Relationship Between Homocysteine Levels and Acute Kidney Injury in Patients with Acute Ischemic Stroke (Postprint)

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Abstract

Background Acute ischemic stroke (AIS) is the second leading cause of death worldwide after coronary heart disease, and acute kidney injury (AKI) is one of the more severe complications following AIS. Homocysteine (Hcy) may be an important factor leading to kidney injury and accelerating renal function deterioration. However, current research on the relationship between Hcy and AKI is still limited, particularly in AIS patients. Objective To investigate the relationship between Hcy levels and the occurrence of AKI in AIS patients, and to provide additional insights for the prevention and treatment of AKI in AIS patients. Methods A total of 1,202 hospitalized AIS patients admitted to the Department of Neurology, Second Hospital of Tianjin Medical University from January 2018 to April 2021 were enrolled as study subjects, and baseline clinical data were collected through the hospital's electronic medical record system. According to the "Expert Consensus on the Diagnosis, Treatment, and Prevention of Hyperhomocysteinemia," patients were divided into three categories: those with normal Hcy (Hcy $\leq$ 15 mol/L, n=618), those with mild hyperhomocysteinemia (HHcy) (Hcy 15-30 mol/L, n=459), and those with moderate to severe HHcy (Hcy $>$ 30 mol/L, n=125). Renal function and urine output were dynamically monitored within 7 days of admission. Based on the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for AKI diagnosis criteria, patients were divided into AKI and non-AKI groups according to whether they developed AKI. Multivariate Logistic regression analysis was used to explore the effect of Hcy as both a continuous and categorical variable on AKI occurrence after AIS. Subgroup analysis was employed to investigate the relationship between Hcy and AKI occurrence after AIS in various subpopulations, and restricted cubic spline models were used to explore the non-linear relationship between Hcy and AKI occurrence after AIS. Results Among the 1,202 AIS patients, 150 (12.48%) developed AKI. Multivariate Logistic regression analysis

showed that after adjusting for confounding variables, each 1 mol/L increase in Hcy increased the risk of AKI after AIS (OR=1.035, 95%CI (1.019, 1.052), P<0.05) ; using the normal Hcy group as reference, the risk of AKI increased in both mild and moderate to severe HHcy groups (OR=1.770, 95%CI (1.150, 2.724), P<0.05; OR=2.927, 95%CI (1.671, 5.126), P<0.05) . Subgroup analysis results showed that when Hcy was treated as a continuous variable, the risk of AKI increased with Hcy levels in AIS patients who were female, aged ≥ 75 years, had hypertension, had diabetes, had moderate to severe stroke at admission, and whose stroke type was large artery atherosclerosis (LAA), small artery occlusion (SAA), or cardioembolism (CE) (P<0.05). When Hcy was treated as a categorical variable, in AIS patients who were male, <75 years old, had hypertension, had diabetes, had a history of stroke, had no coronary heart disease, and had mild stroke at admission, the risk of AKI was higher in mild HHcy patients compared to those with normal Hcy (P<0.05). In AIS patients who were female, had hypertension, had diabetes, regardless of age, presence of coronary heart disease, history of stroke, had moderate or moderate to severe stroke at admission, and whose stroke type was LAA, SAA, or CE, the risk of AKI was higher in moderate to severe HHcy patients compared to those with normal Hcy (P<0.05). Restricted cubic spline model results showed a nonlinear association between Hcy and AKI risk, presenting as an upward convex curve (P=0.026). When admission Hcy < 17 mmol/L, the risk of AKI after AIS increased rapidly with increasing Hcy; when admission Hcy ≥ 17 mmol/L, the risk of AKI after AIS increased slowly with increasing Hcy. Conclusion Hcy is a risk factor for AKI after AIS whether treated as a continuous or categorical variable, and monitoring Hcy levels in patients can help with early identification and prevention of AKI, thereby improving patient prognosis.

Full Text

Relationship between Homocysteine Level and Acute Kidney Injury in Patients with Acute Ischemic Stroke

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Abstract

Background: Acute ischemic stroke (AIS) is the second leading cause of death worldwide after coronary heart disease. Acute kidney injury (AKI) represents one of the most serious complications following AIS, and homocysteine (Hcy)

may be an important factor contributing to renal damage and accelerated deterioration of renal function. However, few studies have examined the relationship between Hcy and AKI, particularly in AIS patients.

Objective: To investigate the association between plasma Hcy levels and AKI occurrence in AIS patients, providing new insights for AKI prevention and treatment in this population.

Methods: We enrolled 1,202 AIS patients admitted to the Department of Neurology at the Second Hospital of Tianjin Medical University between January 2018 and April 2021. Baseline clinical data were collected through the hospital electronic medical record system. According to the Expert Consensus on the Diagnosis, Treatment, and Prevention of Hyperhomocysteinemia, patients were categorized into three groups: normal Hcy (Hcy $\leq$ 15 mol/L, n=618), mild hyperhomocysteinemia (HHcy) (Hcy 15–30 mol/L, n=459), and moderate-to-severe HHcy (Hcy $>$ 30 mol/L, n=125). Renal function and urine output were monitored dynamically within 7 days of admission. Based on the 2021 KDIGO Clinical Practice Guideline for AKI diagnosis, patients were divided into AKI and non-AKI groups. Multivariate logistic regression analysis was used to examine the effect of Hcy on post-AIS AKI, treating Hcy as both a continuous and categorical variable. Subgroup analyses explored the relationship between Hcy and AKI across different populations, while restricted cubic spline modeling investigated potential non-linear relationships.

Results: Among the 1,202 AIS patients, 150 (12.48%) developed AKI. Multivariate logistic regression revealed that after adjusting for confounding variables, each 1 mol/L increase in Hcy elevated the risk of post-AIS AKI by 3.5% (OR=1.035, 95%CI: 1.019–1.052, P<0.05). Compared with normal Hcy, both mild and moderate-to-severe HHcy were associated with increased AKI risk (OR=1.770, 95%CI: 1.150–2.724, P<0.05; OR=2.927, 95%CI: 1.671–5.126, P<0.05, respectively). Subgroup analysis showed that when Hcy was treated as a continuous variable, AKI risk increased with rising Hcy levels in females, patients aged $ $75 years, those with hypertension or diabetes, those with moderate-to-severe stroke at admission, and those with large-artery atherosclerosis (LAA), small artery occlusion (SAO), or cardioembolism (CE) stroke subtypes (P<0.05). When Hcy was analyzed as a categorical variable, mild HHcy conferred higher AKI risk than normal Hcy in males, patients <75 years, those with hypertension, diabetes, stroke history, mild stroke at admission, and those without coronary heart disease (P<0.05). Moderate-to-severe HHcy was associated with elevated AKI risk compared with normal Hcy in females, patients with hypertension or diabetes, those with moderate or moderate-to-severe stroke at admission, and those with LAA, SAO, or CE stroke subtypes, regardless of age, coronary heart disease status, or stroke history (P<0.05). Restricted cubic spline analysis demonstrated a non-linear, convex-shaped relationship between Hcy and AKI risk (P=0.026). When admission Hcy was <17 mmol/L, AKI risk increased rapidly with rising Hcy; when Hcy $ $17 mmol/L, the risk increased more slowly.

Conclusion: Elevated Hcy is a risk factor for AKI in AIS patients whether analyzed as a continuous or categorical variable. Monitoring Hcy levels may facilitate early identification and prevention of AKI, thereby improving patient outcomes.

Keywords: Ischemic stroke; Homocysteine; Acute kidney injury; Logistic regression; Restricted cubic spline

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Introduction

Acute ischemic stroke (AIS) is the second leading cause of death globally after coronary heart disease and represents a major source of disability and reduced life expectancy, imposing substantial economic burdens on families and society. The brain and kidneys share similar physiological characteristics in anatomy, vascular regulation, and hemodynamics, interacting through central autonomic neural networks, sympathetic nervous systems, and inflammatory-immune responses. Acute kidney injury (AKI) constitutes a serious yet often overlooked and underestimated complication of AIS, with approximately 11.60% of ischemic stroke patients developing AKI, which increases the risk of both short-term and long-term adverse outcomes. Therefore, identifying and controlling risk factors for post-AIS AKI is crucial for improving prognosis.

Homocysteine (Hcy) is a naturally occurring sulfur-containing amino acid derived from methionine and cysteine that plays important roles in various biochemical reactions. Elevated Hcy levels have been established as an independent risk factor for multiple diseases, including stroke, coronary heart disease, and peripheral vascular disease. Research has linked Hcy elevation to glomerular sclerosis and renal interstitial fibrosis, and observational studies in general populations have demonstrated an inverse correlation between plasma Hcy levels and estimated glomerular filtration rate. The prevalence of hyperhomocysteinemia (HHcy) is significantly higher in patients with chronic kidney disease than in healthy individuals, suggesting Hcy may be an important contributor to renal injury and accelerated renal function decline. However, few studies have examined the relationship between Hcy and AKI, particularly in the AIS population. This study aims to explore the association between plasma Hcy levels and AKI risk in AIS patients to enable early identification of high-risk individuals and provide novel strategies for AKI prevention and treatment.

Methods

1.1 Study Population We included AIS patients admitted to the Department of Neurology at the Second Hospital of Tianjin Medical University between January 2018 and April 2021. Inclusion criteria were: (1) age $ $18 years; (2) diagnosis of acute ischemic stroke according to the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018, confirmed by experienced neurologists through cranial CT/MRI; (3) completion of plasma

Hcy and renal function tests within 2 days of admission; and (4) at least one repeat renal function test within 7 days of admission. Exclusion criteria included: (1) pre-existing chronic renal insufficiency, nephritis, or kidney disease; (2) malignant tumors; (3) psychiatric disorders or severe cognitive impairment; (4) stroke caused by trauma or iatrogenic factors; and (5) substantially incomplete medical records. Based on these criteria, 1,202 AIS patients were selected for the study. The study was approved by the Ethics Committee of the Second Hospital of Tianjin Medical University (KY2015K003), and all participants or their families provided informed consent.

1.2 Methods 1.2.1 Data Collection

Baseline clinical data were collected through the hospital electronic medical record system, including demographic information (name, sex, age, contact details), medical history (hypertension, diabetes, stroke, coronary heart disease, atrial fibrillation), personal history (smoking defined as current/former use of $ $1 cigarette daily for $ $6 months; alcohol consumption defined as $ $1 drink weekly for $ $1 year), admission NIHSS score, ischemic stroke TOAST classification, and laboratory parameters. Laboratory tests required fasting venous blood samples after at least 6 hours of fasting, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), plasma Hcy, and repeat Cr measurements within 7 days of admission. Serum Cr was measured using the enzyme-linked rate method, and plasma Hcy was determined by enzyme immunoassay.

1.2.2 Diagnostic and Classification Criteria

AKI was diagnosed according to the 2021 KDIGO Clinical Practice Guideline: (1) serum Cr increase >26.5 mol/L (0.3 mg/dl) within 48 hours; (2) serum Cr increase to $ $1.5 times the reference range upper limit known or inferred to have occurred within 7 days; or (3) urine output <0.5 ml/kg/h for >6 hours. Patients were monitored dynamically for renal function and urine output within 7 days of admission and classified into AKI and non-AKI groups based on these criteria.

Hcy levels were analyzed as both continuous and categorical variables. According to the Expert Consensus on the Diagnosis, Treatment, and Prevention of Hyperhomocysteinemia, patients were categorized as: normal Hcy ($ $15 mol/L), mild HHcy (15–30 mol/L), or moderate-to-severe HHcy (>30 mol/L).

1.2.3 Statistical Analysis

Data were analyzed using SPSS 25.0, Stata 15.0, and GraphPad Prism 9.0. Continuous variables were tested for normality using the Shapiro-Wilk method and expressed as mean ± standard deviation ($\bar{x}\pm s$), with group comparisons performed using independent t-tests. Categorical data were expressed as frequencies and percentages, with inter-group comparisons using ^{2} tests. Univari-

ate logistic regression was used to screen variables, with those showing P<0.1 included in multivariate logistic regression analysis. Multivariate logistic regression examined the effect of Hcy on post-AIS AKI as both a continuous and categorical variable. Subgroup analyses stratified patients by age (<60, 60–<75, $ $75 years), sex, hypertension status, diabetes status, coronary heart disease status, stroke history, stroke type, and stroke severity at admission (mild: NIHSS $ $4; moderate: NIHSS 5–<15; moderate-to-severe: NIHSS 15–20; severe: NIHSS $ $21). To explore non-linear relationships, a restricted cubic spline model with four knots (at the 25th, 50th, 75th, and 95th percentiles) was applied based on multivariate logistic regression. A two-sided α level of 0.05 was considered statistically significant.

Results

2.1 General Clinical Data Analysis Among the 1,202 AIS patients, 745 (61.98%) were male and 457 (38.02%) were female, with a mean age of 71.0$±$11.7 years. AKI occurred in 150 patients (12.48%). The cohort included 618 patients with normal Hcy, 459 with mild HHcy, and 125 with moderate-to-severe HHcy. Compared with the non-AKI group, the AKI group had significantly higher admission NIHSS scores (P<0.001) and different stroke type distributions (P<0.05). No significant differences were observed between groups in smoking history or prevalence of hypertension, diabetes, coronary heart disease, stroke history, or atrial fibrillation (P>0.05) .

Laboratory findings showed that the AKI group had significantly higher admission levels of Hcy, BUN, and UA compared with the non-AKI group (P<0.001), while other parameters showed no significant differences (P>0.05) .

2.2 Logistic Regression Analysis of Baseline Hcy Levels and Post-AIS AKI Univariate logistic regression analysis with post-AIS AKI as the dependent variable (1=occurred, 0=did not occur) and all clinical variables as independent factors identified sex, age, alcohol consumption history, stroke type, admission NIHSS score, Hcy, BUN, and UA levels as potential influencing factors (P<0.1) .

Multivariate logistic regression results demonstrated that in Model 1 (unadjusted), each 1 mol/L increase in Hcy significantly increased post-AIS AKI risk (P<0.05). Compared with normal Hcy, both mild and moderate-to-severe HHcy significantly increased AKI risk (P<0.05). Model 2, adjusted for age and sex, showed consistent results, with Hcy remaining a significant predictor as both a continuous and categorical variable (P<0.05). Model 3, adjusted for all variables with P<0.1 in univariate analysis (sex, age, alcohol consumption history, stroke type, admission NIHSS score, Hcy, BUN, and UA), revealed that each 1 mol/L increase in Hcy increased post-AIS AKI risk (P<0.05). As a categorical variable, both mild and moderate-to-severe HHcy were associated with increased AKI risk compared with normal Hcy (P<0.05) .

2.3 Subgroup Analysis Results When Hcy was analyzed as a continuous variable, AKI risk increased with rising Hcy levels in females, patients aged $ $75 years, those with hypertension or diabetes, those with moderate-to-severe stroke at admission, and those with LAA, SAO, or CE stroke subtypes (P<0.05) [Figure 1: see original paper].

When Hcy was analyzed as a categorical variable, mild HHcy was associated with higher AKI risk compared with normal Hcy in males, patients <75 years, those with hypertension, diabetes, stroke history, mild stroke at admission, and those without coronary heart disease (P<0.05) [Figure 2: see original paper]. Moderate-to-severe HHcy was associated with elevated AKI risk compared with normal Hcy in females, patients with hypertension or diabetes, those with moderate or moderate-to-severe stroke at admission, and those with LAA, SAO, or CE stroke subtypes, regardless of age, coronary heart disease status, or stroke history (P<0.05) [Figure 3: see original paper].

2.4 Non-linear Relationship Between Hcy and Post-AIS AKI Restricted cubic spline analysis revealed a non-linear, convex-shaped association between Hcy and AKI risk (P=0.026). When admission Hcy was <17 mmol/L, post-AIS AKI risk increased rapidly with rising Hcy levels. When Hcy $ $17 mmol/L, the risk increased more slowly with further Hcy elevation [Figure 4: see original paper].

Discussion

Hcy is a non-essential sulfur-containing α-amino acid formed from methionine catabolism. Under normal conditions, Hcy is metabolized through the methionine cycle, methylation, and transsulfuration pathways with the assistance of B-complex vitamins, maintaining low physiological concentrations. However, environmental factors, genetic variations, and lifestyle habits can cause Hcy accumulation, leading to HHcy and various health hazards.

Elevated Hcy has been linked to increased risks of cardiovascular and cerebrovascular diseases. A meta-analysis of 10 studies including 10,103 healthy subjects found that Hcy is an independent risk factor for coronary heart disease, with each 5 mol/L increase associated with a 22% increased risk. Wu et al. demonstrated a dose-response relationship between Hcy and stroke risk, with each 1 mol/L increase raising stroke and ischemic stroke risk by 1.06-fold and 1.05-fold, respectively. Furthermore, Hcy plays an important role in acute and chronic kidney injury development. Cohen et al. found that individuals with Hcy $ $15 mol/L had a 7.43-fold higher risk of chronic kidney injury compared with those with normal Hcy levels.

Our findings indicate that Hcy is a risk factor for AKI in AIS patients, whether analyzed as a continuous or categorical variable. As a continuous variable, each 1 mol/L increase in Hcy increased post-AIS AKI risk (OR=1.035). As a categorical variable, mild and moderate-to-severe HHcy were associated with

1.770-fold and 2.927-fold increased AKI risk, respectively, compared with normal Hcy. Early monitoring and intervention of plasma Hcy levels may help prevent AKI, improve outcomes, and reduce healthcare burden.

Notably, Hcy showed more pronounced effects on AKI risk in AIS patients with pre-existing hypertension, diabetes, or stroke history, suggesting Hcy may synergistically enhance the renal damage caused by underlying risk factors. Similar findings were reported by Gao et al., who established HHcy models in hypertensive and non-hypertensive rats, observing that while all HHcy groups showed reduced glomerular filtration rate and renal structural damage, the decline was most severe in hypertensive HHcy rats, indicating that Hcy and hypertension may act synergistically to worsen renal injury. Therefore, patients with chronic underlying diseases require more vigilant Hcy monitoring and intervention to mitigate renal damage and improve survival quality.

The mechanisms linking Hcy elevation to renal injury remain incompletely understood but may involve several pathways: (1) Renal tissue, particularly tubular epithelial cells, has high oxygen consumption and abundant mitochondria. Hcy induces mitochondrial swelling, fragmentation, and dysfunction through mitochondrial damage pathways, promoting renal cell apoptosis and exacerbating kidney injury. (2) Hcy accumulation may inhibit autophagy-mediated renal protection. Zhang et al. found that HHcy reduced expression of transcription factor EB, a key regulator of autophagy-related genes, thereby suppressing autophagy activation and impairing renal clearance of toxic substances. (3) Hcy can inactivate endothelial nitric oxide synthase via protein kinase C-related mechanisms, reducing nitric oxide production, causing endothelial dysfunction, and impairing renal vascular regulation, thereby promoting renal injury. (4) Inflammatory responses and oxidative stress play crucial roles in Hcy-induced renal damage. Elevated Hcy activates nuclear factor- B (NF- B), upregulating pro-inflammatory cytokines while downregulating anti-inflammatory cytokines, causing endothelial dysfunction and renal injury. Additionally, HHcy increases reactive oxygen species production, disrupting oxidative balance and enhancing renal oxidative stress, promoting glomerulosclerosis and tubulointerstitial lesions that lead to AKI. Further research is needed to elucidate these mechanisms to better prevent acute and chronic kidney injury.

This study has several limitations. First, as a single-center retrospective study requiring $ $2 renal function measurements, selection bias may exist. Second, the limited number of patients with moderate and severe HHcy necessitated combining them into a single moderate-to-severe HHcy group, which may affect results. Multi-center, large-sample prospective cohort studies are needed to confirm our findings.

In conclusion, elevated Hcy is a risk factor for AKI in AIS patients, with more pronounced effects in those with chronic underlying diseases. Monitoring Hcy levels may facilitate early AKI identification and prevention, thereby improving patient outcomes.

Author Contributions: WANG Xiaowen, LI Xin, and XIA Xiaoshuang conceived and designed the study and reviewed/edited the manuscript. WANG Xiaowen and XIAO Tongling managed data, performed formal analysis, and wrote the original draft. WANG Xiaowen, WANG Yi, and YANG Ying conducted the investigation. LI Xin acquired funding and provided resources.

Conflict of Interest: The authors declare no conflicts of interest.

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Tables and Figures

Comparison of demographic data between AKI group and non-AKI group

Comparison of baseline laboratory parameters between AKI group and non-AKI group

Univariate Logistic regression analysis of factors associated with AKI after AIS

Multivariate Logistic regression analysis of Hcy (as a continuous variable or a categorical variable) and AKI after AIS

[Figure 1: see original paper] Subgroup analysis of the relationship between Hcy as a continuous variable and AKI after AIS

[Figure 2: see original paper] Subgroup analysis of the relationship between mild HHcy and AKI after AIS using normal Hcy as the reference group

[Figure 3: see original paper] Subgroup analysis of the relationship between moderate-to-severe HHcy and AKI after AIS using normal Hcy as the reference group

[Figure 4: see original paper] Restricted cubic regression of Hcy and AKI risk after AIS

Note: Figure translations are in progress. See original paper for figures.