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ORIGINAL RESEARCH

Association of Homocysteine with Acute Stroke and Its Subtypes in the Chinese Population

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Purpose: Homocysteine (Hcy) is recognized as a risk factor for stroke. Our study examined the relationship between plasma Hcy levels and stroke, along with its subtypes, among Chinese patients who experienced an acute stroke episode.

Patients and Methods: We retrospectively enrolled patients with acute stroke and age- and sex-matched healthy controls admitted to the First Affiliated Hospital of Xi'an Jiaotong University from October 2021 to September 2022. Ischemic stroke subtypes were classified using the modified TOAST criteria. Multivariate logistic regression models were employed to probe the associations of plasma Hcy levels with total stroke, ischemic stroke and its subtypes, and hypertensive intracerebral hemorrhage (HICH), and the correlation between plasma Hcy levels and the National Institute of Health Stroke Scale (NIHSS).

Results: The mean age of the total group was 63 years, with women representing 30.6% (246 individuals). Elevated Hcy levels were significantly associated with total stroke (OR 1.054, 95% CI: 1.038–1.070), HICH (OR 1.040, 95% CI: 1.020–1.060), ischemic stroke (OR 1.049, 95% CI: 1.034–1.065), and the TOAST subtypes of ischemic stroke in large-artery atherosclerosis (LAA) (OR 1.044, 95% CI: 1.028–1.062) and small-artery occlusion (SAO) (OR 1.035, 95% CI: 1.018–1.052), but not with cardioembolic (CE) stroke. Moreover, only in the case of SAO stroke were the Hcy levels positively correlated with the NIHSS score (B=0.030, 95% CI: 0.003–0.056, P=0.030).

Conclusion: Plasma Hcy levels were found to be positively correlated with the risk of stroke, particularly in the context of LAA, SAO stroke, and HICH. Additionally, Hcy levels demonstrated a positive correlation with stroke severity in patients presenting with SAO stroke. These findings suggest potential clinical implications in stroke prevention, particularly for ischemic stroke (LAA, SAO subtypes) and HICH by employing homocysteine-lowering therapies. Future investigations are warranted to fully elucidate these associations.

Keywords: homocysteine, ischemic stroke, hypertensive intracerebral hemorrhage, TOAST, NIHSS

Introduction

Stroke represents the second leading cause of disability and mortality globally, and it holds the grim distinction of being the leading cause of mortality in China.[1,2] In 2019, China reported 24.18 million cases of ischemic stroke and 4.36 million cases of hemorrhagic stroke in China.[3] Additionally, approximately 3.4 million new stroke cases and 2.3 million stroke-related deaths in 2020 among adults aged 40 years and older in China.[4] According to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria,[5] ischemic strokes can be classified into categories as large-artery atherosclerosis (LAA), small-artery occlusion (SAO), cardioembolic (CE), strokes of other determined etiology (SOE), and strokes of undetermined etiology (SUE). Given the limited effective treatments for stroke, the emphasis should be on prevention via early detection and proactive management of modifiable risk factors.

Elevated plasma homocysteine (Hcy) serves as one of the most readily modifiable risk factors for stroke and is typically linked to a deficiency of folate, vitamin B6, and vitamin B12.[6] Hcy, a sulfur-containing amino acid emerges in response to vascular structure damage caused by oxidative stress and inflammation. This can promote the formation of atherosclerosis and the rupture of atherosclerotic plaques, thereby amplifying the risk of stroke.[7] Elevated plasma Hcy levels have a substantial and direct effect on stroke severity and outcomes.[8] Additionally, studies have demonstrated

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a reduced stroke risk associated with lowered plasma Hcy levels.[9–12] Hcy levels show varied associations with different types of stroke;[13,14] due to the diverse underlying mechanisms of stroke's vascular diseases.

Hcy may assume distinct roles in hypertensive arteriosclerosis-related small vessel disease (lacunar stroke) and in atherosclerosis-related macrovascular disease (large infarctions).[15] Research examining the association between Hcy and stroke subtypes remains inconclusive.[11,16,17] Certain studies suggest an association solely between Hcy and SAO,[18] while others point towards a stronger association with LAA than SAO,[19] and yet others propose that Hcy is associated with all subtypes of ischemic stroke.[16] Differing perspectives also exist on whether Hcy is associated with hemorrhagic stroke.[20,21] However, only a few studies in the Chinese population have explored the relationship of plasma Hcy levels with stroke and its subtypes,[16,22–25] leaving these associations yet to be conclusively determined. Moreover, the correlation between Hcy and the severity of acute stroke remains tenuous and contentious.[18,26,27]

Our study seeks to investigate the relationship between plasma Hcy levels and total stroke, ischemic stroke and its TOAST subtypes, hypertensive intracerebral hemorrhage (HICH), and stroke severity in the Chinese population.

Materials and Methods

Study Population

This study retrospectively enrolled acute stroke patients and age- and sex-matched healthy controls, who were admitted to the First Affiliated Hospital of Xi'an Jiaotong University from October 2021 to September 2022. The study consisted of 335 acute stroke patients (including 293 ischemic stroke patients and 42 HICH patients) over 18 years old, all within 7 days of their initial stroke, along with 470 age- and sex-matched healthy controls (Figure 1). All cases adhered to the stroke diagnostic criteria set forth by the American Stroke Association.[28,29] Ischemic stroke patients were further classified according to the modified TOAST criteria.[5] Among patients with acute ischemic stroke, we focused on the LAA, SAO, and CE subtypes. HICH was characterized as deep or infratentorial hemorrhage in individuals with a history

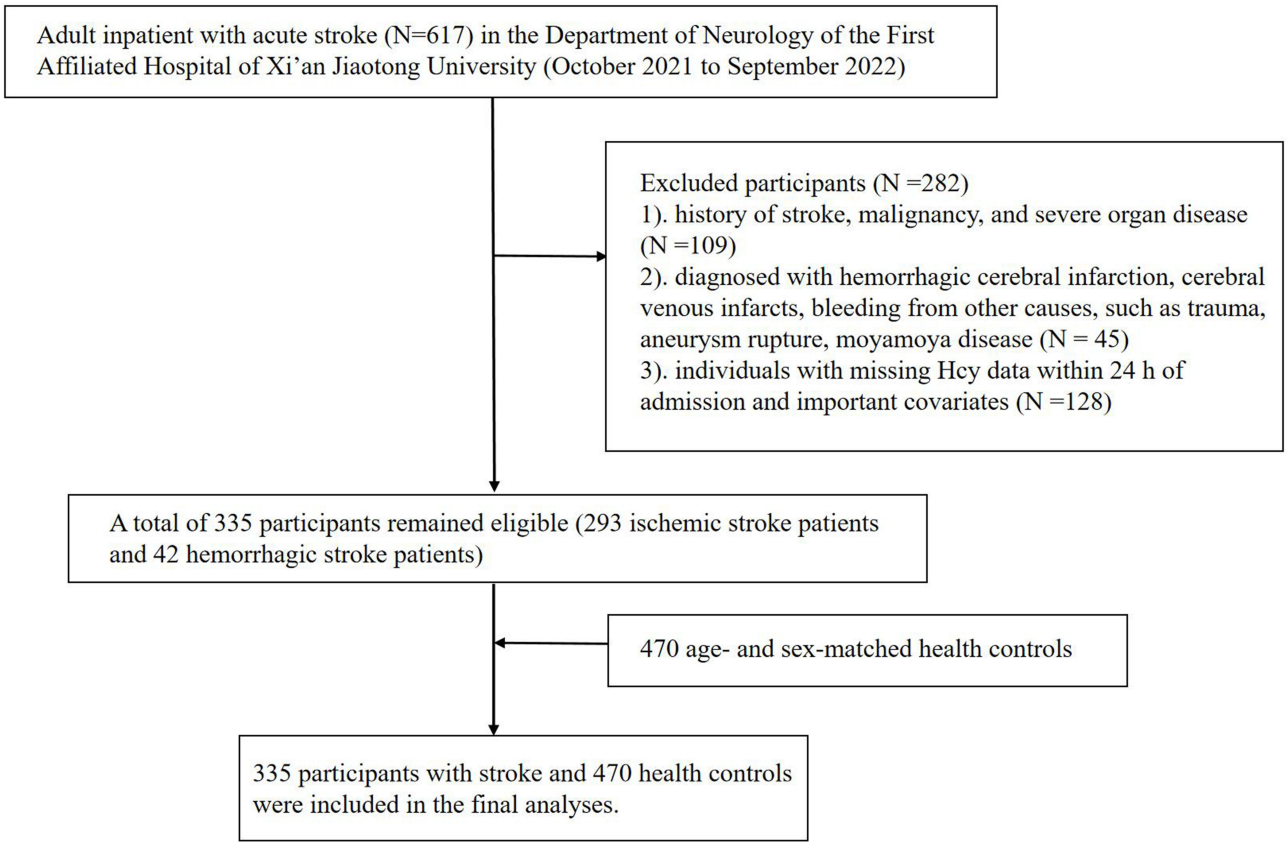

Figure 1 Flowchart of the participants.

of hypertension.[30] The study, aligned with the principles of the Declaration of Helsinki, was approved by the Ethics Committee for Medical Research at the First Affiliated Hospital of Xi'an Jiaotong University. Due to the retrospective design and the absence of study-related interventions, written informed consent was waived and all data were collected anonymously.

Exclusion Criteria

The exclusion criteria were a history of stroke, cerebral venous infarcts, head trauma, or malignancy; complications due to severe hepatic and renal insufficiency; severe immune, hematologic, or cardiovascular system diseases; and bleeding arising from secondary hemorrhagic stroke or other causes, such as trauma, aneurysm rupture, and moyamoya disease.

General Materials and Determination of Hematological Parameters

Baseline demographic data including age (years), sex (female vs male), body mass index (BMI), and traditional cardiovascular risk factors encompassing serum lipid parameters (total cholesterol [TC], triglyceride [TG], low-density lipoprotein [LDL], and high-density lipoprotein [HDL]), alongside medical history of hyperuricemia, hypertension, diabetes mellitus (DM), atrial fibrillation, and coronary heart disease (CHD) were gathered.

Hyperhomocysteinemia (Hhcy) was defined as plasma Hcy levels of ≥15.0 μmol/L. Hypertension was classified as an average systolic blood pressure /average diastolic blood pressure of ≥140/90 mmHg, utilization of antihypertensive medications, or prior diagnosis by a physician. H-type hypertension was identified as hypertension co-existing with plasma Hcy ≥15.0 μmol/L. A self-reported diagnosis formed the basis for identifying a history of diabetes. Furthermore, participants not reporting a diabetes diagnosis but having a fasting HbA1c greater than 6.4% were also categorized as diabetic. Self-reported diagnosis served as the determinant for CHD. We used the National Institutes of Health Stroke Scale (NIHSS) score to evaluate neurological deficits in stroke patients at admission. Fasting venous blood collected within 24 hours of admission, was used to measure plasma total Hcy concentration via a fluorescence polarization immunoassay reagent kit (Abbott Laboratories. Abbott Park, Illinois, USA).

Statistical Analysis

Study participants' descriptive data were reported as means (standard deviation) or medians (interquartile ranges) for continuous variables and as percentages for categorical variables. Continuous and categorical variables were compared using one-way analysis of variance and chi-square tests, respectively. We conducted multivariate logistic regression analyses to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for stroke and its subtypes in relation to Hcy levels. Linear regression analyses were undertaken to ascertain the B-value and 95% CIs of the NIHSS scores in relation to Hcy levels. Considering the significant influence of age as a risk factor for stroke, all logistic regression analyses were adjusted for age (age-adjusted model). The multivariate-adjusted model included additional adjustments for sex, BMI, TG, LDL, and medical history of hypertension, hyperuricemia, AF, and DM. All statistical analyses were conducted using SPSS 25.0 (SPSS Inc., Chicago, USA), with a P-value of <0.05 in a two-tailed test signifying statistical significance.

Results

Characteristics of the Study Population

We evaluated a total of 805 participants, consisting of 335 acute stroke patients and 470 healthy controls. The average age across participants was 63 years, and 30.6% (246/805) were female. LAA accounted for 37% (124/335) of the stroke cases, SAO for 30.7% (103/335), CE for 19.7% (66/335), and HICH for 12.5% (42/335).

Table 1 delineates the baseline characteristics of the study population. Compared to non-stroke, individuals with stroke exhibited higher plasma Hcy levels and lower levels of TC, TG, LDL, and HDL. They were more likely to have a history of hypertension, AF, CHD, and DM, but less likely to have hyperuricemia. Additionally, they had higher percentage of Hhcy and HHYP. BMI showed no significant differences between groups.

Homocysteine Concentration by Stroke Subtype

As displayed in Table 2, plasma Hcy concentrations did not significantly differ among patients with LAA, SAO, and CE stroke subtypes. However, patients with HICH showed the highest plasma Hcy concentration among all stroke classifications, significantly diverging from that of CE stroke.

Associations Between Hcy and Stroke Subtypes

Multivariate logistic regression analysis results are presented in Table 3. A positive association was observed between plasma Hcy concentration and stroke incidence. The age-adjusted OR (95% CI) of total stroke was 1.046 (1.033–1.059). After further adjustment for sex, BMI, TG, LDL, and medical history of hypertension, hyperuricemia, AF, and DM, the OR (95% CI) of total stroke was 1.054 (1.038–1.070). However, this value differed across stroke subtypes. Hcy levels were significantly associated with ischemic stroke (OR 1.049, 95% CI: 1.034–1.065) and the LAA (OR 1.044, 95% CI: 1.028–1.062) and SAO subtypes (OR 1.035, 95% CI: 1.018–1.052). Elevated Hcy levels was also demonstrated significant association with HICH (OR 1.040, 95% CI: 1.020–1.060). However, there was no significant association between Hcy levels and CE stroke (OR 1.017, 95% CI: 0.994–1.041).

Associations Between Hcy and the NIHSS Score

Table 4 presents the linear regression analysis results. The plasma Hcy concentration was not significantly associated with the NIHSS score for total stroke (B=0.036, 95% CI: −0.006 to 0.078). Hcy levels were significantly associated with

Table 1 Characteristics of Study Participants

Characteristic	Total (n=805)	No stroke (n=470)	Stroke (n=335)	P-value
Age (y)	63 (54, 71)	62.5 (54, 71)	64 (55, 71)	0.573
Women, n (%)	246 (30.6)	140 (29.8)	106 (31.6)	0.422
Body Mass Index (kg/m^2)	24.2 (22.3, 26.2)	24.1 (22.4, 26.0)	24.2 (22.1, 26.6)	0.865
Plasma Hcy (μmol/L)	15.7 (12.4, 21.4)	14.0 (11.5, 17.3)	19.1 (14.5, 30.1)	<0.001
TC (mmol/L)	4.40 (3.72, 5.12)	4.67 (3.93, 5.35)	4.03 (3.37, 4.70)	<0.001
TG (mmol/L)	1.29 (0.88, 1.80)	1.39 (0.95, 1.85)	1.16 (0.78, 1.71)	<0.001
HDL (mmol/L)	1.15 (0.96, 1.38)	1.26 (1.10, 1.48)	0.98 (0.84, 1.18)	<0.001
LDL (mmol/L)	2.70 (2.10, 3.35)	2.88 (2.31, 3.51)	2.46 (1.85, 3.07)	<0.001
Medical history, n (%)				
Hyperhomocysteinemia	440 (54.7)	197 (41.9)	243 (72.5)	<0.001
Hyperuricemia	139 (17.3)	100 (21.2)	39 (11.6)	<0.001
Diabetes	175 (21.7)	69 (14.6)	106 (31.6)	<0.001
Hypertension	464 (57.6)	188 (40.0)	276 (82.4)	<0.001
H-type hypertension	285 (35.4)	88 (18.7)	197 (58.8)	<0.001
Atrial fibrillation	61 (7.6)	6 (1.3)	55 (16.4)	<0.001
Coronary heart disease	69 (8.6)	17 (0.36)	52 (15.5)	<0.001

Notes: Unless otherwise indicated, numbers are medians (interquartile range).
Abbreviations: Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2 Homocysteine Concentrations in Stroke Patients by Stroke Etiology

	LAA (n=124)	SAO (n=103)	CE (n=66)	HICH (n=42)
Plasma Hcy (μmol/L) (median, IQR)	19.05 (14.60, 31.05)	19.50 (14.15, 29.15)	16.95 (13.70, 24.50)	25.85 (17.90, 34.00)
LAA	–	NS	NS	NS
SAO		–	NS	NS
CE			–	0.012

Abbreviations: LAA, large-artery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolic; HICH, hypertensive intracerebral hemorrhage; NS, not significant; IQR, interquartile range.

Table 3 Adjusted Associations Between Homocysteine and Stroke Subtypes

	Sample Size (n)	Age-Adjusted Model OR (95% CI)	P-value	Multivariable Adjusted Model OR (95% CI)	P-value
No stroke	470	Reference		Reference	
Total stroke	335	1.046 (1.033, 1.059)	<0.001	1.054 (1.038, 1.070)	<0.001
Ischemic stroke	293	1.041 (1.028, 1.054)	<0.001	1.049 (1.034, 1.065)	<0.001
LAA	124	1.038 (1.024, 1.052)	<0.001	1.044 (1.028, 1.062)	<0.001
SAO	103	1.032 (1.018, 1.046)	<0.001	1.035 (1.018, 1.052)	<0.001
CE	66	1.018 (1.003, 1.034)	0.020	1.017 (0.994, 1.041)	0.153
HICH	42	1.032 (1.015, 1.051)	<0.001	1.040 (1.020, 1.060)	<0.001

Notes: Multivariate adjusted model: age, sex, BMI, TG, LDL, hyperuricemia, hypertension, diabetes, and atrial fibrillation.
Abbreviations: LAA, large-artery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolic; HICH, hypertensive intracerebral hemorrhage.

Table 4 Associations Between Homocysteine and NIHSS

	Sample Size (n)	Multivariable Adjusted Model B-value (95% CI)	P-value
Stroke	335	0.036 (−0.006, 0.078)	0.090
Ischemic Stroke	293	0.034 (−0.010, 0.077)	0.127
LAA	124	0.040 (−0.021, 0.102)	0.197
SAO	103	0.030 (0.003, 0.056)	0.030
CE	66	−0.030 (−0.188, 0.128)	0.706
HICH	42	0.035 (−0.166, 0.184)	0.716

Notes: Adjusted for age, sex, BMI, TG, LDL, hyperuricemia, hypertension, diabetes, and atrial fibrillation.
Abbreviations: LAA, large-artery atherosclerosis; SAO, small-artery occlusion; CE, cardioembolic; HICH, hypertensive intracerebral hemorrhage.

the NIHSS score only in SAO stroke (B=0.030, 95% CI: 0.003–0.056). No significant associations were found between Hcy levels and NIHSS scores in ischemic stroke (B=0.034, 95% CI: −0.010 to 0.077), LAA (B=0.040, 95% CI: −0.021 to 0.102), CE (B= −0.030, 95% CI: −0.188 to 0.128), and HICH (B=0.035, 95% CI: −0.166 to 0.184).

Discussion

In this retrospective study, we observed a positive correlation between plasma Hcy levels and total stroke, LAA and SAO subtypes of ischemic stroke, and HICH. However, no significant association was detected between Hcy levels and the CE subtype of ischemic stroke. Moreover, a positive correlation was found between plasma Hcy levels and NIHSS score solely in SAO. These findings could have significant implications for personalized primary prevention of stroke.

Hhcy and H-type hypertension are prevalent among the Chinese population. A nationwide survey conducted in China showed a geographical distribution pattern of Hhcy, with prevalence ranging from 7.9% to 56.8% across different regions. In addition, the occurrence of H-type hypertension was reported as 14.0%.[31] In this study, we observed a similar Hhcy prevalence of 54.7%, while the incidence of H-type hypertension was considerably higher at 35.4%. This disparity may be attributable to the high proportion (41.6%) of stroke patients (335 out of 805) included in our study.

Previous research have suggested a positive association between Hcy levels and the risk of ischemic stroke,[10–12] a connection substantiated by plausible mechanisms of homocysteine-mediated vascular injury.[7] A literature review indicated a 43% increased risk of ischemic stroke when Hcy levels rose to 5 μmol/L.[32] Our findings align with these previous observations, confirming a significant positive association between Hcy levels and ischemic stroke.[11,32]

Our study supports the finding that plasma Hcy levels are positively correlated with LAA and SAO subtypes, but not with the CE subtype of ischemic stroke. Furthermore, we found no significant difference in Hcy concentrations between LAA and SAO strokes. These results mirror those of previous Chinese studies highlighting a strong correlation between

Hcy levels and ischemic stroke, specifically the LAA and SAO subtypes.[15,22,23] However, conflicting results exist regarding the stroke subtype most closely associated with elevated Hcy levels.[14,16,17,22,23] These discrepancies may stem from regional differences, dietary habits, and genetic variations. For instance, the gene mutations associated with Hcy may differ among various populations.[33,34] Moreover, in the Chinese population, hyperhomocysteinemia prevalence and Hcy levels may be more associated with vitamin intake insufficiency,[35] an area warranting further exploration.

Our study did not uncover a significant correlation between Hcy levels and CE stroke. A handful of studies reported a positive correlation;[36,37] however, their sample size for cardiogenic stroke was limited. The etiology of CE stroke is complex, and its causes may differ across regions and populations. Some minor CE strokes may be misclassified due to limitations in detection methods.

Hemorrhagic stroke carries a higher rate of disability and fatality compared to ischemic stroke.[38] Elevated plasma Hcy levels may compromise the integrity of the vessel wall, resulting in increased cerebrovascular fragility through endothelial dysfunction, vascular elasticity damage, and basal layer injury.[38,39] In line with two recent meta-analyses,[9,20] we found a robust positive correlation between Hcy levels and HICH. Two large case-control studies in China corroborate this finding, identifying Hcy as a critical risk factor for hemorrhagic stroke with independent and additive effects.[11,40] However, the association between Hcy levels and hemorrhagic stroke remains unclear, with some studies reporting non-significant results.[21,41] Other research found the association between elevated Hcy levels and hemorrhagic stroke to be dependent on the bleeding site.[42] Furthermore, the effects of differences in race, diet, and other background factors require clarification.[43]

Given the substantial correlation between stroke severity and stroke outcome, we further investigated the association between Hcy levels and the severity of neurological deficits in patients experiencing their first-ever acute stroke. Consistent with previous studies,[18,26] we did not find a significant correlation between Hcy levels and NIHSS scores for total ischemic stroke and HICH. However, a significant positive correlation was observed in the case of SAO stroke. A couple of studies have highlighted a correlation between Hcy levels and severe neurological impairment in LAA stroke.[24,27] Other studies reported a positive association with the severity of SAO stroke,[44,45] but these did not focus on acute stroke patients.

Stroke prevention is paramount in clinical practice. Our study suggests that elevated Hcy levels are positively associated with stroke, especially LAA, SAO, and HICH subtypes. In addition, high Hcy levels were associated with severe neurological deficits in SAO stroke. While our study advances clinical evidence associating Hcy levels with stroke, certain limitations should be considered. Our study was a single-center retrospective study, hence observational by nature, and potentially subject to selection bias (only 30.6% of participants were females). Therefore, some residual confounding factors cannot be entirely ruled out. Moreover, owing to the limited sample size, we were only able to study the association between Hcy levels and HICH, the most prevalent type of hemorrhagic stroke. Lastly, the retrospective nature of this study meant that plasma Hcy levels were recorded only upon admission, without subsequent follow-ups typical in prospective studies. This prevented us from evaluating the impact of various treatments on Hcy concentration. Future studies are necessary to further elucidate these associations.

Conclusions

Plasma Hcy levels are positively correlated with stroke, notably in LAA and SAO subtypes of ischemic stroke as well as HICH. Furthermore, Hcy levels display a positive correlation with the severity of neurological deficits in patients with SAO stroke. These findings underscore the potential benefits of routine Hcy monitoring and personalized Hcy-targeted therapies in stroke prevention. Future prospective and mechanistic studies are required to clarify the causality of these correlations.

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Disclosure

The authors declare that they have no competing interests.

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