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Article

Early Quantitative Electroencephalography Parameters Predicting Clinical Outcomes of Intravenous rt-PA Thrombolysis in Acute Ischemic Stroke: A Retrospective Cohort Study

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Abstract

Aims/Background: Timely and accurate assessment of the response to intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) is crucial for guiding subsequent interventions in acute ischemic stroke (AIS). Quantitative electroencephalography (qEEG) offers a real-time measure of cerebral function sensitive to ischemia. This study aimed to investigate the predictive value of ultra-early dynamic changes in qEEG parameters following thrombolysis and develop a predictive model for 24-hour clinical efficacy. **Methods**: We conducted a single-center retrospective analysis of 216 patients with AIS who received intravenous rt-PA at the Stroke Center of Xinchang Hospital Affiliated to Shaoxing University between January 2023 and December 2024. qEEG recordings were acquired immediately before (T0) and 1 hour after the initiation of rt-PA infusion (T1). The primary qEEG parameter was the Delta-Theta/Alpha-Beta Ratio (DTABR). We calculated the DTABR reduction value (T0 DTABR–T1 DTABR) to quantify early neurophysiological improvement. The primary outcome was early clinical efficacy at 24 hours, defined as a reduction of $\geq$4 points in the National Institutes of Health Stroke Scale (NIHSS) score or an NIHSS score of 0–1. The cohort was randomized (7:3) into training (n = 151) and validation (n = 65) sets. A nomogram was constructed based on multivariate logistic regression. Model performance was evaluated using the area under the curve (AUC), calibration plots with the Hosmer–Lemeshow test, and decision curve analysis (DCA). SHapley Additive exPlanations (SHAP) analysis was employed for model interpretation. **Results**: Early clinical efficacy was achieved in 53.7% of patients. The DTABR reduction value was significantly higher in responders compared to non-responders (median 1.20 vs. 0.20, $p < 0.001$). In the multivariate analysis, the DTABR reduction value emerged as a strong independent predictor of favorable outcomes (adjusted odds ratio [OR] = 2.745, 95% confidence interval [CI]: 1.283–5.870, $p = 0.009$). A nomogram integrating this dynamic qEEG marker with clinical variables (age, diabetes, onset-to-needle time, baseline diastolic blood pressure, baseline glucose, baseline NIHSS) demonstrated good discriminative ability, with an AUC of 0.77 (95% CI: 0.70–0.85) in the training set and 0.77 (95% CI: 0.65–0.88) in the validation set. The model exhibited excellent calibration and provided significant net clinical benefit across a wide range of threshold probabilities in the DCA. SHAP analysis identified the DTABR reduction value as the most influential feature. **Conclusion**: The magnitude of DTABR reduction within 1 hour of initiating intravenous thrombolysis is a robust, independent biomarker for early neurophysiological recovery. The developed nomogram offers a validated tool for real-time, individualized prediction of early treatment efficacy, potentially facilitating timely optimization of management strategies for AIS.

Keywords: ischemic stroke; electroencephalography; thrombolytic therapy; prognosis; nomograms

1. Introduction

Acute ischemic stroke (AIS) represents a formidable global health challenge. According to the 2022 World Stroke Organization (WSO) report, there are over 12.2 million incident strokes annually, contributing to approximately 6.5 million deaths and the loss of 143 million disability-adjusted life years (DALYs) worldwide [1]. The burden of stroke is particularly acute in China, where it stands as the leading cause of mortality and acquired disability [2,3]. In the hyperacute phase, intravenous administration of recombinant tissue-type plasminogen activator (rt-PA, alteplase) remains the cornerstone reperfusion therapy for eligible patients within 4.5 hours of symptom onset [4,5]. Despite its established benefits, the clinical response to rt-PA is markedly heterogeneous. A comprehensive meta-analysis [6] revealed that intravenous alteplase significantly improves the odds of a favorable functional outcome when administered within 4.5 hours of stroke onset, with greater benefit associated with earlier treatment. Furthermore, patients face the risk of symptomatic intracranial hemorrhage (sICH), occurring in 2%–7% of cases [7]. Consequently, the accurate identification of rt-PA non-responders during the ultra-early phase—specifically within the first hour post-administration—is paramount. Such early risk stratification is critical for clinicians to promptly adjust therapeutic strategies, such as expediting the decision-making process for rescue endovascular treatment (EVT) in patients with large vessel occlusion [8].

Currently, clinical monitoring relies heavily on the National Institutes of Health Stroke Scale (NIHSS). However, the NIHSS remains a clinician-rated scale and may be influenced by inter-rater variability [9]. Moreover, bedside neurological assessment alone may not fully capture the immediate neurophysiological changes occurring after reperfusion. Advanced neuroimaging techniques, such as computed tomography perfusion (CTP) or magnetic resonance imaging (MRI), can quantify the ischemic penumbra but are impractical for high-frequency bedside monitoring and are associated with limitations, including transport delays and contrast agent risks [10].

Electroencephalography (EEG), a non-invasive technique recording the summation of postsynaptic potentials of cortical neurons, is exquisitely sensitive to fluctuations in cerebral blood flow (CBF). Electrophysiological studies have established clear thresholds for cerebral ischemia: EEG fast-wave activity (Alpha, Beta) begins to attenuate when CBF drops to 25–35 mL/100 g/min (functional suppression threshold), while slow-wave activity (Delta, Theta) increases significantly when CBF falls below 12–18 mL/100 g/min (electrical failure threshold) [11,12]. These electrophysiological alterations precede visible structural damage on imaging, offering a theoretical window for early intervention [13]. Quantitative EEG (qEEG) utilizes power spectrum analysis to transform complex EEG waveforms into objective metrics [14]. Among these, the Delta-Theta/Alpha-Beta Ratio (DTABR) and the Delta/Alpha Ratio (DAR) have been shown to correlate strongly with stroke severity and prognosis. For instance, Finnigan et al. [15] found that acute DAR correlated significantly with 30-day NIHSS scores and infarct volume.

Nevertheless, the majority of existing research has focused on utilizing single-time-point (e.g., baseline) qEEG parameters to predict long-term outcomes [16,17]. There is a paucity of studies investigating the dynamic changes in brain electrical activity during the thrombolytic process, particularly shortly after the completion of rt-PA infusion, and their predictive value for early neurologic improvement. Compared to absolute baseline values, the magnitude of change may more directly reflect the immediate physiological effects of reperfusion on ischemic tissue [18].

Based on this rationale, this study aimed to retrospectively analyze qEEG data before and after intravenous thrombolysis in AIS patients to evaluate the efficacy of the 1-hour post-thrombolysis DTABR reduction magnitude (DTABR reduction value) in predicting early clinical efficacy at 24 hours post-thrombolysis. We further developed and validated a nomogram model integrating baseline clinical characteristics with this dynamic electrophysiological index, aiming to provide an objective basis for real-time, precision assessment of acute stroke treatment efficacy.

2. Methods

2.1 Study Design and Participants

This single-center, retrospective observational cohort study was conducted at the Stroke Center of Xinchang Hospital Affiliated to Shaoxing University. We consecutively reviewed the clinical and electrophysiological data of AIS patients who received standard intravenous thrombolysis between January 2023 and December 2024, ultimately enrolling 216 cases. The reporting of this study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [19].

Inclusion criteria included the following: (1) age $\geq$18 years; (2) AIS confirmed by neuroimaging (computed tomography [CT] or MRI), presenting with a unilateral supratentorial hemispheric infarction, and meeting the indications for intravenous thrombolysis recommended by the Chinese guidelines for the diagnosis and treatment of acute ischemic stroke [5]; (3) onset-to-needle time (ONT) $\leq$4.5 hours; and (4) completion of high-quality qEEG recordings before and 1 hour after the initiation of thrombolysis.

Exclusion criteria were as follows: (1) a history of neurological or psychiatric disorders known to significantly affect background EEG activity (e.g., epilepsy, severe dementia); (2) the presence of skull defects or severe scalp lesions preventing standard electrode placement; (3) excessive EEG artifacts (exceeding 15% of the total recording time), rendering power spectrum analysis unreliable; (4) receipt of bridging mechanical thrombectomy immediately after intravenous thrombolysis (to isolate the effect of rt-PA); (5) a pre-stroke modified Rankin Scale (mRS) >2; and (6) use of sedatives or antiepileptic drugs within 24 hours prior to EEG acquisition that could significantly affect background EEG activity.

2.2 Thrombolytic Therapy and Clinical Management

All enrolled patients received standard-dose alteplase (rt-PA, 20 mg/vial; Boehringer Ingelheim, Germany) according to routine clinical practice. The administration protocol was conducted in strict adherence to international and national guidelines [4,5]: a total dose of 0.9 mg/kg (maximum dose 90 mg), with 10% administered as an intravenous bolus over 1 minute, and the remaining 90% infused continuously over the subsequent 60 minutes. Patients underwent standardized monitoring and management in the stroke unit during thrombolysis and for the subsequent 24 hours. According to institutional protocols and guideline-based practice, neurological status and vital signs were monitored at least every 15 minutes during rt-PA infusion and the early post-infusion period, every 30 minutes during the subsequent monitoring period, and hourly thereafter until 24 hours after thrombolysis. Blood pressure was maintained below 180/105 mmHg during the first 24 hours after rt-PA administration.

2.3 Clinical Data Collection

Baseline data were systematically collected via the electronic medical record (EMR) system, including demographic characteristics (age, sex), vascular risk factors (hypertension, history of diabetes mellitus, atrial fibrillation), admission vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP]), and admission random blood glucose measured immediately upon admission. Stroke severity was assessed using the NIHSS scale at baseline (pre-thrombolysis) and 24 hours post-thrombolysis. All NIHSS assessments were performed by trained neurologists blinded to the qEEG analysis results.

2.4 EEG Acquisition and Quantitative Analysis

Signal acquisition EEG monitoring was conducted using a digital video EEG system (NicoletOne, Natus Medical Inc., USA). Sixteen scalp electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6) were placed according to the International 10-20 system, with ipsilateral earlobes (A1, A2) serving as references. Electrode impedance was maintained below 5 kΩ. The sampling rate was set at 500 Hz, with a band-pass filter of 0.5–70 Hz. EEG acquisition was performed at the bedside in the Stroke Unit or Emergency Department by trained neurophysiology technicians, ensuring clinical feasibility. Specifically, ONT was defined as the time interval (in minutes) from the onset of stroke symptoms to the initiation of the intravenous rt-PA infusion. The MRI infarct side was determined based on the hemisphere containing the acute ischemic lesion observed on diffusion-weighted imaging (DWI) sequences.

Monitoring Time Points. Specific monitoring windows were established to capture early neurophysiological changes post-thrombolysis:

• T0 (baseline): Immediately before rt-PA administration;

• T1 (1-hour post-thrombolysis): At the completion of the rt-PA infusion (approximately 60 minutes after initiation);

• T2: 24 hours post-thrombolysis;

• T3: 7 days post-thrombolysis.

Signal Processing and Metric Calculation. All EEG data were preprocessed by a certified neurophysiology technician, who manually excluded artifacts arising from eye movements, muscle activity, and electrode displacement. At least 60 seconds of artifact-free, awake, eyes-closed background EEG segments were selected. Power spectral density (PSD) was calculated using Fast Fourier Transform (FFT). Frequency bands were defined as: δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–30 Hz).

The core parameter of this study was the DTABR, calculated as (δ power + θ power) / (α power + β power). The DTABR value of the lesional hemisphere was calculated based on the infarct location determined by MRI DWI. For each patient, the lesional hemisphere was uniquely defined according to the unilateral supratentorial infarct location. To quantify early thrombolysis-induced neurophysiological improvement, we calculated the DTABR reduction value, which is computed using the formula in the following:

DTABR reduction value = T0 DTABR–T1 DTABR

A larger positive value indicates a more pronounced reduction in slow-wave activity and recovery of fast-wave activity, suggesting improved cerebral function.

2.5 Outcome Definition

The primary study outcome was early clinical efficacy at 24 hours post-thrombolysis. Patients were divided into two groups: efficacy and non-efficacy groups. Based on established criteria for early neurologic improvement [20], we defined "efficacy" as: (1) a reduction in the 24-hour NIHSS score by $\geq$4 points compared to baseline; or (2) a 24-hour NIHSS score of 0 or 1. Patients not meeting these criteria were classified into the "non-efficacy group".

2.6 Statistical Analysis

All statistical analyses and visualizations were performed using R software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria). Normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were expressed as mean $\pm$ standard deviation (SD) and compared using the independent samples *t*-test. Non-normally distributed data were expressed as median (interquartile range [IQR], represented as Q_1, Q_3) and compared using the Mann–Whitney *U* test. Categorical variables were expressed as frequency (percentage) and analyzed using the Chi-square test or Fisher's exact test. The study cohort was randomly split into training and validation sets at a 7:3 ratio. In the training set, potential predictors were initially screened using univariate logistic regression. Subsequently, statistically significant variables were included in a multivariate logistic regression model to construct the nomogram. Multicollinearity among predictors was diagnosed using the variance inflation factor (VIF) and tolerance. A VIF <5 and a tolerance value >0.20 were considered indicative of acceptable multicollinearity. Model performance was assessed in terms of: (1) discrimination, evaluated by the area under the curve (AUC); (2) calibration, evaluated by bootstrap calibration curves (1000 resamples) and the Hosmer–Lemeshow test; and (3) clinical usefulness, evaluated using decision curve analysis (DCA). Furthermore, the SHapley Additive exPlanations (SHAP) algorithm was employed to visualize the importance and contribution direction of model features [21,22]. All tests were two-tailed, and a $p < 0.05$ was considered statistically significant.

3. Results

3.1 Data Distribution Balance of Training and Validation Sets

A total of 216 patients with AIS who underwent intravenous rt-PA thrombolysis were included in this study.

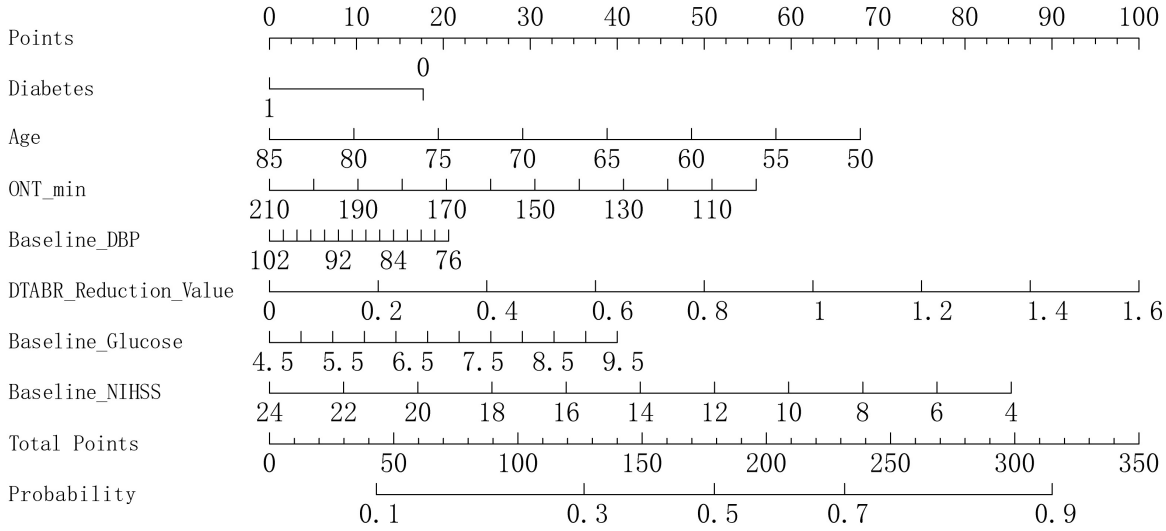

Fig. 1. Nomogram for predicting the probability of early clinical efficacy at 24 hours post-thrombolysis. The nomogram was developed based on the training set. Points for each variable (Age, Diabetes, ONT_min, Baseline_DBP, Baseline_Glucose, Baseline_NIHSS, and DTABR_reduction_value) are located on their respective axes. For the binary variable 'Diabetes', 0 indicates no history of diabetes mellitus while 1 indicates the presence of diabetes. After determining the sum of these points, mark it on the "Total Points" axis and project vertically down to the "Probability" axis to find the predicted probability of the outcome. DTABR, Delta-Theta/Alpha-Beta Ratio.

Patients were randomly assigned to the training set (n = 151) and the validation set (n = 65). As detailed in Table 1, there were no significant differences between the two sets regarding age, baseline blood pressure (SBP, DBP), baseline glucose, ONT, baseline NIHSS score, 24-hour NIHSS, or various qEEG parameters (DTABR T0, T1, T2, T3, reduction value) ($p > 0.05$ for all). Furthermore, the distribution of categorical variables, including sex, vascular risk factors (hypertension, diabetes, atrial fibrillation), MRI infarct side, and early clinical efficacy at 24-hour post-thrombolysis, was also balanced between the two sets ($p > 0.05$ for all). This indicates a balanced distribution and good representativeness of the training and validation cohorts (Table 1).

In the training set (n = 151), based on the early clinical efficacy at 24 hours post-thrombolysis, 84 patients (55.63%) achieved a favorable outcome (Efficacy = 1), while 67 (44.37%) had an unfavorable outcome (Efficacy = 0). Based on results of the comparative analysis (Table 2), the efficacy group was significantly younger (66.06 $\pm$ 8.56 vs. 71.97 $\pm$ 8.80 years, $p < 0.001$), and had lower baseline SBP (148.80 $\pm$ 12.88 vs. 159.48 $\pm$ 14.00, $p < 0.001$) and DBP (88.10 $\pm$ 6.52 vs. 93.24 $\pm$ 6.67, $p < 0.001$), lower baseline glucose levels (6.75 $\pm$ 1.39 vs. 7.79 $\pm$ 1.54 mmol/L, $p < 0.001$), and significantly lower baseline NIHSS scores (median 10.50 vs. 16.00, $p < 0.001$) compared to the non-efficacy group. Regarding qEEG parameters, the DTABR reduction value was significantly higher in the efficacy group (median 1.20 vs. 0.20, $p < 0.001$), suggesting a strong association between early improvement in brain electrical activity and clinical efficacy (Table 2).

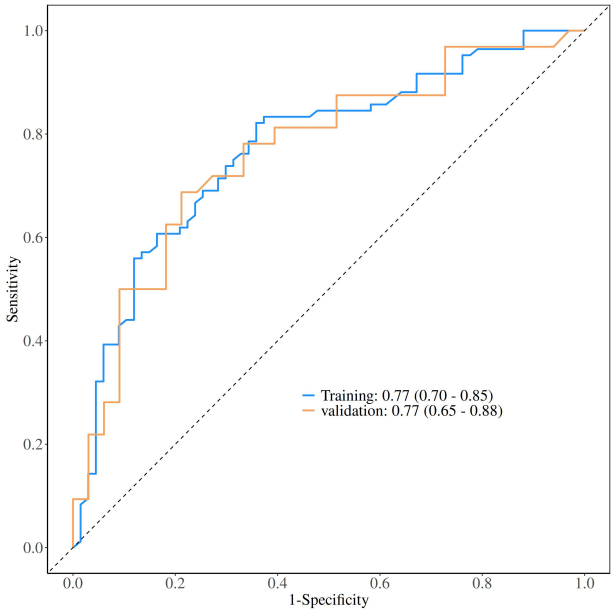

Fig. 2. Receiver operating characteristic (ROC) curves of the prediction model. The model demonstrated comparable performance in the training set (blue line, area under the curve [AUC] = 0.77, $p < 0.001$) and the validation set (orange line, AUC = 0.77, $p < 0.001$), with consistent AUC values indicating good model generalization.

3.2 Predictor Selection and Model Construction

The statistically significant variables identified in the univariate analysis (age, ONT, baseline SBP, baseline DBP, baseline glucose, baseline NIHSS, history of diabetes mel-

Table 1. Demographic, clinical, and neurophysiological characteristics of patients in the training and validation sets.

Variables	Total (n = 216)	Validation (n = 65)	Training (n = 151)	Statistic	p
Age (years), mean ± SD	68.80 ± 8.99	69.08 ± 8.71	68.68 ± 9.13	t = 0.296	0.768
Baseline SBP (mmHg), mean ± SD	153.57 ± 14.35	153.66 ± 14.43	153.54 ± 14.36	t = 0.059	0.953
Baseline DBP (mmHg), mean ± SD	90.43 ± 6.99	90.55 ± 6.92	90.38 ± 7.05	t = 0.170	0.866
Baseline glucose (mmol/L), mean ± SD	7.28 ± 1.53	7.45 ± 1.51	7.21 ± 1.54	t = 1.031	0.304
ONT (min), M (Q_1, Q_3)	146.50 (124.00, 180.00)	146.00 (126.00, 173.00)	147.00 (123.00, 180.00)	Z = –0.176	0.861
DTABR T0 lesional, M (Q_1, Q_3)	5.00 (3.25, 6.53)	5.00 (3.60, 6.70)	5.00 (3.20, 6.50)	Z = –1.026	0.305
DTABR T1 lesional, M (Q_1, Q_3)	4.10 (2.05, 6.43)	4.65 (2.20, 6.60)	3.90 (2.00, 6.40)	Z = –1.268	0.205
DTABR reduction value, M (Q_1, Q_3)	0.60 (0.20, 1.30)	0.20 (0.15, 1.20)	1.20 (0.20, 1.30)	Z = –1.583	0.113
DTABR T2 lesional, M (Q_1, Q_3)	2.40 (1.70, 4.71)	3.00 (1.80, 4.70)	2.30 (1.65, 4.78)	Z = –0.654	0.513
DTABR T3 lesional, M (Q_1, Q_3)	1.83 (1.35, 4.57)	2.85 (1.45, 4.55)	1.80 (1.35, 4.65)	Z = –0.603	0.546
Baseline NIHSS, M (Q_1, Q_3)	12.00 (9.00, 17.00)	12.00 (9.00, 17.00)	12.00 (8.00, 17.00)	Z = –0.457	0.648
24-hour NIHSS, M (Q_1, Q_3)	5.00 (2.00, 17.25)	9.00 (2.00, 17.00)	5.00 (2.00, 18.00)	Z = –1.013	0.311
Sex, n (%)				χ^2 = 0.285	0.594
Female	99 (45.83)	28 (43.08)	71 (47.02)		
Male	117 (54.17)	37 (56.92)	80 (52.98)		
MRI infarct side, n (%)				χ^2 = 0.008	0.930
Left	104 (48.15)	31 (47.69)	73 (48.34)		
Right	112 (51.85)	34 (52.31)	78 (51.66)		
Hypertension, n (%)				χ^2 = 0.730	0.393
No	79 (36.57)	21 (32.31)	58 (38.41)		
Yes	137 (63.43)	44 (67.69)	93 (61.59)		
Diabetes, n (%)				χ^2 = 0.506	0.477
No	147 (68.06)	42 (64.62)	105 (69.54)		
Yes	69 (31.94)	23 (35.38)	46 (30.46)		
Atrial fibrillation, n (%)				χ^2 = 0.061	0.804
No	129 (59.72)	38 (58.46)	91 (60.26)		
Yes	87 (40.28)	27 (41.54)	60 (39.74)		
Clinical efficacy*, n (%)				χ^2 = 0.748	0.387
No	100 (46.30)	33 (50.77)	67 (44.37)		
Yes	116 (53.70)	32 (49.23)	84 (55.63)		

Notes: t, t-test statistic; Z, Mann–Whitney U test statistic; χ^2, Chi-square test statistic; *Early clinical efficacy at 24 hours post-thrombolysis. Diabetes refers to a documented history of diabetes mellitus in the medical records. Baseline glucose refers to admission random blood glucose measured immediately upon admission.

DBP, diastolic blood pressure; DTABR, Delta-Theta/Alpha-Beta Ratio; M, Median; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; ONT, onset-to-needle Time; Q_1, 1st Quartile; Q_3, 3rd Quartile; SBP, systolic blood pressure; SD, standard deviation; T0, immediately before rt-PA administration; T1, at the completion of the rt-PA infusion (approximately 60 minutes after initiation); T2, 24 hours post-thrombolysis; T3, 7 days post-thrombolysis.

litus, and DTABR-related metrics) were assessed for multicollinearity prior to multivariate modeling. Baseline SBP was excluded due to a VIF >5. After excluding baseline SBP, all retained predictors in the final multivariable model showed acceptable multicollinearity diagnostics, with VIF values ranging from 1.285 to 3.539 and tolerance values ranging from 0.283 to 0.778. Consequently, the final multivariate logistic regression model included the following seven variables: age, history of diabetes mellitus, ONT, baseline DBP, baseline glucose, baseline NIHSS, and the DTABR reduction value.

The results of the multivariate logistic regression analysis are presented in Table 3. The DTABR reduction value emerged as an independent favorable factor for thrombolytic efficacy (adjusted odds ratio [OR] = 2.745, 95% confidence interval [CI]: 1.283–5.870, p = 0.009) (Table 3).

Based on the multivariate logistic regression, a visualized nomogram was constructed (Fig. 1) using a "Full Model" strategy. It is important to note that although the DTABR reduction value was the only variable to maintain statistical significance (p = 0.009) in the multivariate analysis, likely due to its dominant predictive effect in this sample. Other clinical variables, such as age, diabetes, ONT, baseline DBP, glucose, and baseline NIHSS, were retained in the final nomogram. Retaining these clinically relevant variables ensures the model's biological plausibility and minimizes omitted variable bias.

Table 2. Differential analysis in the training set.

Variables	Total (n = 151)	Non-efficacy group (n = 67)	Efficacy group (n = 84)	Statistic	p
Age (years), mean ± SD	68.68 ± 9.13	71.97 ± 8.80	66.06 ± 8.56	t = 4.164	<0.001
Baseline SBP (mmHg), mean ± SD	153.54 ± 14.36	159.48 ± 14.00	148.80 ± 12.88	t = 4.871	<0.001
Baseline DBP (mmHg), mean ± SD	90.38 ± 7.05	93.24 ± 6.67	88.10 ± 6.52	t = 4.768	<0.001
Baseline glucose (mmol/L), mean ± SD	7.21 ± 1.54	7.79 ± 1.54	6.75 ± 1.39	t = 4.359	<0.001
ONT (min), M (Q_1, Q_3)	147.00 (123.00, 180.00)	164.00 (136.00, 194.00)	138.50 (118.00, 166.00)	Z = –3.488	<0.001
DTABR T0 lesional, M (Q_1, Q_3)	5.00 (3.20, 6.50)	5.90 (4.85, 6.90)	3.95 (3.10, 5.70)	Z = –4.233	<0.001
DTABR T1 lesional, M (Q_1, Q_3)	3.90 (2.00, 6.40)	5.70 (3.60, 6.70)	2.55 (1.80, 5.51)	Z = –4.338	<0.001
DTABR reduction value, M (Q_1, Q_3)	1.20 (0.20, 1.30)	0.20 (0.15, 1.20)	1.20 (0.20, 1.30)	Z = –4.228	<0.001
DTABR T2 lesional, M (Q_1, Q_3)	2.30 (1.65, 4.78)	4.50 (2.52, 5.22)	1.85 (1.65, 2.40)	Z = –5.619	<0.001
DTABR T3 lesional, M (Q_1, Q_3)	1.80 (1.35, 4.65)	4.35 (2.52, 5.03)	1.50 (1.30, 1.80)	Z = –5.627	<0.001
Baseline NIHSS, M (Q_1, Q_3)	12.00 (8.00, 17.00)	16.00 (11.50, 19.00)	10.50 (7.00, 14.00)	Z = –4.772	<0.001
24-hour NIHSS, M (Q_1, Q_3)	5.00 (2.00, 18.00)	18.00 (15.00, 20.00)	2.00 (1.00, 3.00)	Z = –10.579	<0.001
Sex, n (%)				χ^2 = 1.322	0.250
Female	71 (47.02)	28 (41.79)	43 (51.19)		
Male	80 (52.98)	39 (58.21)	41 (48.81)		
MRI infarct side, n (%)				χ^2 = 0.208	0.648
Left	73 (48.34)	31 (46.27)	42 (50.00)		
Right	78 (51.66)	36 (53.73)	42 (50.00)		
Hypertension, n (%)				χ^2 = 3.730	0.053
No	58 (38.41)	20 (29.85)	38 (45.24)		
Yes	93 (61.59)	47 (70.15)	46 (54.76)		
Diabetes, n (%)				χ^2 = 7.295	0.007
No	105 (69.54)	39 (58.21)	66 (78.57)		
Yes	46 (30.46)	28 (41.79)	18 (21.43)		
Atrial fibrillation, n (%)				χ^2 = 3.240	0.072
No	91 (60.26)	35 (52.24)	56 (66.67)		
Yes	60 (39.74)	32 (47.76)	28 (33.33)		

Notes: t, t-test statistic; Z, Mann–Whitney U test statistic; χ^2, Chi-square test statistic.

3.3 Model Performance and Calibration

Receiver operating characteristic (ROC) curve analysis (Fig. 2) demonstrated the model's discriminative ability. In the training set, the AUC was 0.77 (95% CI: 0.70–0.85, $p < 0.001$), with a sensitivity of 0.82 and a specificity of 0.64. In the validation set, the AUC remained robust at 0.77 (95% CI: 0.65–0.88, $p < 0.001$), with a sensitivity of 0.81 and a specificity of 0.52. The high consistency in AUC values between the two datasets indicates that the model did not suffer from overfitting.

Furthermore, the calibration curves demonstrated excellent agreement between the predicted probabilities and the actual observed outcomes. In both the training set (Fig. 3A, Hosmer–Lemeshow test $p = 0.4854$) and the validation set (Fig. 3B, Hosmer–Lemeshow test $p = 0.4157$), the bias-corrected curve closely tracked the ideal diagonal line, indicating good calibration of the model.

3.4 Clinical Usefulness

Decision curve analysis (DCA) was employed to evaluate the clinical utility of the model. Within a wide range of threshold probabilities, the net benefit derived from clinical decisions based on the nomogram model (Model curve) consistently exceeded that of the "treat all" (All curve) or "treat none" (None curve) strategies (Fig. 4). This advantage was confirmed in the validation set (Fig. 4B), supporting the model's potential application in real-world clinical scenarios.

3.5 Evaluation of Model Interpretability via SHAP Analysis

SHAP analysis elucidated the mechanisms of specific impact of each feature on the predicted outcome. The SHAP feature importance plot confirmed that the DTABR reduction value was the most important predictive feature (Fig. 5A). In the beeswarm plot (Fig. 5B), higher DTABR reduction values (red dots) were predominantly distributed in the positive SHAP value region, indicating a positive contribution to the prediction of "efficacy". Conversely, higher NIHSS scores and age were mainly distributed in the negative SHAP values. The waterfall plot illustrates an individual case (Fig. 5C), intuitively demonstrating how the DTABR reduction value significantly increased the patient's predicted outcome.

The SHAP analysis further demonstrated that, beyond the DTABR reduction value, several clinical variables—

Table 3. Logistic regression analysis for predicting early clinical efficacy at 24 hours post-thrombolysis.

Variables	Univariate					Multivariate				
	β	SE	Z	p	OR (95% CI)	β	SE	Z	p	OR (95% CI)
Sex										
Female					1.000 (Reference)					
Male	–0.379	0.330	–1.148	0.251	0.685 (0.358–1.307)					
MRI infarct side										
Left					1.000 (Reference)					
Right	–0.150	0.328	–0.456	0.649	0.861 (0.453–1.638)					
Hypertension										
No					1.000 (Reference)					
Yes	–0.663	0.345	–1.920	0.055	0.515 (0.262–1.014)					
Diabetes										
No					1.000 (Reference)					1.000 (Reference)
Yes	–0.968	0.363	–2.663	0.008	0.380 (0.186–0.774)	–0.286	0.448	–0.638	0.524	0.752 (0.312–1.808)
Atrial fibrillation										
No					1.000 (Reference)					
Yes	–0.604	0.337	–1.792	0.073	0.547 (0.283–1.058)					
Age	–0.076	0.020	–3.836	<0.001	0.926 (0.891–0.963)	–0.031	0.026	–1.201	0.230	0.969 (0.921–1.020)
ONT	–0.020	0.006	–3.499	<0.001	0.981 (0.970–0.991)	–0.008	0.008	–1.080	0.280	0.992 (0.977–1.007)
Baseline DBP	–0.115	0.027	–4.267	<0.001	0.891 (0.846–0.940)	–0.013	0.049	–0.263	0.793	0.987 (0.897–1.086)
Baseline glucose	–0.469	0.118	–3.988	<0.001	0.626 (0.497–0.788)	0.117	0.224	0.525	0.600	1.125 (0.725–1.744)
Baseline NIHSS	–0.168	0.036	–4.605	<0.001	0.845 (0.787–0.908)	–0.069	0.063	–1.087	0.277	0.933 (0.824–1.057)
DTABR reduction value	1.446	0.320	4.522	<0.001	4.247 (2.269–7.948)	1.010	0.388	2.603	0.009	2.745 (1.283–5.870)
Baseline SBP	–0.057	0.013	–4.354	<0.001	0.945 (0.921–0.969)					

Notes: OR, odds ratio; CI, confidence interval; SE, standard error. The multivariate model was adjusted for all variables listed in the table.

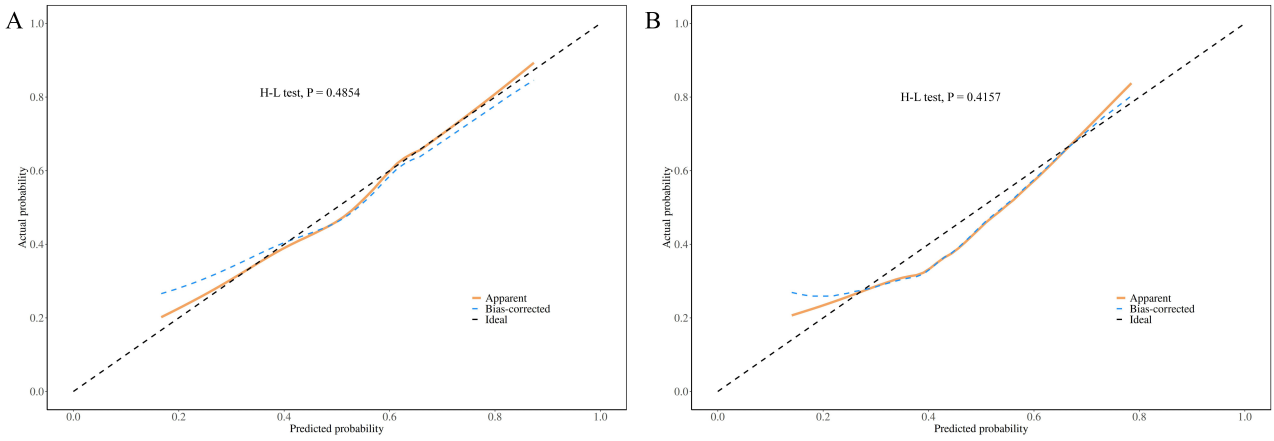

Fig. 3. Calibration curves of the nomogram for the training set (A) and the validation set (B). The x-axis represents the predicted probability, and the y-axis represents the actual observed probability. The diagonal dotted line represents ideal prediction. The solid line (bias-corrected) closely tracking the ideal line indicates good calibration in both cohorts.

particularly age and baseline NIHSS—continued to contribute meaningfully to individual probability prediction. This finding supports their inclusion in the final model, despite their relatively higher p-values in the multivariate regression analysis.

4. Discussion

In the context of reperfusion therapy for AIS, the real-time and accurate assessment of tissue-level reperfusion and the salvage of neuronal function are paramount. This study, through a retrospective analysis of 216 AIS patients undergoing intravenous thrombolysis, systematically investigated the predictive value of ultra-early (1-hour post-thrombolysis) dynamic qEEG changes. Our central finding is that the DTABR reduction value is an independent and potent biomarker for predicting early clinical efficacy at 24-hour post-thrombolysis. The nomogram model, integrating this parameter with key clinical variables, demonstrated fa-

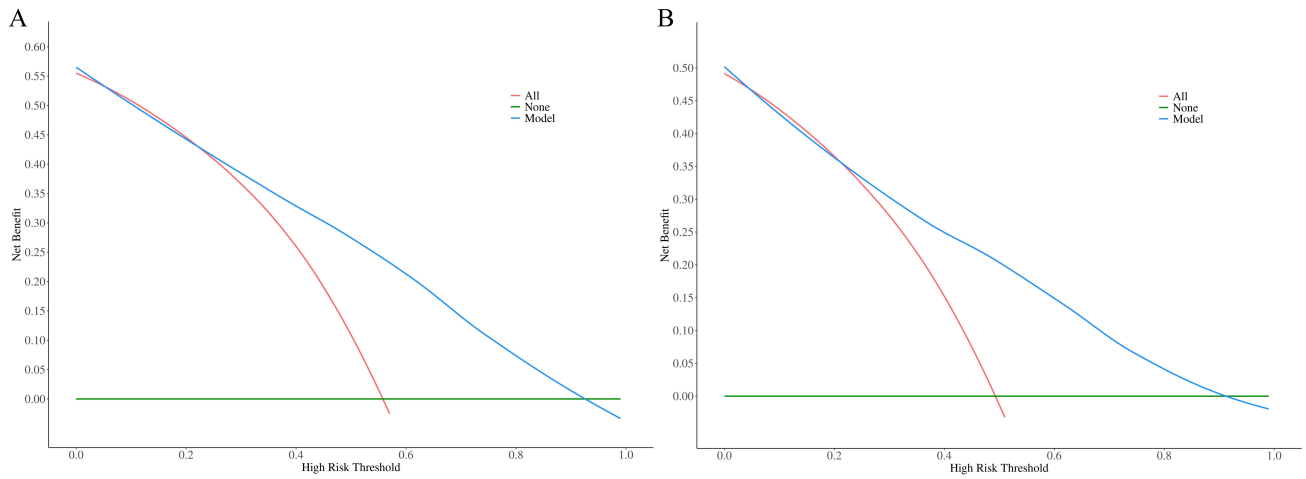

Fig. 4. Decision curve analysis (DCA) for the prediction model: (A) training set, and (B) validation set. The y-axis represents net benefit. The blue line denotes the nomogram model, the red line assumes intervention in all patients, and the green line assumes that no patients receive intervention. The model shows a positive net benefit across a wide range of threshold probabilities in both datasets.

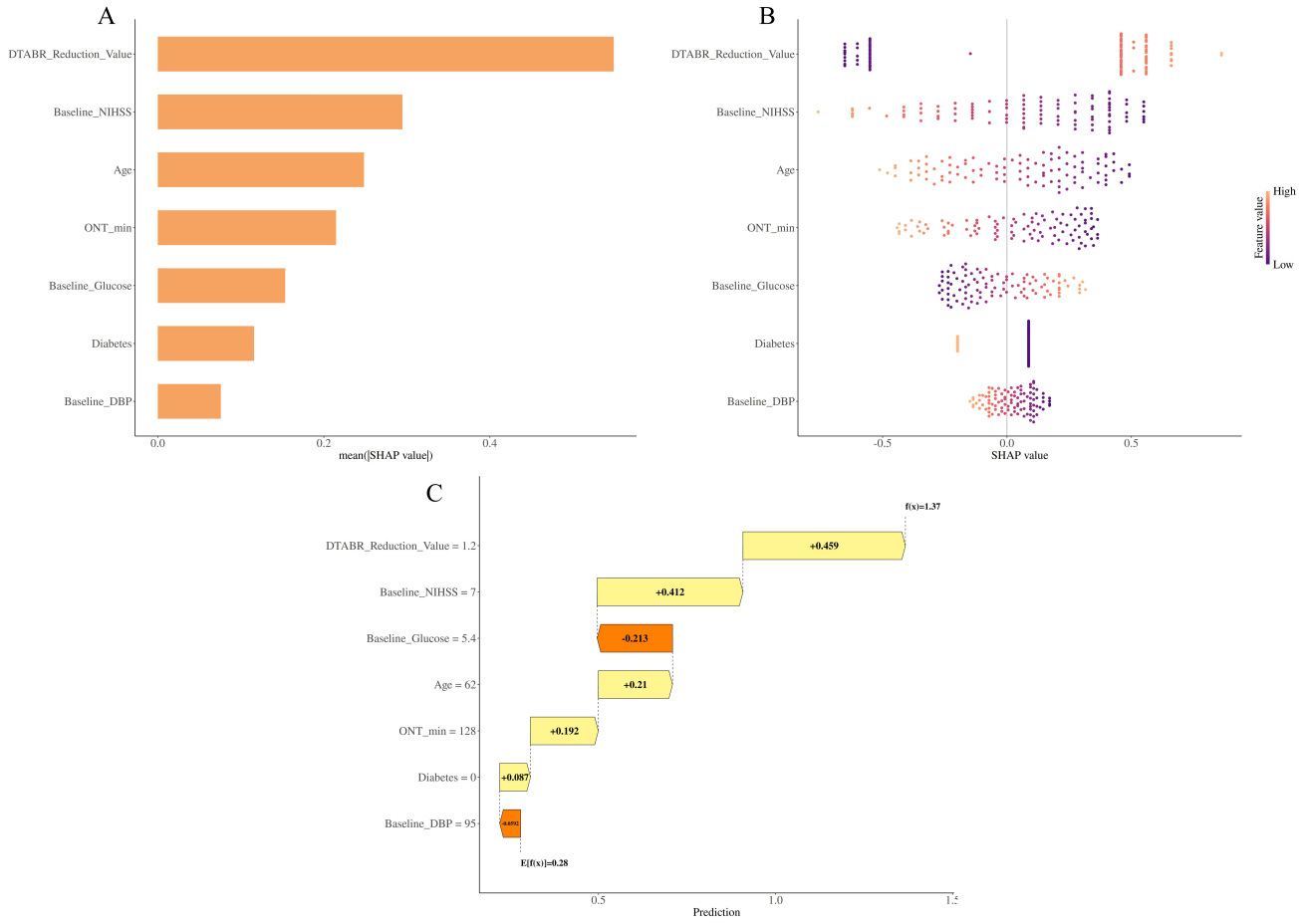

Fig. 5. SHapley Additive exPlanations (SHAP) analysis for model interpretability. (A) SHAP feature importance plot ranking predictors by their mean absolute SHAP values. The DTABR reduction value is identified as the most important feature. (B) SHAP summary (beeswarm) plot. Red dots (high feature values) for DTABR reduction value are associated with positive SHAP values (better outcome). (C) SHAP waterfall plot illustrating details of prediction for a representative patient, highlighting the strong positive contribution of DTABR.

vorable predictive performance (AUC = 0.77) and clinical utility.

The pathophysiological cascade of cerebral ischemia originates from energy metabolism failure. As CBF declines, neuronal adenosine triphosphate (ATP) synthesis is impeded, leading to ion pump dysfunction, loss of cell membrane potential stability, and subsequent synaptic transmission blockade [23]. Electrophysiologically, this process manifests as rapid suppression of high-frequency cortical neuronal oscillations (Alpha, Beta waves, representing active cortical information processing) and a marked increase in low-frequency slow waves (Delta, Theta waves) [24,25]. DTABR, as a composite index reflecting this "fast-slow wave imbalance", has been validated as a sensitive marker of ischemic brain injury [26]. Prior studies, such as those by Finnigan et al. [27] and Shreve et al. [13] have established that elevated baseline DTABR or DAR correlates closely with infarct core volume and clinical severity.

This study uniquely focused on the "dynamic changes" during the thrombolytic process rather than static indices. We observed that in patients with favorable outcomes (efficacy), DTABR exhibited a significant downward trend within 1 hour post-thrombolysis (median reduction value 1.20 vs. 0.20). The physiological basis for this phenomenon is likely the successful reperfusion of the ischemic penumbra. Reperfusion restores the supply of oxygen and glucose, enabling neurons to restart aerobic metabolism, restore membrane potential (repolarization), and gradually recover synaptic function [8,28]. This aligns with the "ischemic penumbra" theory proposed by Astrup et al. [23]—the rapid decline in DTABR may signify the restoration of CBF from dysfunctional levels to normal perfusion levels. Conversely, the minimal change in DTABR in the non-efficacy group suggests persistent vessel occlusion or a microcirculatory "no-reflow" phenomenon [29].

Most previous qEEG studies have concentrated on using baseline data to predict long-term functional recovery [16]. For example, Sheorajpanday et al. [30] found a correlation between baseline qEEG and 6-month functional status. While these studies confirm the potential of qEEG as a prognostic biomarker, they do not provide real-time guidance for acute-phase treatment decisions. A few studies have explored early changes in qEEG. de Vos et al. [31] showed that continuous EEG monitoring during thrombolysis was technically feasible and provided real-time information on the effect of thrombolysis. Zhang et al. [18] preliminarily demonstrated that qEEG indices may have predictive value for outcomes in AIS, although their study was limited by a small sample size and focused on patients undergoing mechanical thrombectomy. By clearly defining the critical 1-hour window, utilizing the "reduction value" as the core parameter, and constructing a validated multivariate nomogram model, this study advances the field methodologically and clinically. Compared to baseline values, the dynamic nature of reduction value better reflects the patient's immediate response to treatment, minimizing the impact of individual variability.

The selection of the 1-hour post-thrombolysis time point (i.e., at the completion of rt-PA infusion) as the assessment node is strategically significant, marking the peak pharmacological effect of intravenous thrombolysis [32]. However, serial NIHSS-based assessments may not fully capture subtle neurologic changes when compared with a comprehensive neurologic examination [33]. Our study confirms that qEEG can objectively capture this micro-level neurophysiological response within 1 hour, closely aligning with the concept of very early neurologic improvement (VENI) [20]. For clinical practice, this early objective assessment is crucial. If, at the 1-hour node, the patient shows no clinical improvement and qEEG reveals no significant decrease in DTABR, it strongly suggests potential failure of intravenous thrombolysis. For patients with suspected large vessel occlusion, this physiology-based "futility warning" can significantly shorten the clinical decision-making time, accelerating the transition to bridging therapy or rescue endovascular treatment (EVT) [34,35]. Given the highly time-dependent efficacy of EVT [36], in the "drip-and-ship" model, real-time qEEG information may facilitate optimization of transfer decisions by prioritizing patients most likely to benefit from EVT.

Stroke prognosis is the result of multifactorial interactions. While the baseline NIHSS score is a strong prognostic factor, it primarily reflects the extent of baseline anatomical injury and cannot fully represent the tissue's salvage potential [37]. Our nomogram achieves complementarity of multidimensional information by integrating ONT (reflecting the "time window"), age and comorbidities (reflecting "physiological reserve"), baseline NIHSS (reflecting "anatomical injury"), and, most critically, the DTABR reduction value (reflecting "dynamic physiological recovery"). In addition, baseline DBP and blood glucose were retained in the final model as indicators of systemic hemodynamic and metabolic status. DBP may influence cerebral perfusion at the microvascular level, while elevated blood glucose reflects acute stress responses and metabolic dysregulation, both of which can modulate tissue-level response to thrombolytic therapy. The model demonstrated good discrimination (AUC = 0.77) and excellent calibration. More importantly, DCA confirmed that the model provides significant net benefit across a wide range of clinically relevant threshold probabilities, indicating its practical value in assisting clinical decision-making. SHAP analysis was conducted to further enhance model transparency. SHAP results explicitly identified the DTABR reduction value as the most important feature in the model. This finding has profound clinical implications, suggesting that early physiological recovery may be a more critical indicator of thrombolytic efficacy than baseline stroke severity. It underscores the potential value of incorporating dynamic

electrophysiological monitoring into the multimodal acute stroke assessment [38], advancing stroke treatment toward precision medicine.

From a pragmatic perspective, the 1-hour post-thrombolysis window represents a critical window for decision-making. In current clinical workflows, physicians often face a dilemma when neurological deficits remain unchanged shortly after rt-PA administration. Our study suggests that dynamic qEEG monitoring can serve as an objective "futility warning" approach. A stagnant DTABR value (low reduction value) at the 1-hour mark may indicate inadequate microcirculatory reperfusion. This objective information provides a rationale for initiating rescue endovascular treatment or transferring the patient to a comprehensive stroke center ("drip-and-ship"), rather than waiting passively for the full pharmacological effect of rt-PA.

This study has several limitations that warrant consideration. First, as a single-center retrospective study, there may be selection bias. We excluded patients with poor-quality EEG (often those who are severely ill or uncooperative), and patients with bilateral hemispheric infarctions or infratentorial lesions, which may limit the applicability of the current model to these stroke subtypes. Second, we used 24-hour NIHSS improvement as a surrogate endpoint for early efficacy, rather than long-term functional prognosis (e.g., 90-day modified Rankin Scale [mRS]) or evidence of vascular recanalization (e.g., Thrombolysis in Cerebral Infarction [TICI] grade). Despite the strong correlation of early neurological improvement with long-term prognosis [39], future confirmation through analysis of vascular imaging data and long-term follow-up is still necessary. Third, EEG is generally more sensitive to cortical ischemia than to deep subcortical or lacunar infarctions. Due to data limitations, we could not perform a stratified analysis based on infarct depth/location (cortical vs. lacunar), which may affect the model's sensitivity for specific stroke subtypes. Fourth, EEG signals may be influenced by confounders such as sedative medications and metabolic disturbances; future prospective studies should control these variables more rigorously. Finally, this study utilized traditional frequency band ratio methods. Future research could explore more advanced EEG analysis techniques, such as brain network connectivity analysis or deep learning-based end-to-end analysis [40], to dissect the more intricate pathophysiological network.

5. Conclusion

In conclusion, a reduction in DTABR within 1 hour of intravenous thrombolysis in patients with AIS is an independent and sensitive biomarker of early neurophysiological recovery. The nomogram constructed using this dynamic qEEG parameter provides an accurate prediction of early clinical efficacy at 24-hour post-thrombolysis and demonstrates good clinical utility. This study supports the integration of qEEG as a real-time, non-invasive bedside monitoring tool into the precision treatment decision-making process for AIS, enabling early identification of thrombolytic response and guiding individualized treatment decisions.

Key Points

• The study establishes the Delta-Theta/Alpha-Beta Ratio (DTABR) reduction value within 1 hour post-thrombolysis as a robust, independent predictor of clinical efficacy at 24 hours following thrombolysis in patients with acute ischemic stroke (AIS).

• Dynamic changes in qEEG—measured via DTABR reduction value—better reflect the immediate physiological response to reperfusion compared to static baseline measurements.

• A nomogram integrating the DTABR reduction value and key clinical variables was developed and validated, showing good discrimination (AUC = 0.77), good calibration based on calibration curves and the Hosmer–Lemeshow test, and clinical utility based on decision curve analysis.

• The DTABR reduction value was identified in the SHAP analysis as the most influential feature in the model, surpassing baseline NIHSS score in importance for predicting early efficacy.

• Ultra-early (1-hour) identification of non-responders using this qEEG-based model can facilitate timely clinical decision-making, particularly in accelerating the administration of rescue endovascular treatment (EVT).

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

HTL and YCC designed the research study. HTL performed the research. YCC analyzed the data. HTL drafted the article. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Xinchang Hospital Affiliated to Shaoxing University (approval number: 2022-K-046-01). Given the retrospective design and anonymized data analysis, the Ethics Committee waived the requirement for obtaining informed consent from patients. The study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

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