546 (84.2)	
Yes	2043 (9.5)	62 (1.2)	353 (6.4)	778 (14.4)	850 (15.8)	
Cerebral hernia, n (%)						< 0.001
No	21278 (99.2)	5110 (99.6)	5515 (99.5)	5332 (98.9)	5321 (98.6)	
Yes	181 (0.8)	20 (0.4)	27 (0.5)	59 (1.1)	75 (1.4)	
Hydrocephalus, n (%)						< 0.001
No	21178 (98.7)	5092 (99.3)	5493 (99.1)	5304 (98.4)	5289 (98)	
Yes	281 (1.3)	38 (0.7)	49 (0.9)	87 (1.6)	107 (2)	
Gender, n (%)						< 0.001
Female	10616 (49.5)	1628 (31.7)	2337 (42.2)	3048 (56.5)	3603 (66.8)	
Male	10843 (50.5)	3502 (68.3)	3205 (57.8)	2343 (43.5)	1793 (33.2)	
Age, Mean ± SD	66.4 ± 12.4	59.0 ± 8.1	66.0 ± 10.3	67.8 ± 13.7	72.4 ± 12.5	< 0.001
PLT, Mean ± SD	189.9 ± 27.0	194.9 ± 27.0	189.4 ± 27.7	192.8 ± 25.8	182.8 ± 26.0	< 0.001
WBC,	8.5 ± 1.6	8.1 ± 1.3	8.2 ± 1.4	8.5 ± 1.4	9.1 ± 2.0	< 0.001

Mean ± SD						
RBC, Mean ± SD	4.3 ± 0.3	4.5 ± 0.4	4.4 ± 0.3	4.3 ± 0.3	4.2 ± 0.3	< 0.001
CRP,Median (IQR)	9.4 (4.7, 19.1)	4.2 (2.6, 7.1)	7.4 (4.2, 12.6)	11.3 (6.7, 19.1)	24.4 (13.4, 42.5)	< 0.001
TG, Mean ± SD	1.5 ± 0.4	1.7 ± 0.5	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	< 0.001
LDL, Mean ± SD	2.7 ± 0.4	2.8 ± 0.4	2.7 ± 0.3	2.7 ± 0.3	2.6 ± 0.3	< 0.001
HDL, Mean ± SD	1.2 ± 0.1	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.1	1.3 ± 0.1	< 0.001
AST, Mean ± SD	26.6 ± 13.4	21.0 ± 5.6	25.4 ± 12.9	27.8 ± 15.3	31.9 ± 14.8	< 0.001
ALT, Mean ± SD	24.4 ± 10.2	23.0 ± 6.9	23.1 ± 6.2	23.8 ± 10.2	27.6 ± 14.4	< 0.001
Bilirubin, Mean ± SD	15.3 ± 4.0	13.9 ± 3.7	15.9 ± 4.7	15.1 ± 3.3	16.1 ± 3.8	< 0.001
Albumin, Mean ± SD	40.9 ± 2.2	42.7 ± 1.7	41.4 ± 1.6	40.3 ± 1.7	39.3 ± 2.4	< 0.001
Urea, Mean ± SD	6.4 ± 1.4	6.1 ± 1.7	6.3 ± 1.2	6.5 ± 1.5	6.6 ± 1.2	< 0.001
Creatinine, Mean ± SD	84.9 ± 51.2	74.8 ± 40.2	81.9 ± 37.5	95.0 ± 77.4	87.4 ± 35.2	< 0.001
BUA, Mean ± SD	344.1 ± 58.8	343.1 ± 53.7	346.8 ± 51.2	352.8 ± 61.3	333.8 ± 66.3	< 0.001
PT, Mean ± SD	13.8 ± 1.1	14.0 ± 1.9	13.8 ± 0.9	13.7 ± 0.7	13.9 ± 0.8	< 0.001
APTT, Mean ± SD	35.7 ± 2.3	34.6 ± 2.1	35.6 ± 2.1	35.8 ± 1.9	36.6 ± 2.6	< 0.001
INR, Mean ± SD	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	< 0.001
D-dimer, Median (IQR)	0.9 (0.7, 1.5)	0.5 (0.4, 0.6)	0.8 (0.7, 0.8)	1.1 (1.0, 1.3)	2.1 (1.7, 2.8)	< 0.001
fibrinogen, Mean ± SD	3.6 ± 0.5	3.3 ± 0.5	3.6 ± 0.4	3.7 ± 0.4	3.8 ± 0.5	< 0.001
CK, Median (IQR)	130.2 (103.4, 196.5)	111.6 (96.5, 135.4)	133.0 (105.8, 186.5)	136.7 (108.4, 223.2)	155.8 (109.4, 351.4)	< 0.001
CK-MB, Median (IQR)	12.6 (11.3, 15.2)	11.6 (10.7, 12.8)	12.6 (11.4, 14.5)	13.1 (11.6, 15.7)	14.5 (11.7, 19.4)	< 0.001
LDH, Mean ± SD	218.8 ± 79.0	178.7 ± 30.4	211.9 ± 88.0	227.7 ± 84.5	255.2 ± 76.7	< 0.001

Na, Mean ± SD	138.6 ± 1.8	139.0 ± 1.7	138.6 ± 1.7	138.5 ± 1.8	138.1 ± 1.7	< 0.001
K, Mean ± SD	3.8 ± 0.2	3.8 ± 0.2	3.8 ± 0.2	3.8 ± 0.2	3.7 ± 0.2	< 0.001
CL, Mean ± SD	103.4 ± 2.0	104.0 ± 2.0	103.3 ± 2.0	103.3 ± 2.0	102.9 ± 1.7	< 0.001
Ca, Mean ± SD	2.2 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	< 0.001
lactate, Mean ± SD	2.5 ± 0.4	2.6 ± 0.5	2.4 ± 0.3	2.4 ± 0.3	2.6 ± 0.5	< 0.001
Anion gap, Mean ± SD	12.4 ± 1.4	12.1 ± 1.6	12.4 ± 1.4	12.4 ± 1.2	12.6 ± 1.3	< 0.001
NIHSS, Mean ± SD	8.0 ± 2.9	6.9 ± 2.7	7.3 ± 2.3	8.1 ± 2.6	9.8 ± 3.3	< 0.001

Table 2. Association between D-dimer and post-stroke epilepsy in multivariable logistic regression models.

	Non-adjusted		Adjusted I		Adjusted II		Adjusted III	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
D-dimer	1.74 (1.68-1.80)	<0.001	1.61 (1.55-1.67)	<0.001	1.98 (1.88-2.08)	<0.001	1.46 (1.37~1.57)	<0.001
D-dimer quartiles								
Q1+Q2	ref		ref		ref		ref	
Q3	5.74 (4.40-7.47)	<0.001	7.07 (5.38-9.30)	<0.001	8.58 (6.47-11.38)	<0.001	9.13 (6.49-12.85)	<0.001
Q4	18.99 (14.94-24.15)	<0.001	20.16 (15.59-26.08)	<0.001	29.49 (22.48-38.67)	<0.001	15.23 (10.7-21.67)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001

Non-adjusted: no covariates were adjusted;

the adjusted I model: adjusted for age+ gender+ NIHSS scores;

the adjusted II model: adjusted for the adjusted I + DVT +Fatty liver +Diabetes +Hypertension +Cerebral hernia +Atrial fibrillation

the adjusted III model: adjusted for the adjusted II +WBC +PLT +CRP +TG +AST +ALT +Bilirubin +Albumin +Urea +Creatinine +BUA

Table 3. Threshold effect analysis of the relationship between D-dimer and incidence of post-stroke epilepsy.

Threshold of D-dimer	n (%)	OR (95%CI)	*p*
<0.867	65 (0.67%)	-	-
≥0.867	871 (7.45%)	1.254 (1.113~1.413)	<0.001
Likelihood Ratio test		-	<0.001

Data were adjusted for all the factors of Adjusted III model of Table 2.

Table 4. Comparison of D-dimer with other laboratory indicators for predicting post-stroke epilepsy using AUC.

Indicators	AUC (95% CI)	*p*
D-dimer	0.822 (0.810-0.835)	ref
AST	0.810 (0.795-0.825)	0.123
ALT	0.617 (0.599-0.634)	<0.001
BUA	0.538 (0.517-0.560)	<0.001
Creatinine	0.571 (0.555-0.588)	<0.001
Urea	0.527 (0.507-0.547)	<0.001

Table 5. Incremental predictive value of D-dimer (NRI and IDI).

Model	NRI (95% CI)	*p*	IDI (95% CI)	*p*
Baseline risk model		ref		ref
Baseline risk model+ D-dimer	0.8438 (0.7829-0.9047)	< 0.001	0.2031 (0.1826-0.2236)	< 0.001