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NOVEL SERUM BIOMARKERS, MEDICATION ADHERENCE, AND A PREDICTIVE NOMOGRAM IN PATIENTS WITH TYPE 2 DIABETES AND ISCHEMIC STROKE

NOVI SERUMSKI BIOMARKERI, PRIDRŽAVANJE TERAPIJE I PREDIKTIVNI NOMOGRAM KOD PACIJENATA SA DIJABETES MELITUSOM TIPA 2 I ISHEMIJSKIM MOŽDANIM UDAROM

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Summary

Background: Long-term management of pharmacotherapy in patients with type 2 diabetes mellitus (T2DM) and ischemic stroke is challenging due to comorbidities, neurological impairment and functional limitations. Although clinical factors are known to influence adherence, the contribution of circulating biomarkers of neurological injury and repair remains poorly characterised. To investigate the clinical and biomarker-related factors associated with suboptimal medication adherence, and to develop a biomarker-enhanced nomogram for predicting poor adherence in patients with T2DM complicated by ischemic stroke.

Methods: A retrospective cohort study was conducted in which 100 patients were screened, 100 enrolled, and 0 were excluded based on predefined inclusion and exclusion criteria. All the patients were treated from March 2025 to July 2025. Demographics, comorbidities, medication classes, National Institutes of Health Stroke Scale, Barthel Index, rehabilitation guidance, and circulating biomarkers, including neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), brain-derived neurotrophic factor (BDNF), high-sensitivity C-reactive protein, and HbA1c, were collected. Medication adherence was evaluated at 6 months post-discharge using the Morisky Medication Adherence Scale. Patients were randomly assigned to a training cohort (n=70) and a validation cohort (n=30). Univariate and multivariable logistic regressions were performed to find factors associated with poor ad-

Kratak sadržaj

Uvod: Dugoročno upravljanje farmakoterapijom kod pacijenata sa dijabetes melitusom tipa 2 (T2DM) i ishemijskim moždanim udarom predstavlja izazov zbog komorbiditeta, neurološkog oštećenja i funkcionalnih ograničenja. Iako je poznato da klinički faktori utiču na pridržavanje terapije, doprinos cirkulišućih biomarkera neurološke povrede i reparacije još uvek nije dovoljno razjašnjen.

Cilj: Ispitati kliničke i faktore vezane za biomarkere povezane sa suboptimalnim pridržavanjem terapije, kao i razviti nomogram zasnovan na biomarkerima za predikciju slabog pridržavanja terapije kod pacijenata sa ishemijskim moždanim udarom komplikovanim sa T2DM.

Metode: Sprovedena je retrospektivna kohortna studija u kojoj je skrining obuhvatio 100 pacijenata, gde su svi uključeni, a nijedan nije isključen na osnovu unapred definisanih kriterijuma. Svi pacijenti su lečeni u periodu od marta 2025. do jula 2025. Prikupljeni su demografski podaci, komorbiditeti, klase lekova, NIHSS skor, Bartel indeks, rehabilitaciona podrška i cirkulišući biomarkeri, uključujući neuron-specifičnu enolazu (NSE), S100 kalcijum-vezujući protein B (S100B), moždani neurotrofni faktor (BDNF), visokoosetljivi C-reaktivni protein i HbA1c. Pridržavanje terapije je procenjeno 6 meseci nakon otpusta pomoću Morisky skale adherencije na lekove. Pacijenti su nasumično podeljeni na trening kohortu (n=70) i validacionu kohortu (n=30). Za identifikaciju faktora povezanih sa slabim pridržavanjem terapije su primenjene univarijantna i multivarijantna logistička regresija, a razvijen je nomo-

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herence, and a biomarker-enhanced nomogram was built. Model performance was evaluated by the concordance index, calibration curves, receiver operating characteristic curves and net reclassification improvement (NRI). For NRI analysis, patients were categorised into three clinically interpretable predicted-risk groups: low risk (<30%), intermediate risk (30%–60%), and high risk (>60%).

Results: Forty-three patients showed poor adherence to medication. Independent predictors of poor adherence were age ≥60 years, primary education or less, ≤2 types of medication, NIHSS score ≥4, Barthel Index ≤60, no guidance for rehabilitation, high NSE (>15 ng/mL), high S100B (>110 pg/mL) and low BDNF (<22 ng/mL). Discrimination of the nomogram, including the biomarker, was good, with C-indexes of 0.851 in the training cohort and 0.838 in the validation cohort. The area under the curve values were 0.873 and 0.851, respectively. Calibration plots showed little difference between predicted and observed probabilities. The inclusion of NSE, S100B, and BDNF in the clinical-only model improved risk classification of patients (NRI 0.324, 95% CI: 0.112–0.536) using the predefined low, intermediate, and high-risk categories.

Conclusion: Clinical characteristics, neurological function, rehabilitation guidance and serum neurological injury/repair biomarkers were related to the medication adherence of the patients with T2DM and ischemic stroke. A nomogram combining NSE, S100B, and BDNF biomarkers improved the prediction of poor adherence. They may facilitate the identification of high-risk patients who need early, individualised adherence-support interventions.

Keywords: type 2 diabetes, ischemic stroke, medication adherence, nomogram, predictive model, biomarkers, NSE, S100B, BDNF

gram zasnovan na biomarkerima. Performanse modela su procenjene pomoću C-indeksa, kalibracionih krivih, ROC krivih i neto reklasifikacionog poboljšanja (NRI). Za NRI analizu, pacijenti su podeljeni u tri klinički interpretabilne grupe rizika: nizak (<30%), srednji (30–60%) i visok rizik (>60%).

Rezultati: četrdeset tri pacijenta su pokazala slabo pridržavanje terapije. Nezavisni prediktori slabog pridržavanja bili su starost ≥60 godina, osnovno obrazovanje ili niže, ≤2 vrste lekova, NIHSS ≥4, Bartel indeks ≤60, odsustvo rehabilitacionih preporuka, visoke vrednosti NSE (>15 ng/mL), povišen S100B (>110 pg/mL) i nizak BDNF (<22 ng/mL). Diskriminacija nomograma koji uključuje biomarkere je bila dobra, sa C-indeksom od 0,851 u trening kohorti i 0,838 u validacionoj kohorti. AUC vrednosti su bile 0,873 i 0,851. Kalibracione krive su pokazale minimalno odstupanje između predviđenih i stvarnih verovatnoća. Uključivanje NSE, S100B i BDNF u klinički model je poboljšalo klasifikaciju rizika (NRI 0,324; 95% CI: 0,112–0,536) u definisanim grupama rizika.

Zaključak: Kliničke karakteristike, neurološki status, rehabilitaciona podrška i serumski biomarkeri neurološke povrede i reparacije su povezani sa pridržavanjem terapije kod pacijenata sa T2DM i ishemijskim moždanim udarom. Nomogram koji uključuje NSE, S100B i BDNF poboljšava predikciju slabog pridržavanja terapije i može doprineti ranoj identifikaciji visokorizičnih pacijenata kojima je potrebna individualizovana podrška u adherenciji.

Ključne reči: dijabetes tip 2, ishemijski moždani udar, pridržavanje terapije, nomogram, prediktivni model, biomarkeri, NSE, S100B, BDNF

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder with a global epidemic, and the incidence has continuously increased in recent years (1). The prevalence of T2DM in adults is estimated at approximately 12–14%, and many patients develop chronic complications (2). Ischemic stroke is a frequent and severe complication of T2DM. Chronic hyperglycaemia damages the vascular endothelium and is a risk factor for atherosclerosis, stroke occurrence and recurrence (3, 4). The presence of multiple comorbidities and neurological impairment due to the coexistence of T2DM and ischaemic stroke is linked to poorer quality of life, greater disability and higher healthcare burden; therefore, the need for early intervention and long-term management (5).

The management of both T2DM and ischemic stroke requires long-term pharmacotherapy including oral hypoglycaemic agents, insulin, antiplatelet therapy and adjunctive medications for blood-pressure and lipid control (6). Compliance with medication is of great significance for patients with T2DM complicated by ischaemic stroke in controlling blood glucose, blood pressure and blood lipids, reducing the risk of stroke recurrence, supporting neurological recovery and improving quality of life. However, patients with chronic diseases often demonstrate poor medication adherence, including missed doses, reduced dosages, or self-discontinuation of medication (7, 8). Multiple factors determine medication adherence, and early identification of high-risk patients, followed by personalised interventions such as medication education, guidance in rehabilitation care, and follow-up reminders, may improve adherence and clinical outcomes (9).

While demographic and clinical factors associated with medication adherence have been studied, the potential role of circulating biomarkers indicative of neurological injury and recovery has not been sufficiently explored. Biomarkers collected during the acute hospitalisation period may provide objective information beyond conventional clinical scales. They may help identify patients at increased risk of medication non-adherence after discharge due to neurological injury, impaired neuroplasticity, or reduced self-management capacity. Therefore, this retrospective study includes patients with T2DM complicated by ischemic stroke, who were administered the Morisky Medication Adherence Scale to evaluate their medication adherence at 6 months after discharge, along with their demographic, clini-

cal, functional, rehabilitation-related, and biomarker variables. Using these data, independent predictors of poor adherence were identified, and a biomarker-enhanced nomogram was developed to enable early risk stratification and individualised intervention.

Subjects and methods

Study population

We retrospectively collected the clinical datasets from 100 patients with type 2 diabetes mellitus and ischemic stroke who were treated at our institution from March 2025 to July 2025.

Inclusion criteria

① Meeting the World Health Organisation diagnostic criteria for type 2 diabetes (10)

② Meeting diagnostic criteria for ischemic stroke (11) and confirmed by cranial imaging scans

③ Being conscious and having stable vital signs at discharge, capable of self-administering medication and completing relevant questionnaires or interviews

④ Possessing complete clinical records

Exclusion criteria

① Presence of psychiatric disorders, cognitive impairment, impaired language expression, or intellectual disability

② Dysphagia

③ Impairment of major organ function (e.g., cardiac, hepatic, renal dysfunction) was documented in the study cohort

④ Concurrent malignant neoplasms

⑤ Participation in other concurrent studies

⑥ Inability to complete follow-up

Ethical approval for the present investigation was granted by the Institutional Review Board of Xingtai People's Hospital.

Research methods

Follow-up period and methods

The patient was discharged, and follow-up was initiated, but there was no guidance for medication intervention after discharge. Adherence was assessed by telephone, WeChat or outpatient follow-up assessments at 6 months. The follow-up phase was completed in January 2026, and the median follow-up duration of the study cohort was 11 months (11).

Data collection

Collected data included medical records, questionnaires completed during the patient's inpatient treatment, and laboratory biomarkers. Demographic and clinical data including age, sex, education level, marital status, place of residence, employment status, duration of diabetes mellitus, comorbidities (hypertension, hyperlipidaemia, hyperhomocysteinemia, hyperuricemia, anaemia, atrial fibrillation, etc.), types of antidiabetic medications used, National Institutes of Health Stroke Scale (NIHSS) score (12), Barthel Index score (13) and receiving rehabilitation care guidance were obtained.

In this study, rehabilitation guidance specifically refers to structured rehabilitation nursing guidance after discharge, including individualised medication education, rehabilitation exercise instructions, caregiver involvement, reminder strategies, and follow-up guidance before discharge or early post-discharge contact. Routine inpatient verbal advice or general discharge instructions were not considered rehabilitation advice unless they included a documented individualised rehabilitation and medication management plan.

Functional independence in activities of daily living was measured using the Barthel Index. Scores range from 0 to 100, with a higher score indicating greater independence. A cut-off value of ≤60 points was chosen since this threshold is often used to discriminate patients with severe functional dependence from patients with moderate or mild dependence. In previous categorisations of the Barthel Index, scores of 21–60, 61–90 and 91–99 were generally categorised as severe, moderate and slight dependence, respectively. Thus, patients with scores of 60 or below were considered to have clinically meaningful functional dependence that could impact their ability to reliably self-administer medications.

Venous blood samples were obtained within 48 hours of admission. Samples were centrifuged at 3000 rpm for 10 min, and serum/plasma was stored at -80 °C until analysis. The following novel biomarkers were measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits (all assays were performed in duplicates according to manufacturer's protocols and with intra- and inter-assay coefficients of variation <8%):

Neuron-Specific Enolase (NSE): Marker of acute neuronal damage (CanAg Diagnostics, Gothenburg, Sweden).

S100 calcium-binding protein B (S100B): Marker of astroglial damage and blood-brain barrier disruption (BioVendor, Brno, Czech Republic).

Brain-Derived Neurotrophic Factor (BDNF): Neuroplasticity and cognitive reserve marker (R&D Systems, Minneapolis, MN, USA).

High-sensitivity C-reactive protein (hs-CRP): Systemic inflammation marker (Roche Diagnostics, Basel, Switzerland).

HbA1c: Long-term glycaemic control (Bio-Rad Laboratories, Hercules, CA, USA).

Medication adherence assessment

Medication adherence was measured using the Morisky Medication Adherence Scale (14) during patient follow-up. The scale measured ① missed doses times; ② whether there are days in the past two weeks when the medication was not taken on time, one or more days; ③ ④ Whether the medication dose was independently reduced or stopped when symptoms worsened or other discomforts appeared during the treatment; ⑤ Whether the medication was occasionally forgotten when going out; Whether the antiviral medication was taken as prescribed yesterday and today; ⑥ 7) Medication was stopped independently after symptoms improved or disappeared; 8. Difficulties with adherence to the antiviral treatment regimen. Do you have difficulty remembering to take your antiviral medication at the correct time and in the correct dose?

For Questions 1–7, responses are scored as follows: »Yes« = 0 points and »No« = 1 point. Frequency-based responses are scored as follows: Never = 1 point, Occasionally = 0.75 points, Sometimes = 0.50 points, Often = 0.25 points, and All the time = 0 points. Question 8 is scored according to response frequency. A total questionnaire score of <6 indicates poor medication adherence, whereas a score of ≥ 6 indicates good medication adherence (15).

Grouping method

One hundred patients with type 2 diabetes mellitus and ischaemic stroke were randomly allocated to the training cohort (n=70) and the validation cohort (n=30) using simple randomisation techniques. The predictive model was developed and internally validated in the training cohort. The validation set was used only for external validation of the model. To identify determinants of medication non-adherence, the training set was further divided into poor-adherence and good-adherence subgroups based on patient adherence patterns.

Predictive model construction and validation

Univariate analyses and multivariate logistic regression models were used to identify determinants associated with medication adherence among individuals with T2DM and ischaemic stroke, and to identify independent risk factors for poor adherence. Optimal cut-off values for continuous biomarkers (NSE, S100B, BDNF, hs-CRP, HbA1c) were obtained using maximally selected rank statistics.

Based on regression analysis results, a biomarker-enhanced linear graphical predictive model (nomogram) for suboptimal medication adherence was developed in R, yielding an early-warning tool. Each variable in the model is represented by a scale on the chart. The value of each independent variable was plotted on the scale axis, and a vertical line was drawn upwards to obtain the corresponding score. For all risk factors (clinical variables and significant biomarkers), the scores were summed to create an overall score, and the location on the total score axis was identified. A vertical line was then drawn downwards to the risk axis, and the point of intersection was taken to represent the estimated likelihood of suboptimal medication adherence for the individual patient.

Finally, the developed predictive model underwent both internal and external validation procedures.

Missing data handling

The completeness of all demographic, clinical, functional, rehabilitation, medication adherence, and biomarker variables was assessed before statistical analysis. As the study included only patients with complete clinical records, complete follow-up information and available biomarker measurements, there were no missing values for variables included in the final analysis. Hence, we conducted a complete case analysis and no statistical imputation was required. Predefined exclusion criteria were used to exclude patients with incomplete clinical records or those unable to complete follow-up.

Sample size justification

This was a retrospective cohort study of all eligible patients with T2DM complicated by ischemic stroke treated at our institution from March 2025 to July 2025 who had fulfilled the predefined inclusion and exclusion criteria. 100 patients were screened,

100 patients were enrolled, and no patients were excluded post-screening. At 6 months after discharge, 43 of these patients had poor medication adherence, and 57 had good medication adherence. Hence, the sample size was the number of eligible patients available during the study period.

The cohort was randomly divided into a training set and a validation set at a 7:3 ratio for model development, including 70 patients for model construction and internal validation and 30 patients for validation. This single-centre, retrospective prediction-model study was exploratory. Because of the limited number of outcome events, multivariable model development was limited to clinically relevant variables and to variables significant in univariate analysis, while considering model parsimony. Hence, the findings should be considered preliminary and confirmed in larger multicentre cohorts.

TRIPOD statement compliance

The design, analysis and reporting of this prediction-model study were performed according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement. As recommended by TRIPOD, we clearly defined the source population, eligibility criteria, outcome definition, candidate predictors, sample size, handling of missing data, model development procedure, measures of model performance, and validation strategy. The model was evaluated for discrimination, calibration, and reclassification metrics, including the concordance index, receiver operating characteristic curve, area under the curve, calibration curve, DeLong test, and net reclassification improvement.

Statistical analysis

The statistical analyses of the datasets were conducted using SPSS 27.0 software. Categorical data were presented as frequency and proportion. Between-group comparisons were performed with the chi-square test or Fisher's exact test. For continuous variables (biomarkers), the Mann-Whitney U test was used. Logistic regression models were used to examine factors associated with medication compliance. Values of $P<0.05$ were considered statistically significant.

We constructed a column chart prediction model for medication adherence using the R programming environment (version 3.5.3) and the Rms package. Internal and external validation of the model was performed by bootstrap sampling. The predictive performance of the established model was evaluated using concordance index (C-index), calibration plots and receiver operating characteristic (ROC) curves. The C-index was computed with the rms package, and calibration plots were produced jointly with the rms and caret packages. ROC curves were generated with the ROCR and rms packages (1-specificity on the x-axis, sensitivity on the y-axis), and the area under the curve (AUC) was used as a measure of the model's predictive accuracy. The added predictive value of biomarkers was assessed by comparing the AUCs of the model with only clinical data and the model with clinical data and biomarkers using the DeLong test. We quantified the proportion of patients correctly reclassified in appropriate risk categories using net reclassification improvement (NRI).

First, the Mann-Whitney U test was used to compare continuous biomarker variables (NSE, S100B, BDNF, hs-CRP, HbA1c) between good-adherence and poor-adherence groups. The optimal cut-off values for continuous biomarkers in the training cohort were determined using the maximally selected rank statistics to allow clinical interpretation and integration into the nomogram. The resulting thresholds were subsequently used in the multivariable logistic regression model and validation analysis. The cut-off values for the identified biomarkers were NSE>15 ng/mL, S100B>110 pg/mL, BDNF<22 ng/mL, hs-CRP>5 mg/L, and HbA1c>7.5%. Internal validation of the nomogram was performed using the bootstrap resampling method with 1,000 resamples. In each bootstrap iteration, the model was refitted, and its predictive performance was reassessed to estimate optimism-corrected discrimination and calibration. The C-index, calibration curve, calibration intercept, and calibration slope were then calculated to evaluate model performance.

Results

Baseline characteristics of the training and validation cohort

One hundred patients with type 2 diabetes mellitus complicated with ischemic stroke were randomly divided into a training cohort (n=70) and a verification cohort (n=30). We compared the baseline characteristics of the two cohorts to assess the balance of randomisation. As presented in *Table I*, there were no statistically significant differences in demographic characteristics, clinical variables, neurological function scores, Barthel Index, rehabilitation guidance, medication adherence status, and levels of biomarkers, including NSE, S100B, BDNF, hs-CRP, and HbA1c between the training and validation cohorts (all $P>0.05$). These results suggest that the two cohorts were generally comparable at baseline and suitable for subsequent model development and validation.

Table I Baseline characteristics of the training and validation cohorts.

Characteristic	Training cohort (n=70)	Validation cohort (n=30)	χ^2 / Z	P value
Demographic characteristics				
Age, n (%)			0.000	1.000
<60 years	14 (20.00)	6 (20.00)		
≥60 years	56 (80.00)	24 (80.00)		
Sex, n (%)			0.008	0.930
Male	39 (55.71)	17 (56.67)		
Female	31 (44.29)	13 (43.33)		
Education level, n (%)			0.008	0.927
Primary school or below	24 (34.29)	10 (33.33)		
Secondary school or above	46 (65.71)	20 (66.67)		
Marital status, n (%)			0.052	0.820
Married	57 (81.43)	25 (83.33)		
Divorced/Widowed	13 (18.57)	5 (16.67)		
Residence, n (%)			0.021	0.885
Rural	20 (28.57)	9 (30.00)		
Urban	50 (71.43)	21 (70.00)		
Employment status, n (%)			0.008	0.930
Employed	38 (54.29)	16 (53.33)		
Retired/Unemployed	32 (45.71)	14 (46.67)		
Clinical characteristics				
Comorbid chronic diseases, n (%)			0.000	1.000
Yes	63 (90.00)	27 (90.00)		
No	7 (10.00)	3 (10.00)		
Duration of diabetes, n (%)			0.045	0.978
<3 years	22 (31.43)	10 (33.33)		
3–6 years	15 (21.43)	6 (20.00)		
>6 years	33 (47.14)	14 (46.67)		
Medication categories, n (%)			0.014	0.905
>2 types	11 (15.71)	5 (16.67)		
≤2 types	59 (84.29)	25 (83.33)		
NIHSS score, n (%)			0.016	0.900
<4 points	60 (85.71)	26 (86.67)		
≥4 points	10 (14.29)	4 (13.33)		
Barthel Index, n (%)			0.016	0.900
≤60 points	10 (14.29)	4 (13.33)		
>60 points	60 (85.71)	26 (86.67)		
Rehabilitation guidance, n (%)			0.004	0.948
Yes	9 (12.86)	4 (13.33)		
No	61 (87.14)	26 (86.67)		
Medication adherence status, n (%)			0.002	0.965
Good adherence	40 (57.14)	17 (56.67)		
Poor adherence	30 (42.86)	13 (43.33)		
Biomarkers, median (IQR)				
NSE, ng/mL	14.9 (10.8–19.2)	15.3 (11.0–19.8)	−0.22	0.826
S100B, pg/mL	108 (74–151)	112 (76–156)	−0.31	0.757
BDNF, ng/mL	24.9 (19.4–30.8)	24.5 (18.9–31.1)	−0.18	0.857
hs-CRP, mg/L	4.5 (2.4–7.9)	4.7 (2.6–8.2)	−0.27	0.787
HbA1c, %	7.8 (6.8–8.9)	7.9 (6.9–9.1)	−0.25	0.803

Table II Comparison of clinical and biomarker data between good and poor adherence groups.

Characteristic	Good compliance (n=57)	Poor compliance (n=43)	χ^2 / Z	P
Demographic				
Age			3.982	0.016
<60 years	15 (26.32)	5 (11.63)		
≥60 years	42 (73.68)	38 (88.37)		
Gender			0.774	0.435
Male	29 (50.88)	27 (62.79)		
Female	28 (49.12)	16 (37.21)		
Education Level			4.364	0.008
Primary school or below	13 (22.81)	21 (48.84)		
Secondary school or above	44 (77.19)	22 (51.16)		
Marital Status			1.327	0.202
Married	45 (78.95)	37 (86.05)		
Divorced/Widowed	12 (21.05)	6 (13.95)		
Residence			4.003	0.010
Rural	14 (24.56)	15 (34.88)		
Urban	43 (75.44)	28 (65.12)		
Employment Status			0.015	0.891
Employed	30 (52.63)	24 (55.81)		
Retired/Unemployed	27 (47.37)	19 (44.19)		
Clinical				
Comorbid Chronic Conditions			4.204	0.006
Yes	49 (85.96)	41 (95.35)		
No	8 (14.04)	2 (4.65)		
Duration of Diabetes			1.458	0.187
<3 years	14 (24.56)	18 (41.86)		
3č6 years	15 (26.32)	6 (13.95)		
>6 years	28 (49.12)	19 (44.19)		
Medication Status			7.506	0.001
>2 types	13 (22.81)	3 (6.98)		
≤2 types	44 (77.49)	40 (93.02)		
NIHSS Score			3.842	0.015
<4 points	51 (89.47)	35 (81.40)		
≥4 points	6 (10.53)	8 (18.60)		
Barthel Index			4.121	0.009
≤60 points	5 (8.77)	9 (20.93)		
>60 points	52 (91.23)	34 (79.07)		
Rehabilitation Guidance			3.996	0.011
Yes	9 (15.79)	4 (9.30)		
No	48 (84.21)	39 (90.70)		
Biomarkers (Median, IQR)				
NSE (ng/mL)	12.3 (9.8–15.1)	18.7 (14.2–24.5)	-4.21	<0.001
S100B (pg/mL)	85 (62–112)	145 (108–189)	-4.85	<0.001
BDNF (ng/mL)	28.5 (24.1–33.2)	19.3 (15.0–24.8)	-5.02	<0.001
hs-CRP (mg/L)	3.2 (1.8–5.9)	6.8 (3.5–11.2)	-3.56	<0.001
HbA1c (%)	7.2 (6.5–8.0)	8.5 (7.4–9.6)	-3.89	<0.001

Comparison of patient demographics and biomarkers

Among the 100 patients diagnosed with type 2 diabetes mellitus and ischaemic stroke, 43 achieved a score <6 on the Morisky Medication Adherence Scale after discharge (poor adherence group), and 57 achieved a score ≥6 (good adherence group). *Table II* summarises the differences in clinical characteristics and biomarker levels between the two groups.

No statistically significant differences were found between groups for sex, marital status, or employment status (P>0.05). On the contrary, the good adherence cohort had significantly higher proportions than the poor adherence cohort in the following characteristics (P<0.05): age <60 years, educational attainment at secondary school level or above, urban residence, absence of other chronic diseases, >2 types of medications, NIHSS score <4 points, Barthel Index >60 points, and receiving rehabilitation care guidance.

In terms of biomarkers, the poor adherence group had significantly higher levels of NSE (median 18.7 vs 12.3 ng/mL, P<0.001), S100B (median 145 vs 85 pg/mL, P<0.001), hs-CRP (median 6.8 vs 3.2 mg/L, P<0.001) and HbA1c (median 8.5% vs 7.2%, P<0.001) than the good adherence group, and significantly lower levels of BDNF (median 19.3 vs 28.5 ng/mL, P<0.001).

Multivariable logistic regression analysis of determinants impacting medication compliance

Multivariate logistic regression was used to examine determinants of medication adherence. The independent variables were the significantly different variables (age, educational attainment, residence, presence of other chronic diseases, number of medications taken, NIHSS score, Barthel Index, presence of rehabilitation care guidance, and all five biomarkers), and the dependent variable was medication adherence, as shown in *Table III*.

Results: The independent clinical determinants associated with suboptimal medication adherence were: age ≥60 years, educational attainment at the elementary school level or below, taking ≤2 types of medications, NIHSS score ≥4, Barthel Index ≤60, and no rehabilitation care delivery (P<0.05).

Among the biomarkers, high NSE (>15 ng/mL, OR=6.632, 95% CI: 2.431–18.095, P<0.001), high S100B (>110 pg/mL, OR=8.176, 95% CI: 2.794–23.926, P<0.001), and low BDNF (<22 ng/mL, OR=0.233, 95% CI: 0.091–0.596,

Table III Multivariate logistic regression analysis of factors influencing patient medication adherence (clinical + biomarkers).

Factors	β	S.E.	Wald χ^2	P	OR	95% CI
Age (≥60 years)	0.789	0.331	5.68	0.017	2.201	1.150–4.213
Education Level (Primary or below)	0.702	0.345	4.14	0.042	2.018	1.026–3.968
Place of Residence (Rural)	0.698	0.478	2.13	0.144	2.010	0.788–5.126
Comorbid Chronic Diseases (Yes)	0.789	0.289	7.45	0.106	2.201	0.845–5.732
Types of Medications Taken (≤2)	0.956	0.398	5.77	0.016	2.601	1.192–5.677
NIHSS Score (≥4)	1.123	0.339	10.96	<0.001	3.074	1.581–5.976
Barthel Index (≤60)	1.423	0.468	9.25	0.002	4.149	1.658–10.380
Rehabilitation Nursing Guidance (No)	1.245	0.618	4.06	0.044	3.473	1.034–11.665
NSE (>15 ng/mL)	1.892	0.512	13.65	<0.001	6.632	2.431–18.095
S100B (>110 pg/mL)	2.101	0.548	14.70	<0.001	8.176	2.794–23.926
BDNF (<22 ng/mL)	-1.456	0.479	9.24	0.002	0.233	0.091–0.596
hs-CRP (>5 mg/L)	0.589	0.401	2.16	0.142	1.802	0.821–3.955
HbA1c (>7.5%)	0.521	0.387	1.81	0.178	1.684	0.789–3.595
Constant Term	-4.892	1.045	21.92	<0.001	0.007	

Note: Independent variable assignments are as follows: age (≥60 years = 1, <60 years = 0), education level (primary school and below = 1, secondary school and above = 0), place of residence (rural = 1, urban = 0), other chronic diseases (yes = 1, no = 0), duration of diabetes (>6 years = 2, 3č6 years = 1, <3 years = 0), types of medications taken (>2 types = 1, ≤2 = 0), NIHSS score (≥4 points = 1, <4 points = 0), Barthel index (≤60 points = 1, >60 points = 0), rehabilitation nursing guidance (no = 1, yes = 0). Maximally selected rank statistics determined biomarker cut-offs: NSE>15 ng/mL, S100B>110 pg/mL, BDNF<22 ng/mL, hs-CRP>5 mg/L, HbA1c>7.5%.

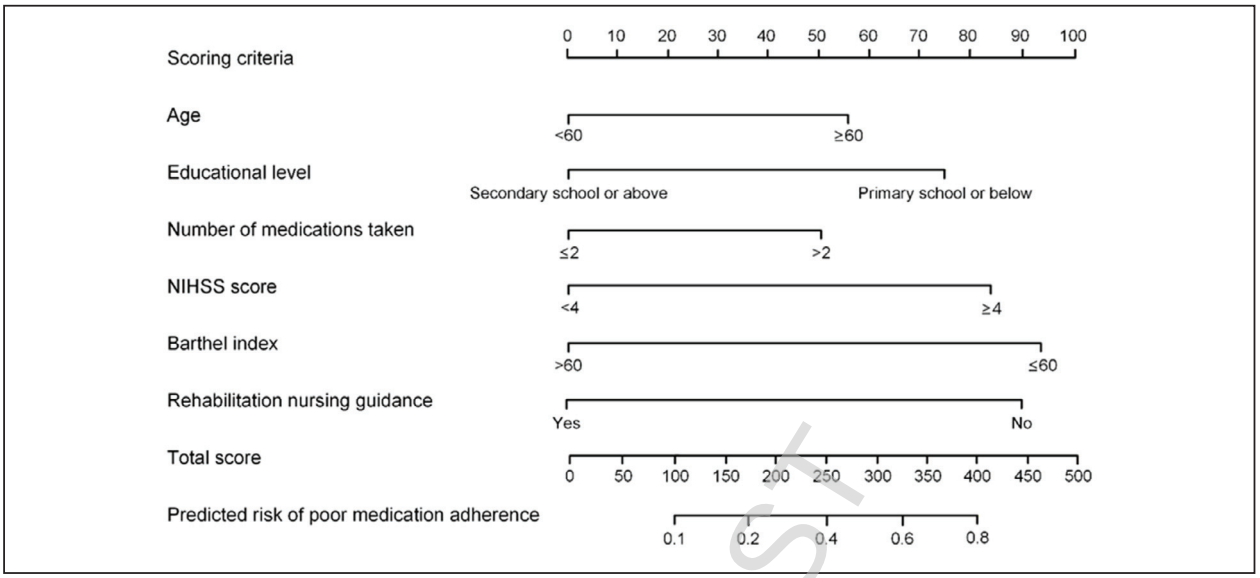

Figure 1 Nomogram predicting poor medication adherence in T2DM and ischemic stroke patients.

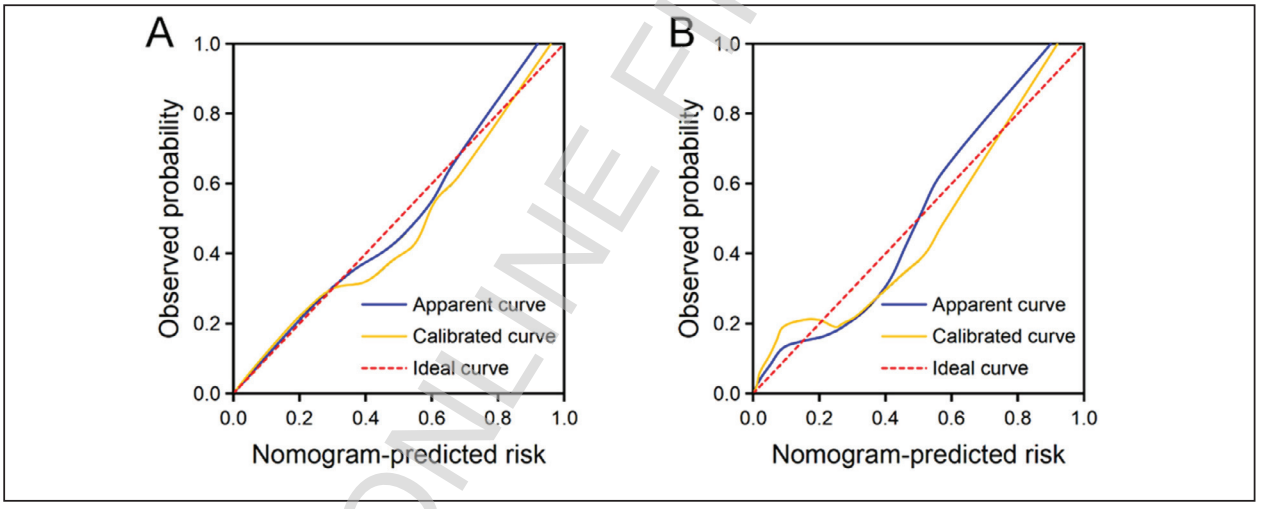

Figure 2 Calibration curves of the nomogram model for predicting poor patient medication adherence.

(A) Calibration curve for training set (C-index=0.851); (B) Calibration curve for validation set (C-index=0.838). Both curves demonstrate excellent agreement between predicted and observed probabilities.

P=0.002) were also independent predictors of poor adherence. In the multivariable model, hs-CRP (>5 mg/L) and HbA1c (>7.5%) were not significant after adjustment for other factors (P>0.05).

Construction of a predictive nomogram model for poor medication adherence

The model included 6 clinical variables (age, education level, number of medicines, NIHSS score, Barthel index, rehabilitation guidance) and 3 key biomarkers (NSE, S100B, BDNF). To apply the nomogram, the value of each variable was found on the corresponding axis, and a vertical line was drawn to the »Points« axis to assign individual points. All points were then totalled to obtain a total score. A vertical line was drawn downward from the »Total Points« axis to the »Risk of Poor Adherence« axis, and the point of intersection corresponded to the predicted probability of suboptimal medication adherence. The results demonstrated that the constructed predictive nomogram had a risk range of 10–90%.

The nomogram was constructed using independent predictors identified by multivariable logistic regression analysis in the training cohort. The final model included six clinical predictors, namely age ≥60 years, primary education or below, ≤2 medica-

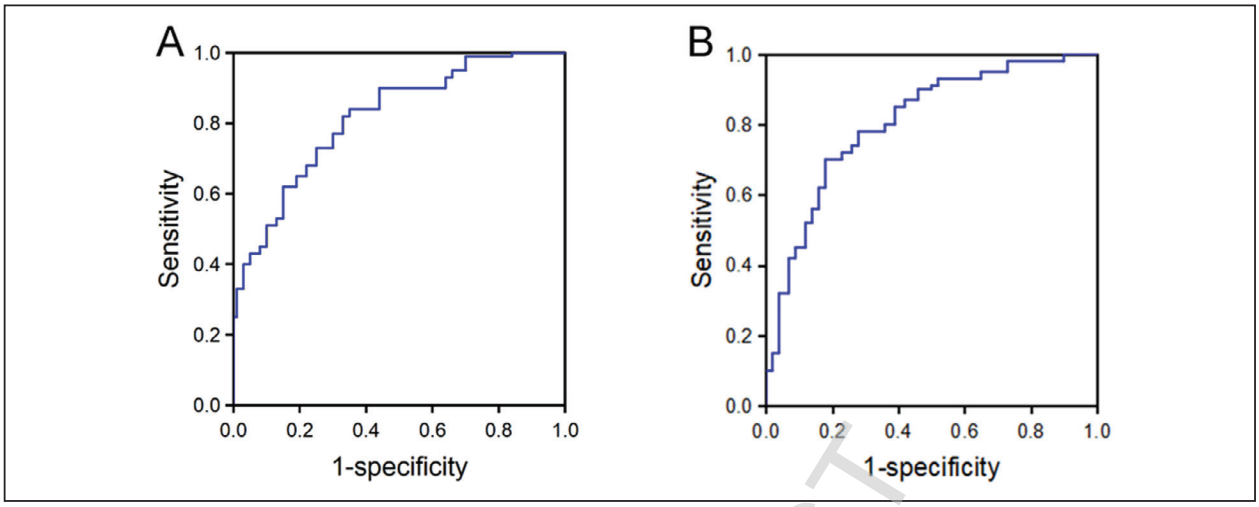

Figure 3 ROC curves of the nomogram model for predicting poor patient medication adherence.
(A) ROC curve of the training set (AUC=0.873); (B) ROC curve of the validation set (AUC=0.851). The biomarker-enhanced model (solid line) significantly outperformed the clinical-only model (dashed line) in both cohorts.

tion types, NIHSS score ≥4, Barthel Index ≤60, and absence of rehabilitation guidance, together with three biomarker predictors, namely NSE>15 ng/mL, S100B>110 pg/mL, and BDNF<22 ng/mL. Each predictor was assigned a point value according to its regression coefficient. For each patient, the points assigned to all predictors are summed to obtain the total score, which is then mapped to the risk scale to estimate the probability of poor medication adherence.

Validation of the poor medication adherence prediction nomogram

The suboptimal medication adherence predictive nomogram in T2DM and ischaemic stroke patients underwent both internal and external validation procedures. The calibration plots for training and validation cohorts are presented in *Figure 2*.

The biomarker-enhanced model achieved a C-index of 0.851 (95% CI: 0.792–0.910) in the training cohort and 0.838 (95% CI: 0.810–0.866) in the validation cohort, compared with the clinical-only model, which achieved a C-index of 0.808 and 0.795, respectively. Calibration plots showed good approximation to the ideal reference line, indicating good agreement between the predicted and observed probabilities. The calibration intercept and slope also assessed calibration performance. Calibration intercept and slope were -0.034 and 0.962, respectively, in the training cohort, indicating little systematic over- or underestimation and good agreement between predicted and observed probabilities. In the validation cohort, the calibration intercept was 0.071, and the calibration slope was 0.918, indicating an acceptable external calibration with slight overfitting. The numerical calibration indices confirmed the visual findings of the calibration curves, with calibration intercepts being near 0 and calibration slopes near 1.

The ROC curves for the training and validation cohorts are presented in *Figure 3*. The biomarker-enhanced model had an AUC of 0.873 (95% CI, 0.845–0.920) in the training cohort and 0.851 (95% CI, 0.835–0.879) in the validation cohort. The DeLong test demonstrated that the biomarker-enhanced model was significantly better than the clinical-only model (P=0.014 for training, P=0.021 for validation). The net reclassification improvement (NRI) was 0.324 (95% confidence interval, 0.112 to 0.536), indicating that the addition of biomarkers correctly reclassified 32% of patients into appropriate risk categories.

Discussion

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disorder globally. It has been proven that its persistent hyperglycaemic state contributes to vascular endothelial damage, atherosclerosis and multi-organ complications. Among these, ischaemic stroke is known to be one of the most common and serious neurological complications among patients with T2DM (16, 17). Patients with T2DM are at approximately 2–3 times greater risk of ischaemic stroke than the general population, with significantly higher rates of stroke recurrence and disability (18). Stroke not only exacerbates the neurological impairment but also leads to cognitive decline, loss of independence in daily living and limitations in activities of daily living. Therefore, the patients' quality of life is significantly affected, and the socioeconomic burden on the community and families is worsened (19–21).

In the long term, regular and timely medication adherence is a key step to control blood glucose, blood pressure and blood lipids and prevent the recurrence of stroke for T2DM patients with ischemic stroke (22). However, in clinical practice, these patients are often characterised by poor medication adherence. Advanced age, cognitive decline, complexity of medications, and lack of guidance for rehabilitation care may lead to missed doses, dose reductions, or self-discontinuation of medications (23). Therefore, regular analysis of medication adherence change patterns, identification of high-risk groups, and the establishment of prediction models can provide scientific evidence for clinical practice and formulate individualised intervention strategies to improve long-term patient outcomes. That is the core purpose of this work.

Clinical risk factors for poor medication adherence

The independent clinical risk factors influencing medication compliance in the present investigation were as follows: age ≥60 years, primary school or lower education level, <2 medication types, NIHSS score ≥4, Barthel Index ≤60, and no rehabilitation care guidance. First, older people often experience cognitive decline and memory impairment, which makes them vulnerable to forgetting to take medications on time. Low adherence is also due to their ignorance about the effectiveness of drugs and diseases (24). Second, patients with lower educational attainment were less aware of disease management and medication adherence, underestimated the importance of drugs and could not self-adjust and monitor their regimen (25, 26). Third, patients taking fewer types of medication may have engaged in »selective medication adherence« or arbitrarily stopped drugs because they thought they were unimportant, indicating that fewer medications are not necessarily better and that patient education plays an important role. Fourth, higher NIHSS scores are associated with a more severe neurological deficit, cognitive impairment, and physical limitations that impede the ability of patients to self-administer medications (27). Fifth, less independence in activities of daily living in patients with a lower Barthel Index, some of whom require assistance with medication administration. Without nursing and family support, adherence inevitably declined (28). Finally, the lack of guidance for rehabilitation nursing does not provide patients with systematic medication education, reminders, and follow-up support, further weakening adherence (29). These factors highlight the importance of demographic characteristics, neurological function and the ability to perform activities of daily living in adherence management.

Novel biomarkers as independent predictors of medication adherence

This study innovated in demonstrating that NSE, S100B and BDNF are strong independent predictors of poor medication adherence in T2DM-ischemic stroke patients even after adjustment for traditional clinical factors. High levels of NSE and S100B (both among the best known markers of acute neuronal injury and blood-brain barrier disruption) were associated with 6.6- and 8.2-fold increased risk of poor adherence, respectively, while low BDNF (a marker of impaired neuroplasticity) was associated with better adherence (OR=0.23 for high BDNF levels). The findings represent a biological link between the severity of stroke and subsequent medication-taking behaviour that is beyond clinical observation. Those with more underlying neuronal injury (higher NSE/S100B) may have more profound executive dysfunction, apathy, or memory deficits, all of which are mediated by damage to frontal-subcortical circuits and the hippocampus. These cognitive and motivational impairments directly impact the ability to plan, initiate and maintain complex medication regimens. On the other hand, low BDNF has previously been associated with depression and cognitive decline of stroke survivors and may predispose to motivational deficits, learned helplessness, and poor health engagement. Of note, in the multivariable model, hs-CRP (systemic inflammation) and HbA1c (glycaemic control) did not reach significance, suggesting that markers of acute neurological injury may be more specific predictors of adherence than broad measures of inflammatory or metabolic status in this cohort.

The application of these biomarkers in prediction models provides pathophysiological insight that cannot be achieved with clinical scales (NIHSS, Barthel Index) alone. For example, two patients with identical NIHSS scores of 3 (mild deficit) may have very different NSE/S100B levels, depending on the extent of subclinical neuronal injury. Our model would identify patients with high NSE/S100B as high risk for poor adherence to early intervention.

Biomarker-enhanced model improves predictive accuracy

The C-index of the model increased from 0.808 to 0.851 (AUC from 0.841 to 0.873) with the addition of NSE, S100B, and BDNF to the training set, representing a clinically meaningful improvement in risk discrimination. The net reclassification improvement (NRI) of 0.324 indicates that approximately 32% of patients were correctly reclassified into appropriate risk categories with the addition of biomarkers. This implies that the biomarker status

can identify patients at high risk who would not be identified solely by clinical assessment.

Clinically, NSE, S100B and BDNF measured within 48 h of admission may trigger early, targeted interventions before discharge and may prevent the emergence of poor adherence patterns. Clinicians may apply for patients with high risk (e.g., high NSE/S100B, low BDNF):

1. intensive medication education with simplified and pictographic instructions adapted to cognitive impairment;

2. training and involvement of caregivers, particularly in patients with low BDNF who may be at risk for post-stroke depression;

3. simplifying the medication regimen (e.g., once-a-day dosing, pill boxes, electronic reminders);

4. scheduled follow-up with telephone or video-based medication reminders;

5. early referral to neuropsychology for cognitive rehabilitation and mood management.

Beyond global cognitive impairment, several neurobehavioral mechanisms may plausibly explain the association between NSE, S100B, BDNF, and medication adherence. NSE is widely regarded as a marker of neuronal injury, whereas S100B reflects astroglial injury and blood–brain barrier dysfunction (30). Increased levels of these biomarkers may therefore indicate more extensive disruption of neural networks involved in executive control, emotional regulation, motivation, planning, and goal-directed behaviour. Previous studies have shown that cognitive impairment after stroke is associated with medication non-adherence (31). In addition, apathy after stroke is increasingly recognised as a common neuropsychiatric syndrome characterised by reduced goal-directed activity and poorer functional recovery (32). Apathy has also been linked to executive dysfunction and impaired processing speed, suggesting that motivational and executive-control deficits may share overlapping vascular and neural substrates (33). Therefore, patients with elevated NSE and S100B may have difficulty organising medication schedules, initiating medication-taking behaviour, maintaining routines, and engaging consistently in long-term secondary-prevention strategies, even when basic orientation or global cognition appears relatively preserved.

BDNF may also influence adherence through pathways related to neuroplasticity, mood regulation, and motivational recovery. Lower serum BDNF has been reported in patients with post-stroke depression compared with stroke patients without depression (34). Post-stroke depression is also associated with impaired functional recovery and reduced quality of life (35). Depression and apathy may reduce treatment engagement by decreasing motivation, perceived benefit of therapy, participation in rehabilitation, and capacity for sustained self-management (32, 34). In this context, reduced BDNF may reflect impaired adaptive neuroplasticity and vulnerability to depressive or apathetic symptoms, which can subsequently compromise medication-taking behaviour. Taken together, NSE, S100B, and BDNF may represent a broader neurobiological vulnerability involving neuronal injury, glial activation, blood–brain barrier disruption, impaired neuroplasticity, depression, apathy, and executive dysfunction, all of which may contribute to poor adherence in patients with T2DM and ischemic stroke.

Clinical utility of the nomogram

For the identified risk factors, this study developed a nomogram that quantifies and aggregates scores for each independent risk factor (clinical and biomarker variables) and maps them to the predicted risk of poor adherence. The intuitiveness and ease of use of the nomogram model enable clinicians to rapidly assess each patient's risk and develop intervention strategies based on the contribution of different factors to the overall risk (36–38). The high C-index and AUC values confirmed the model's strong discriminative performance in both internal and external validation. Calibration curves showed high consistency between predicted and actual risks, confirming the model's stability and reliability.

Limitations

This study has several limitations. First, this was a single-centre retrospective study with a relatively small sample size, which may limit the generalizability of the findings. Although the model showed good performance in both the training and validation cohorts, further validation in larger, prospective, multicentre cohorts is required. Second, medication adherence was assessed using the self-reported Morisky Medication Adherence Scale, which may be affected by recall bias and social desirability bias. Future studies could combine self-reported scales with objective adherence measures, such as pharmacy refill records, pill counts, or electronic medication monitoring. Third, serum biomarkers were measured at a single time point within 48 hours of admission; therefore, the present study could not evaluate dynamic changes in NSE, S100B, BDNF, hs-CRP, or HbA1c over time. Longitudinal biomarker assessment may better clarify whether temporal trajectories of biomarkers are associated with post-discharge adherence behaviour.

Fourth, although NSE, S100B, and BDNF were independently associated with poor medication ad-

herence, the observational design does not allow causal inference. These biomarkers should be interpreted as predictive and associative indicators rather than direct mechanistic determinants of adherence. Fifth, some potentially relevant factors were not fully captured, including cognitive test results, depression and anxiety status, caregiver support, medication cost, health literacy, medication regimen complexity, and post-discharge follow-up intensity. These unmeasured variables may have influenced medication-taking behaviour and model performance. Finally, the validation cohort was derived from the same institution as the training cohort. Therefore, although the cohort split provided preliminary validation, true external validation in independent populations is still needed before the nomogram is routinely applied in clinical practice.

Conclusion

Age, educational attainment, type of medication, delivery of neurological function and rehabilitation care were identified as key clinical determinants associated with medication adherence among individuals with a diagnosis of T2DM and ischaemic stroke. Furthermore, high NSE (>15 ng/mL), high S100B (>110 pg/mL), and low BDNF (<22 ng/mL) were robust independent biomarker predictors of poor adherence, suggesting the biological impact of neuronal injury and impaired neuroplasticity on self-management capacity. The developed biomarker-enhanced nomogram predicts poor adherence risk with greater accuracy than clinical variables alone. It may serve as a useful reference for early clinical identification and individualised intervention strategies for high-risk patients.

Authors' contribution

Research design, data collection and analysis: Xuexue Wang, Mengmeng Pu, Yalin Liu, manuscript drafting; Data organisation and statistical analysis: Zhongmin Zhao, Yanhong Wang; Manuscript revision and academic guidance: Xuexue Wang; All authors are responsible for the final manuscript content and consent to its publication.

Ethical approval

The hospital's Medical Ethics Committee approved this study.

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Data availability

Research data are available upon reasonable request to the corresponding author.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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