Elevated Total Homocysteine Levels in Acute Ischemic Stroke Are Associated With Long-Term Mortality

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Background and Purpose—Total homocysteine (tHcy) levels are associated with secondary vascular events and mortality after stroke. The aim of this study was to investigate whether tHcy levels in the acute phase of a stroke contribute to the recurrence of cerebro-cardiovascular events and mortality.

Methods—A total of 3799 patients were recruited after hospital admission for acute ischemic stroke. Levels of tHcy were measured within 24 hours after primary admission. Patients were followed for a median of 48 months.

Results—During the follow-up period, 233 (6.1%) patients died. After adjustment for age, smoking status, diabetes mellitus, and other cardiovascular risk factors, patients in the highest tHcy quartile (>18.6 μmol/L) had a 1.61-fold increased risk of death (adjusted hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.03–2.53) compared with patients in the lowest quartile (≤10 μmol/L). Further subgroup analysis showed that this correlation was only significant in the large-artery atherosclerosis stroke subtype (adjusted HR, 1.80; 95% CI, 1.05–3.07); this correlation was not significant in the small-vessel occlusion subtype (adjusted HR, 0.80; 95% CI, 0.30–2.12). The risk of stroke-related mortality was 2.27-fold higher for patients in the third tHcy quartile (adjusted HR, 2.27; 95% CI, 1.06–4.86) and 2.15-fold more likely for patients in the fourth quartile (adjusted HR, 2.15; 95% CI, 1.01–4.63) than for patients in the lowest tHcy quartile. The risk of cardiovascular-related mortality and the risk of recurrent ischemic stroke were not associated with tHcy levels.

Conclusions—Our findings suggest that elevated tHcy levels in the acute phase of an ischemic stroke can predict mortality, especially in stroke patients with the large-vessel atherosclerosis subtype. (***Stroke***. 2015;46:2419-2425. DOI: 10.1161/STROKEAHA.115.009136.)

Key Words: acute ischemic stroke ■ atherosclerosis ■ homocysteine ■ long-term mortality ■ stroke

Worldwide, Asia, Russia, and Eastern Europe experience the highest rates of mortality and disability-adjusted life years lost because of stroke.[1] In China, the incidence of stroke is expected to dramatically increase because of the combination of an aging population and the high prevalence of smoking and hypertension, which are risk factors for stroke.[2] However, conventional vascular risk factors, such as age, hypertension, dyslipidemia, diabetes mellitus, and smoking do not fully explain recurrent stroke and cerebro-cardiovascular mortality rates.[3] Identification of modifiable risk factors may lead to more effective stroke prevention and reduced mortality rates.

Numerous studies have demonstrated that plasma total homocysteine (tHcy) is a strong, graded, and independent risk factor for coronary heart disease and stroke.[4–8] Studies have also demonstrated that elevated tHcy levels are associated with higher mortality rates from stroke and coronary heart disease.[9,10] However, the timing of these tHcy measurements is unclear: some of these studies did not state when tHcy was measured, and in others, tHcy was measured several weeks after a stroke. The time of tHcy measurement is particularly important because plasma concentrations of tHcy can change with lifestyle and dietary modifications. Many patients are motivated to change these habits after a stroke, so examining tHcy levels weeks after a stroke may not be accurate for predicting a patient's risk of mortality and stroke recurrence, especially in the short-term. Furthermore, elevated tHcy levels have been found to cause oxidative stress, endothelial dysfunction, and atherothrombosis.[11] Considering the vulnerability of the penumbra, it may be more appropriate to measure tHcy concentrations in the acute phase of a stroke.

Concentrations of tHcy represent a potentially modifiable risk factor for stroke. Earlier studies have not provided

evidence that B vitamin therapy reduces the risk of stroke or other cardiovascular events, and these studies failed to account for the effects of renal function on response to vitamin therapy. It is now widely recognized that B vitamin therapy reduces tHcy levels, which leads to a reduced risk of stroke. Several studies and meta-analyses, including the HOPE-2 trial, the French SuFolOM3 trial, a subgroup analysis of the Vitamin Intervention for Stroke Prevention trial that excluded patients with renal failure, and a subgroup analysis of the VITATOPS trial that excluded patients on antiplatelet therapy, all showed a reduced risk of stroke. However, in patients with diabetic nephropathy or a glomerular filtration rate <50 mL/min/1.73 m², vitamin B12 supplementation results in cyanide production and is harmful to patients.[12,13]

The relationship between tHcy levels and vascular events and death after stroke remains inconclusive as a result of short follow-up periods[14,15] and small sample sizes[16,17] of many studies. Therefore, we conducted a prospective study of a large stroke population with a median follow-up period of 48 months to investigate whether elevated plasma tHcy levels in the acute phase of an ischemic stroke contribute to the risk of stroke recurrence and all-cause mortality.

Methods

Study Design

All patients admitted into the neurological department at Tianjin Huanhu Hospital in Tianjin, China, from September 2005 to March 2011were assessed for eligibility for the study. Inclusion criteria included first ischemic stroke within 48 hours, which was confirmed by imaging studies of the head (magnetic resonance imaging or computed tomography). Exclusion criteria for this study were (1) age <18 or ≥80 years; (2) death during the hospital admission; (3) nonischemic stroke with a life expectancy <1 year; (4) renal failure; (5) B vitamin or statin therapy within 2 weeks of hospital admission; (6) residence outside the hospital's catchment area; (7) unwillingness to participate; and (8) previous admission resulting in inclusion in the study.

A total of 3799 patients met the inclusion criteria and provided informed consent for participation. Patients were classified into stroke subtypes of large-artery atherosclerosis and small-vessel occlusion according to the Trial of Org 10172 in Acute Stroke Treatment criteria.[18] The primary outcome measure was all-cause mortality and the median follow-up time was 48 months. Confirmation of survival and dates of death were obtained from the official population registry. Eleven patients, who emigrated from Tianjin, were lost to follow-up and considered alive at the day of emigration. The secondary outcome was incidence of recurrent ischemic stroke (ICD-9 codes 431, 432, 433, or 436 or ICD-10 codes I61, I62, I63, or I64). Patient comorbidities, such as type 2 diabetes mellitus, hyperlipidemia, and hypertension, were retrieved from patient files and confirmed in patient interviews during the initial hospital admission. The diagnosis of hyperlipidemia was based on the guidelines established by the American Heart Association,[19] and the diagnosis of type 2 diabetes mellitus was based on the guidelines established by the American Diabetes Association.[20] Hypertension was diagnosed as a systolic blood pressure >140 mm Hg.[21] A smoker was defined as an individual who smoked >5 cigarettes per day for at least 2 years, and an alcohol drinker was defined as an individual who drank >1 standard drink (10 g of alcohol) per week for >2 years. A person was considered to have low physical activity if they performed <30 minutes of moderate exercise per day, 5 days per week, for at least 2 years. The Regional Ethics Committee approved the study protocol.

Blood Sample Collection

Blood samples were obtained from all patients within 24 hours of admission, after an overnight fast of 12 to 14 hours. Peripheral venous blood was drawn from the antecubital vein. Blood samples were then placed into plasma separator tubes with K2-EDTA and serum separator tubes for centrifugation. Levels of tHcy, high-sensitivity C-reactive protein (hsCRP), triglycerides, fasting glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, and Apo AI were measured within 2 hours of collection.

Laboratory Measurements

Levels of tHcy and hsCRP were measured using nephelometric technology, which was conducted on a BNII system (SIEMENS, Erlangen, Germany). Fasting glucose was determined by the glucose-oxidase method. Triglycerides were measured using the enzymatic colorimetric method with glycerol phosphate oxidase, and high-density lipoprotein cholesterol and LDL-C were measured using the enzymatic, monophasic, colorimetric method. Apo B and Apo AI were measured using transmission turbidimetry, and the ratio of Apo B/Apo AI was calculated. These biochemical measurements were performed using a commercial kit (Shanghai Hua Chen Inc, Shanghai, China) and ADVIA2400 auto-analyzer (SIEMENS).

Statistical Methods

Categorical variables are reported as proportions and continuous variables are reported as median values or means±standard deviations (SD). The associations between tHcy levels and baseline demographic variables and cerebrovascular risk factors were tested using the Mann–Whitney U test for categorical variables and χ^2 statistics for continuous variables.

Cox proportional hazards regression analyses were used to calculate crude and adjusted hazard ratio (HR) estimates associated with tHcy levels and end points, including mortality from all causes, cardiovascular disease, and ischemic stroke. In the multivariate analyses, we adjusted for potential clinically relevant confounders, including age, sex, smoking status, diabetes mellitus, hypertension, LDL-C, hyperuricemia, coronary artery disease, obesity, and markers of inflammation, such as hsCRP. Statistical significance was defined as a P value <0.05.

Results

Baseline Characteristics

A total of 3799 patients (75.6% male; median age, 62 years; interquartile range, 54–71 years) were included in the study. The tHcy levels of all patients were obtained within 24 hours of admission for ischemic stroke. The mean±SD (range) tHcy level of all patients was 16.9±12.5 (2.13–162) µmol/L. Overall, 2732(71.9%) patients had hypertension, 1150 (30.3%) had diabetes mellitus, 1157 (30.5%) had hyperlipidemia, 712 (18.7%) were alcohol drinkers, 1495 (39.4%) were smokers, 368 (9.7%) had hyperuricemia, 374 (9.8%) were obese, 903 (23.8%) had coronary artery disease, and 412 (10.8%) had low physical activity. The baseline characteristics of the patients, stratified according to tHcy quartiles, are presented in Table 1. Patients with elevated tHcy levels were more likely than patients with low tHcy levels to be older, male, smokers, and alcohol drinkers and have hyperuricemia, large-artery atherosclerosis stroke subtype, elevated LDL-C levels, and elevated ApoB/ApoAI ratios; patients with elevated tHcy levels were less likely to have type 2 diabetes mellitus and high fasting glucose levels.

Mortality and tHcy Levels

During a median follow-up period of 48 months, 233 (6.1%) patients died. The mortality rate was significantly higher in patients in the fourth (highest) tHcy quartile than in patients

Table 1.   Baseline Characteristics of All Patients According to Quartiles of tHcy Levels

	Quartile of Plasma tHcy Levels, μmol/L				
	Q1 (≤10), n=973	Q2 (10–12.9), n=949	Q3 (12.9–18.6), n=932	Q4 (>18.6), n=945	P Value
Age, y, mean (SD)	61.0 (11.0)	62.8 (11.4)	64.3 (11.2)	62.3 (12.1)	<0.001
Male, n (%)	509 (52.3)	604 (63.6)	650 (69.7)	748 (79.2)	<0.001
TOAST subtype:					0.019
Large-artery atherosclerosis, n, (%)	662 (68.0)	664 (70.0)	683 (73.3)	695 (73.5)	
Small-vessel occlusion, n, (%)	311 (32.0)	285 (30.0)	249 (26.7)	250 (26.5)	
Risk factors:					
Hypertension, n (%)	715 (73.5)	664 (70.0)	675 (72.4)	678 (71.7)	0.377
Type 2 DM, n (%)	394 (40.5)	325 (34.2)	233 (25.0)	198 (21.0)	<0.001
Hyperlipidemia, n (%)	274 (28.2)	282 (29.7)	283 (30.4)	318 (33.7)	0.065
CAD	236 (24.3)	240 (25.3)	205 (22.0)	222 (23.5)	0.392
Alcohol drinker, n (%)	170 (17.5)	152 (16.0)	187 (20.1)	203 (21.5)	0.010
Smoking, n (%)	319 (32.8)	373 (39.3)	369 (39.6)	434 (45.9)	<0.001
Hyperuricemia n (%)	59 (6.1)	69 (7.3)	117 (12.5)	143 (15.1)	<0.001
Low physical activity, n (%)	105 (10.8)	95 (10.0)	122 (13.1)	90 (9.5)	0.064
Obesity	109 (11.2)	81 (8.5)	94 (10.1)	90 (9.5)	0.259
Laboratory findings*					
TG, mmol/L	1.68	1.65	1.63	1.72	0.644
HDL-C, mmol/L	1.06	1.03	1.06	1.05	0.053
LDL-C, mmol/L	3.07	3.05	3.13	3.15	0.036
Apo AI, g/L	1.51	1.56	1.15	1.57	0.808
ApoB, g/L	1.12	1.02	1.04	1.02	0.513
ApoB/ApoAI ratio	0.89	0.93	0.94	0.94	<0.001
Fasting glucose, mmol/L	6.85	6.52	6.0	5.8	<0.001
hsCRP, mg/L	2.00	1.88	2.11	2.50	0.264
Heart rate times/min*	72	70	72	72	0.102

Apo indicates apolipoprotein; CAD, coronary artery disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; and tHcy, total homocysteine.

*Median values.

in the first (lowest) quartile (unadjusted HR, 1.95; 95% confidence interval [CI], 1.28–2.97; P=0.002). Similarly, the mortality rate was significantly higher in patients in the third quartile than in patients in the first quartile (unadjusted HR, 1.83; 95% CI, 1.18–2.82; P=0.006). This association remained significant for patients in the fourth quartile compared with patients in the first quartile after adjustment for age, smoking status, LDL-C level, hsCRP level, and ApoB/ApoAI ratio and the presence of hypertension, type 2 diabetes mellitus, hyperuricemia, coronary artery disease, and obesity (adjusted HR, 1.61; 95% CI, 1.03–2.53; P=0.039; Table 2).

In the subgroup analysis, patients with the large-artery atherosclerosis stroke subtype in the highest tHcy quartile had a significantly higher risk of mortality than patients in the lowest quartile (unadjusted HR, 1.97; 95% CI, 1.20–3.22; P=0.007). This association was not significant for the small-vessel occlusion subgroup (unadjusted HR, 1.45; 95% CI, 0.61–3.44; P=0.404). Multivariate analysis did not affect this association (Table 2).

Recurrent Ischemic Stroke and tHcy Levels
The risk of recurrent ischemic stroke was not significantly increased in patients with elevated tHcy levels (Table 2).

Causes of Mortality
During the follow-up period, 233 deaths occurred: 95 were caused by ischemic stroke, 39 were caused by cardiovascular disease, and 99 were caused by other causes. Among patients who died of stroke, the mortality rate was significantly higher in patients in the fourth quartile of tHcy levels than in patients in the first quartile (unadjusted HR, 2.41; 95% CI, 1.19–4.90; P=0.015). Similarly, the mortality rate was significantly higher in patients in the third quartile than in patients in the first quartile (unadjusted HR, 2.45; 95% CI, 1.19–5.03; P=0.015). After adjustment for confounders, the association remained significant for patients in the third tHcy quartile and was borderline significant for patients in the fourth quartile compared with patients in the first quartile (adjusted HR, 2.27; 95% CI, 1.06–4.86; P=0.029 and adjusted HR, 2.15; 95% CI, 1.01–4.63; P=0.049, respectively; Table 3).

Among patients who died of cardiovascular disease, the mortality rate was significantly higher in patients in the fourth quartile of tHcy levels than in patients in the first quartile (unadjusted HR, 3.29; 95% CI, 1.11–9.74; P=0.031). This association was not significant after adjustment for confounding variables.

Table 2.   Associations of tHcy Level Quartiles With Mortality and Recurrent Ischemic Stroke

Variables	Quartile of Plasma tHcy Levels			
	Q1	Q2	Q3	Q4
Recurrent ischemic stroke, n (N)	107 (973)	130 (949)	141 (932)	164 (945)
Crude HR (95% CI)	1	1.20 (0.94–1.61)	1.06 (0.81–1.40)	1.08 (0.82–1.41)
Adjusted HR (95% CI)*	1	1.23 (0.95–1.61)	1.10 (0.84–1.43)	1.10 (0.85–1.43)
Mortality, n (N)	30(973)	48 (949)	67 (932)	88 (945)
Crude HR (95% CI)	1	1.57 (0.99–2.48)	1.83 (1.18–2.82)†	1.95 (1.28–2.97)†
Adjusted HR (95% CI)	1	1.25 (0.77–2.03)	1.46 (0.92–2.30)	1.61 (1.03–2.53)†
Subgroup analysis for mortality:				
Large-arteryatherosclerosis, n (N)	21 (662)	37 (664)	49 (683)	76 (695)
Crude HR (95% CI)	1	1.63 (0.95–2.78)	1.64 (0.98–2.74)	1.97 (1.20–3.22)†
Adjusted HR (95% CI)	1	1.41 (0.80–2.50)	1.37 (0.79–2.37)	1.80 (1.05–3.07)†
Small-vessel occlusion, n (N)	9 (311)	11 (285)	18 (249)	12 (250)
Crude HR (95% CI)	1	1.35 (0.56–3.26)	2.21 (0.99–4.94)	1.45 (0.61–3.44)
Adjusted HR (95% CI)	1	0.81 (0.31–2.13)	1.62 (0.71–3.72)	0.80 (0.30–2.12)

CI indicates confidence interval; HR, hazard ratio; and tHcy, total homocysteine.

*Adjusted for age, smoking status, low-density lipoprotein cholesterol level, high-sensitivity C-reactive protein level, Apolipoprotein B/Apoliprotein AI ratio, and the presence of hypertension, type 2 diabetes mellitus, hyperuricemia, coronary artery disease, and obesity.

†$P<0.05$ compared with Q1.

Discussion

Our results demonstrate that elevated tHcy levels during the acute phase of an ischemic stroke significantly predict mortality in Chinese patients. Patients in the third and fourth quartiles of tHcy levels had a 1.83-fold or higher increased risk of death 48 months after stroke compared with patients in the first quartile. After multivariate analysis, this association in the highest (fourth) quartile remained statistically significant. Subgroup analysis showed that the association between tHcy levels and all-cause mortality was only significant in patients with the large-artery atherosclerosis stroke subtype; the association was not significant in the small-vessel stroke subtype. Examination of the causes of mortality revealed that patients in the 2 highest quartiles of tHcy levels had a 2.15-fold or higher increased risk of mortality from ischemic stroke compared with patients in the lower quartiles. These findings suggest that quantifying tHcy levels in patients with acute, ischemic, large-vessel stroke may help to determine a patient's prognosis and, thus, initiate methods to improve survival.

To the best of our knowledge, these are the first published results demonstrating that elevated tHcy levels during the first 24 hours after admission for an acute stroke significantly predict mortality within 48 months. Previous studies have only examined tHcy levels that were measured at least months before or after the first stroke.[9,10,22,23] For the present study, we obtained plasma samples for tHcy measurements during the admission for acute stroke. In previous studies, blood levels of lipid were affected by furosemide therapy or dehydration.[24,25] Therefore, plasma tHcy may also be affected by hemodilution in the recumbent position or the effects of dehydration. However, we obtained blood samples from all patients in the morning, after an overnight fast of 12 to 14 hours without fluid restriction. None of the patients were receiving furosemide therapy, and the patients who had dehydration before

Table 3.   Associations Between tHcy Levels and Causes of Mortality in 233 Patients Who Died During the Follow-up Period

Cause of death	Quartile of plasma tHcy levels			
	Q1	Q2	Q3	Q4
Initial ischemic stroke (n)	10	19	30	36
Crude HR (95% CI)	1	1.87 (0.87–4.020)	2.45 (1.19–5.03)*	2.41 (1.19–4.90)*
Adjusted HR (95% CI)		1.69 (0.75–3.80)	2.27 (1.06–4.86)*	2.15 (1.01–4.63)*
CVD (n)	4	8	6	21
Crude HR (95% CI)	1	1.93 (0.58–6.427)	1.18 (0.33–4.22)	3.29 (1.11–9.74)*
Adjusted HR (95% CI)	1	1.31 (0.37–4.69)	0.64 (0.5–2.60)	2.56 (0.82–8.04)
Other causes (n)	16	21	31	31
Crude HR (95% CI)	1	1.29 (0.67–2.47)	1.61 (0.876–2.96)	1.31 (0.71–2.42)
Adjusted HR (95% CI)	1	0.96(0.48–1.94)	1.19 (0.63–2.26)	1.02 (0.53–1.98)

CI indicates confidence interval; CVD, cardiovascular disease; HR, hazard ratio; and tHcy, total homocysteine.

*$P<0.05$ compared with Q1.

admission were given fluid and salt replacement. Therefore, dehydration may not have affected the results. Still, our results are almost identical to a previous study that reported that elevated tHcy levels 6 weeks after a stroke increased all-cause mortality by 1.75-fold when patients in the highest and lowest quartiles of tHcy levels were compared.[22] Naess et al[23] measured tHcy on an average of 6 years after primary stroke and found a smaller, though significant, HR for mortality of 1.02 (*P*=0.02). These findings indicate that tHcy levels are better predictors of mortality if measured before or within 6 weeks after the first stroke.

It is well established that tHcy increases the risk of developing large and small vessel strokes,[8,26,27] but our study is the first to demonstrate that the association between tHcy levels and all-cause mortality is only significant in the large-vessel atherosclerosis stroke subtype and is not significant in the small-vessel occlusion subtype. These findings suggest that either (1) elevated tHcy levels in the acute phase of a stroke may be more detrimental in large-vessel strokes compared with small-vessel strokes or (2) tHcy levels increase in large-vessel strokes, but tHcy levels remain stable in serious and minor small-vessel strokes. Taken together, elevated tHcy may be a useful prognostic marker for large-artery atherosclerosis stroke subtypes.

In this study, we aimed to evaluate whether the relationship between tHcy levels and all-cause mortality is confounded by other risk factors. The univariate HR of mortality from ischemic stroke was significantly higher in patients in the third and fourth quartiles of tHcy levels than in patients in the first quartile. After adjustment for confounding factors including age, sex, smoking status, LDL-C level, and glucose level, the presence of diabetes mellitus, hypertension, hyperuricemia, coronary artery disease, and obesity and markers of inflammation, such as hsCRP, the association remained significant. This indicates that high tHcy levels are an independent risk factor for increased mortality from ischemic stroke. Cui et al[10] also reported that patients in the highest tHcy quartile had a significantly increased risk of mortality from ischemic stroke (adjusted odds ratio, 4.35; 95% CI, 1.12–16.9) compared with patients in the lowest quartile.

However, a vital question still remains: do elevated plasma tHcy levels cause more serious strokes or do more serious strokes result in higher tHcy levels? Both scenarios are likely true. Studies have found that elevated tHcy levels induce oxidative injury to vascular endothelial cells and impair the production of nitric oxide, an effective vasodilator, from the endothelium.[28,29] This results in higher arterial pressure, which increases the risk of stroke and can worsen a stroke that has already happened.[30] Elevated tHcyalso enhances platelet adhesion to endothelial cells,[31] promotes the growth of vascular smooth muscle cells,[32] and is associated with higher levels of prothrombotic factors, such as [beta]-thromboglobulin, tissue plasminogen activator, and factor VIIc.[33] These mechanisms increase the risk of developing an ischemic stroke and are likely detrimental to the vulnerable penumbra. However, Perini et al[34] observed no association between plasma tHcy and stroke severity, suggesting that elevated tHcy is not a cause of stroke and not associated with stroke severity. Future prospective studies examining the risk of stroke and the changes

in tHcy levels before and after stroke are necessary to clarify these associations.

Concentrations of tHcy represent a modifiable risk factor for stroke, so an understanding of the prognostic impact of tHcy levels is clinically relevant. Therapy to lower tHcy levels with B vitamins has been found to reduce the risk of stroke, as well as the risk of myocardial infarction, in several recent trials and meta-analyses. The lack of efficacy of vitamin therapy reported in most large clinical trials is likely because of the failure to consider the metabolic deficiency of vitamin B12 and the influence of impaired renal function. Metabolic B12 deficiency is present in 30% of vascular patients over the age of 70 years, and higher doses of vitamin B12 are needed in elderly patients than in younger patients. However, high doses of cyanocobalamin increase cyanide levels in patients with renal failure. Therefore, B vitamin therapy is beneficial for patients with adequate renal function but detrimental for those with a glomerular filtration rate <50 mL/min/1.73 m².[13,14]

Dolichocarotids are geometric abnormalities of the internal carotid artery characterized by atypical elongation, angulations, and undulations. The clinical role of dolichocarotids is currently unclear, and studies have denied an association between these carotid abnormalities and cerebrovascular events. One study found kinking to be more frequently associated with cardiovascular death than tortuosity,[35] and another study showed that dolichocarotids are associated with dilated cardiomyopathy.[36] However, only a small proportion of patients (2% to 6%) have dolichocarotids and, in our study, we did not consider dolichocarotids as a confounding factor associated with cardiovascular-related mortality. Future studies are needed to assess the correlation between dolichocarotids and tHcy levels.

Our study has numerous strengths, including the large number of strokes confirmed by imaging studies and the analysis of serum tHcy within 24 hours of hospital admission. However, this study also has limitations that need to be considered when interpreting the results. First, the follow-up period was only 48 months. However, a previous prospective study with a follow-up period of 4.5 years reported nearly identical all-cause mortality rates when comparing patients in the highest and lowest quartiles of tHcy levels.[22] Second, there was no control group in this study. An appropriate control group would include patients who had their first ischemic stroke 6 months previously and were matched for age, sex, and cardiovascular risk factors to the patients in this study. This would clarify if measuring tHcy within 24 hours of a stroke has more prognostic value for stroke recurrence and mortality than measuring tHcy 6 months after a stroke. Third, patients' medications at the time of admission were not recorded in this study. Future studies should assess the associations between numerous medications, such as antihypertensives, aspirin, statins, and β-blockers, and the risk of cerebrovascular events and mortality. However, compliance with these medications and medication dose and duration varies among patients, and this study measured the biological impact of such medications by measuring serum cholesterol and fasting glucose levels. Future studies should also measure variability in heart rate, which may have affected cardiovascular mortality.[37,38] Fourth, the initial severity of stroke in the acute phase was

not measured. This would have been interesting to determine to observe whether elevated tHcy levels were associated with more serious strokes and, thus, a higher mortality rate or if tHcy was independent of the severity of the stroke. All patients who died from ischemic stroke in the first hospital admission were excluded from our study. Future prospective studies are needed to define the relationships between tHcy levels and stroke severity.

In conclusion, we observed that elevated plasma tHcy levels in the acute phase of an ischemic stroke are a strong predictor of mortality in patients with the large-artery atherosclerosis stroke subtype. There is a strong, independent association between elevated tHcy levels and the risk of mortality from ischemic stroke.

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Disclosures

None.

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