

The Impact of Plasma Homocysteine Level and Estimated Glomerular Filtration Rate on Neurological Function at Admission in Patients with Acute Ischemic Stroke: A Retrospective Cross-Sectional Study

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Objective: To investigate the effects of homocysteine (Hcy) and estimated glomerular filtration rate (eGFR) on neurological function in patients with ischemic stroke (IS) on admission.

Methods: 248 IS patients admitted to the Third Affiliated Hospital of Heilongjiang University of Chinese Medicine from January 2023 to January 2025 were studied. Basic information, disease history, laboratory test indicators and other information of patients were recorded at admission. According to admission mRS scores, patients were divided into two groups: the control group with good neurological function (mRS 0–1) and the neurological dysfunction group (mRS 2–5). The relationship between Hcy and eGFR on the neurological function of IS patients at admission was analyzed using a multivariate logistic regression model and an additive interaction model.

Results: Among 248 patients, there were 118 patients with neurological dysfunction and 130 patients with good neurological function. After adjusting for confounding factors, it was found that eGFR and Hcy were independent influencing factors of neurological function in IS patients on admission ($P < 0.05$). The risk of neurological dysfunction in patients with elevated Hcy and decreased eGFR on admission was 4.28 times higher than that in patients with both indicators normal [OR = 4.28 (95% CI 2.62–7.24), $P < 0.001$]. There was a significant negative correlation between HCY and eGFR, and Hcy and eGFR had an additive interaction effect on the risk of neurological dysfunction on admission (RERI = 2.02, 95% CI 0.02–4.01; AP = 0.45, 95% CI 0.13–0.79).

Conclusion: Hcy and eGFR are the influencing factors of neurological dysfunction in IS patients, and the two are significantly negatively correlated with the risk of neurological dysfunction in IS patients, and there is an additive interaction.

Keywords: ischemic stroke, homocysteine, glomerular filtration rate, neurological function recovery

Introduction

Ischemic stroke (IS) remains a major global public health challenge, with persistently high incidence, disability, and mortality rates. According to the Global Burden of Disease Report 2023, the annual incidence of IS worldwide has exceeded 24 million, and approximately 50% of survivors suffer from permanent neurological impairments, imposing a substantial economic and caregiving burden on families and society.¹ The underlying pathology of IS involves arterial occlusion leading to cerebral ischemia and hypoxia, which not only triggers acute neuronal necrosis but also initiates complex cascades of inflammation and oxidative stress, further expanding the infarct volume and exacerbating



neurological deficits.² Although reperfusion therapies such as intravenous thrombolysis and mechanical thrombectomy have significantly improved patient outcomes, 30–40% of patients still experience poor prognosis due to delayed admission or unsuccessful recanalization.³ Thus, the identification of potential biomarkers associated with neurological recovery in IS is of great clinical importance for optimizing treatment strategies.

Homocysteine (Hcy), an intermediate product of methionine metabolism, has been consistently linked to IS in multiple large-scale cohort studies. A meta-analysis including 120 studies reported that each 5 $\mu\text{mol/L}$ increase in plasma Hcy was associated with a 12–25% higher risk of IS, and this association remained significant after adjustment for conventional risk factors.⁴ Mechanistic studies have shown that Hcy contributes to brain injury through several pathways: (1) inducing endothelial dysfunction and promoting platelet aggregation and thrombosis; (2) enhancing oxidative stress, leading to neuronal apoptosis and blood–brain barrier disruption; and (3) activating N-methyl-D-aspartate (NMDA) receptors to aggravate excitotoxic injury.⁵ The neurotoxic effects of Hcy appear to be more pronounced in individuals with impaired renal function, suggesting a potential synergistic relationship between Hcy and renal impairment.

In recent years, estimated glomerular filtration rate (eGFR), a key indicator of renal function, has emerged as a research focus in cerebrovascular disease. Declined eGFR is not only a hallmark of chronic kidney disease (CKD) but also an independent predictor of cardiovascular and cerebrovascular events. The Framingham Heart Study demonstrated that individuals with eGFR <60 mL/min/1.73 m² had a 1.8-fold higher risk of IS compared with those with normal renal function, with risk increasing progressively as renal impairment worsened.⁶ Moreover, renal ischemia and hypoxia may influence cerebral hemodynamics through neurohumoral regulation.⁷ Of particular interest, the brain and kidneys share hemodynamic similarities, both relying on high perfusion to sustain normal physiological function, which may explain the intrinsic link between renal impairment and cerebral injury.⁸

Although Hcy and eGFR have each been extensively studied in relation to IS,⁹ their combined effects and potential synergistic influence on neurological recovery remain underexplored. Recent evidence suggests that elevated Hcy may accelerate eGFR decline by promoting renal microvascular injury, while reduced eGFR may impair Hcy metabolism, creating a vicious cycle of “high Hcy–low eGFR”.¹⁰ Research on the joint evaluation of Hcy and eGFR in predicting neurological outcomes in IS patients is still in its early stage, particularly in the acute phase, and their dynamic interplay has not been fully elucidated.

The present study was designed to examine the independent and combined effects of eGFR and Hcy levels on neurological deficits at admission in patients with acute IS. Findings from this study may provide a rationale for early identification of high-risk patients and contribute to the development of individualized intervention strategies.

Materials and Methods

Study Population and Design

This retrospective cross-sectional study was conducted at the Third Affiliated Hospital of Heilongjiang University of Chinese Medicine (Harbin, China). A total of 248 patients with acute ischemic stroke (AIS) admitted between January 2023 and January 2025 were included. According to admission mRS scores, patients were divided into two groups: the control group with good neurological function (mRS 0–1) and the neurological dysfunction group (mRS 2–5). Clinical and laboratory data were extracted from electronic medical records.

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) age ≥ 18 years; (2) diagnosis of AIS according to the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018,¹¹ confirmed by typical symptoms (eg, monocular vision loss, limb numbness, memory impairment) and neuroimaging evidence (head CT or MRI showing ischemic changes such as thrombosis or atherosclerosis).

The exclusion criteria were: (1) pre-existing neurological dysfunction prior to the index stroke; (2) comorbidities significantly affecting limb function; (3) incomplete medical records.

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Heilongjiang University of Chinese Medicine (Approval No. 2022-TCM-073). All procedures were performed in accordance with the ethical

standards of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians.

Data Collection

The following data were collected from patient records upon admission: Demographic characteristics: age, gender, body mass index (BMI); Clinical scores: modified Rankin Scale (mRS) score; Lifestyle factors: smoking history, drinking history (including past smokers or drinkers); Medical history: hypertension, diabetes, hyperlipidemia, previous cerebral infarction; Laboratory parameters: plasma homocysteine (Hcy) level, serum creatinine.

Hypertension was defined as a self-reported history, ongoing use of antihypertensive drugs for >2 weeks prior to admission, or a new diagnosis at discharge. Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L and/or postprandial blood glucose ≥ 11.1 mmol/L, use of hypoglycemic agents, self-reported history, or new diagnosis at discharge. Hyperlipidemia was defined as triglycerides (TG) >2.30 mmol/L and/or total cholesterol (TC) >5.17 mmol/L, use of lipid-lowering drugs, self-reported history, or new diagnosis at discharge. Previous cerebral infarction was confirmed by evidence of old infarction on admission CT/MRI or prior diagnosis by a healthcare institution based on neurological signs and imaging.

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, based on admission serum creatinine, age, and gender. Renal impairment was defined as eGFR <60 mL/min/1.73 m². Hyperhomocysteinemia (high Hcy) was defined as Hcy >15 μ mol/L.¹²

Statistical Analysis

Statistical analyses were performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA), R (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism (version 8.0.2; GraphPad Software, San Diego, CA, USA). Patients were categorized into two groups based on the admission modified Rankin Scale (mRS) score: a neurologically good group (mRS 0–1) and a neurological dysfunction group (mRS 2–5).

Continuous variables were expressed as mean \pm standard deviation (SD) or median (interquartile range) based on their distribution, and compared using the Student's *t*-test or Mann–Whitney-*U* test, as appropriate. Categorical variables were presented as frequencies (percentages) and compared using the χ^2 -test or Fisher's exact test.

A multivariate binary logistic regression model was employed to assess the independent associations of estimated glomerular filtration rate (eGFR) and homocysteine (Hcy) with neurological outcome (dichotomized mRS group). Variables included in the model were those that showed significant differences in univariate analyses or were considered clinically relevant to the outcome. Given that age and gender are integral components of the eGFR calculation, they were not included as separate covariates in the regression model to avoid collinearity.

To assess the additive interaction between eGFR and Hcy on neurological impairment, we calculated three interaction metrics: the Relative Excess Risk due to Interaction (RERI), the Attributable Proportion due to Interaction (AP), and the Synergy Index (S). The following formulae were applied, where OR₁₁ represents the odds ratio for the joint effect of low eGFR and high Hcy, OR₁₀ represents the odds ratio for low eGFR alone, and OR₀₁ represents the odds ratio for high Hcy alone, using the group with normal eGFR and normal Hcy as the reference (OR₀₀/gcl = 1): RERI = OR₁₁ - OR₁₀ - OR₀₁ + 1; AP = RERI / OR₁₁; S = (OR₁₁ - 1) / [(OR₁₀ - 1) + (OR₀₁ - 1)]. An additive interaction was considered statistically significant if the 95% confidence intervals (CIs) for RERI or AP did not include zero.

The correlation between eGFR and Hcy levels was evaluated using Pearson or Spearman correlation analysis, as appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population

This study ultimately included 248 patients, comprising 130 in the control group (good neurological function, mRS 0–1) and 118 in the neurological dysfunction group (mRS 2–5). The baseline characteristics of the study population are compared in Table 1. Patients in the control group were significantly younger (65.55 vs 72.67 years, P < 0.001), had

Table 1 Comparison of Baseline Characteristics Between the Neurological Dysfunction Group and the Control Group

Variable	Neurological Dysfunction Group (n = 118)	Control Group (n = 130)	P-value
Age ($\bar{x} \pm s$, years)	72.67±10.39	65.55±7.15	<0.001
Male [n(%)]	72(61.0)	72(55.4)	0.206
BMI[M (P ₂₅ , P ₇₅), (kg/m ²)]	23.6(22.1,26.6)	25.3(23.0,27.7)	<0.001
Smoking history [n(%)]	49(41.5)	47(36.2)	0.178
Drinking history [n(%)]	31(26.3)	38(29.2)	0.037
Medical history			
Hypertension [n(%)]	99(83.8)	107(82.3)	0.647
Diabetes [n(%)]	49(41.5)	55(42.3)	0.870
Hyperlipidemia [n(%)]	38(32.2)	44(33.8)	0.680
Coronary heart disease [n(%)]	37(31.4)	38(29.2)	0.613
Previous cerebral infarction [n(%)]	73(61.8)	76(58.4)	0.378
Laboratory indicators			
Scr[M (P ₂₅ , P ₇₅), mg/dl]	0.8(0.6,1.0)	0.9(0.6,1.1)	0.997
eGFR[M (P ₂₅ , P ₇₅), mL/min · 1.73m ²]	62.3(45.3,97.8)	82.5(60.3,106.2)	<0.001
Hcy [M (P ₂₅ , P ₇₅), μmol / L]	16.7(12.6,23.2)	13.6(11.0,17.5)	<0.001

Notes: Data are presented as mean ± standard deviation, median (P₂₅, P₇₅), or n (%).

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; Scr, serum creatinine.

a higher eGFR (82.5 vs 62.3 mL/min/1.73 m², P < 0.001), lower Hcy levels (13.6 vs 16.7 μmol/L, P < 0.001), higher BMI (25.3 vs 23.6 kg/m², P < 0.001), and a higher rate of alcohol consumption history (29.2% vs 26.3%, P = 0.037) compared to patients in the neurological dysfunction group. No statistically significant differences were observed between the two groups in terms of gender, smoking history, medical history (hypertension, diabetes, hyperlipidemia, coronary heart disease, previous cerebral infarction), or blood creatinine (Scr) levels.

Notably, while Scr levels were not significantly different between the groups (P = 0.997), eGFR was significantly lower in the neurological dysfunction group. This divergence can be explained by the fact that eGFR is a more comprehensive measure of renal function than Scr alone, as it incorporates age, gender, and race (via the CKD-EPI equation), providing a more accurate reflection of glomerular filtration rate, especially in older populations where muscle mass (a major determinant of Scr production) may be reduced.

Univariable and Multivariable Logistic Regression Analyses of Neurological Function at Admission

First, univariable logistic regression analyses were performed to assess the crude associations between various baseline factors and neurological dysfunction (Table 2). Variables with a P-value < 0.10 in the univariable analysis (specifically, age, BMI, drinking history, eGFR, and Hcy) were identified as potential candidates for the multivariable model. Additionally, variables considered clinically relevant based on existing literature (eg, smoking history, hypertension, diabetes, hyperlipidemia, coronary heart disease, and previous cerebral infarction) were also considered for inclusion to ensure comprehensive adjustment.^{13,14} The final multivariable logistic regression model was constructed using a purposeful selection method, adjusting for BMI, smoking history, drinking history, and the aforementioned medical histories. Age was not included as a separate covariate due to its incorporation into the eGFR calculation, preventing collinearity.

As shown in Table 3, after adjustment, both Hcy and eGFR were identified as independent factors associated with neurological dysfunction at admission in AIS patients. The risk of neurological dysfunction was 2.2 times higher in

Table 2 Univariable Logistic Regression Analysis of Factors Associated with Neurological Dysfunction at Admission in Patients with Acute Ischemic Stroke

Variable	β	SE	Wald χ^2	OR (95% CI)	P
Age (per year increase)	0.084	0.015	45.213	1.083 (1.063–1.104)	< 0.001
Male (vs Female)	0.236	0.181	1.634	1.259 (0.884–1.793)	0.201
BMI (per kg/m ² increase)	-0.129	0.035	12.345	0.905 (0.854–0.959)	< 0.001
Smoking history (Yes vs No)	-0.221	0.175	1.676	0.803 (0.576–1.120)	0.196
Drinking history (Yes vs No)	0.451	0.196	4.381	1.492 (1.028–2.165)	0.036
Hypertension (Yes vs No)	0.099	0.221	0.178	1.094 (0.710–1.686)	0.681
Diabetes (Yes vs No)	-0.031	0.170	0.035	0.970 (0.696–1.353)	0.865
Hyperlipidemia (Yes vs No)	0.073	0.174	0.173	1.073 (0.769–1.497)	0.68
Coronary heart disease (Yes vs No)	0.091	0.183	0.256	1.094 (0.770–1.555)	0.614
Previous cerebral infarction (Yes vs No)	0.145	0.167	0.771	1.150 (0.841–1.573)	0.38
eGFR (<60 vs \geq 60 mL/min/1.73m ²)	1.150	0.223	25.051	3.004 (1.948–4.633)	< 0.001
Hcy (>15 vs \leq 15 μ mol/L)	0.954	0.218	20.455	2.586 (1.712–3.906)	< 0.001

Notes: P-values indicate statistical significance ($P < 0.10$), which was the threshold for consideration in the multivariable model.

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; Hcy, homocysteine.

Table 3 Multivariable Logistic Regression Analysis of Factors Associated with Neurological Dysfunction at Admission

Exposure Factors	β	SE	Wald χ^2	OR (95% CI)	P
Hcy	0.832	0.208	15.810	2.200(1.519–3.501)	<0.001
eGFR	0.613	0.208	8.584	1.851(1.231–2.776)	0.003
BMI	-0.092	0.026	11.557	0.921(0.865–0.961)	0.001
Smoking history	-0.111	0.235	0.234	0.876(0.548–1.432)	0.631
Drinking history	0.388	0.259	2.189	1.479(0.879–2.521)	0.141
Hypertension	0.006	0.244	0.001	1.006(0.611–1.659)	0.979
Diabetes	0.084	0.201	0.210	1.097(0.742–1.626)	0.641
Hyperlipidemia	-0.034	0.204	0.014	0.986(0.654–1.459)	0.906
Coronary heart disease	0.038	0.226	0.050	1.055(0.687–1.604)	0.831
Previous cerebral infarction	0.033	0.186	0.012	1.024(0.697–1.502)	0.907

Notes: The model was adjusted for BMI, smoking history, drinking history, hypertension, diabetes, hyperlipidemia, coronary heart disease, and previous cerebral infarction.

Abbreviations: eGFR, estimated glomerular filtration rate; Hcy, homocysteine; OR, odds ratio; CI, confidence interval.

patients with Hcy >15 μ mol/L compared to those with Hcy \leq 15 μ mol/L (OR = 2.200, 95% CI: 1.519–3.501, $P < 0.001$). Similarly, patients with renal dysfunction (eGFR <60 mL/min/1.73 m²) had a 1.851-fold increased risk compared to those with preserved renal function (eGFR \geq 60 mL/min/1.73 m²) (OR = 1.851, 95% CI: 1.231–2.776, $P = 0.003$). Higher BMI was associated with a reduced risk of neurological dysfunction (OR = 0.921, 95% CI: 0.865–0.961, $P = 0.001$).

Correlation and Interaction Between Hcy Levels and eGFR

Pearson correlation analysis revealed a significant negative correlation between Hcy levels and eGFR ($r = -0.267$, $P < 0.001$; Figure 1), indicating that poorer renal function was associated with higher homocysteine levels.

The additive interaction between eGFR and Hcy on the risk of neurological dysfunction is presented in Table 4. The results showed that patients with both high Hcy and low eGFR on admission had a 4.28-fold increased risk of neurological dysfunction

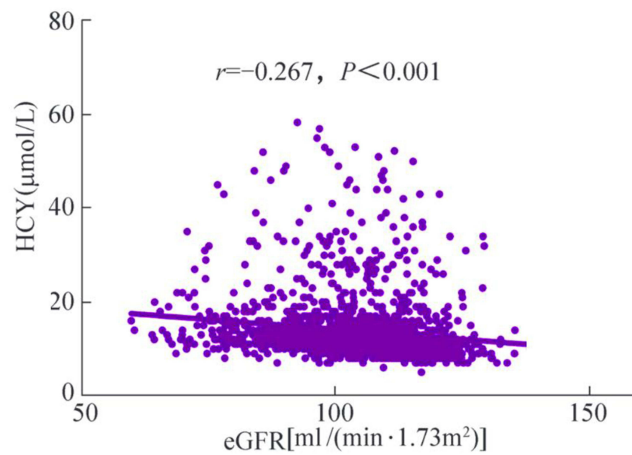


Figure 1 Pearson correlation analysis of HCY level and eGFR.

compared to patients with normal levels of both indicators [OR = 4.28 (95% CI: 2.62–7.24), $P < 0.001$]. The interaction analysis indicated a significant additive interaction between Hcy and eGFR. The relative excess risk due to interaction (RERI) was 2.02 (95% CI: 0.02–4.01), and the attributable proportion due to interaction (AP) was 0.45 (95% CI: 0.13–0.79), suggesting that the interaction between these two factors accounts for a substantial portion of the total effect. The synergy index (S) was 2.46 (95% CI: 0.90–6.77). **Figure 2** visually represents the relative risk distribution across different exposure combinations.

Table 4 Additive Interaction Analysis Between Homocysteine (Hcy) and Estimated Glomerular Filtration Rate (eGFR) on the Risk of Neurological Dysfunction at Admission

A Odds ratios for neurological dysfunction by Hcy and eGFR categories			
Hcy Category	eGFR Category	OR (95% CI) for Neurological Dysfunction	P
≤ 15 µmol/L	≥ 60 mL/min/1.73m ²	1.00 (Reference)	–
≤ 15 µmol/L	< 60 mL/min/1.73m ²	1.32 (0.75, 2.66)	0.341
> 15 µmol/L	≥ 60 mL/min/1.73m ²	1.84 (1.17, 3.25)	0.012
> 15 µmol/L	< 60 mL/min/1.73m ²	4.28 (2.62, 7.24)	< 0.001
B Measures of additive interaction between Hcy and eGFR.			
Measures of Additive Interaction		Value (95% CI)	Interpretation
RERI (Relative Excess Risk due to Interaction)		2.02 (0.02, 4.01)	Significant
AP (Attributable Proportion due to Interaction)		0.45 (0.13, 0.79)	Significant
S (Synergy Index)		2.46 (0.90, 6.77)	

Notes: The reference group for the interaction analysis is patients with Hcy ≤15 µmol/L and eGFR ≥60 mL/min/1.73m². An additive interaction is considered statistically significant if the 95% CI for RERI or AP does not include zero. The model was adjusted for body mass index, smoking history, drinking history, hypertension, diabetes, hyperlipidemia, coronary heart disease, and previous cerebral infarction.

Abbreviations: CI, confidence interval; OR, odds ratio; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index.

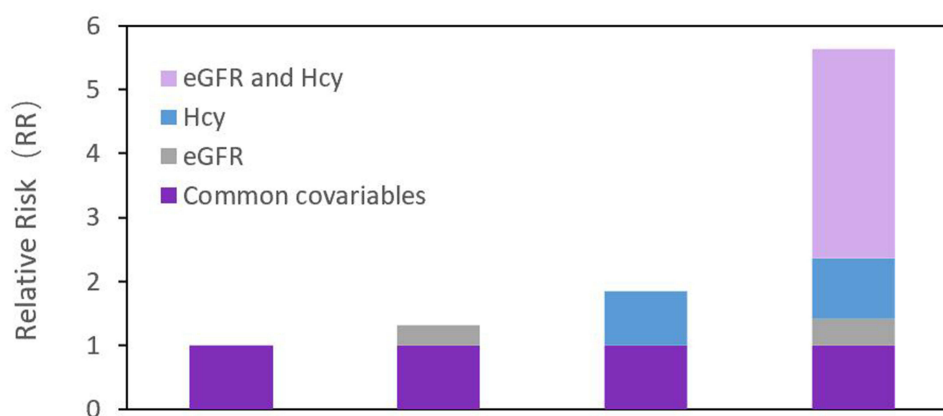


Figure 2 Relative risk distribution of different exposure situations of neurological dysfunction in the study population.

Discussion

This retrospective cross-sectional study demonstrated that both elevated homocysteine (Hcy) levels and reduced estimated glomerular filtration rate (eGFR) are independent risk factors for neurological dysfunction at admission in patients with acute ischemic stroke (AIS). A significant negative correlation was observed between Hcy and eGFR. Moreover, a significant additive interaction was identified between these two factors, indicating that patients with concomitant hyperhomocysteinemia and renal impairment face a substantially higher risk of severe neurological deficits than would be expected from the sum of their individual effects.

As a high-risk area for stroke, China faces a significant public health challenge from ischemic stroke (IS), which accounts for approximately 69.6% of the about 2.80 million new stroke cases annually, according to the “China Stroke Prevention and Treatment Report 2022”.¹⁵ The findings of this study underscore the importance of assessing both renal and metabolic pathways in the initial evaluation of AIS patients. Our results align with the growing body of evidence positioning eGFR not merely as a marker of kidney health but as a clinically relevant predictor of neurological damage and prognosis in IS patients.¹⁶ The relationship between renal dysfunction and stroke is bidirectional. On one hand, renal dysfunction is a well-established risk factor for incident stroke, contributing to cerebrovascular damage through mechanisms like accelerated atherosclerosis, hypertension, and chronic inflammation.¹⁷ On the other hand, the acute phase of a major stroke can lead to subsequent renal impairment due to neurohormonal activation, systemic inflammation, and complications like dehydration or rhabdomyolysis.¹⁸ Our study, focusing on admission status, captures the impact of pre-existing or acute-on-chronic renal dysfunction on initial stroke severity.

The clinical value of eGFR is widely recognized. Approximately one-third of AIS patients present with renal insufficiency.¹⁹ Our findings further confirm that lower eGFR levels are significantly associated with more severe neurological damage upon admission, which is highly consistent with previous research conclusions on the correlation between renal function and brain health.^{20,21} The detrimental impact of renal dysfunction on the brain may be mediated through several mechanisms: firstly, the accumulation of uremic toxins (eg, asymmetric dimethylarginine) can induce cerebrovascular endothelial dysfunction and compromise blood-brain barrier integrity;²² secondly, chronic renal ischemia and associated conditions like anemia can exacerbate cerebral hypoperfusion, potentially inducing white matter lesions and accelerating neurodegeneration.²³

Homocysteine (Hcy) is a key biomarker in cardiovascular and cerebrovascular diseases, with elevated levels linked to endothelial dysfunction, abnormal lipid metabolism, and atherosclerosis.²⁴ Hcy metabolism is intrinsically linked to renal function, as the kidneys are a major site for its clearance. Consequently, renal impairment often leads to elevated Hcy levels, creating a synergistic pathophysiological state.²⁵ Serum Hcy concentration is influenced by genetic factors, age, gender, obesity, and nutritional status (eg, vitamin B and folate intake).²⁶ While hyperhomocysteinemia is common in stroke patients,^{27,28} its role as an independent prognostic factor has been debated. In our cohort, after adjusting for confounders including renal function, elevated Hcy remained an independent predictor of worse neurological status at admission. This suggests a direct or additive role of Hcy beyond its association with renal impairment. Mechanistically,

elevated Hcy exacerbates vascular injury by damaging endothelial cells, promoting oxidative stress, activating coagulation cascades, and accelerating atherosclerosis.^{29,30}

The most salient finding of this study is the significant additive interaction between eGFR and Hcy. The risk of neurological dysfunction in patients with both low eGFR and high Hcy was 4.28-fold higher than in those with normal values, exceeding the sum of the risks associated with each factor alone. This synergistic effect, quantified by a significant RERI of 2.02, implies that the coexistence of these conditions creates a pathophysiological milieu far more detrimental to the brain than either condition in isolation. This result resonates with studies in other populations, such as the work by Suliman et al³¹ in metabolic syndrome, which found that the interaction between Hcy and renal dysfunction markedly increased cardiovascular risk. The discordant patterns—where Hcy and eGFR are inversely correlated yet exert a synergistic effect on neurological outcome—can be interpreted through their shared and complementary pathways. Both conditions promote endothelial dysfunction, oxidative stress, and a pro-thrombotic state. When combined, these pathways are likely amplified, leading to more severe cerebral endothelial injury, impaired cerebrovascular autoregulation, and ultimately, greater ischemic damage.^{32,33}

Several limitations of this study warrant consideration. Its single-center, retrospective cross-sectional design limits the ability to infer causality or generalize the findings. The sample size, while adequate for the primary analysis, may limit the stability of subgroup and interaction analyses. Furthermore, we lacked data on specific nutritional markers (eg, folate, vitamin B12) and detailed imaging correlates of stroke severity (eg, infarct volume), which could provide deeper mechanistic insights. Future prospective, multi-center studies incorporating longitudinal data and more detailed biomarker profiling are needed to validate these findings and explore the underlying causal mechanisms, potentially using methods like Mendelian randomization.

Conclusion

In conclusion, this retrospective study suggests a potential synergistic interaction between reduced eGFR and elevated Hcy on the severity of neurological dysfunction at admission in patients with AIS. These preliminary findings highlight the potential clinical value of a combined assessment of renal and metabolic function upon hospitalization. However, given the inherent limitations of the retrospective design and sample size, these results should be interpreted with caution. They primarily generate a hypothesis that needs to be validated in future large-scale, prospective studies. If confirmed, such an assessment may aid in identifying patients who could be candidates for more intensive monitoring and management strategies in a research setting.

Funding

This study was supported by the Clinical study of Qutan Tongyang Tang in treating diabetic nephropathy complicated with chronic heart failure (NO.zxykt202304).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Herpich F, Rincon F. Management of Acute Ischemic Stroke. *Crit Care Med*. 2020;48(11):1654–1663. PMID: 32947473; PMCID: PMC7540624. doi:10.1097/CCM.0000000000004597
2. Olugbo P, Ariëns RAS. Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke. *Stroke*. 2021;52(3):1131–1142. PMID: 33563020; PMCID: PMC7610448. doi:10.1161/STROKEAHA.120.032810
3. Ekkert A, Šliachtenko A, Grigaitė J, Burnytė B, Utkus A, Jatužis D. Ischemic stroke genetics: what is new and how to apply it in clinical practice? *Genes*. 2021;13(1):48. PMID: 35052389; PMCID: PMC8775228. doi:10.3390/genes13010048
4. Rabelo NN, Telles JPM, Pipek LZ, et al. Homocysteine is associated with higher risks of ischemic stroke: a systematic review and meta-analysis. *PLoS One*. 2022;17(10):e0276087. PMID: 36227950; PMCID: PMC9560514. doi:10.1371/journal.pone.0276087
5. Pinzon RT, Wijaya VO, Veronica V. The role of homocysteine levels as a risk factor of ischemic stroke events: a systematic review and meta-analysis. *Front Neurol*. 2023;12:1144584. Erratum in: *Front Neurol*. 2024 Apr 04;15:1404808. doi: 10.3389/fneur.2024.1404808. PMID: 37251231; PMCID: PMC10216881. doi:10.3389/fneur.2023.1144584
6. Liu H, Zheng H, Wu P, et al. Estimated glomerular filtration rate, anemia and outcomes in patients with ischemic stroke. *Ann Transl Med*. 2020;8(1):2. PMID: 32055593; PMCID: PMC6995746. doi:10.21037/atm.2019.11.148
7. Kang MK, Lee D, Oh MS, et al. Association of high-estimated glomerular filtration rate with the severity of ischemic stroke during non-vitamin K antagonist oral anticoagulants therapy: a nationwide cohort study. *Front Neurol*. 2023;14:1277855. PMID: 38107638; PMCID: PMC10722199. doi:10.3389/fneur.2023.1277855

8. Eun MY, Park JW, Cho BH, Cho KH, Yu S. Influence of estimated glomerular filtration rate on clinical outcomes in patients with acute ischemic stroke not receiving reperfusion therapies. *J Clin Med*. 2021;10(20):4719.PMID: 34682842; PMCID: PMC8541215. doi:10.3390/jcm10204719
9. Cheng Y, Kong FZ, Dong XF, et al. Influence of renal function on the association between homocysteine level and risk of ischemic stroke. *Am J Transl Res*. 2017;9(10):4553–4563. PMID: 29118917; PMCID: PMC5666064.
10. Mizuno T, Hoshino T, Ishizuka K, et al. Hyperhomocysteinemia increases vascular risk in stroke patients with chronic kidney disease. *J Atheroscler Thromb*. 2023;30(9):1198–1209.PMID: 36436876; PMCID: PMC10499453. doi:10.5551/jat.63849
11. Chinese Stroke Association, Chinese Interventional Neuroradiology Society, Intervention Group of Committee of Stroke Prevention and Control of Chinese Preventive Medicine Association. Chinese guideline for endovascular treatment of acute ischemic stroke 2018. *Chin J Stroke*. 2018;13(07):706–729.
12. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–Based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737–1749. doi:10.1056/NEJMoa2102953
13. Ebinger M, Siegerink B, Kunz A, et al. Berlin_prehospital or usual delivery in stroke care (B_PROUD) study group. Association between dispatch of mobile stroke units and functional outcomes among patients with acute ischemic stroke in Berlin. *JAMA*. 2021;325(5):454–466. Erratum in: *JAMA*. 2021 Apr 6;325(13):1335. doi: 10.1001/jama.2021.2565. PMID: 33528537; PMCID: PMC7856548. doi:10.1001/jama.2020.26345
14. Zhang S, Zhang J, Wang C, et al. COVID-19 and ischemic stroke: mechanisms of hypercoagulability (Review). *Int J Mol Med*. 2021;47(3):21. PMID: 33448315; PMCID: PMC7849983. doi:10.3892/ijmm.2021.4854
15. Chao CH, Wu CL, Huang WY. Association between estimated glomerular filtration rate and clinical outcomes in ischemic stroke patients with high-grade carotid artery stenosis. *BMC Neurol*. 2021;21(1):124.PMID: 33740899; PMCID: PMC7977561. doi:10.1186/s12883-021-02154-3
16. Zhang C, Zhang X, Meng P, Gao H, Bai B, Li D. The association between serum uric acid and cognitive performance in patients with ischemic stroke is modified by estimated glomerular filtration rate. *Sci Rep*. 2023;13(1):7097.PMID: 37130897; PMCID: PMC10154290. doi:10.1038/s41598-023-34352-z
17. Kelly DM, Georgakakis MK, Franceschini N, Blacker D, Viswanathan A, Anderson CD. Interplay between chronic kidney disease, hypertension, and stroke: insights from a multivariable mendelian randomization analysis. *Neurology*. 2023;101(20):e1960–e1969. Epub 2023 Sep 29. Erratum in: *Neurology*. 2024 Jul 9;103(1):e209573. doi: 10.1212/WNL.000000000209573. doi: 10.1212/WNL.000000000209596. Erratum in: *Neurology*. 2024 Jul 9;103(1):e209596. PMID: 37775316; PMCID: PMC10662984. doi:10.1212/WNL.000000000207852
18. Omer Sultan M, Farooque U, Javed R, et al. Correlation of homocysteine level and age in patients with ischemic stroke. *Cureus*. 2020;12(4):e7785. PMID: 32461857; PMCID: PMC7243624. doi:10.7759/cureus.7785
19. Dong WC, Guo JL, Xu L, et al. Impact of homocysteine on acute ischemic stroke severity: possible role of aminothiols redox status. *BMC Neurol*. 2024;24(1):175.PMID: 38789928; PMCID: PMC11127353. doi:10.1186/s12883-024-03681-5
20. Ghose M, Das M, Das R, et al. Homocysteine, vitamins B6, B12, and folate and the risk of ischemic and hemorrhagic stroke: a case-control study from northeast India. *Ann Neurosci*. 2023;30(1):33–39.PMID: 37313333; PMCID: PMC10259151. doi:10.1177/09727531221124425
21. Chermitti R, Burtey S, Dou L. Role of uremic toxins in vascular inflammation associated with chronic kidney disease. *J Clin Med*. 2024;13(23):7149. doi:10.3390/jcm13237149
22. Tang X, Han YP, Chai YH, et al. Association of kidney function and brain health: a systematic review and meta-analysis of cohort studies. *Ageing Res Rev*. 2022;82:101762. doi:10.1016/j.arr.2022.101762
23. Bi R, Wei Y, Li P, et al. Associations of cerebral small vessel disease and chronic kidney disease in patients with acute ischemic stroke. *J Am Heart Assoc*. 2025;14(9):e038711. doi:10.1161/JAHA.124.038711
24. Assem M, Lando M, Grissi M, et al. The impact of uremic toxins on cerebrovascular and cognitive disorders. *Toxins*. 2018;10(7):303. doi:10.3390/toxins10070303
25. Saija C, Currò M, Ientile R, Caccamo D, Bertuccio MP. Impact of alterations in homocysteine, asymmetric dimethylarginine and vitamins-related pathways in some neurodegenerative diseases: a narrative review. *Int J Mol Sci*. 2025;26(8):3672. doi:10.3390/ijms26083672
26. Rao ZZ, Gu HQ, Wang XW, et al. Renal dysfunction and in-hospital outcomes in patients with acute ischemic stroke after intravenous thrombolytic therapy. *J Am Heart Assoc*. 2019;8(20):e012052. doi:10.1161/JAHA.119.012052
27. Wang Y, Jing J, Meng X, et al. The third china national stroke registry (CNSR-III) for patients with acute ischaemic stroke or transient ischaemic attack: design, rationale and baseline patient characteristics. *Stroke Vasc Neurol*. 2019;4(3):158–164. doi:10.1136/svn-2019-000242
28. Guo C, Shang L, Li Y. Application and effect analysis of refined nursing mode on physical and mental health of patients with post-stroke epilepsy. *J Mod Nurs Pract Res*. 2021;1(1):4. doi:10.53964/jmnp.2021004
29. Miglinas M, Cesniene U, Janusaite MM, Vinikovas A. Cerebrovascular disease and cognition in chronic kidney disease patients. *Front Cardiovasc Med*. 2020;7:96. doi:10.3389/fcvm.2020.00096
30. Chen Y, Wu J, Yang Y, Xiong M, Yu X, Lei S. Causal effects of sarcopenia-related traits on ischemic stroke: a two-sample mendelian randomization study. *Clin Mol Epidemiol*. 2024;1:9. doi:10.53964/cme.2024009
31. Suliman ME, Lindholm B, Bárány P, Bergström J. Hyperhomocysteinemia in chronic renal failure patients: relation to nutritional status and cardiovascular disease. *Clin Chem Lab Med*. 2001;39(8):734–738.PMID: 11592443. doi:10.1515/CCLM.2001.122
32. Zhao Q, Yan T, Chopp M, Venkat P, Chen J. Brain-kidney interaction: renal dysfunction following ischemic stroke. *J Cereb Blood Flow Metab*. 2020;40(2):246–262. doi:10.1177/0271678X19890931
33. Zhang C, Xue G, Hou Y, et al. Association between kidney measurements and cognitive performance in patients with ischemic stroke. *PLoS One*. 2023;18(12):e0292506.PMID: 38096197; PMCID: PMC10721055. doi:10.1371/journal.pone.0292506

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