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Original Article

Factors associated with non-adherence of secondary prophylactic drugs in ischemic stroke subjects and its correlation with chronic cognitive and motor performance

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Abstract: Objectives: To determine predictors of suboptimal medication adherence in patients with ischemic stroke and to examine the relationship between adherence and long-term cognitive, motor and clinical outcomes. Methods: This retrospective cohort study included 276 patients with ischemic stroke. Medication adherence was evaluated using the 8-item Morisky Medication Adherence Scale (MMAS-8). Patients scoring 6 or higher were categorized as having high adherence (n = 182), while those scoring below 6 were classified as having low adherence (n = 94). Laboratory assessments, including low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), and homocysteine, were performed at baseline and at 12 months. Cognitive and motor functions were evaluated at baseline and at 3, 6, and 12 months. The primary clinical endpoints at 12 months comprised recurrent ischemic stroke, major adverse cardiovascular events (MACE), and all-cause mortality. Results: Independent predictors of low adherence included older age (OR = 1.035), lower education (OR = 0.906), self-pay insurance (OR = 1.743), higher baseline NIHSS (OR = 1.336), and more discharge medications (OR = 1.295) (all $P < 0.05$). At 12 months, the high adherence group had significantly lower LDL-C, HbA1c, and homocysteine (all $P < 0.05$) than the low adherence group. They also exhibited superior cognitive and motor scores, and significantly better functional independence (all $P < 0.001$). The composite outcome rate was significantly lower in the high adherence group (15.93% vs. 32.98%, $P = 0.001$). Conclusion: Multiple patient-level factors predict poor adherence. Poor adherence is associated with worse metabolic control, higher rates of recurrent vascular events and mortality, and inferior long-term cognitive and functional recovery.

Keywords: Ischemic stroke, medication adherence, secondary prevention, cognitive function, motor rehabilitation, risk factors

Introduction

Ischemic stroke remains a major global health challenge as a leading cause of long-term disability and mortality. According to the Global Burden of Disease Study 2021, approximately 7.63 million new cases were reported globally in 2021, with the total number of prevalent cases reaching 77.2 million [1, 2]. Although age-standardized mortality rates have modestly declined, stroke incidence is rising among younger populations, particularly in low- and middle-income countries [3, 4]. The enduring high disability burden following stroke highlights the pressing need for effective secondary prevention measures [5, 6]. Reducing long-term sequelae therefore demands effective secondary prevention.

Secondary prevention pharmacotherapy is the cornerstone of long-term management after ischemic stroke, aiming to lower the risk of recurrent cerebrovascular events and halt progressive neurological deterioration. Current evidence-based guidelines, including the Chinese Guideline for Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack (2022) and the recommendations from the American

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Heart Association/American Stroke Association, consistently recommend antiplatelet agents, statins, and appropriate antihypertensive and hypoglycemic therapies [1, 7, 8]. When used consistently as secondary prevention, these interventions reduce the relative risk of recurrent stroke by approximately 25-30% and improve survival [9, 10]. However, clinical effectiveness critically depends on patients' long-term adherence, which remains suboptimal across healthcare settings. Systematic reviews and meta-analyses report that medication adherence rates among stroke survivors range from only 40% to 60%, and adherence declines progressively after hospital discharge [9, 10]. Thus, poor adherence threatens the very benefits that secondary prevention aims to provide.

The consequences of poor adherence extend beyond elevated recurrence risk. Emerging evidence suggests that sustained exposure to secondary prevention medications may influence long-term functional outcomes, including cognitive and motor recovery trajectories [11, 12]. High adherence has been associated with significantly lower recurrence risk (e.g., relative risk reduction of approximately 1.85 for non-adherent patients with atrial fibrillation) and improved survival [11]. Nevertheless, the relationship between medication adherence and nuanced dimensions of neurological recovery-particularly cognitive function and motor recovery-remains insufficiently characterized in current literature. Neuroplasticity, the brain's capacity for reorganization after injury, underpins post-stroke recovery and is modulated by vascular risk factor control, inflammatory processes, and neural repair mechanisms [13, 14]. Clarifying how adherence modulates these processes is therefore an unmet need.

Contemporary research reveals substantial gaps in understanding how sustained pharmacological secondary prevention interacts with neuroplastic processes to influence long-term functional outcomes. Neuroimaging studies have elucidated reorganization of motor networks, including involvement of the contralesional hemisphere, premotor cortex, and supplementary motor area, but the potential modifying effect of medication adherence on these neural adaptations has not been systematically investigated [13, 14]. Moreover, existing post-stroke management predominantly focuses on acute intervention efficacy and short-term functional gains, with limited attention to the longitudinal interplay between medication adherence behavior and cognitive-motor recovery over extended follow-up [15, 16]. Additionally, functional recovery assessment remains heavily reliant on subjective clinical scales, highlighting the need for more objective, quantifiable approaches [16]. These gaps collectively impede the optimization of post-stroke treatment.

Several conflicting findings persist in the current literature. While some studies have reported positive associations between medication adherence and improved functional outcomes [11, 12], others have failed to demonstrate significant relationships after adjusting for confounders [9, 10]. These discrepancies may arise from heterogeneous study designs, varying adherence measurement tools, and insufficient adjustment for baseline prognostic factors. Moreover, the majority of existing investigations have focused on short-term outcomes (≤ 6 months) and have not systematically examined the longitudinal trajectory of cognitive and motor recovery in relation to adherence status. Critically, whether poor adherence independently contributes to worse functional recovery-beyond its effect on recurrent vascular events-remains unresolved. To date, no study has comprehensively evaluated the simultaneous impact of adherence on both cognitive and motor domains using validated, multi-dimensional assessments over a 12-month follow-up period in a Chinese ischemic stroke cohort. The present study was therefore designed to address these gaps by: (1) identifying independent predictors of medication non-adherence in a real-world clinical setting; (2) examining the longitudinal association between adherence status and trajectories of cognitive and motor recovery; and (3) assessing the impact of adherence on hard clinical endpoints including recurrent stroke, major adverse cardiovascular events and mortality. This integrated approach represents a novel contribution to the literature and provides evidence to inform targeted adherence-improving interventions in post-stroke management.

Materials and methods

Study design and case selection

We conducted a retrospective cohort study that consecutively enrolled 276 patients with a

primary diagnosis of ischemic stroke, also termed cerebral infarction, who were admitted to our institution between March 2023 and February 2025. The sample size was determined by consecutive enrollment. Post hoc power analysis using G*Power for the primary continuous outcome (MMSE) indicated that 105 patients per group were required (α = 0.05, power = 0.95, Cohen's d = 0.5). Our enrollment of 276 patients exceeded this threshold. For the composite endpoint, post hoc analysis using PASS 15.0 achieved 92.3% power. These results confirm adequate statistical power for both primary and secondary outcomes.

The inclusion criteria were as follows: (1) age over 18 years; (2) previously clinically diagnosed with ischemic stroke or transient ischemic attack, diagnosed by head CT or MRI, excluding intracranial hemorrhage or non-ischemic neurological diseases [17]; (3) time from symptom onset to enrollment was at least 3 months. This threshold was chosen to ensure enrollment during the stable chronic phase, minimizing confounding from spontaneous neurological improvement typically occurring within the first 3 months [13]. This design allows for a more reliable assessment of the impact of long-term medication adherence on functional outcomes over the 12-month follow-up period; and (4) completeness of clinical and follow-up data. The exclusion criteria were: (1) stroke caused by brain tumors, head trauma, or other systemic diseases, or other non-ischemic strokes; (2) serious internal medical conditions, including severe heart, liver, kidney, hematopoietic, or immune system diseases; (3) other neurological disorders; (4) vascular dementia; and (5) cognitive impairment resulting from causes other than stroke. Baseline demographic and clinical data were collected from electronic medical records using a standardized case report form.

Approval for the study protocol was obtained from the General Hospital of Ningxia Medical University ethics committee (No. KYLL-2024-1601). We conducted this retrospective study in full compliance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legally authorized representatives prior to enrollment. The ethics committee approved the informed consent procedure, and all personal data were anonymized before analysis to ensure participant confidentiality.

Adherence evaluation and group assignment

All patients received standardized secondary prevention medications according to the Chinese Guidelines for Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack [18], including antiplatelet agents (aspirin, clopidogrel, or dual antiplatelet therapy as indicated), statins (primarily atorvastatin or rosuvastatin), and, when clinically indicated, antihypertensive agents (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, or diuretics) and/or hypoglycemic agents (metformin, sulfonylureas, DPP-4 inhibitors, insulin, etc.). Thus, most patients were prescribed a combination of multiple cardiovascular and antidiabetic agents, reflecting the polypharmacy typical of secondary prevention after ischemic stroke. Adherence to medication was evaluated using the validated 8-item Morisky Medication Adherence Scale (MMAS-8). The scale consists of eight items: for the first seven items, "no" answers are scored 1 and "yes" answers 0, with item 5 reverse-scored. The eighth item is rated on a 5-point Likert scale, where 1 corresponds to never, 0.75 to rarely, 0.5 to sometimes, 0.25 to often, and 0 to always. Total scores range from 0 to 8, with higher scores reflecting better adherence. Based on established thresholds, scores of 8 were considered high adherence, scores of 6-7 medium adherence, and scores below 6 low adherence. For the purposes of this study, participants with MMAS-8 scores of 6 or greater were grouped as high adherence (n = 182), and those with scores < 6 as low adherence (n = 94). This binary grouping was employed to assess how adherence affects cognitive function, motor recovery, and clinical endpoints over the long term. The rationale for merging medium and high adherence was twofold: (1) preliminary analyses revealed that patients with medium adherence (scores 6-7) had clinical outcomes and laboratory parameters comparable to those with high adherence (score 8), while both groups differed significantly from the low adherence group (score < 6), and (2) the threshold of MMAS-8 $\geq$ 6 has been previously established in the literature as indicating "adequate adherence" associated with optimal clini-

cal outcomes in cardiovascular and cerebrovascular populations. This dichotomous classification (adequate adherence ≥ 6 vs. inadequate adherence < 6) facilitates clinically meaningful interpretation and aligns with prior published studies [19-21].

Data collection and evaluation methods

Baseline demographic and clinical data: At admission, the following demographic and clinical variables were collected from electronic medical records using a standardized case report form. Stroke subtype was recorded as acute cerebral infarction or transient ischemic attack. The National Institutes of Health Stroke Scale (NIHSS) score at admission (range 0-42, higher = more severe neurological impairment) was obtained for each patient. The scale demonstrated a Cronbach's alpha coefficient of 0.685 [22]. Discharge medication categories (antiplatelet agents, statins, antihypertensives, hypoglycemic agents, and others) and the total number of discharge medications were recorded for each patient to quantify the medication burden.

Laboratory assessments: We collected 5 mL of fasting venous blood from each patient before 8 am. Biochemical assessments included total cholesterol, LDL-C, HDL-C, triglycerides, fasting glucose, and homocysteine. Lipid and glucose levels were reported in mmol/L, and homocysteine in μmol/L. A BECKMAN Synchron lx20 automated chemistry analyzer (Beckman Coulter, Inc., Brea, CA, USA) was used for these analyses. For HbA1c determination, we employed high-performance liquid chromatography using the Bio-Rad Variant II Turbo system (Bio-Rad Laboratories, Hercules, CA, USA). The CKD-EPI formula was applied to calculate the estimated glomerular filtration rate.

Cognitive function assessment: Cognitive function was evaluated at baseline and at 3, 6, and 12 months using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). The MoCA covers multiple domains including visuospatial/executive abilities, naming, attention, language, abstraction, delayed recall, and orientation. Total scores range from 0 to 30, with higher scores indicating better cognitive status. Its reliability is supported by a Cronbach's alpha coefficient of 0.839 [23]. The MMSE, a 30-point questionnaire, assesses orientation, registration, attention and calculation, recall, language, and visuospatial construction. To interpret MMSE results, education-adjusted thresholds were adopted: greater than 17 for patients with no formal education, greater than 20 for primary school graduates, and greater than 24 for those with secondary education or beyond. The MMSE has been reported to have a Cronbach's alpha of 0.78 [24]. Semantic memory and executive function were further evaluated using a verbal fluency task, in which patients were asked to generate as many animal names as possible in 60 seconds, and the total correct responses were counted.

Motor function assessment: A combination of standardized scales was administered at baseline and at 3, 6, and 12 months to assess motor function and independence in daily living. The Fugl-Meyer Assessment for Upper Extremity (FMA-UE) was applied to evaluate upper limb recovery, with scores spanning 0 to 66 and higher scores representing better motor performance. This scale has demonstrated high inter-rater reliability (ICC = 0.98) and excellent internal consistency, with Cronbach's alpha ranging from 0.96 to 0.99 [25]. Lower limb motor recovery was quantified using the Fugl-Meyer Assessment for Lower Extremity (FMA-LE), which has a total score range of 0 to 34; it also exhibits robust inter-rater reliability (ICC = 0.85) and good internal consistency (Cronbach's alpha = 0.70-0.92) [25]. The Berg Balance Scale (BBS) comprises 14 items, each rated from 0 to 4, for a maximum score of 56, with higher scores indicating superior balance. Test-retest reliability for the BBS has been reported as ICC = 0.92 [26]. The modified Barthel Index (mBI) was employed to measure functional independence across ten domains, namely feeding, bathing, grooming, dressing, bowel and bladder management, toilet use, transfers, walking, and stair climbing; scores range from 0 to 100, and higher values denote greater independence. The mBI has outstanding inter-rater reliability (ICC = 0.94), making it a reliable instrument for evaluating disability in stroke survivors [27].

Follow-up and clinical outcomes

Follow-up assessments were conducted at 3, 6, and 12 months to evaluate clinical out-

comes. These evaluations were performed via outpatient visits or structured telephone interviews. The primary clinical outcomes measured at twelve months included a composite of several key events: any occurrence of recurrent ischemic stroke, defined as a new focal neurological deficit lasting more than 24 hours with confirmation of a new infarction via neuroimaging; major adverse cardiovascular events (MACE) [28], which encompass non-fatal myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization procedures; and all-cause mortality.

Statistical methods

Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and R 3.0.2 (Free Software Foundation, Inc., Boston, MA, USA). Normality was examined for all continuous variables using the Kolmogorov-Smirnov test. Continuous data with normal distribution are presented as mean ± standard deviation, while non-normally distributed data are presented as median (interquartile range). Categorical variables are summarized as frequencies and percentages. Differences between the high adherence group (n = 182) and the low adherence group (n = 94) were evaluated with independent-sample t-tests for continuous variables and Pearson's chi-square tests for categorical variables.

For the primary comparative analyses of cognitive function, motor function, and clinical outcomes between adherence groups, unadjusted comparisons were performed using independent-sample t-tests and chi-square tests, as these baseline differences reflect intrinsic characteristics of the adherence groups rather than confounders requiring adjustment. The independent predictive role of these variables for adherence was already established through multivariate logistic regression. We also constructed a separate multivariate logistic regression model to evaluate the independent association between adherence and 12-month MACE, adjusting for baseline covariates (including age, education, NIHSS score, number of discharge medications, insurance type, and gender).

To determine factors independently associated with poor medication adherence, we performed both univariate and multivariate logistic regression analyses. Results from these models are presented as odds ratios (OR) with 95% confidence intervals (CI). Longitudinal changes in cognitive and motor scores across groups were compared using repeated-measures analysis of variance (ANOVA) with post-hoc pairwise comparisons adjusted by the Bonferroni method. The relationship between adherence status (high versus low) and clinical outcomes at 12 months was examined using chi-square tests. For all analyses, a two-sided p value below 0.05 was interpreted as statistically significant.

Results

General information

Baseline characteristics of the two groups are compared in **Table 1**. Patients with low medication adherence were significantly older (65.63 ± 10.27 vs. 62.28 ± 9.91 years, $P = 0.009$) and had fewer years of education (9.34 ± 3.28 vs. 10.88 ± 3.61, $P < 0.001$) than their high-adherence counterparts. The proportion of self-paying patients was markedly higher in the low adherence group (25.53% vs. 11.54%, $P = 0.009$). Moreover, a higher baseline NIHSS score (5.81 ± 2.46 vs. 4.31 ± 2.18, $P < 0.001$) and a larger number of discharge medications (4.03 ± 1.27 vs. 3.59 ± 1.21, $P = 0.005$) characterized the low adherence group. No significant between-group differences were observed for sex, BMI, marital status, income, smoking, drinking, living area, stenting procedure, medical history, or stroke subtype.

Factors associated with medication adherence

To identify independent predictors of low adherence, logistic regression analyses were performed (**Table 2**). After multivariate adjustment, each additional year of age increased the odds of low adherence by 3.5% (OR = 1.035, 95% CI: 1.006-1.064, $P = 0.016$), whereas each additional year of education was associated with a 9.4% reduction in the odds of low adherence (OR = 0.906, 95% CI: 0.836-0.982, $P = 0.017$). Self-pay patients had a 74.3% higher likelihood of low adherence compared with those who had medical insurance (OR = 1.743, 95% CI: 1.221-2.487, $P = 0.002$). Higher baseline NIHSS score (OR per point = 1.336, 95% CI: 1.176-1.517, $P < 0.001$) and a greater number of discharge medications (OR

Table 1. Baseline characteristics of the high- and low-adherence groups

Variable	High adherence (n = 182)	Low adherence (n = 94)	t/χ^2 value	*P* value
Age (years)	62.28 ± 9.91	65.63 ± 10.27	2.633	0.009
Gender [n (%)]			1.551	0.213
Male	111 (60.99%)	50 (53.19%)		
Female	71 (39.01%)	44 (46.81%)		
BMI (kg/m^2)	24.79 ± 3.30	25.38 ± 3.51	1.369	0.172
Education level (years)	10.88 ± 3.61	9.34 ± 3.28	3.472	< 0.001
Marital status [n (%)]			2.713	0.258
Married	149 (81.87%)	69 (73.40%)		
Unmarried	14 (7.69%)	10 (10.64%)		
Widowed	19 (10.44%)	15 (15.96%)		
Monthly income (CNY) [n (%)]			2.109	0.348
< 3000	56 (30.77%)	37 (39.36%)		
3000-5000	66 (36.26%)	31 (32.98%)		
> 5000	60 (32.97%)	26 (27.66%)		
Current smoking [n (%)]	47 (25.82%)	32 (34.04%)	2.049	0.152
Current drinking [n (%)]	40 (21.98%)	26 (27.66%)	1.100	0.294
Living area [n (%)]			2.827	0.093
Rural	57 (31.32%)	39 (41.49%)		
Urban	125 (68.68%)	55 (58.51%)		
Insurance type [n (%)]			9.337	0.009
Medical insurance	139 (76.37%)	58 (61.7%)		
Government-funded	22 (12.09%)	12 (12.77%)		
Self-paying	21 (11.54%)	24 (25.53%)		
Intra-/extracranial stenting during hospitalization [n (%)]			0.858	0.354
Yes	31 (17.03%)	12 (12.77%)		
No	151 (82.97%)	82 (87.23%)		
Medical history [n (%)]				
Hypertension	129 (70.88%)	73 (77.66%)	1.452	0.228
Diabetes mellitus	57 (31.32%)	34 (36.17%)	0.66	0.417
Hyperlipidemia	95 (52.2%)	46 (48.94%)	0.264	0.607
Prior ischemic stroke	47 (25.82%)	30 (31.91%)	1.143	0.285
Coronary artery disease	24 (13.19%)	16 (17.02%)	0.735	0.391
Atrial fibrillation	15 (8.24%)	11 (11.7%)	0.87	0.351
Stroke subtype [n (%)]			0.373	0.542
Acute cerebral infarction	158 (86.81%)	84 (89.36%)		
Transient ischemic attack	24 (13.19%)	10 (10.64%)		
NIHSS (score)	4.31 ± 2.18	5.81 ± 2.46	5.166	< 0.001
Discharge medication category [n (%)]				
Statins	173 (95.05%)	88 (93.62%)	0.249	0.618
Antiplatelet agents	172 (94.51%)	89 (94.68%)	0.004	0.951
Antihypertensives	126 (69.23%)	71 (75.53%)	1.205	0.272
Hypoglycemic agents	58 (31.87%)	37 (39.36%)	1.542	0.214
Number of discharge medications (n)	3.59 ± 1.21	4.03 ± 1.27	2.857	0.005

Note: BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale. Number of discharge medications refers to the total count of distinct cardiovascular, antithrombotic, and antidiabetic agents prescribed at discharge.

Table 2. Logistic regression analysis of factors associated with poor medication adherence

Variable	Univariate logistic regression			Multivariate logistic regression		
	Coefficient	*P* value	OR (95% CI)	Coefficient	*P* value	OR (95% CI)
Age (per year)	0.033	0.010	1.034 (1.008-1.061)	0.034	0.016	1.035 (1.006-1.064)
Education level (per year)	-0.127	< 0.001	0.880 (0.815-0.947)	-0.099	0.017	0.906 (0.836-0.982)
Insurance type (ref: Medical insurance)	0.479	0.003	1.615 (1.173-2.230)	0.555	0.002	1.743 (1.221-2.487)
NIHSS score (per point)	0.283	< 0.001	1.327 (1.184-1.498)	0.290	< 0.001	1.336 (1.176-1.517)
Number of discharge medications (per drug)	0.299	0.005	1.348 (1.097-1.671)	0.259	0.029	1.295 (1.026-1.634)

Note: NIHSS, National Institutes of Health Stroke Scale.

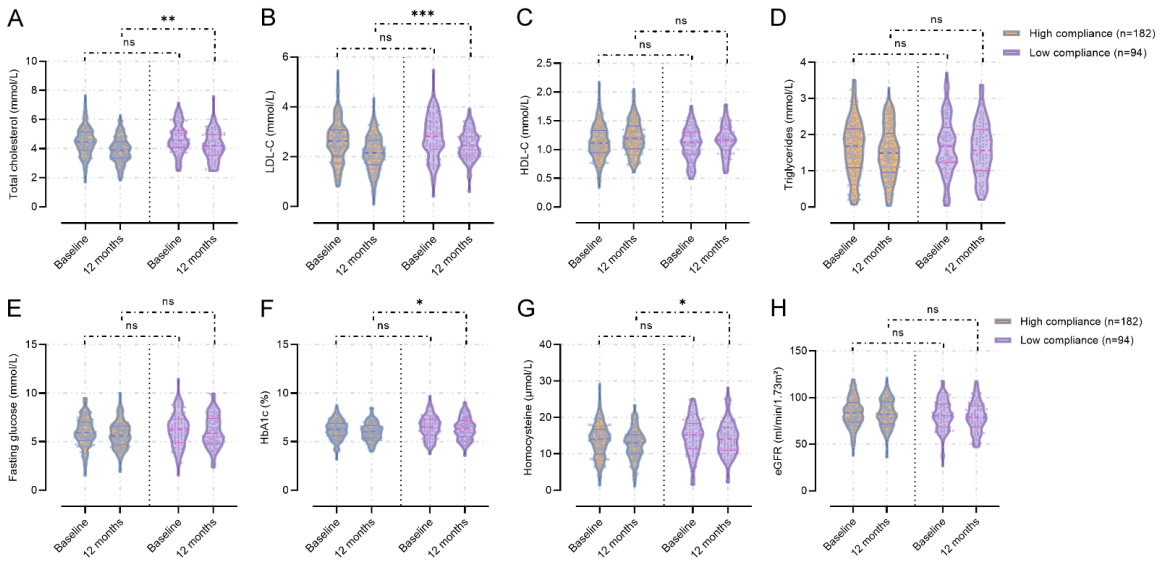


Figure 1. Comparison of baseline and 12-month laboratory findings between groups. A. Total cholesterol (mmol/L). B. LDL-C (mmol/L). C. HDL-C (mmol/L). D. Triglycerides (mmol/L). E. Fasting glucose (mmol/L). F. HbA1c (%). G. Homocysteine (μmol/L). H. eGFR (ml/min/1.73 m^2). Note: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; ns: No significant difference; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

per drug = 1.295, 95% CI: 1.026-1.634, P = 0.029) also independently predicted low adherence. Thus, these five variables remained significant after adjustment for confounders.

Laboratory and imaging findings

Longitudinal laboratory changes are shown in **Figure 1**. At 12 months, the high adherence group showed significantly lower total cholesterol (3.92 ± 0.87 vs. 4.24 ± 0.99 mmol/L, P = 0.007, **Figure 1A**) and LDL-C (2.14 ± 0.71 vs. 2.46 ± 0.60 mmol/L, P < 0.001, **Figure 1B**) than the low adherence group. No significant differences were observed for HDL-C or triglycerides (**Figure 1C** and **1D**). Fasting glucose at 12 months was lower in the high adherence group, but the difference did not reach statistical significance (5.71 ± 1.41 vs. 6.08 ± 1.69 mmol/L, P = 0.072, **Figure 1E**). By contrast, HbA1c at 12 months was significantly lower in the high adherence group (6.04 ± 0.93% vs. 6.35 ± 1.13%, P = 0.025, **Figure 1F**). Homocysteine levels were favorable in the high adherence group at both baseline (13.63 ± 4.67 vs. 14.84 ± 5.09 μmol/L, P = 0.048) and 12 months (12.71 ± 4.18 vs. 14.13 ± 4.82 μmol/L, P = 0.012, **Figure 1G**). Estimated GFR did not differ significantly between groups at either time point (**Figure 1H**). Good adherence was associated with better metabolic control, particularly for LDL-C, HbA1c, and homocysteine.

Longitudinal impact of adherence on cognitive function

The high adherence group consistently outperformed the low adherence group on the MoCA at every assessment (baseline: 21.38 ± 3.78 vs. 20.24 ± 3.96, P = 0.020; 12 months: 23.56 ± 3.18 vs. 22.02 ± 3.49, P < 0.001). A similar pattern was observed for the MMSE, with significant differences favoring the high adherence group at all visits (baseline: 25.13 ± 2.18 vs. 24.18 ± 2.41, P = 0.001; 12 months: 26.82 ± 1.58 vs. 25.64 ± 1.77, P < 0.001). Verbal fluency (animals per minute) also showed better performance in the high adherence group across all time points, with the largest gap at 12 months (16.63 ± 3.28 vs. 15.11 ± 3.57, P < 0.001, **Table 3**).

Repeated-measures ANOVA (Supplementary Tables 1, 2, 3) further confirmed that medication adherence had a significant main effect on all three cognitive measures (MoCA: F = 32.524, P < 0.001; MMSE: F = 73.776, P < 0.001; verbal fluency: F = 28.634, P < 0.001).

Table 3. Longitudinal comparison of cognitive function between the two groups

Variable	Time	High adherence (n = 182)	Low adherence (n = 94)	t value	*P* value
MoCA (score)	Baseline	21.38 ± 3.78	20.24 ± 3.96	2.332	0.020
	3 months	22.19 ± 3.61	20.97 ± 3.85	2.601	0.010
	6 months	23.01 ± 3.44	21.68 ± 3.71	2.971	0.003
	12 months	23.56 ± 3.18	22.02 ± 3.49	3.686	< 0.001
MMSE (score)	Baseline	25.13 ± 2.18	24.18 ± 2.41	3.293	0.001
	3 months	25.74 ± 2.07	24.71 ± 2.32	3.761	< 0.001
	6 months	26.29 ± 1.97	25.21 ± 2.22	4.093	< 0.001
	12 months	26.82 ± 1.58	25.64 ± 1.77	5.649	< 0.001
Verbal Fluency (animals/min)	Baseline	14.06 ± 3.72	12.92 ± 3.89	2.375	0.018
	3 months	15.12 ± 3.59	13.79 ± 3.82	2.851	0.005
	6 months	15.91 ± 3.43	14.53 ± 3.69	3.089	0.002
	12 months	16.63 ± 3.28	15.11 ± 3.57	3.555	< 0.001

Note: MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination.

Table 4. Longitudinal comparison of motor function between the two groups

Variable	Time	High adherence (n = 182)	Low adherence (n = 94)	t value	*P* value
FMA-UE (score)	Baseline	43.82 ± 9.88	41.32 ± 10.46	1.952	0.052
	3 months	47.94 ± 9.16	44.84 ± 9.49	2.629	0.009
	6 months	50.73 ± 8.58	47.27 ± 9.37	3.071	0.002
	12 months	51.82 ± 6.19	48.22 ± 6.98	4.379	< 0.001
FMA-LE (score)	Baseline	21.62 ± 4.79	20.51 ± 5.08	1.786	0.075
	3 months	23.83 ± 4.47	22.43 ± 4.78	2.393	0.017
	6 months	25.13 ± 4.08	23.73 ± 4.39	2.638	0.009
	12 months	26.22 ± 3.46	24.53 ± 3.88	3.668	< 0.001
BBS (score)	Baseline	42.2 ± 7.19	40.22 ± 7.79	2.104	0.036
	3 months	44.93 ± 6.56	42.03 ± 7.21	3.365	< 0.001
	6 months	46.83 ± 5.94	43.73 ± 6.57	3.960	< 0.001
	12 months	47.92 ± 3.48	44.82 ± 3.99	6.670	< 0.001
mBI (score)	Baseline	63.02 ± 11.92	59.51 ± 13.18	2.232	0.026
	3 months	69.82 ± 10.81	64.2 ± 12.28	3.905	< 0.001
	6 months	73.92 ± 10.19	68.03 ± 11.39	4.372	< 0.001
	12 months	76.62 ± 7.91	71.29 ± 9.14	5.032	< 0.001

Note: FMA-UE, Fugl-Meyer Assessment - Upper Extremity; FMA-LE, Fugl-Meyer Assessment - Lower Extremity; BBS, Berg Balance Scale; mBI, modified Barthel Index.

Time effects were also significant (all $P < 0.001$), whereas the group-by-time interactions were not (all $P > 0.05$). This non-significant interaction indicates that the cognitive benefit of high adherence was established early and remained stable over the 12-month period. Thus, although both groups improved cognitively over time, the high adherence group consistently maintained superior cognitive function.

Longitudinal impact of adherence on motor function

As shown in **Table 4**, motor function recovery was also associated with adherence status. Although baseline FMA-UE scores did not differ significantly between groups (43.82 ± 9.88 vs. 41.32 ± 10.46, $P = 0.052$), the high adherence group showed significantly better upper extremity function at 3, 6, and 12 months, with

Table 5. Association between medication adherence and 12-month clinical outcomes

Outcome	Total cohort (n = 276)	High adherence (n = 182)	Low adherence (n = 94)	χ^2 value	*P* value
Composite outcome events	60 (21.74%)	29 (15.93%)	31 (32.98%)	10.585	0.001
Recurrent ischemic stroke	32 (11.59%)	14 (7.69%)	18 (19.15%)	7.937	0.005
MACE	21 (7.61%)	9 (4.95%)	12 (12.77%)	5.393	0.020
All-cause death	15 (5.43%)	6 (3.30%)	9 (9.57%)	4.753	0.029

the most pronounced difference at 12 months (51.82 ± 6.19 vs. 48.22 ± 6.98, $P < 0.001$). FMA-LE scores followed a similar trajectory: no baseline difference ($P = 0.075$), but significantly higher scores in the high adherence group from 3 months onward (12-month: 26.22 ± 3.46 vs. 24.53 ± 3.88, $P < 0.001$). The Berg Balance Scale scores were already higher in the high adherence group at baseline (42.20 ± 7.19 vs. 40.22 ± 7.79, $P = 0.036$), and the gap widened over time (12-month: 47.92 ± 3.48 vs. 44.82 ± 3.99, $P < 0.001$). The modified Barthel Index also demonstrated superior daily living independence in the high adherence group at every follow-up (12-month: 76.62 ± 7.91 vs. 71.29 ± 9.14, $P < 0.001$).

The robustness of these motor benefits was supported by repeated-measures ANOVA (Supplementary Tables 4, 5, 6, 7). A significant main effect of group was evident for FMA-UE ($F = 30.947$, $P < 0.001$), FMA-LE ($F = 24.485$, $P < 0.001$), BBS ($F = 49.215$, $P < 0.001$), and mBI ($F = 56.822$, $P < 0.001$). Time effects were also highly significant for all motor scales (all $P < 0.001$), while none of the group-by-time interactions reached significance (all $P > 0.05$). The absence of significant group-by-time interactions for all motor scales suggests that the motor recovery advantage associated with high adherence was not due to a differential rate of improvement, but rather reflected a consistently superior functional status that was maintained throughout the 12-month follow-up period.

Association of medication adherence with 12-month clinical outcomes

The impact of adherence on clinical endpoints at 12 months is summarized in **Table 5**. The composite outcome (recurrent ischemic stroke, major adverse cardiovascular events, or all-cause death) occurred in 15.93% of the high adherence group versus 32.98% of the low adherence group ($P = 0.001$). Specifically, recurrent ischemic stroke was less frequent in the high adherence group (7.69% vs. 19.15%, $P = 0.005$), as were MACE (4.95% vs. 12.77%, $P = 0.020$) and all-cause death (3.30% vs. 9.57%, $P = 0.029$). Thus, poor adherence to secondary prevention medication was associated with a substantially higher risk of adverse clinical events at one year. In the multivariate logistic regression analysis adjusting for baseline covariates (Supplementary Table 8), low medication adherence remained a significant independent predictor of 12-month MACE (OR = 2.815, 95% CI: 1.124-7.052, $P = 0.027$). Higher baseline NIHSS score (OR = 1.201 per point increase, 95% CI: 1.015-1.422, $P = 0.033$) was also independently associated with an increased risk of MACE.

Discussion

This retrospective cohort study investigated factors influencing medication adherence to secondary prevention in ischemic stroke patients and examined the impact of adherence on long-term cognitive and motor recovery. Our findings revealed that older age, lower educational level, self-pay insurance status, higher baseline stroke severity, and a greater number of discharge medications independently predicted poor adherence. Over the 12-month follow-up, patients with good adherence demonstrated better metabolic control, superior cognitive performance across multiple domains, better functional status, and more favorable clinical outcomes compared to those with poor adherence.

Consistent with our observations, age has been repeatedly identified as a determinant of medication adherence in stroke survivors. Ruksakulpiwat et al. [9] reported in their systematic review that older patients often face physical limitations, cognitive decline, and polypharmacy, all of which complicate medication

taking behaviors. Conversely, younger patients may perceive lower recurrence risk and exhibit higher rates of intentional non adherence. The association between educational level and adherence is well documented. Cao et al. [10] found that limited health literacy, more common among less educated individuals, impedes understanding of medication indications and the consequences of non-adherence. Mechanistically, lower education may reduce comprehension of discharge instructions and diminish perceived personal control over disease management [29, 30]. The strong effect of insurance type in our study aligns with reports from low- and middle-income settings where out-of-pocket costs pose substantial barriers. Specifically, self-pay patients were significantly more likely to have poor adherence, consistent with the notion that financial constraints may lead patients to skip doses or discontinue medications, particularly given the lifelong nature of secondary prevention [9, 31].

Higher baseline NIHSS score emerged as a robust predictor of poor adherence, a finding corroborated by Yeo et al. [12] Greater initial neurological impairment may restrict physical ability to obtain and ingest medications, increase dependency on caregivers, and exacerbate depressive symptoms, all of which undermine adherence. Additionally, more severe strokes often necessitate complex medication regimens. Our observation that a higher number of discharge medications independently predicted poor adherence echoes the work of Mafruhah et al. [11] Polypharmacy increases pill burden, raises the risk of adverse effects, and complicates dosing schedules, leading to both unintentional and intentional non-adherence.

Regarding laboratory outcomes, patients with good adherence had significantly lower total cholesterol, LDL-C, HbA1c, and homocysteine levels at 12 months compared to their poorly adherent counterparts. These differences are clinically meaningful because sustained control of these biomarkers represents the mechanistic pathway through which secondary prevention reduces recurrent events [33-35]. Mafruhah et al. [9] reported in their meta-analysis that failure to adhere to statin and antihypertensive therapy is directly associated with elevated lipid levels and blood pressure values during treatment. The homocysteine reduction observed in the good adherence group may reflect better adherence with B vitamin supplementation or improved dietary patterns that often accompany diligent medication taking behavior, although residual confounding cannot be ruled out.

At each follow-up visit, the high adherence group exhibited superior cognitive performance relative to the low adherence group across all three measures: the Montreal Cognitive Assessment, the MMSE, and verbal fluency. While both groups improved over time, the advantage of good adherence remained stable throughout the 12 month period. Emerging literature supports a link between medication adherence and post stroke cognitive outcomes. Takeuchi and Izumi [32] proposed that optimal control of vascular risk factors mediated by consistent pharmacotherapy preserves cerebral white matter integrity and reduces silent ischemic burden, thereby protecting cognitive reserve. Furthermore, antiplatelet agents and statins may exert direct neuroprotective effects beyond their vascular actions, including attenuation of neuroinflammation and stabilization of atherosclerotic plaques, as reported by Yu et al. [14] Our verbal fluency findings, which showed better semantic memory and executive function in the adherent group, align with the concept that subcortical ischemic changes disproportionately affect frontal subcortical circuits.

Motor function recovery, assessed by upper and lower extremity Fugl Meyer Assessment scores, the Berg Balance Scale, and the modified Barthel Index, also favored the high adherence group. Notably, group differences emerged over time for upper and lower extremity scores even when baseline scores were comparable, suggesting that adherence is not merely a marker of baseline motor status but may be associated with better recovery trajectories. The observed association between adherence and better functional status is likely mediated through vascular and metabolic pathways. Poor adherence leads to suboptimal control of LDL-C, HbA1c, and homocysteine, which increases the risk of recurrent ischemic events. Such recurrent strokes may directly cause additional neurological damage, leading to cumulative disability [33, 34]. Furthermore, persistent

inflammation and oxidative stress resulting from uncontrolled vascular risk factors may indirectly impair long-term neurological function [35, 36]. Thus, the functional advantage of good adherence can be explained by more effective secondary prevention of new vascular insults, rather than by enhanced "recovery" from the index stroke alone.

The clinical outcomes at 12 months confirmed the prognostic importance of adherence. The composite endpoint of recurrent stroke, major adverse cardiovascular events, or death occurred approximately twice as often in the low adherence group, with each individual component showing a consistent pattern. These findings are in agreement with the meta analysis by Mafruhah et al. [11] and the registry study by Yeo et al. [12], both of which demonstrated that non-adherence substantially elevates the risk of recurrent vascular events and mortality. The mechanistic basis is well established. Secondary prevention medications reduce platelet aggregation, lower LDL cholesterol, control blood pressure and glucose, and stabilize endothelial function. Discontinuation or intermittent use undermines these protective effects, leaving patients vulnerable to thrombotic events and disease progression.

Our findings have several clinical implications. First, identifying patients at risk for poor adherence, particularly older individuals, those with limited education, self-pay patients, and those with severe strokes or polypharmacy, should trigger targeted interventions. These may include simplified dosing regimens, fixed dose combinations, medication reminder systems, and financial assistance programs. Second, the association between adherence and better cognitive and motor recovery suggests that improving medication adherence could serve as an adjunct to therapeutic management. Clinicians should emphasize both the reduction of recurrence risk and the potential functional benefits during patient counseling. Third, longitudinal monitoring of adherence using validated tools such as the MMAS-8 could be integrated into routine follow up visits to enable early detection of non-adherence and timely intervention.

Several limitations of this study should be noted. First, the retrospective design precludes causal inference. Unmeasured confounders may have influenced both adherence and outcomes, including social support, depression, anxiety, sleep quality, rehabilitation adherence, dietary patterns, and physical activity. These factors are known to affect post-stroke functional recovery and recurrent vascular events, and their omission represents a significant limitation of this study. Although we adjusted for several potential confounders in multivariate analyses, residual confounding cannot be excluded. Prospective studies that include comprehensive assessments of psychosocial and lifestyle variables are required to confirm the independent effect of medication adherence. Because our study was conducted at a single institution, the generalizability of our findings to other healthcare systems or cultural settings is limited. The MMAS-8, which relies on patient self-report, was used to measure adherence, and this approach is inherently prone to recall bias and social desirability bias. We acknowledge that this represents a significant limitation of our study. However, the MMAS-8 is a well-validated instrument with established psychometric properties and has been widely employed in stroke populations. Importantly, the significant differences observed between adherence groups in objective laboratory parameters - including LDL-C, HbA1c, and homocysteine-provide external biochemical validation of the MMAS-8 classification, as these biomarkers are directly influenced by the pharmacological effects of secondary prevention medications and would not be expected to differ solely due to reporting bias. Nevertheless, we concur with the reviewer that objective measures such as pharmacy refill records, electronic medication monitoring, or therapeutic drug monitoring would provide more accurate adherence data. Future prospective studies should incorporate such objective adherence measures to confirm our findings and to more precisely quantify the relationship between adherence and long-term outcomes. The 12 month follow up period, while adequate for detecting differences in metabolic control and functional recovery, may not capture very late outcomes such as dementia or progressive motor decline. Additionally, we did not assess adherence to individual drug classes separately, and different medications may have distinct adherence patterns and effects on outcomes. Future prospective cohort studies with longer follow up,

objective adherence monitoring, and incorporation of neuroimaging markers such as white matter hyperintensity progression or cortical thickness are needed to confirm our findings and elucidate underlying mechanisms. Randomized controlled trials testing adherence enhancing interventions with functional outcomes as primary endpoints would provide the highest level of evidence.

Conclusion

Multiple patient-level factors, including age, education, insurance type, stroke severity, and medication burden, are associated with poor adherence to secondary prevention in ischemic stroke. In this cohort, low adherence correlated with worse metabolic control, higher rates of recurrent vascular events and mortality, as well as inferior long-term cognitive and motor recovery. These findings highlight medication adherence as a potentially modifiable factor associated with functional prognosis after ischemic stroke. Prospective studies with objective adherence measures are warranted to confirm these findings.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Repeated measures ANOVA of MoCA scores

Effect	DFn	DFd	F	*P* value	ges
Group	1	274	32.524	< 0.001	0.029
Time	3	822	14.593	< 0.001	0.038
Group × Time	3	822	0.145	0.933	0.000396

Supplementary Table 2. Repeated measures ANOVA of MMSE scores

Effect	DFn	DFd	F	*P* value	ges
Group	1	274	73.776	< 0.001	0.057
Time	2.87	785.54	26.436	< 0.001	0.07
Group × Time	2.87	785.54	0.139	0.93	0.000394

Supplementary Table 3. Repeated measures ANOVA of verbal fluency

Effect	DFn	DFd	F	*P* value	ges
Group	1	274	28.634	< 0.001	0.036
Time	3	822	21.907	< 0.001	0.051
Group × Time	3	822	0.238	0.869	0.0006

Supplementary Table 4. Repeated measures ANOVA of FMA-UE scores

Effect	DFn	DFd	F	P	ges
Group	1	274	30.947	< 0.001	0.029
Time	2.86	782.4	36.042	< 0.001	0.089
Group × Time	2.86	782.4	0.195	0.891	0.000527

Supplementary Table 5. Repeated measures ANOVA of FMA-LE scores

Effect	DFn	DFd	F	P	ges
Group	1	274	24.485	< 0.001	0.023
Time	2.88	788.86	46.558	< 0.001	0.111
Group × Time	2.88	788.86	0.183	0.901	0.000493

Supplementary Table 6. Repeated measures ANOVA of BBS

Effect	DFn	DFd	F	P	ges
Group	1	274	49.215	< 0.001	0.044
Time	2.64	723.33	33.395	< 0.001	0.083
Group × Time	2.64	723.33	0.472	0.678	0.001

Supplementary Table 7. Repeated measures ANOVA of mBI

Effect	DFn	DFd	F	P	ges
Group	1	274	56.822	< 0.001	0.048
Time	2.89	791.09	63.893	< 0.001	0.150
Group × Time	2.89	791.09	0.619	0.596	0.002

Supplementary Table 8. Multivariate logistic regression analysis of factors associated with 12-month MACE

Variable	β	SE	Wald	OR	95% CI for OR	P
Medication adherence (Low vs. High)	1.035	0.469	4.865	2.815	1.124-7.052	0.027
Age (per 1-year increase)	0.040	0.021	3.802	1.041	1.000-1.084	0.051
Education level (per 1-year increase)	-0.053	0.047	1.278	0.948	0.863-1.041	0.258
Baseline NIHSS (per 1-point increase)	0.183	0.086	4.543	1.201	1.015-1.422	0.033
No. of discharge medications (per 1-drug increase)	0.138	0.126	1.205	1.148	0.897-1.468	0.272
Insurance type (Self-pay vs. Medical insurance)	0.404	0.425	0.903	1.498	0.651-3.448	0.338
Gender (Male vs. Female)	0.188	0.391	0.232	1.207	0.561-2.596	0.630

Note: MACE, Major Adverse Cardiovascular Events; NIHSS, National Institutes of Health Stroke Scale.