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ORIGINAL RESEARCH

Delirium is a Potential Predictor of Unfavorable Long-term Functional Outcomes in Patients with Acute Ischemic Stroke: A Prospective Observational Study

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Purpose: Delirium is an acute fluctuating impairment of attention and awareness, common in acute ischemic stroke (AIS). This study aimed to evaluate the prognostic significance of delirium for neurological function at 3 months post-stroke, and develop a predictive model integrating delirium and biomarkers to enhance prognostic accuracy.

Methods: We conducted a prospective cohort study of patients admitted to the stroke unit (n=722). All patients were screened for daily delirium during clinical care. Plasma biomarkers were measured within 24 hours after admission. The main outcomes were evaluated with the 3-months modified Rankin Scale (mRS).

Results: Delirium developed in 10.2% of patients during the acute phase of stroke. Patients with post-stroke delirium (PSD) was significantly older (median age 74 vs 68 years, $P<0.001$), more likely to have pre-stroke cognitive impairment (14.9% vs 4.8%, $P=0.001$), a higher prevalence of cardiovascular history (35.1% vs 16.2%, $P<0.001$). PSD was also associated with higher scores of NIHSS (14.3 vs 9.1, $P<0.001$) and greater scores of mRS (3.0 vs 1.5, $P<0.001$) at admission. PSD patients showed worse outcomes, with elevated NIHSS and mRS scores at discharge and 3-month follow-up, as well as higher mortality rates (5.4% vs 1.4%, $P=0.025$). Biomarker analysis revealed increased plasma levels of inflammatory (white blood cells, neutrophils, C-reactive protein) and coagulation biomarkers (fibrinogen, D-dimer) in PSD patients, particularly those with poorer outcomes ($P<0.01$). Our model, which incorporated delirium and biomarkers of inflammation and coagulation dysfunction, demonstrated strong predictive accuracy for adverse outcomes at 3 months with an AUC of 0.779 (95% CI=0.736–0.822), with clinical utility confirmed by decision curve analysis.

Conclusion: PSD is a strong independent predictor of poor 3-month outcomes in AIS, including higher mortality and disability. Our findings highlight the critical role of inflammation and coagulation dysfunction in the pathogenesis of PSD. Furthermore, we present the clinical utility of a predictive model integrating delirium and relevant biomarkers to assess the risk of adverse outcomes at 3 months, suggesting potential targets for intervention.

Keywords: acute ischemic stroke, AIS, delirium, post-stroke delirium, PSD, biomarkers, modified rankin scale, mRS, neuroinflammation, coagulation dysfunction

Introduction

Delirium is s complex neuropsychiatric disorder, characterized by a disturbance of attention, consciousness, cognitive, and behavior, which shows an acute onset and fluctuates in severity during the day.[1] It is common in elderly hospitalized

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adults, correlated with a longer length of hospital stay, functional decline during hospitalization, adverse effect on functional outcomes, and higher risk of death.[1] Delirium is a frequent neuropsychiatric complication of several healthcare settings, arising from a wide range of factors including medical conditions, diseases, substances, drug abuse or combined causation.[2,3] With occurrence rates of up to one-third of general medical patients aged 70 years or older, the condition is present in half of these patients on admission and develops during hospitalization in the other half.[4] Delirium is extremely common but can be challenging to diagnose, representing a medical condition that is severe, costly and recognized as an indicator of patient safety.[5] However, if recognized early, delirium can be prevented in a large percentage of cases. It is often reversible with the timely identification and treatment of the underlying cause.[3]

Delirium is commonly classified by psychomotor presentation as hyperactive, hypoactive and mixed syndromes.[6] Hyperactive delirium is characterized by agitation, restlessness, hallucinations and aggression.[6,7] Hypoactive delirium is characterized by somnolence, lethargy and inattentiveness, and is less frequently recognized.[6,7] Hyperactive and mixed delirium are associated with higher symptom fluctuation than hypoactive delirium.[7] Besides, many patients exhibit a mixed picture, with symptoms predominantly of hypoactive delirium and occasional agitation.[6,8]

Delirium is best understood as a multifactorial behavioral syndrome predominantly affecting elder patients. Mounting evidence indicates that various interacting biological factors contribute to disruption of large-scale neuronal networks in the brain, resulting in sudden cognitive dysfunction.[9,10] The findings of Glumac et al offered a foundational perspective that could be extended to explore the impact of delirium on outcomes in acute ischemic stroke. Their emphasis on the association between cognitive decline and adverse long-term outcomes underscored the potential prognostic implications of delirium.[11] Additionally, Rollo et al recently demonstrated that delirium was an independent predictor of poor functional recovery in the context of acute stroke.[12] Incorporating these findings would offer valuable understanding of delirium as a predictor of unfavorable outcomes.

Delirium is usually related with acute physical stressors, such as surgery, pulmonary infection, intensive care, and acute stroke.[9] Stroke, characterized by the sudden onset of neurological deficits likely caused by vascular events, is a well-established risk factor for delirium.[13] Globally, it is the second-leading cause of mortality and the third most significant contributor to combined death and disability.[14] Delirium affects approximately one in four patients with acute stroke and is associated with significantly worse clinical outcomes.[15,16] However, post-stroke delirium (PSD) remains an underexplored area, despite growing evidence suggesting that delirium episodes may not always be fully reversible.[7,17] There are only a small number of studies on delirium in the context of stroke, and PSD remains understudied with little known about its effect on clinical outcomes and long-term prognosis.[18] Furthermore, the limited published data on prognosis of delirium in AIS shows inconsistent findings.[6,19] Despite being a frequent complication of stroke, the pathophysiological mechanisms of delirium remain poorly understood, with leading hypotheses involving neurotransmitter imbalance and neuroinflammatory processes.[9] This gap in understanding highlights the urgent need for further research and development of targeted interventions.

The purpose of this prospective, observational study was to measure the prevalence of delirium in the acute ischemic stroke (AIS) in the setting of a stroke unit, identify the clinical features and risk factors of delirium post-stroke and determine the outcomes of PSD. In addition, we aim to develop a clinical model integrating delirium and biomarkers to enhance its predictive performance for 3-month outcomes post-stroke. We hypothesized that PSD would be an independent predictor of poor functional outcomes and increased mortality at 3 months after AIS, and that the integration of biomarkers into the prediction model would enhance the predictive accuracy of this model for long-term outcomes.

Materials and Methods

Participants

In this prospective observational study, we have compiled and analyzed clinical data pertaining to patients with AIS, admitted to the First Affiliated Hospital of Wenzhou Medical University between July 2021 and December 2023. The study adhered stringently to the ethical guidelines outlined in the Declaration of Helsinki. Approval was granted by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (approval no.YS-2018026). Prior to

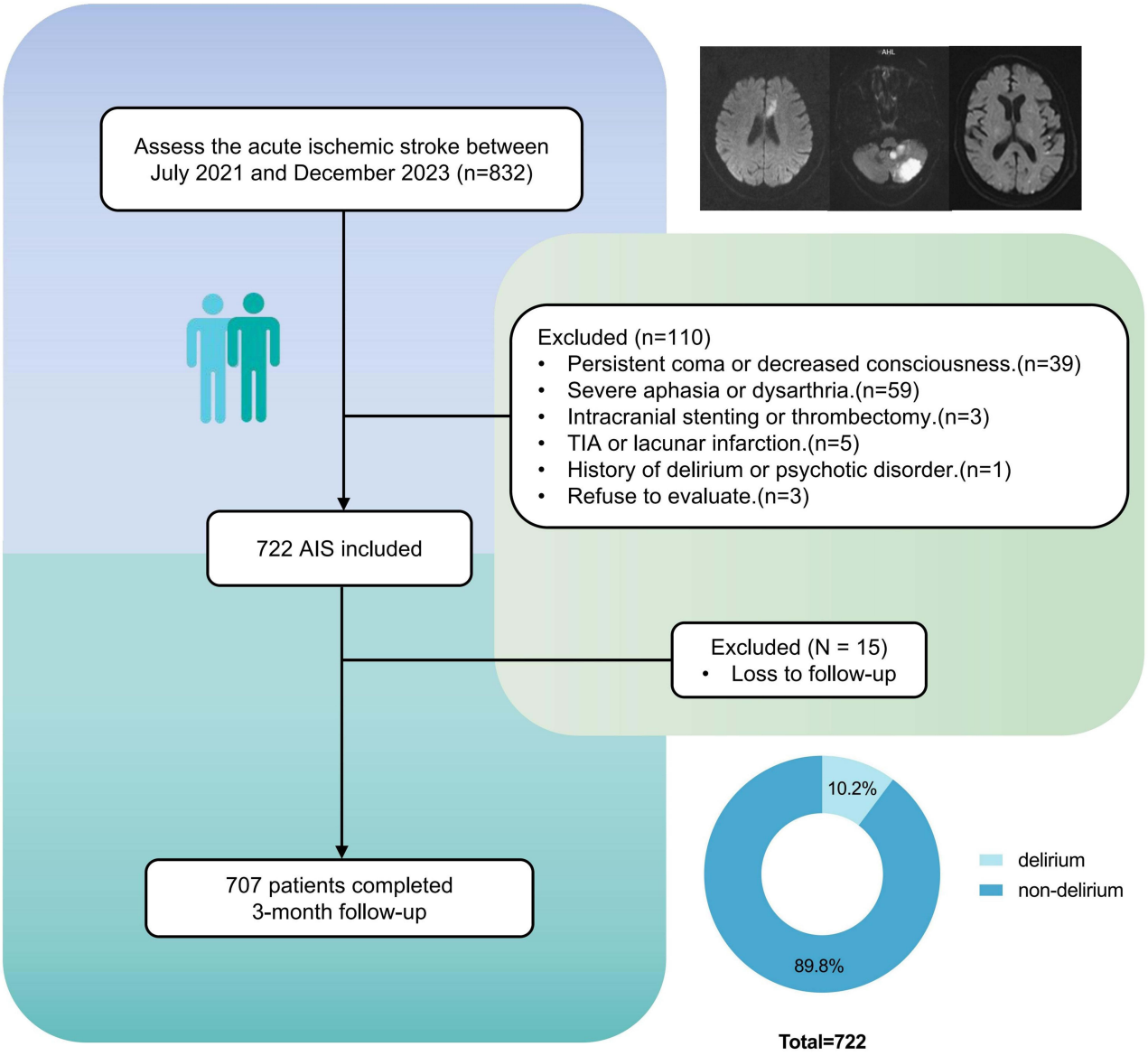

Figure 1 Flow chart of enrolled patients.
Abbreviations: AIS, acute ischemic stroke; TIA, transient ischemic attack.

participation, all eligible patients provided informed consent, ensuring that their data remained anonymous throughout the study period.

The inclusion criteria for this study were as follows: (a) AIS confirmed by cranial CT or MRI; (b) age ≥ 18 years; (c) admission to the hospital within a week of symptom onset; (d) ability and willingness to follow up. Conversely, patients were excluded if they exhibited: (a) persistent coma or decreased consciousness during the evaluation period; (b) severe aphasia or dysarthria; (c) TIA or lacunar infarction; (d) intracranial stenting or thrombectomy; (e) history of delirium and mental disorders; (f) incomplete medical records. The flow chart is shown in Figure 1.

Diagnostic Criteria for AIS and Delirium

The clinical presentation of ischemic stroke involves the sudden onset of a focal clinical deficit, referable to a specific site in the central nervous system (CNS). Symptoms can include hemiparesis, hemianesthesia, aphasia, homonymous hemianopia and hemi spatial inattention. It requires differentiation from common mimics including migraine, seizures,

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vestibular disturbances, metabolic disturbances and functional disorders. Subsequently, an experienced neurologist confirms the diagnosis through neuroimaging modalities, MRI or CT.[20] Ischemic stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria.[21]

Commencing from the time of admission and extending until discharge, patients underwent daily delirium screening, facilitated by an experienced neurologist. This screening was standardized to occur at a fixed time each day (5–6 p.m)., employing the 4 'A's Test (4AT).[22,23] Delirium was subsequently confirmed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), in conjunction with the Delirium Rating Scale Revised 98 (DRS-R-98).[24,25] Additionally, the severity of delirium symptoms was appraised using the DRS-R-98 scale and further typed according to specific DRS-R-98 entries and clinical presentations.

Neurological Functions Evaluation

Stroke severity was assessed upon admission by an experienced neurologist using the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale for Stroke (mRS).[26,27] To identify individuals with pre-stroke dementia, the Questionnaire on Cognitive Decline in the Elderly (IQCODE) was administered.[28]

Measurement of Plasma Biomarkers

Plasma biomarkers were measured within 24 hours of admission, under fasting conditions, and obtained through blood centrifugation. The laboratory results encompassed white blood cells (WBC), neutrophils (N), monocytes (M), lymphocytes (L), C-reactive protein (CRP), prothrombin time (PT), prothrombin activity (PTA), international normalized ratio (INR), fibrinogen (FIB), activated partial thromboplastin time (APTT), activated partial thromboplastin time ratio (APTT ratio), thrombin time (TT), and D-dimer. Blood cell counts were examined using an automated hematology analyzer (Mindray, BC-6800 vet, China). Biochemistry parameters were tested by an AU5800 (Beckman Coulter). The coagulation analyses were performed using an STA R Max Coagulation Analyzer (Stago).

Data Collection and Outcome Measures

Baseline characteristics were collected using an electronic medical record system. Upon admission, the following baseline characteristics were extracted: demographic parameters (age, sex), clinical characteristics (years of education, thrombolysis, NIHSS score, mRS score, indwelling urinary catheterization), medical history (cardiovascular accidents, atrial fibrillation, cognitive impairment), laboratory characteristics, and data from discharge and 3-month follow-up (NIHSS score, mRS score, death).

Follow-up

A dedicated follow-up staff evaluated patients' neurological prognosis using the mRS on the day of discharge. Patients or their family members were contacted by telephone three months after discharge to assess their activities of daily living (ADL) and mRS.[29] Importantly, the follow-up staff remained unaware of the results of the delirium screening to avoid potential bias.

Statistical Analysis

The continuous Statistics analysis and graphical representations was conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, NY, USA), R software (https://www.r-project.org/, version 4.3.1) and GraphPad Prism (version 10.0, 2024). For the independent two-sample *t*-test, the sample size required for the study was analyzed using the pwr package in R software. Initially, the Kolmogorov–Smirnov Test was administered to ascertain the normality of the distributed variables. Normally distributed continuous variables were compared using Student's *t*-test for two groups and one-way analysis of variance (ANOVA) for multiple groups, and results were expressed as mean ± standard deviation (SD). Conversely, non-normally distributed continuous variables were analyzed with the Mann–Whitney *U*-Test for two groups and the Kruskal–Wallis Test for three or more groups, and results were reported as medians with interquartile ranges (IQR). Categorical variables were analyzed utilizing χ^2-Test or Fisher's exact Test, and results were presented as numbers (n) and percentages (%).

To enhance clinical applicability, we identified all risk factors associated with poor three-month prognosis through a three-step process. First, potential factors were selected based on clinicians' experience and observed differences in baseline characteristics, including clinical features and laboratory indicators among patients. Second, a univariate binary logistic regression model was employed for further selection of risk factors. Finally, a multivariate binary logistic regression model was used for stepwise backward selection to determine the final set of risk factors.

On this basis, a predictive model for joint biomarker indicators of delirium was constructed using the nomogram package in R. Subsequently, the model underwent rigorous evaluation to ascertain its capabilities in identification, calibration, and clinical validation. The discriminative performance of the model was quantified using the area under the receiver operating characteristic curve (AUC-ROC). To verify the model's calibration, the Hosmer-Lemeshow goodness-of-fit test was employed, complemented by bootstrap correction plots with 1,000 samples. Furthermore, the clinical utility of the nomogram was appraised using decision curve analysis (DCA), a methodology tailored for assessing predictive model effectiveness. The significance level was set at a two-tailed $p < 0.05$.

To elucidate the potential mechanisms linking delirium to a poor 3-month prognosis, mediated effects analyses were carried out using the PROCESS V4.2 by Andrew F. Hayes in SPSS. We took delirium as the independent variable, and 3-month mRS as the dependent variable, to explore whether neutrophil, D-dimer levels, and other indicators play a mediating effect.

Results

Patient Baseline and Clinical Characteristics

During the recruitment period, a total of 832 patients with stroke were admitted to the stroke unit. After screening for inclusion and exclusion criteria, 722 patients were included for analysis. Of the 722 patients, 15 patients were lost at the 3-months follow-up. The final study cohort consisted of 707 patients. In this population, 74/722 (10.2%) patients developed delirium during the acute phase of stroke. A consort diagram depicting the enrollment process was reported in Figure 1. The median age of the study population was 68 years (interquartile range, 60–75); 499 of 727 (69.1%) were men (Table 1). Demographic and clinical baseline features of the study cohort, and of the subgroups with and without delirium, were described in Table 1. Stroke causes were large artery atherosclerosis in 60.7% (n=437), cardioembolism in 15.4% (n=111), small-vessel occlusion in 19% (n=137), other causes in 1.0% (n=7), and undetermined in 3.9% (n=28) (Table 1), by Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[14]

Table 1 Baseline Characteristics of Patients with Stroke According to the Univariate Logistic Regression Analyses of Delirium and Associated Predisposing Factor

	Total (n=722)	Non-Delirium (n=648)	Delirium (n=74)	OR (95% CI)	*P*-Value
Patient characteristics					
Male, n (%)	499 (69.1)	448 (69.1)	51 (68.9)	0.990 (0.589–1.665)	0.969
Age (years)	68.00 [60.00, 75.00]	68.00 [59.00, 74.00]	74.00 [68.00, 81.75]	1.050 (1.026–1.074)	<0.001
Thrombolysis, n (%)	89 (12.3)	77 (11.9)	12 (16.2)	1.435 (0.740–2.783)	0.285
Education (years)	6.00 [0.00, 9.00]	6.00 [0.00, 9.00]	6.00 [0.00, 6.00]	0.917 (0.862–0.975)	0.006
Cardiovascular accidents history, n (%)	131 (18.1)	105 (16.2)	26 (35.1)	2.801 (1.664–4.716)	<0.001
Atrial fibrillation, n (%)	78 (10.8)	61 (9.4)	17 (23.0)	2.865 (1.569–5.233)	0.001
Cognitive impairment, n (%)	42 (5.8)	31 (4.8)	11 (14.9)	3.475 (1.666–7.248)	0.001
Admission mRS score	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	4.00 [2.00, 4.00]	1.625 (1.337–1.975)	<0.001
Admission NIHSS score	3.00 [2.00, 7.00]	3.00 [1.00, 6.00]	8.00 [4.00, 13.00]	1.164 (1.115–1.214)	<0.001
Laboratory characteristics					
WBC ($\times 10^9$/L)	6.88 [5.72, 8.47]	6.77 [5.67, 8.34]	7.54 [6.53, 9.50]	1.156 (1.065–1.255)	0.001
N ($\times 10^9$/L)	4.69 [3.68, 6.16]	4.57 [3.61, 6.01]	5.50 [4.64, 7.24]	1.184 (1.091–1.284)	<0.001
M ($\times 10^9$/L)	0.43 [0.34, 0.53]	0.42 [0.34, 0.52]	0.47 [0.39, 0.63]	9.240 (2.578–33.118)	0.001
L ($\times 10^9$/L)	1.46 [1.14, 1.86]	1.49 [1.16, 1.87]	1.29 [0.99, 1.61]	0.485 (0.298–0.788)	0.003

(*Continued*)

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Table 1 (Continued).

	Total (n=722)	Non-Delirium (n=648)	Delirium (n=74)	OR (95% CI)	*P*-Value
CRP (mg/L)	6.20 [2.40, 13.00]	5.70 [2.30, 12.00]	11.00 [5.10, 26.25]	1.008 (1.002–1.014)	0.013
PT (s)	13.50 [13.00, 14.00]	13.50 [13.00, 14.00]	13.90 [13.40, 14.40]	1.147 (1.001–1.314)	0.048
PTA (%)	93.00 [86.00, 101.00]	94.00 [87.00, 102.00]	87.50 [82.25, 95.75]	0.980 (0.964–0.995)	0.011
INR	1.04 [0.99, 1.10]	1.04 [0.99, 1.09]	1.08 [1.02, 1.13]	3.074 (0.831–11.364)	0.092
FIB (g/L)	3.01 [2.65, 3.59]	2.98 [2.64, 3.55]	3.41 [2.85, 3.94]	1.359 (1.078–1.713)	0.009
APTT (s)	35.70 [33.20, 38.60]	35.65 [33.20, 38.42]	36.45 [33.00, 39.48]	0.999 (0.980–1.020)	0.959
APTT ratio	0.99 [0.92, 1.07]	0.99 [0.92, 1.07]	1.01 [0.91, 1.10]	1.312 (0.338–5.101)	0.695
TT (s)	17.20 [16.60, 18.10]	17.20 [16.60, 18.02]	17.20 [16.45, 18.20]	0.980 (0.893–1.075)	0.672
D-dimer (mg/L)	0.40 [0.22, 0.96]	0.38 [0.22, 0.92]	0.80 [0.37, 1.75]	1.175 (1.068–1.292)	<0.001
Imaging characteristics					
TOAST, n (%)					
Large-artery atherosclerosis	437 (60.7)	389 (60.1)	48 (65.8)	1.674 (0.939–2.983)	0.081
Cardioembolism	111 (15.4)	92 (14.2)	19 (26.0)	0.244 (0.086–0.689)	0.008
Small-vessel occlusion	137 (19.0)	133 (20.6)	4 (5.5)	1.351 (0.159–11.459)	0.783
Other	7 (1.0)	6 (0.9)	1 (1.4)	0.300 (0.040–2.259)	0.243
Undetermined	28 (3.9)	27 (4.2)	1 (1.4)	-	-
Intracranial occlusion location, n (%)					
Temporal lobe	389 (83.9)	329 (50.8)	60 (81.1)	2.536 (1.451–4.433)	0.001
Insular lobe	348 (48.2)	300 (46.3)	48 (64.9)	2.385 (1.220–4.662)	0.011
Basal ganglia	434 (60.1)	379 (58.5)	55 (74.3)	1.312 (0.742–2.320)	0.350
Anterior and posterior circulation, n (%)					
Anterior circulation	509 (70.9)	451 (69.9)	58 (79.5)	0.543 (0.284–1.035)	0.063
Posterior circulation	184 (25.6)	172 (26.7)	12 (16.4)	1.111 (0.321–3.839)	0.868
Both	25 (3.5)	22 (3.4)	3 (4.1)	-	1.000
Discharge characteristics					
Discharge NIHSS score	2.00 [1.00, 5.00]	2.00 [1.00, 4.75]	6.00 [3.00, 12.00]	1.166 (1.11.0–1.224)	<0.001
Discharge mRS score	2.00 [1.00, 3.00]	1.00 [1.00, 3.00]	4.00 [2.00, 4.00]	1.906 (1.580–2.299)	<0.001
mRS>2 at discharge, n (%)	265 (36.7)	211 (32.6)	54 (73.0)	5.592 (3.263–9.583)	<0.001
Discharge 3-month mRS score	1.00 [1.00, 2.00]	1.00 [0.00, 2.00]	3.00 [1.00, 5.00]	1.771 (1.534–2.044)	<0.001
Discharge 3-month death, n (%)	13 (1.8)	9 (1.4)	4 (5.4)	3.962 (1.189–13.199)	0.025

Notes: Comparing baseline characteristics of AIS with delirium and non-delirium groups; Finding independent risk factors for developing delirium using logistic regression. **Abbreviations**: WBC, White blood cells; N, Neutrophils; M, Monocyte; L, Lymphocytes; CRP, C-reactive protein; PT, Prothrombin time; PTA, Prothrombin time activity; INR, International normalized ratio; FIB, Fibrinogen; APTT, Activated par_x0002_tial thromboplastin time; TT, Thrombin time; NIHSS, National insti_x0002_tutes of health stroke scale; mRS, modified Rankin Scale; TOAST, the trial of ORG 10172 in acute stroke. OR, odds ratios; CI, Confidence interval;

Stroke localization was as follows: temporal lobe involvement in 83.9% (n=389), insular cortex involvement in 48.2% (n=348), and basal ganglia involvement in 60.1% (n=434). Anterior circulation stroke accounted for 70.9% (n=509), posterior circulation stroke for 25.6% (n=184), and involved both anterior and posterior circulation stroke for 3.5% (n=25).

Comparison of Clinical Characteristics Between Delirium and No Delirium Patients

Patients who developed delirium (74.00 [68.00, 81.75]) during their hospitalization, as compared to those who did not develop delirium (68.00 [59.00, 74.00]), tended to be older (P<0.001). Gender was not significant predictors for delirium. In the univariate comparison between subgroups with and without delirium, the subgroup with delirium more often had prestroke cognitive impairment (14.9% versus 4.8%, P=0.001), previous cardiovascular accidents history (35.1% versus 16.2%, P<0.001) and atrial fibrillation (23% versus 9.4%, P=0.001). Regarding to numerical variables, the subgroup with delirium had higher NIHSS scores and greater scores of mRS prestroke than the subgroup without delirium (P<0.001). A summary of the population characteristics is shown in Table 1. Unadjusted models (logistic regression with the group with delirium as the dependent variable), suggested associations between WBC, neutrophils, monocyte, CRP,

prothrombin time, fibrinogen, D-dimer variables with greater incidence of delirium than those without delirium (P<0.05) (Table 1). In the unadjusted models, significant associations were absorbed in the incidence of cardioembolism stroke (OR: 0.244; 95% CI=0.086–0.689, P=0.008), and infarct location in the temporal lobe (OR: 2.536; 95% CI=1.451–4.433, P=0.001) and the insular lobe (OR: 2.385; 95% CI=1.220–4.662, P=0.011) between patients with delirium and without delirium (Table 1).

Delirium Was Associated with Poor Functional Outcomes in AIS Patients

Clinical outcomes were worse in patients who developed delirium during their hospitalization (Table 1). In this study, discharge NHISS scores were higher for patients who developed delirium (P<0.001). For the unadjusted models (logistic regression with the group with delirium as the dependent variable), obvious associations were found for discharge NHISS scores (OR: 1.166; 95% CI=1.110–1.224) and mRS scores (OR: 1.906; 95% CI=1.580–2.229) (P<0.001) (Table 1). Worse outcomes (mRS>2) were more frequent in patients with delirium compared to non-delirium (73% versus 32.6%; OR: 5.592; 95% CI=3.263–9.583, P<0.01) at discharge (Table 1).

Our study found delirium remained as an independent predictor of poor functional outcome and mortality at 3 months. At 3-month follow-up, the mortality in the delirium group was higher than that in the non-delirium group (5.4% vs 1.4%; OR: 3.962; 95% CI=1.189–13.199, P=0.025) (Table 1). Poor outcomes (mRS>2) were more frequent in patients with delirium compared to non-delirium (OR: 1.771; 95% CI=1.534–2.044, P<0.01) at 3 months (Table 1) (Figure 2). At discharge 3 months post-stroke, patients with poor outcomes (mRS>2) exhibited significantly higher plasma levels of WBC, neutrophils, monocyte, CRP, prothrombin time, international normalized ratio, fibrinogen and D-dimer (P<0.01) compared to the subgroup with favorable outcomes (mRS≤2). Conversely, plasma levels of lymphocytes and prothrombin time activity counted lower in the poor prognosis group (Table 2). Age, gender, atrial fibrillation, cognitive impairment, WBC, neutrophils, monocyte, CRP, fibrinogen, D-dimer and delirium were identified to be associated with poor outcomes at 3 months in the univariate logistic regression (Table 3). For the multivariate logistic regression, independent associations were observed in age (OR: 1.026; 95% CI=1.003–1.049, P=0.026), neutrophils (OR: 1.890; 95% CI=1.289–2.733, P=0.01), D-dimer (OR: 1.200; 95% CI=1.047–1.376, P=0.009) and delirium (OR: 3.853; 95% CI=2.068–7.178, P=0.000). The independent determinants of poor outcomes are shown in Table 3.

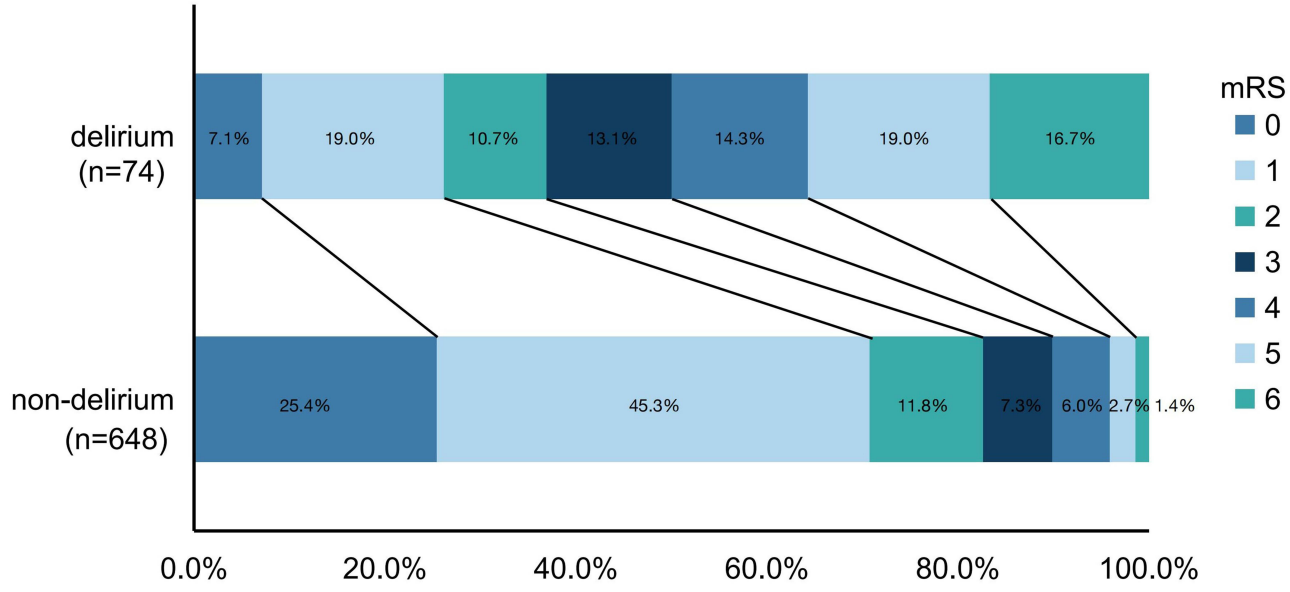

Figure 2 Comparison of 3-month mRS in AIS patients with delirium versus non-delirium.
Abbreviations: mRS, modified Rankin Scale; AIS, acute ischemic stroke.

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Table 2 Baseline Characteristics Between 3-month mRS≤2 and 3-month mRS>2 Groups

	Total (n=707)	mRS≤2 (n=555)	mRS>2 (n=152)	*P*-Value
Patient characteristics				
Male, n (%)	489 (69.2)	394 (71.0)	95 (62.5)	0.056
Age (years)	68.00 [60.00, 75.00]	67.00 [58.00, 73.50]	73.00 [67.00, 80.25]	<0.001
Thrombolysis, n (%)	89 (12.3)	62 (11.2)	26 (17.1)	0.068
Education (years)	6.00 [0.00, 9.00]	6.00 [6.00, 9.00]	6.00 [0.00, 6.00]	0.001
Cardiovascular accidents history, n (%)	131 (18.1)	94 (16.9)	35 (23.0)	0.109
Atrial fibrillation, n (%)	78 (10.8)	49 (8.8)	29 (19.1)	0.001
Cognitive impairment, n (%)	42 (5.8)	24 (4.3)	18 (11.8)	0.001
Admission mRS score	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]	4.00 [4.00, 4.00]	<0.001
Admission NIHSS score	3.00 [2.00, 7.00]	3.00 [1.00, 5.00]	10.00 [7.00, 14.00]	<0.001
Delirium	74 (10.2)	31 (5.6)	43 (28.3)	<0.001
Laboratory characteristics				
WBC (×109/L)	6.88 [5.72, 8.47]	6.63 [5.54, 8.05]	8.11 [6.80, 9.73]	<0.001
N (×109/L)	4.69 [3.68, 6.16]	4.38 [3.46, 5.65]	5.90 [4.77, 7.33]	<0.001
M (×109/L)	0.43 [0.34, 0.53]	0.42 [0.34, 0.51]	0.47 [0.39, 0.61]	<0.001
L (×109/L)	1.46 [1.14, 1.86]	1.51 [1.17, 1.90]	1.33 [1.00, 1.73]	<0.001
CRP (mg/L)	6.20 [2.40, 13.00]	5.00 [2.10, 11.20]	9.74 [4.97, 19.52]	<0.001
PT (s)	13.50 [13.00, 14.00]	13.50 [13.00, 14.00]	13.70 [13.20, 14.30]	<0.001
PTA (%)	93.00 [86.00, 101.00]	94.00 [87.00, 102.00]	90.50 [83.00, 97.00]	<0.001
INR	1.04 [0.99, 1.10]	1.04 [0.99, 1.09]	1.06 [1.02, 1.12]	<0.001
FIB (g/L)	3.01 [2.65, 3.59]	2.95 [2.60, 3.51]	3.30 [2.84, 3.98]	<0.001
APTT (s)	35.70 [33.20, 38.60]	35.70 [33.20, 38.32]	36.00 [33.30, 39.50]	0.107
APTT ratio	0.99 [0.92, 1.07]	0.99 [0.92, 1.06]	1.00 [0.93, 1.10]	0.124
TT (s)	17.20 [16.60, 18.10]	17.20 [16.60, 18.00]	17.40 [16.50, 18.10]	0.988
D-dimer (mg/L)	0.40 [0.22, 0.96]	0.35 [0.21, 0.86]	0.77 [0.37, 1.69]	<0.001

Notes: Data are expressed as mean (SD), median [IQR] or n (%); P values considered statistically significant.
Abbreviations: WBC, White blood cells; N, Neutrophils; M, Monocyte; L, Lymphocytes; CRP, C-reactive protein; PT, Prothrombin time; PTA, Prothrombin time activity; INR, International normalized ratio; FIB, Fibrinogen; APTT, Activated par_x0002_tial thromboplastin time; TT, Thrombin time; NIHSS, National insti_x0002_tutes of health stroke scale; mRS, modified Rankin Scale.

Table 3 Univariate and Multivariate Binary Logistic Regression Analysis for the Potential Factors Associated With 3-month Poor Prognosis

Variables	Univariate Binary Logistic Regression			Multivariate Binary Logistic Regression		
	β	*P*-Value	OR (95% CI)	β	*P*-Value	OR (95% CI)
Age	0.048	0.000	1.049 (1.031–1.067)	0.026	0.026	1.026 (1.003–1.049)
Gender	0.384	0.045	1.468 (1.008–2.139)	−0.439	0.094	0.645 (0.386–1.078)
AF	0.888	0.000	2.430 (1.474–4.005)	0.592	0.080	1.808 (0.931–3.512)
CI*	1.089	0.001	2.972 (1.567–5.635)	0.403	0.362	1.496 (0.629–3.558)
WBC	0.240	0.000	1.272 (1.181–1.369)	−0.392	0.047	0.676 (0.459–0.996)
N	0.278	0.000	1.321 (1.222–1.428)	0.637	0.001	1.890 (1.289–2.733)
M	2.798	0.000	16.410 (5.553–48.497)	0.578	0.535	1.783 (0.288–11.052)
CRP	0.008	0.007	1.008 (1.012–1.015)	−0.010	0.040	0.990 (0.980–1.000)
PT	0.081	0.167	1.085 (0.967–1.217)	-	-	-
APTT	0.017	0.254	1.017 (0.988–1.046)	-	-	-
FIB	0.380	0.000	1.462 (1.213–1.761)	0.257	0.087	1.293 (0.964–1.734)
D-dimer	0.159	0.001	1.173 (1.071–1.284)	0.183	0.009	1.200 (1.047–1.376)
Delirium	1.897	0.000	6.668 (4.021–11.058)	1.349	0.000	3.853 (2.068–7.178)

Notes: Univariate and multivariate logistic regression analyses of susceptibility factors associated with 3-month adverse prognosis in stroke patients; Delirium, neutrophils, D-dimer, and age considered risk factors for poor prognosis at 3 months.
Abbreviations: AF, Atrial fibrillation; CI*, Cognitive impairment; WBC, White blood cells; N, Neutrophils; M, Monocyte; L, Lymphocytes; CRP, C-reactive protein; PT, Prothrombin time; APTT, Activated par_x0002_tial thromboplastin time; FIB, Fibrinogen; OR, odds ratio; CI, confidence interval.

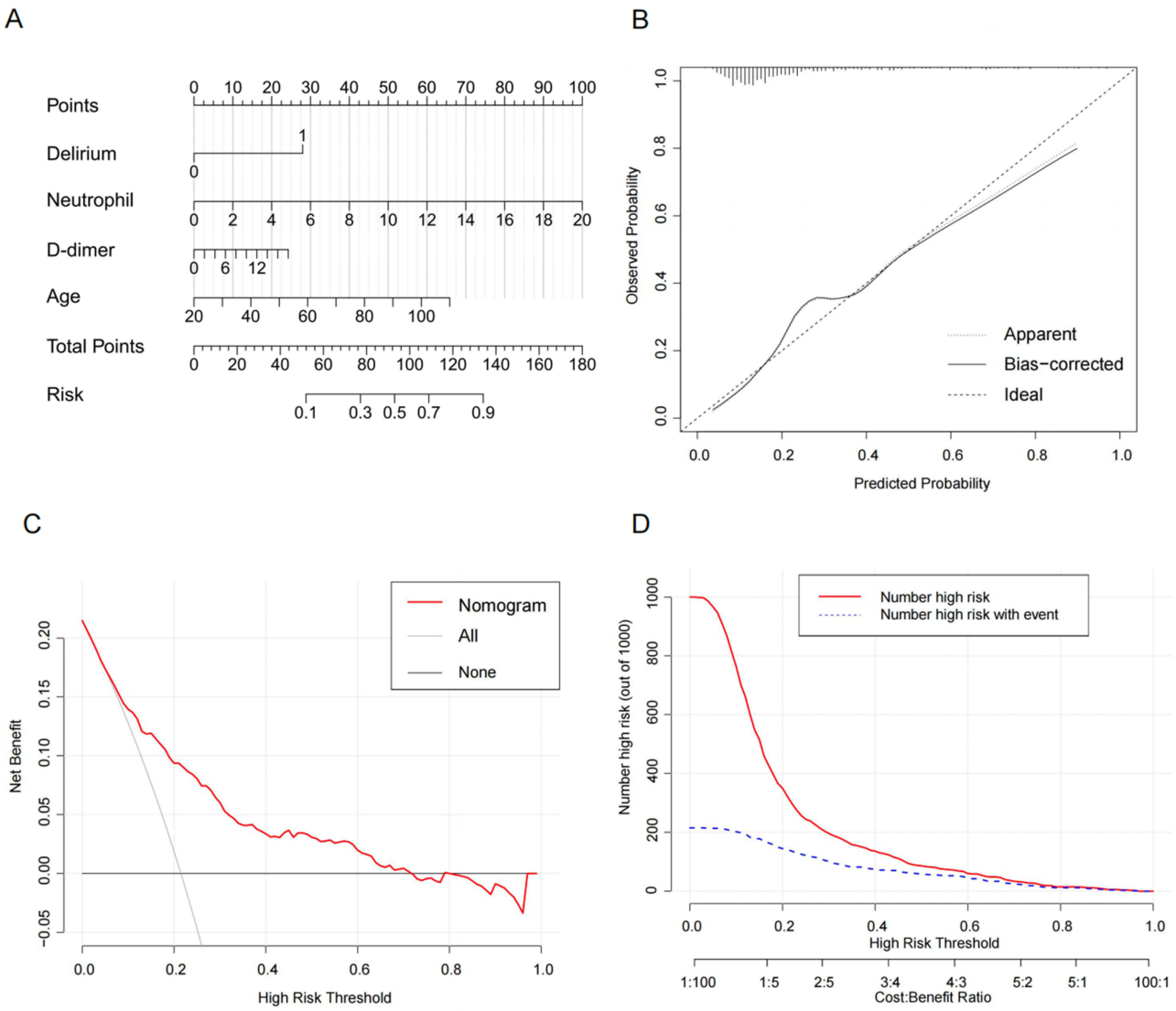

Figure 3 Nomogram and its validation of effectiveness.
Notes: (**A**), Nomogram was plotted based on four optimal predictors (Delirium, Neutrophil,D-dimer and Age) to predict the neurological function outcome in AIS patients at 3 months; (**B**), Calibration plots of the nomogram; (**C**), Decision curve analysis (DCA) for the predictive model; (**D**), Clinical impact curves for the predictive model.
Abbreviations: AIS, acute ischemic stroke; DCA, Decision curve analysis.

About forty-five percent of patients (n=33) with stroke developed delirium within 24 hours of admission and fifty-five percent of patients (n=41) occurred after 24 hours. The onset timing of delirium was not significantly associated with neurological function at discharge, mortality and the outcome at 3 months (Table S1). Motor subtypes were hyperactive in 55% (n=41), hypoactive in 23% (n=17), and mixed in 22% (n=16). Our analysis revealed that patients experiencing delirium suppression tended to have poorer outcomes, but the association did not reach statistical significance (Table S2).

Construction of Nomogram Models for Predicting the Progression of AIS

Based on the results of multifactorial logistic regression analysis, we developed a nomogram model to visualize individual risk estimates and facilitate intuitive prediction of the 3-month neurological function for patients with AIS (Figure 3A). In the nomogram, each predictor was assigned a specific point, and the total points in the nomogram were used to estimate the risk of adverse outcomes at 3 months post-stroke. Our analysis revealed that the AUC for a model incorporating delirium, inflammation and coagulation biomarkers was higher than that included delirium combining with only one of these indicators (Figure 4A and B). Specifically, the model of delirium in conjunction with neutrophils and

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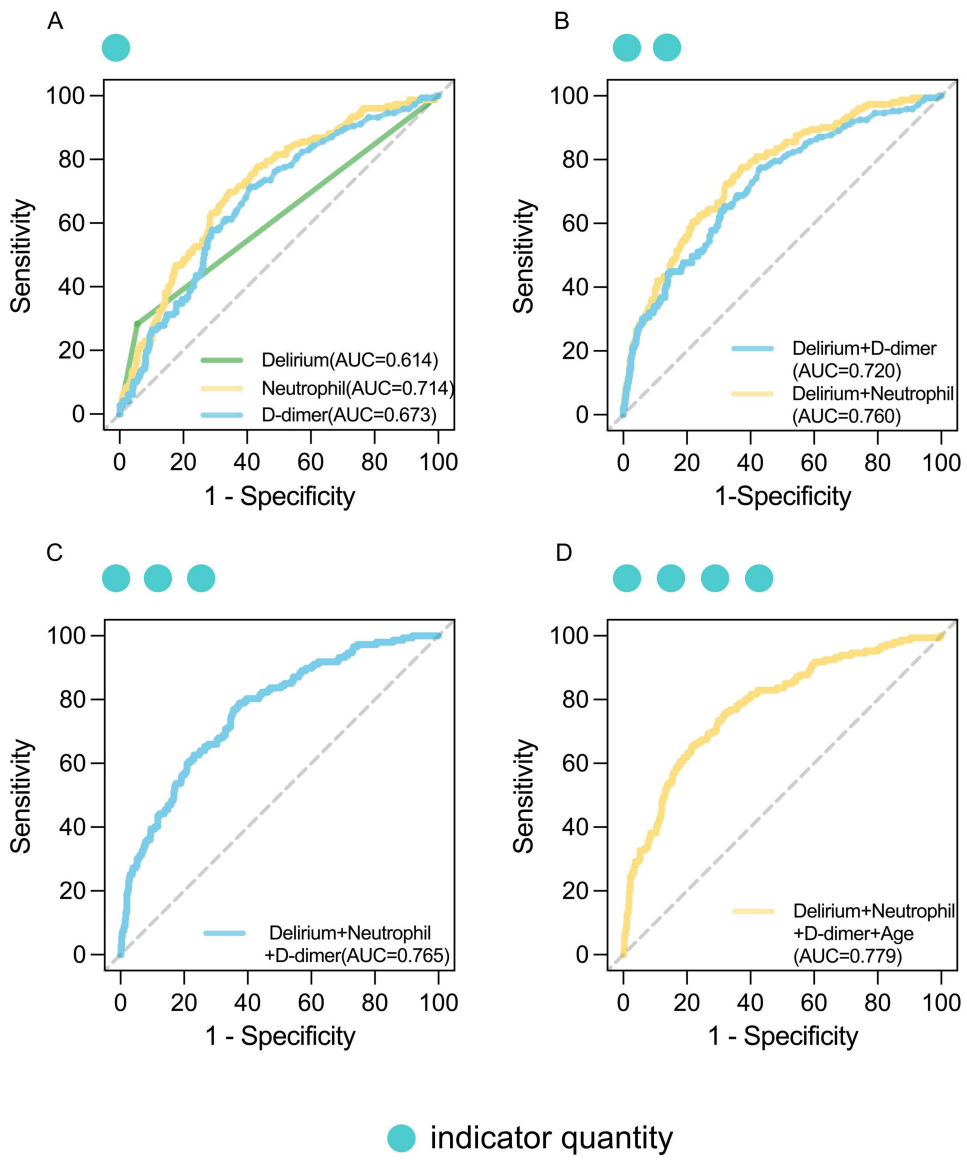

Figure 4 The AUC-ROC curves of predictive nomogram in (**A** - **D**).
Notes: AUC-ROC curve for predicting 3-month adverse prognosis using different numbers of indicators; (**A**), AUC-ROC of a single predictive indicator; (**B**), AUC-ROC of two predictive indicators; (**C**), AUC-ROC of three predictive indicator; (**D**), AUC-ROC of four predictive indicator.
Abbreviations: AUC-ROC, Area Under the Receiver Operating Characteristic Curve.

D-dimer yielded AUC=0.765 (95% CI=0.723–0.807, *P*=0.000) (Hosmer-Lemeshow test, *P*=0.043), indicating poor calibration. When age was added to the model, alongside delirium, neutrophil count, and D-dimer, the AUC increased to 0.779 (95% CI=0.736–0.822, *P*=0.000) (Hosmer-Lemeshow test, *P*=0.364), indicating this model provided a more robust prediction of 3-month poor outcomes in AIS patients (Figure 4C and D).

To ensure the internal validity of the nomogram, a 1,000-bootstrap analysis was conducted. The calibration curves (Figure 3B) indicated that the predicted risk closely aligned with the ideal 45°diagonal, demonstrating significant accuracy in predicting 3-month poor outcomes. To assess the clinical utility of these models, decision curve analysis (DCA) was employed. The result of DCA demonstrated the benefit of the models in a range from 0 to 1. The model demonstrated a clinically significant net benefit when the high-risk threshold ranged from 0.08 to 0.72, underscoring its predictive value in 3 months poor outcomes (Figure 3C). Furthermore, the clinical impact curve confirmed that the nomogram effectively predicted 3-month poor prognoses in AIS patients (Figure 3D).

Table 4 Binary Logistic Regression Analysis Between Delirium and AIS Patients With 3-month mRS >2

	3-Month mRS>2	
	OR (95% CI)	***P*-Value**
Unadjusted	6.668 (4.021–11.058)	0.000
Model 1	5.773 (3.431–9.713)	0.000
Model 2	2.816 (1.442–5.500)	0.002
Model 3	2.295 (1.139–4.624)	0.020

Notes: As a reference without delirium occurring. Model 1: After adjusting for age, gender.Model 2: After adjusting for age, gender, NIHSS score, history of atrial fibrillation, history of cognitive impairment. Model 3: After adjusting for age, gender, NIHSS score, history of atrial fibrillation, history of cognitive impairment, WBC, N, FIB, D-dimer.
Abbreviations: AIS, acute ischemic stroke; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval.

Mediation Analysis the Relationship Between Delirium and 3-month Functional Outcomes in AIS

Our study revealed that the incidence of poor outcomes at 3 months was significantly higher in the delirium group (58.1%) compared to those with non-delirium (Table 1). The results of the binary logistic stepwise regression, presented in Table 4, demonstrated a strong correlation between delirium and 3-month mRS scores. In the unadjusted model, patients with delirium experienced a substantially higher risk of poor outcomes compared to those without delirium (OR: 6.668; 95% CI= 4.021–11.058, $P<0.001$). In Model 1, adjusting for age and gender, delirium remained significantly associated with adverse outcomes (OR: 5.773; 95% CI= 3.431–9.713, $P<0.001$). Model 2, adjusting for NIHSS score, history of atrial fibrillation, and cognitive impairment, also demonstrated a significant association (OR: 2.816; 95% CI=1.442–5.500, $P=0.002$). To investigate the relationship between delirium, inflammation, coagulation, and neurological outcomes, inflammatory (WBC and neutrophils) and coagulation markers (fibrinogen and D-dimer) were included in Model 3. The results indicated that delirium was still significantly related with mRS scores (OR: 2.295; 95% CI=1.139–4.624, $P=0.020$); however, both the OR decreased and P values became more substantial, suggesting that inflammation and coagulation factors may mediate the impact of delirium on neurological outcomes.

The findings from binary logistic regression implied that the poor outcomes at 3-month in post-stroke with delirium may be linked to inflammatory and coagulation pathways (Table 4). To identify key mediators, we analyzed the mediating role of WBC, neutrophils, monocytes, CRP, PT, APTT, fibrinogen, and D-dimer between delirium and 3-month neurological outcome. Based on the total effect of delirium on the 3-month mRS (c=1.431; 95% CI=1.087–1.774, $P<0.001$), after adjusting for age, literacy, and history of atrial fibrillation, we found a mediating effect of WBC, neutrophils, and monocytes among inflammatory biomarkers. Of these, neutrophils accounted for the highest proportion (14%) of the total effect. As concerned coagulation indicators, there was a mediating effect of FIB and D-dimer, with D-dimer accounting for the largest proportion (4.3%) of the total effect. Other biomarkers, such as CRP, PT and APTT, did not show significant mediation effects (Figure 5).

In addition, as shown in Figure 6, we explored whether inflammation and coagulation factors jointly mediated the effect of delirium on 3-month poor outcomes by parallel mediation analysis. Based on the total effect of delirium on 3-month mRS (c=1.419; 95% CI=1.074–1.764, $P<0.001$), after adjustment for literacy, age, and atrial fibrillation history, we found that delirium co-influenced the 3-month neurological outcomes through monocytes (prop.=5.8%) and D-dimers (prop.=4.3%), as well as monocytes (prop.=5.4%) and fibrinogen (prop.=3.0%). This suggested that delirium may contribute to the poor 3-month outcomes via inflammatory and coagulation pathways (Figure 6).

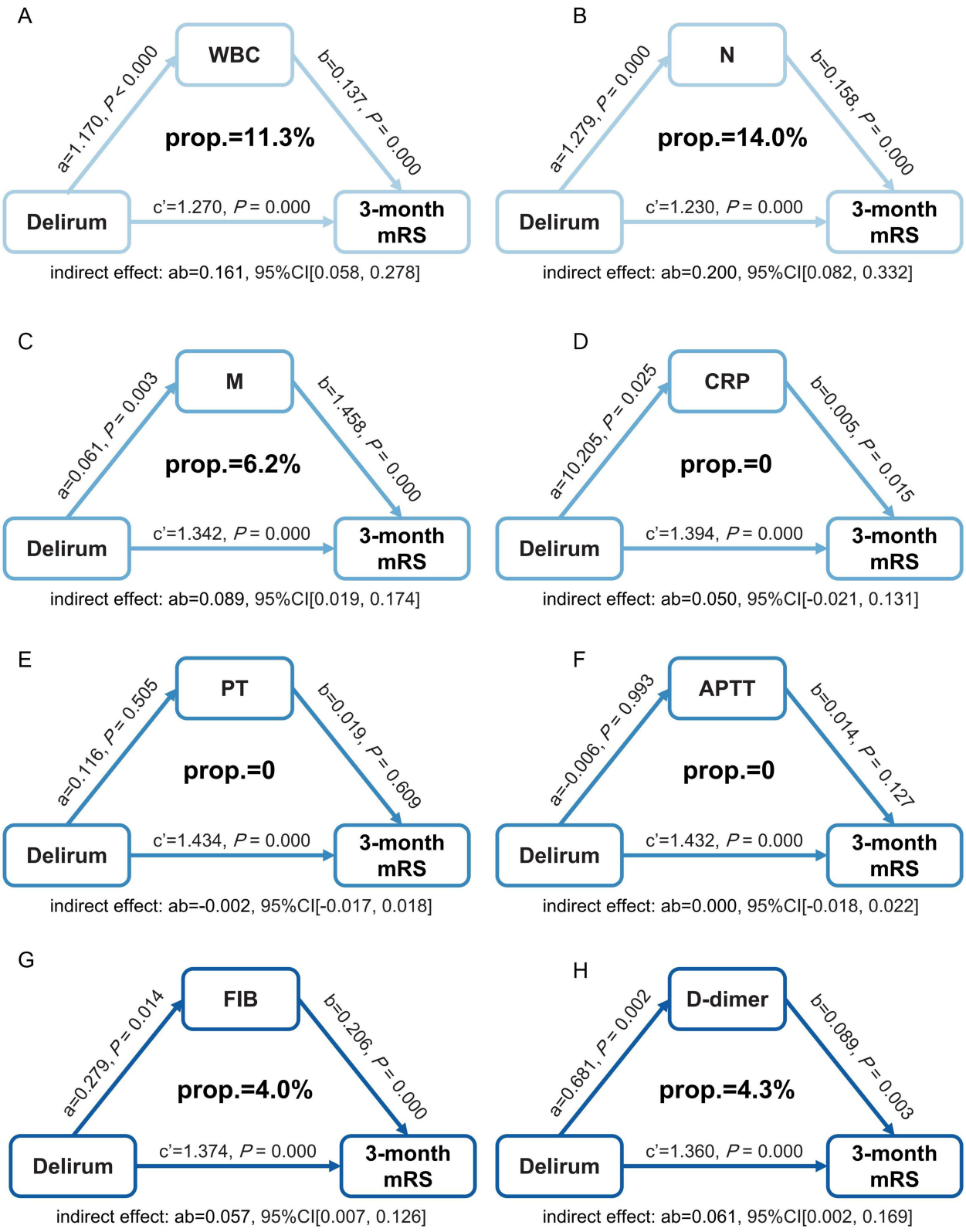

Figure 5 The flow of mediating effect of laboratory indicators between delirium and 3-month mRS.

Notes: (**A** - **D**) are the mediating role of inflammatory markers in delirium and 3-month mRS; (**E** - **H**) are the mediating role of coagulation markers in delirium and 3-month mRS; total effect c=1.431, 95% CI[1.087,1.774], *p*=0.000;

Abbreviations: mRS, modified Rankin Scale; WBC, White blood cells; N, Neutrophils; M, Monocyte; CRP, C-reactive protein; PT, Prothrombin time; APTT, Activated par_x0002_tial thromboplastin time; FIB, Fibrinogen; CI, Confidence interval; prop., proportion.

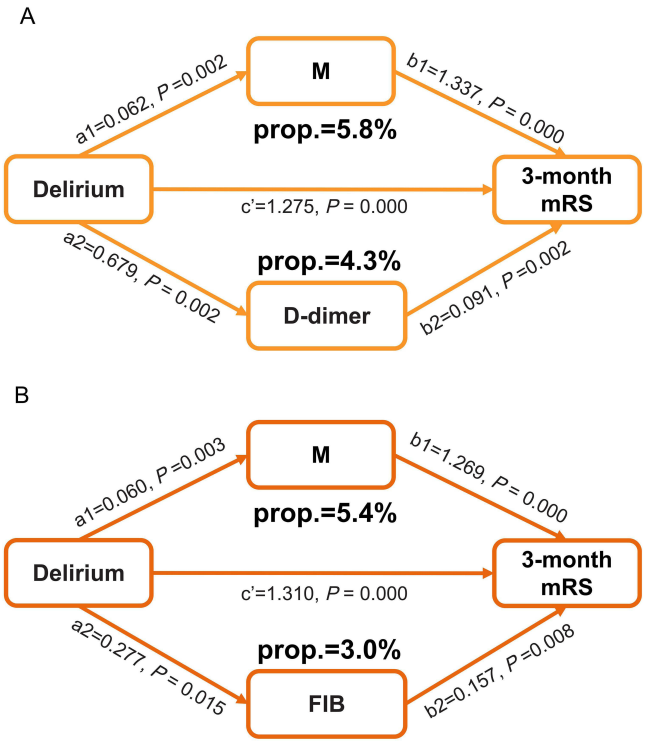

Figure 6 The flow of the parallel mediating effect of laboratory indicators between delirium and 3-month mRS.
Notes: (**A** and **B**) are the parallel mediating effects of inflammation and coagulation indicators between delirium and 3-month mRS. Total effect c=1.419,95% CI [1.074,1.764], p=0.000.
Abbreviations: mRS, modified Rankin Scale; M, Monocyte; FIB, Fibrinogen; CI, Confidence interval; prop., proportion.

Discussion

The main finding of this study is that PSD serves as an independent predictor of poor functional outcomes and increased mortality at 3 months following AIS. Our results confirm that delirium in the acute phase of stroke is associated with worse neurological recovery, higher rates of disability, and greater mortality, emphasizing the prognostic significance of PSD in AIS patients. This study also identified several key factors associated with the development of delirium, including older age, pre-stroke cognitive impairment, a history of cardiovascular events, and the severity of the initial stroke, as indicated by higher NIHSS scores. While gender did not differ between the patients with delirium and those without. These findings are consistent with previous research highlighting similar risk factors for PSD. Additionally, the elevated levels of inflammatory and coagulation biomarkers in delirium patients further suggest that systemic inflammation and coagulation dysfunction may play a role in the pathophysiology of PSD.

To the best of the author's knowledge, this is the first study that has reported the predictive performance of these clinical model at discharge 3 months post-stroke. In our cohort, the delirium incidence rate of 10.2% was relatively lower than previously reported 25%.[30] The differences in incidence rate may be caused by the definition of delirium diagnosis, introduction of organized stroke unit care, case ascertainment, sample size, methodology and accuracy. Notably, other studies have reported delirium incidence ranging from 10–13%,[30,31] which closely aligned with our findings. As concerns the severity of stroke, expressed as NIHSS score, and pre-stroke mRS score were associated with delirium, which is in line with previous studies.[31] Factors predictive of delirium were a combination of premorbid and stroke-specific variables. Additional potential risk factors for developing PSD included advanced age, atrial fibrillation, pre-existing cardiovascular conditions, pre-existing cognitive impairment and mRs score in the current study, which align with prior findings.[32] These risk factors are nonmodifiable but could potentially serve as valuable indicators to identify patients at risk of delirium where preventative measures could be used.

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PSD represents a frequent complication of stroke, with an adverse impact on clinical outcomes.[33] Our study confirmed that PSD was a common yet overlooked predictor of poor prognosis, associating it with increased mortality and greater functional dependence in AIS. Our results underscored the profound effect of PSD on both short-term and 3-month long-term outcomes, consistent with previous studies linking PSD to increased mortality and poor functional recovery.[16,34,35] Specifically, our study identified a significantly higher mortality rate in PSD patients than delirium-free patients at 3-month follow-up, echoing findings that PSD independently increased mortality risk in AIS, particularly in the months following the acute event.[16] These findings are consistent with existing literature that links delirium with worse short- and long-term outcomes in stroke patients. In a prospective cohort study, Rollo et al highlighted that delirium in AIS resulted in higher mRS scores at 3 months, marking PSD as a powerful predictor of disability and survival.[12] Fleischmann et al found that PSD increased healthcare utilization, leading to prolonged hospital stays and elevated care dependency at discharge, further burdening healthcare resources and impacting patient quality of life. Similarly, a prospective study observed that delirium was an independent predictor of mRS>2 at 3-months post-stroke.[7] Additionally, the elevated prevalence and severity of PSD in hypoactive subtypes emphasize the need for targeted diagnostic approaches, as hypoactive delirium often remains unrecognized, despite its association with poorer outcomes.[6] Given the significant morbidity and mortality associated with PSD, early recognition and intervention could play a critical role in improving clinical outcomes.

In view of the complex multifactorial pathophysiology of PSD, which combines neural and systemic factors.[9] Some of the leading mechanisms postulated to lead to delirium include neurotransmitters, inflammation, physiological stressors, metabolic derangements, coagulation responses and genetic factors.[9,36] PSD pathogenesis appears to be mediated by an acute systemic inflammatory response, as supported by various studies that highlight the role of inflammatory and coagulation markers in the development and prognosis of delirium.[37,38] Previous studies demonstrated that high concentrations of baseline inflammatory markers were associated with risk of developing delirium.[36] Inflammatory pathways, including activation of microglia and the release of pro-inflammatory cytokines, have been linked to delirium in various settings, including stroke.[39] Neuroinflammation has been recognized as a critical component of stroke pathophysiology, affecting both the disease's acute and chronic phases.[40] Systemic inflammation, measured by elevated WBC, CRP, and other biomarkers, has been shown to exacerbate neuronal injury leading to secondary injury and contribute to cognitive dysfunction, both in the acute phase and in the long term.[40] The role of inflammation in PSD was corroborated by elevated plasma levels of biomarkers such as WBC, neutrophils, and monocytes observed in our cohort, particularly among patients with poorer outcomes, which aligns with studies suggesting that systemic inflammation can exacerbate neural injury and accelerate neurodegenerative processes.[37] The inflammatory cascade contributes to oxidative stress, neurotransmitter imbalances, and synaptic dysregulation, which may promote both acute and persistent cognitive dysfunction.[31] Elevated plasma levels of neutrophils and monocytes in our cohort align with findings by Khodadadi et al, who reported that heightened inflammatory markers in delirium patients correlate with worse outcomes, further supporting the hypothesis that inflammation accelerates the neurodegenerative processes underlying PSD.[41]

Similarly, the coagulation system has been increasingly recognized for its role in the development of PSD. Coagulation dysfunction, indicated by elevated D-dimer and fibrinogen levels, was also significantly higher in PSD patients, supporting the hypothesis that vascular and coagulation abnormalities may contribute to PSD development.[35] Our study found significantly higher levels of these biomarkers in PSD patients, supporting the growing body of literature that suggests vascular and coagulation abnormalities contribute to delirium development. For example, proinflammatory cytokines also activate the endothelium, leading to coagulation system activation, microvascular thrombosis, and impaired blood flow, consistent with the hypothesis that endothelial activation from inflammatory cytokines initiates a po-coagulant state, enhancing the risk of microvascular thrombosis and neuronal ischemia.[38,42] These processes are believed to trigger a cascade of oxidative stress, neurotransmitter imbalances, and synaptic dysregulation, all of which are implicated in both acute and persistent cognitive dysfunction.[43] Such coagulation pathways, combined with inflammatory mechanisms, suggest potential targets for intervention that may reduce PSD incidence and outcomes. This inflammatory cascade and coagulation dysregulation in the brain can lead to enhanced cytokine transport across the disrupted blood–brain barrier and infiltration of leukocytes and cytokines into the central nervous system, producing ischemia and neuronal apoptosis.[37,42] Recent studies have highlighted the potential for

targeting these inflammatory and coagulation pathways as therapeutic strategies for preventing or mitigating PSD. Anti-inflammatory drugs, such as corticosteroids or cytokine inhibitors, and anticoagulants, like heparin or direct oral anticoagulants, have been explored for their potential to modulate these pathways and reduce delirium incidence in critical care and stroke patients.[44]

These findings highlighted the potential of inflammatory and coagulation pathways as targets for therapeutic intervention, which may help to reduce the incidence or severity of PSD and improve clinical outcomes. Further research is needed to identify whether these changes in biomarkers are a direct result of delirium, whether they are caused by indirect associations with delirium, or whether they are due to dementia via progressive neurodegeneration, or a combination of these factors.

To our knowledge, this is the first study to integrate predictive value for PSD, combining inflammation and coagulation indicators to date. Our findings highlight the mediating roles of leukocytes, neutrophils, monocytes, fibrinogen, and D-dimer in this relationship. This predictive model reliably predicted the outcomes of PSD at 3-month. Several studies indicate that addressing modifiable risk factors, such as inflammation and coagulopathy, could reduce PSD incidence or severity. Anti-inflammatory and anticoagulant therapies, administered during the acute phase of stroke, may mitigate these pathways and, by extension, lower the risk or severity of PSD. Our findings indicate the practical value of this integrated model in clinical settings, where identifying and modifying risk factors may facilitate the use of preventive measures and improve patient outcomes.

Limitation

This study has several limitations. Firstly, this study did not collect data on preexisting medications, such as antiplatelet and anticoagulant therapies, which may have influenced patient outcomes and affected the reliability of laboratory characteristics obtained at admission. Future research should consider including comprehensive information on medication history to control for potential confounding effects and better understand how these drugs interact with delirium onset and outcomes. Secondly, while standardized clinical assessment tools were employed to identify PSD, subtle presentations may have been missed. Future studies should consider using advanced imaging techniques, such as functional MRI or positron emission tomography, to better understand neural correlates and provide more objective diagnostic criteria. Additionally, while our analysis identified key inflammatory and coagulation markers as potential mediators of PSD, the precise role of these biomarkers in delirium pathogenesis remains uncertain. Further investigation is necessary to clarify whether these biomarkers are direct contributors to delirium, secondary responses, or indicators of overlapping conditions like progressive neurodegeneration or underlying cardiovascular diseases. Longitudinal studies with larger sample sizes and more comprehensive data collection would provide greater insight into the long-term impact of these biomarkers and their potential as therapeutic targets. Additionally, this observational study design limits our ability to infer causality between the identified risk factors and PSD outcomes. To address this limitation, future studies could incorporate randomized controlled trials to test interventions targeting inflammation or coagulation pathways, with the goal of reducing the incidence or severity of PSD.

Conclusions

Our study confirms PSD as a significant risk factor for poor neurological outcomes at 3 months, demonstrating its association with increased mortality, functional dependence, and disability. In combination integrating inflammatory and coagulation biomarkers, our model could effectively predict 3-month outcomes. The study highlights the roles of neuroinflammation and coagulation dysfunction in PSD pathogenesis, indicating potential therapeutic targets that may reduce PSD incidence, severity or improve outcomes. Early identification and management of PSD could facilitate timely intervention and improve recovery, underscoring the clinical value of our model in guiding preventive and therapeutic measures. Further research should aim to clarify the mechanistic pathways of PSD and assess the long-term cognitive effects, offering insights into targeted therapies to mitigate the impact of PSD on stroke recovery.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Author Contributions

Chenhui Lin and Heyu Zhang analyzed the data and drafted the manuscript. Yujie Tu and Yaoyao Lin recruited the participants. Fangyi Xiao, Luqian Zhan, Yisi Lin and Yanwei Li made substantial contributions to conception and replenished the required data. Chenglong Xie and Yanyan Chen were involved in revising draft, tables and figures. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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