# Postprint: Relationship Between Homocysteine Levels and Acute Kidney Injury in Patients with Acute Ischemic Stroke

**Authors:** Wang Xiaowen, Xiao Tongling, Wang Yi, Yang Ying, Xia Xiaoshuang, Li Xin, Li Xin

**Date:** 2023-04-03T00:00:00+00:00

## Abstract

Background Acute ischemic stroke (AIS) is the second leading cause of death globally after coronary heart disease. Acute kidney injury (AKI) is one of the more serious complications following AIS. Homocysteine (Hcy) may be an important factor that causes kidney injury and accelerates deterioration of renal function. However, current research on the relationship between Hcy and AKI is scarce, particularly in AIS patients.

Objective To investigate the relationship between Hcy levels and AKI occurrence 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. 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 divided into three categories: 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 dynamically monitored within 7 days of admission. Based on the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) AKI diagnostic criteria, patients were divided into AKI group and non-AKI group according to whether AKI occurred. Multivariate logistic regression analysis was used to investigate the effect of Hcy as both a continuous and categorical variable on AKI occurrence after AIS. Subgroup analysis was used to explore the relationship between Hcy and AKI occurrence after AIS in various subpopulations. Restricted cubic spline model was 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, for each 1 mol/L increase in Hcy, the risk of AKI after AIS increased [OR=1.035, 95%CI (1.019, 1.052), P<0.05]. Using normal Hcy as the reference group, both mild and moderate-to-severe HHcy patients had increased risk of AKI [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 showed that when Hcy was treated as a continuous variable, in AIS patients who were female, aged $ $75 years, had hypertension, had diabetes, had moderate-to-severe stroke at admission, and had stroke types of large artery atherosclerosis (LAA), small artery occlusion (SAA), or cardioembolism (CE), the risk of AKI increased with Hcy levels (P<0.05). When Hcy was treated as a categorical variable, in AIS patients who were male, <75 years, had hypertension, had diabetes, had stroke history, had no coronary heart disease, and had mild stroke at admission, mild HHcy patients had higher risk of AKI than normal Hcy patients (P<0.05). In AIS patients who were female, had hypertension, had diabetes, regardless of age, coronary heart disease status, stroke history, had moderate or moderate-to-severe stroke at admission, and had stroke types of LAA, SAA, or CE, moderate-to-severe HHcy patients had higher risk of AKI than normal Hcy patients (P<0.05). Restricted cubic spline model results showed a non-linear association between Hcy and AKI risk, presenting as an upper convex curve (P=0.026). When admission Hcy $<$ 17 mmol/L, the risk of AKI after AIS increased rapidly with Hcy elevation; when admission Hcy $\geq$ 17 mmol/L, the risk of AKI after AIS increased slowly with Hcy elevation.

Conclusion Hcy is a risk factor for AKI after AIS, both as a continuous and categorical variable. Monitoring Hcy levels helps early identification and prevention of AKI, improving patient prognosis.

## Full Text

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

**WANG Xiaowen, XIAO Tongling, WANG Yi, YANG Ying, XIA Xiaoshuang, LI Xin***

Department of Neurology, the Second Hospital of Tianjin Medical University, Tianjin 300211, China

*Corresponding author: LI Xin, Professor/Doctoral supervisor; E-mail: Jessielx@126.com

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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 injury 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 relationship between plasma Hcy level and AKI occurrence in AIS patients, and to provide new insights for the prevention and treatment of AKI in this population.

**Methods:** We enrolled 1,202 hospitalized 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' s 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 analysis explored the relationship between Hcy and AKI across different subpopulations, and restricted cubic spline modeling was used to investigate potential nonlinear relationships.

**Results:** Among the 1,202 AIS patients, 150 (12.48%) developed AKI. Multivariate logistic regression analysis revealed that after adjusting for confounding variables, each 1 mol/L increase in Hcy was associated with a 1.035-fold increase in AKI risk [OR=1.035, 95%CI (1.019, 1.052), P<0.05]. Compared with the normal Hcy group, 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 Hcy level 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 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). Moderate-to-severe HHcy was associated with higher 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 revealed a nonlinear, 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 $\geq$

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

## Introduction

Acute ischemic stroke (AIS) is the second leading cause of death globally after coronary heart disease [1] and represents a major cause of disability and reduced life expectancy [2], imposing substantial health, economic, and social burdens. The brain and kidneys share similar physiological characteristics in terms of anatomy, vascular regulation, and hemodynamics, and interact through multiple mechanisms including central autonomic neural networks, sympathetic nervous systems, and inflammatory immune responses [3]. Acute kidney injury (AKI) is a serious and often underrecognized complication of AIS, with studies indicating that approximately 11.60% of ischemic stroke patients develop AKI [4], 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 patient prognosis.

Homocysteine (Hcy) is a naturally occurring sulfur-containing amino acid derived from methionine and cysteine that plays important roles in various biochemical reactions [5]. Elevated Hcy levels have been established as an independent risk factor for multiple diseases, including stroke, coronary heart disease, and peripheral vascular disease [6]. Research has demonstrated that Hcy elevation is associated with glomerulosclerosis and renal interstitial fibrosis [7], and population studies have observed an inverse correlation between plasma Hcy levels and estimated glomerular filtration rate, with hyperhomocysteinemia (HHcy) prevalence significantly higher in chronic kidney disease patients than in healthy individuals [8]. Hcy may thus be an important contributor to renal injury and accelerated renal function decline. However, research on the relationship between Hcy and AKI remains limited, particularly in AIS patients. This study aims to explore the association between plasma Hcy level and AKI risk in AIS patients to facilitate early identification of high-risk individuals and provide novel strategies for AKI prevention and management in this population.

## Methods

**Study Population** We included hospitalized 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 the Diagnosis and Treatment of Acute Ischemic Stroke 2018 [9], 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 or examination data. 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 informed consent was obtained from all participants or their families.

**Data Collection and Definitions** Baseline clinical data were collected from the hospital' s electronic medical record system, including demographic information (name, sex, age, contact details), medical history (hypertension, diabetes, stroke, coronary heart disease, atrial fibrillation), lifestyle factors (smoking defined as current/former use of $ $1 cigarette daily for $ $6 months; alcohol consumption defined as $ $1 drink per week for $ $1 year), admission NIHSS score, ischemic stroke TOAST classification, and laboratory results. 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. Serum Cr was measured using the enzyme-linked rate method, and plasma Hcy was measured by enzyme immunoassay.

**Diagnostic Criteria** AKI was diagnosed according to the 2021 KDIGO Clinical Practice Guideline [10] based on any of the following criteria: (1) increase in serum Cr >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 presumed to have occurred within 7 days; or (3) urine output $< 0.5 ml \cdot kg^{\{-1\} \cdot h}\{-1\}$ for >6 hours. Patients were monitored for renal function and urine output changes within 7 days of admission and classified into AKI and non-AKI groups.

**Statistical Analysis** Data analysis was performed using SPSS 25.0, Stata 15.0, and GraphPad Prism 9.0. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent t-tests. Categorical variables were expressed as frequencies and percentages and compared using $^2$ tests. Variables with P<0.1 in univariate logistic regression analysis were included in multivariate logistic regression analysis. Multivariate logistic regression was used to examine the effect of Hcy on post-AIS AKI, treating Hcy as both a continuous and categorical variable. Subgroup analyses were conducted by stratifying patients according to age (<60,

60–<75, $ $75 years), sex, hypertension status, diabetes status, coronary heart disease status, stroke history, stroke severity at admission (mild: NIHSS $ $4; moderate: NIHSS 5–<15; moderate-to-severe: NIHSS 15–20; severe: NIHSS $ $21), and stroke type to explore the relationship between Hcy and AKI in different subpopulations. To further investigate the nonlinear relationship between Hcy and post-AIS AKI, a restricted cubic spline model with four knots (at the 25th, 50th, 75th, and 95th percentiles) was constructed based on multivariate logistic regression analysis. A two-sided $\alpha$ level of 0.05 was considered statistically significant.

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## Results

**Baseline Clinical Characteristics** 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.AKIoccurredin150patients$(12.48±8.2$vs$.6.0±$6.1, P<0.001). The distribution of stroke subtypes differed significantly between groups (P<0.05). No significant differences were observed in smoking history or prevalence of hypertension, diabetes, coronary heart disease, stroke history, or atrial fibrillation (P>0.05) .

Regarding laboratory parameters, the AKI group had significantly higher admission levels of Hcy (22.61$±11.86$vs$.17.09±9.48$\mu mol/L, P < 0.001$), $BUN$(9.21±5.70$vs$.6.09±2.69$mmol/L, P < 0.001$), $andUA$(378.0±144.3$vs$.330.1±$99.9 mol/L, P<0.001) compared with the non-AKI group. Other laboratory parameters showed no significant between-group differences (P>0.05) .

**Association Between Baseline Hcy Level and Post-AIS AKI** Univariate logistic regression analysis identified sex, age, alcohol consumption history, stroke type, admission NIHSS score, Hcy, BUN, and UA levels as factors associated with post-AIS AKI (P<0.1) .

To explore the relationship between Hcy and post-AIS AKI, Hcy was analyzed as both a continuous and categorical variable. According to the Expert Consensus on the Diagnosis, Treatment, and Prevention of Hyperhomocysteinemia [11], patients were categorized as normal Hcy (Hcy $ $15 mol/L), mild HHcy (Hcy 15–30 mol/L), or moderate-to-severe HHcy (Hcy >30 mol/L).

Multivariate logistic regression results showed that in Model 1 (unadjusted), each 1 mol/L increase in Hcy was associated with increased AKI risk (P<0.05). Compared with normal Hcy, both mild and moderate-to-severe HHcy were associated with increased AKI risk (P<0.05). Model 2, adjusted for age and sex, yielded similar results (P<0.05). Model 3, adjusted for all variables with P<0.1 in univariate analysis (sex, age, alcohol consumption, stroke type, admission NIHSS score, Hcy, BUN, and UA), showed that each 1 mol/L increase in Hcy increased 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) .

**Subgroup Analysis Results** When Hcy was treated as a continuous variable, AKI risk increased with Hcy level 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 higher 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].

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

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## Discussion

Hcy is a non-essential sulfur-containing $\alpha$-amino acid formed by terminal methyl cleavage of methionine [12]. Under normal conditions, Hcy is maintained at low concentrations through resynthesis to methionine or cysteine via the methionine cycle, methylation, and transsulfuration pathways, with assistance from B-complex vitamins [13]. However, environmental factors, genetic variations, and lifestyle habits can cause Hcy accumulation, leading to HHcy and various health hazards [14].

Studies have demonstrated that elevated Hcy is associated with increased risk of cardiovascular and cerebrovascular diseases [15-16]. 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 in Hcy associated with a 22% increase in coronary heart disease risk [17]. Wu et al. [18] identified dose-response relationships between Hcy and stroke risk, with each 1  mol/L increase in Hcy associated with 1.06-fold and 1.05-fold increases in overall stroke and ischemic stroke risk, respectively. Furthermore, Hcy plays an important role in the development and progression of acute and chronic kidney injury. Cohen et al. [19] analyzed 17,010 Israeli subjects and found that those with Hcy

$ $15  mol/L had 7.43 times higher risk of chronic kidney injury compared with those with normal Hcy. Similarly, Gao et al. [20] established HHcy models in hypertensive and non-hypertensive rats, finding that all HHcy models exhibited reduced glomerular filtration rate and renal structural damage, with the most severe changes observed in hypertensive HHcy rats, suggesting that Hcy may synergize with hypertension to exacerbate renal injury.

Our study demonstrates that elevated 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 was associated with increased AKI risk (OR=1.035). As a categorical variable, mild and moderate-to-severe HHcy were associated with increased AKI risk compared with normal Hcy (OR=1.770 and 2.927, respectively). Early monitoring and intervention of plasma Hcy levels may help prevent AKI, improve patient outcomes, and reduce healthcare burden.

The mechanisms linking Hcy elevation to renal injury remain incompletely understood but may include: (1) Mitochondrial damage in renal tubular epithelial cells, which have high oxygen consumption, leading to mitochondrial swelling, fragmentation, and dysfunction that induces and exacerbates renal cell apoptosis [21]; (2) Impaired autophagy, as HHcy downregulates transcription factor EB, a key regulator of autophagy-related genes, reducing renal clearance of toxic substances [22]; (3) Endothelial dysfunction through inactivation of protein kinase C-related endothelial nitric oxide synthase, reducing nitric oxide production and impairing renal arterial vasomotor function [23]; (4) Inflammation and oxidative stress, as HHcy activates nuclear factor- B (NF- B), upregulating pro-inflammatory cytokines and downregulating anti-inflammatory cytokines, while increasing reactive oxygen species production and disrupting redox balance, promoting glomerulosclerosis and tubulointerstitial lesions [24-25]. Further research is needed to elucidate these mechanisms to better prevent acute and chronic kidney injury.

Our 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 required 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 comorbidities. Monitoring Hcy levels may facilitate early identification and prevention of AKI, thereby improving patient prognosis.

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**Author Contributions:** Wang Xiaowen, Li Xin, and Xia Xiaoshuang conceptualized 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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*Received: December 22, 2022; Revised: March 1, 2023*
*Edited by: MAO Yamin*

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