Original Article

Hyperhomocysteinemia in Young Adults with Ischemic Stroke: Association with Stroke Etiology

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Abstract

Background: Hyperhomocysteinemia has been implicated in ischemic stroke through endothelial dysfunction, oxidative stress, thrombogenicity, and vascular injury. However, its relationship with specific etiologic subtypes of ischemic stroke in young adults remains incompletely defined. This study evaluated the prevalence of hyperhomocysteinemia and its association with stroke etiology in young adults with first-ever ischemic stroke. **Material and Methods:** In this prospective observational study, 150 consecutive patients aged <50 years with first-ever acute ischemic stroke were enrolled. Demographic characteristics, vascular risk factors, biochemical parameters, and neurovascular and cardiac findings were systematically recorded. Fasting serum total homocysteine, vitamin B12, and folate concentrations were measured. Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Hyperhomocysteinemia was defined as homocysteine >15 µmol/L. Multivariable logistic regression was performed to assess associations with stroke etiology after adjustment for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, vitamin B12, folate, and renal function. **Results:** Hyperhomocysteinemia was present in 61 (40.7%) patients, with a mean homocysteine concentration of 18.6 ± 9.4 µmol/L. Mean concentrations were highest in large-artery atherosclerosis (23.4 ± 10.2 µmol/L), followed by small-vessel occlusion (18.7 ± 7.9), undetermined etiology (17.6 ± 8.6), cardioembolism (14.9 ± 6.3), and other determined etiologies (13.8 ± 5.7; P<0.001). Hyperhomocysteinemia was more frequent in large-artery atherosclerosis than in other etiologic subtypes (60.0% vs 35.0%; P=0.012). After adjustment, hyperhomocysteinemia remained independently associated with large-artery atherosclerosis (adjusted OR, 2.84; 95% CI, 1.31–6.16; P=0.008). Each 5-µmol/L increase in homocysteine was associated with higher odds of large-artery atherosclerosis (adjusted OR, 1.31; 95% CI, 1.08–1.59; P=0.006). **Conclusion:** Hyperhomocysteinemia was common among young adults with ischemic stroke and was independently associated with large-artery atherosclerosis. These findings support an association between elevated homocysteine and the atherosclerotic stroke phenotype in young adults and highlight homocysteine as a potentially relevant metabolic marker for etiologic characterization.

Keywords: Hyperhomocysteinemia, Homocysteine, Ischemic stroke, Young adults, Large-artery atherosclerosis, Stroke etiology, TOAST.

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Introduction

Ischemic stroke in young adults represents an important clinical and public-health problem because cerebrovascular events occurring during the productive years of life can result in substantial long-term disability and socioeconomic consequences.[1-3] Although traditionally considered uncommon in younger populations, the incidence of stroke among young adults has increased in several regions, with conventional vascular risk factors increasingly recognized alongside non-traditional and age-specific causes.[4-6] The etiological spectrum in young adults is also considerably heterogeneous, encompassing large-artery atherosclerosis, cardioembolism, small-vessel occlusion, cervical or cerebral arterial dissection, thrombophilic disorders, inflammatory and other vascular diseases, and strokes of undetermined origin.[7-9] Recent studies indicate that the contribution of large-artery atherosclerosis and small-vessel occlusion increases with advancing age even within young-adult populations, emphasizing the importance of identifying potentially modifiable metabolic and vascular determinants.[11,12]

Homocysteine is a sulfur-containing amino acid involved in methionine metabolism, and elevated circulating total homocysteine has been associated with vascular disease. Hyperhomocysteinemia may promote vascular injury through endothelial dysfunction, oxidative stress, impaired nitric-oxide bioavailability, smooth-muscle proliferation, and prothrombotic effects, providing biologically plausible mechanisms linking elevated homocysteine with cerebrovascular disease,[13-15] Nutritional factors, particularly folate and vitamin B12 status, as well as renal function and genetic determinants, can influence circulating homocysteine concentrations and therefore represent

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important potential confounders when evaluating its vascular associations.[16-18]

Epidemiological evidence supports an association between elevated homocysteine and ischemic stroke. Prospective cohort data have demonstrated a dose-dependent relationship between circulating homocysteine and subsequent stroke risk, while systematic reviews and meta-analyses have consistently reported higher homocysteine concentrations among individuals with ischemic stroke compared with controls.[9,10] However, an elevated homocysteine concentration may not have the same clinical significance across different stroke mechanisms. Young-adult stroke cohorts have demonstrated substantial variation in the distribution of etiological subtypes, with atherosclerotic mechanisms becoming increasingly prominent with age and traditional vascular risk burden.[5,6,19] Nevertheless, evidence specifically examining whether hyperhomocysteinemia is differentially associated with particular ischemic stroke etiologies in young adults remains limited.

Etiological classification is clinically relevant because the underlying mechanism influences diagnostic evaluation, secondary prevention, and assessment of recurrent vascular risk. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) system categorizes ischemic stroke into large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined etiology, and undetermined etiology.[11,20] Determining whether homocysteine concentrations differ systematically across these categories may help clarify whether hyperhomocysteinemia is predominantly associated with an atherosclerotic stroke phenotype or represents a broader marker of cerebrovascular risk.

Therefore, the present study evaluated the prevalence of hyperhomocysteinemia among young adults with first-ever ischemic stroke and investigated its association with specific stroke etiologies classified according to TOAST criteria, while accounting for conventional vascular risk factors, vitamin B12, folate, and renal function.

Materials and Methods

Study Design and Participants: This prospective observational study enrolled 150 consecutive patients aged <50 years with a first-ever acute ischemic stroke. Patients were recruited after presentation to the study center and underwent standardized clinical, biochemical, neuroimaging, vascular, and cardiac evaluation. Patients with previous stroke, intracerebral hemorrhage, age ≥50 years, or inadequate information for etiological classification were excluded. Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki following approval from the institutional ethics committee.

Clinical and Laboratory Assessment: Demographic characteristics, vascular risk factors, smoking status, and relevant clinical findings were systematically recorded. Routine investigations included complete blood count, fasting glucose, lipid profile, serum creatinine, and other clinically indicated investigations. Fasting venous blood samples were obtained for measurement of total serum homocysteine, vitamin B12, and folate using standardized laboratory methods. Hyperhomocysteinemia was defined a priori as a total homocysteine concentration >15 μmol/L. Renal function was assessed using serum creatinine and estimated glomerular filtration rate.

Stroke Evaluation and Etiological Classification: All patients underwent brain imaging with computed tomography and/or magnetic resonance imaging, together with vascular imaging and cardiac evaluation as clinically indicated. Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria into large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined etiology, and undetermined etiology. The etiological classification was based on the complete clinical, neuroimaging, vascular, and cardiac evaluation.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation or median (interquartile range), according to distribution, while categorical variables were presented as frequencies and percentages. Homocysteine concentrations and the prevalence of hyperhomocysteinemia were compared across TOAST subtypes using appropriate parametric or non-parametric tests and χ^2/Fisher's exact tests. Multivariable logistic regression was performed to evaluate the independent association of hyperhomocysteinemia and homocysteine concentration with large-artery atherosclerosis, adjusting for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, vitamin B12, folate, and renal function. Effect estimates were reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided $P<0.05$ was considered statistically significant. Analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Results

[Table 1] summarizes the baseline demographic, clinical, vascular risk, and biochemical characteristics of the 150 young adults with first-ever ischemic stroke. The cohort had a mean age of 41.2 ± 6.7 years, with male predominance, and hyperhomocysteinemia was identified in 40.7% of participants.

[Table 2] compares biochemical and metabolic parameters according to hyperhomocysteinemia status, demonstrating significantly lower vitamin B12 and folate levels and modestly impaired renal function among participants with elevated homocysteine. [Table 3] presents the TOAST etiological distribution, with small-vessel occlusion being the most frequent subtype, followed by undetermined etiology and large-artery atherosclerosis.

[Table 4] demonstrates substantial variation in homocysteine concentrations across TOAST subtypes, with the highest levels observed in large-artery atherosclerosis and the greatest prevalence of hyperhomocysteinemia in this group. [Table 5] shows that hyperhomocysteinemia remained independently associated with large-artery atherosclerosis after adjustment for demographic, vascular, nutritional, and renal factors.

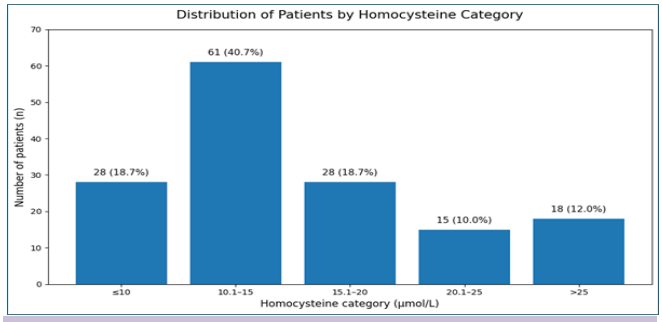


Figure 1: Distribution of Serum Homocysteine Concentrations Across TOAST Stroke Etiological Subtypes

[Table 6] demonstrates a concentration-dependent association between increasing serum homocysteine and large-artery atherosclerosis, with progressively higher odds observed at increasing homocysteine exposure levels. [Figure 1] illustrates the overall distribution of serum homocysteine concentrations across predefined concentration categories. [Figure 2] illustrates the prevalence of hyperhomocysteinemia across the individual TOAST etiological subtypes.

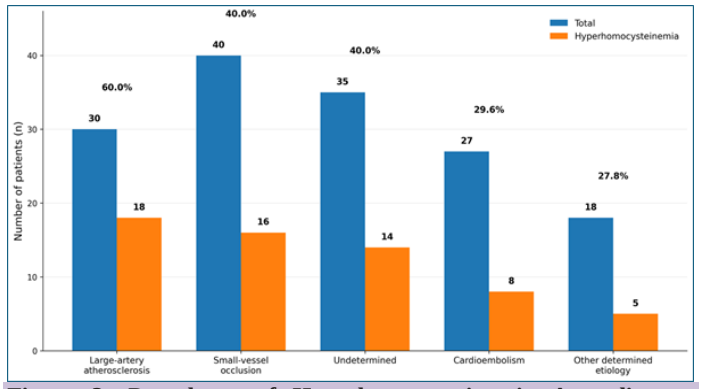


Figure 2: Prevalence of Hyperhomocysteinemia According to Stroke Etiological Subtype

Table 1: Baseline Demographic, Clinical, and Vascular Risk Characteristics of Young Adults with First-Ever Ischemic Stroke (N=150)

Variable	Overall (N=150)
Age, years	41.2 ± 6.7
Age group, n (%)	
<30 years	14 (9.3)
30–39 years	39 (26.0)
40–49 years	97 (64.7)
Male sex, n (%)	96 (64.0)
Female sex, n (%)	54 (36.0)
Body mass index, kg/m²	24.6 ± 3.8
Hypertension, n (%)	55 (36.7)
Diabetes mellitus, n (%)	29 (19.3)
Dyslipidemia, n (%)	48 (32.0)
Current smoking, n (%)	52 (34.7)
Current alcohol use, n (%)	43 (28.7)
Family history of premature vascular disease, n (%)	21 (14.0)
Previous coronary artery disease, n (%)	8 (5.3)
Chronic kidney disease, n (%)	12 (8.0)
Systolic blood pressure, mmHg	139.8 ± 18.6
Diastolic blood pressure, mmHg	86.2 ± 11.4
Fasting plasma glucose, mg/dL	108.6 ± 31.7
HbA1c, %	6.1 ± 1.2
Total cholesterol, mg/dL	186.4 ± 42.5
LDL cholesterol, mg/dL	113.7 ± 34.6
HDL cholesterol, mg/dL	42.8 ± 9.7
Triglycerides, mg/dL	151.6 ± 67.4
Serum creatinine, mg/dL	0.91 ± 0.24
eGFR, mL/min/1.73 m²	96.4 ± 18.7
Vitamin B12, pg/mL	342.6 ± 128.4
Folate, ng/mL	8.7 ± 3.2
Total homocysteine, µmol/L	18.6 ± 9.4
Hyperhomocysteinemia (>15 µmol/L), n (%)	61 (40.7)

Table 2: Biochemical Profile According to Hyperhomocysteinemia Status

Variable	Overall (N=150)	Normal Homocysteine ≤15 µmol/L (n=89)	Hyperhomocysteinemia >15 µmol/L (n=61)	P value
Total homocysteine, µmol/L	18.6 ± 9.4	12.1 ± 2.1	28.1 ± 8.0	<0.001
Vitamin B12, pg/mL	342.6 ± 128.4	369.8 ± 125.7	303.0 ± 123.2	0.002
Folate, ng/mL	8.7 ± 3.2	9.2 ± 3.3	7.9 ± 2.9	0.014
Serum creatinine, mg/dL	0.91 ± 0.24	0.87 ± 0.18	0.97 ± 0.30	0.018
eGFR, mL/min/1.73 m²	96.4 ± 18.7	99.2 ± 16.4	92.3 ± 21.0	0.028
Fasting plasma glucose, mg/dL	108.6 ± 31.7	104.7 ± 27.8	114.3 ± 36.1	0.071
HbA1c, %	6.1 ± 1.2	6.0 ± 1.1	6.3 ± 1.3	0.118
Total cholesterol, mg/dL	186.4 ± 42.5	181.7 ± 39.8	193.3 ± 45.7	0.091
LDL cholesterol, mg/dL	113.7 ± 34.6	110.1 ± 32.1	119.0 ± 37.5	0.116

HDL cholesterol, mg/dL	42.8 ± 9.7	43.5 ± 9.4	41.8 ± 10.1	0.296
Triglycerides, mg/dL	151.6 ± 67.4	147.8 ± 61.9	157.1 ± 74.6	0.413

Table 3: Distribution of Ischemic Stroke According to TOAST Etiological Classification

TOAST stroke subtype	n	%
Large-artery atherosclerosis	30	20.0
Cardioembolism	27	18.0
Small-vessel occlusion	40	26.7
Other determined etiology	18	12.0
Undetermined etiology	35	23.3
Total	150	100.0

Clinical and Diagnostic Characteristics by TOAST Subtype

Characteristic	Large-artery atherosclerosis (n=30)	Cardioembolism (n=27)	Small-vessel occlusion (n=40)	Other determined etiology (n=18)	Undetermined etiology (n=35)	P value
Age, years	43.8 ± 4.7	39.8 ± 7.1	42.7 ± 5.4	37.9 ± 8.0	40.8 ± 6.9	0.009
Male sex, n (%)	22 (73.3)	14 (51.9)	28 (70.0)	10 (55.6)	22 (62.9)	0.289
Hypertension, n (%)	17 (56.7)	6 (22.2)	19 (47.5)	4 (22.2)	9 (25.7)	0.006
Diabetes mellitus, n (%)	9 (30.0)	3 (11.1)	10 (25.0)	2 (11.1)	5 (14.3)	0.173
Dyslipidemia, n (%)	13 (43.3)	5 (18.5)	13 (32.5)	4 (22.2)	13 (37.1)	0.196
Current smoking, n (%)	13 (43.3)	7 (25.9)	16 (40.0)	4 (22.2)	12 (34.3)	0.358
Acute infarction on MRI/CT, n (%)	30 (100.0)	27 (100.0)	40 (100.0)	18 (100.0)	35 (100.0)	—
Multiple vascular-territory infarction, n (%)	7 (23.3)	13 (48.1)	2 (5.0)	5 (27.8)	7 (20.0)	<0.001
Relevant arterial stenosis, n (%)	30 (100.0)	2 (7.4)	1 (2.5)	4 (22.2)	5 (14.3)	<0.001
Potential cardiac source identified, n (%)	2 (6.7)	27 (100.0)	1 (2.5)	2 (11.1)	5 (14.3)	<0.001

Table 4: Homocysteine Concentrations and Prevalence of Hyperhomocysteinemia Across TOAST Stroke Etiological Subtypes

TOAST subtype	n	Homocysteine, µmol/L, mean ± SD	Hyperhomocysteinemia, n (%)	Normal homocysteine, n (%)
Large-artery atherosclerosis	30	23.4 ± 10.2	18 (60.0)	12 (40.0)
Small-vessel occlusion	40	18.7 ± 7.9	16 (40.0)	24 (60.0)
Undetermined etiology	35	17.6 ± 8.6	14 (40.0)	21 (60.0)
Cardioembolism	27	14.9 ± 6.3	8 (29.6)	19 (70.4)
Other determined etiology	18	13.8 ± 5.7	5 (27.8)	13 (72.2)
Overall	150	18.6 ± 9.4	61 (40.7)	89 (59.3)

Table 5: Multivariable Logistic Regression Analysis of Factors Associated With Large-Artery Atherosclerosis

Predictor	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Hyperhomocysteinemia (>15 µmol/L)	2.79	1.31–5.96	0.008	2.84	1.31–6.16	0.008
Age, per 1-year increase	1.08	1.02–1.14	0.009	1.06	0.99–1.13	0.082
Male sex	1.64	0.70–3.82	0.255	1.48	0.59–3.70	0.405
Hypertension	3.14	1.42–6.94	0.005	2.41	1.02–5.70	0.045
Diabetes mellitus	1.82	0.76–4.37	0.179	1.39	0.54–3.58	0.493
Dyslipidemia	1.58	0.70–3.56	0.271	1.31	0.54–3.17	0.552
Current smoking	1.55	0.70–3.43	0.279	1.42	0.60–3.39	0.426
Vitamin B12, per 100-pg/mL increase	0.84	0.69–1.02	0.078	0.89	0.72–1.10	0.281
Folate, per 1-ng/mL increase	0.86	0.76–0.98	0.024	0.92	0.79–1.07	0.286
eGFR, per 10-mL/min/1.73 m² increase	0.91	0.80–1.04	0.171	0.94	0.81–1.09	0.406

Table 6: Dose–Response Association Between Increasing Serum Homocysteine and Large-Artery Atherosclerosis

Homocysteine exposure	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Per 1 µmol/L increase	1.05	1.02–1.08	0.003	1.06	1.02–1.10	0.004
Per 5 µmol/L increase	1.28	1.07–1.53	0.007	1.31	1.08–1.59	0.006
≤10 µmol/L	Reference	—	—	Reference	—	—
10.1–15 µmol/L	1.34	0.57–3.15	0.504	1.28	0.52–3.15	0.588
15.1–20 µmol/L	2.18	0.93–5.12	0.073	2.05	0.82–5.11	0.124
>20 µmol/L	3.76	1.54–9.18	0.004	3.42	1.31–8.94	0.012

Discussion

The present prospective observational study demonstrates that

hyperhomocysteinemia is common among young adults with first-ever ischemic stroke and, importantly, is disproportionately associated with the large-artery atherosclerosis phenotype. Among 150 patients younger than 50 years, 40.7% had total homocysteine concentrations >15 μmol/L, with an overall mean concentration of 18.6 ± 9.4 μmol/L. Homocysteine concentrations were highest among patients with large-artery atherosclerosis, followed by small-vessel occlusion and undetermined stroke, whereas the lowest concentrations were observed in cardioembolic and other determined etiologies. After adjustment for conventional vascular risk factors, vitamin B12, folate, and renal function, hyperhomocysteinemia remained independently associated with large-artery atherosclerosis (adjusted OR, 2.84; 95% CI, 1.31–6.16; P=0.008). Furthermore, the association strengthened with increasing homocysteine concentration, with a 31% higher adjusted odds of large-artery atherosclerosis for every 5-μmol/L increase in homocysteine.

The demographic and vascular-risk profile of the cohort is consistent with the changing epidemiology of stroke in younger adults. In the present study, nearly two-thirds of participants were aged 40–49 years, and hypertension, smoking, dyslipidemia, and diabetes were frequent. These findings are broadly consistent with contemporary young-stroke cohorts demonstrating that conventional vascular risk factors increasingly contribute to ischemic stroke even before the age of 50 years. Ekker et al. reported substantial heterogeneity in the causes and risk-factor profiles of 1322 young adults with ischemic stroke, with conventional vascular risk factors contributing substantially to stroke risk.[7] Similarly, Tang et al. identified hypertension, dyslipidemia, smoking, and other vascular factors as important contributors to ischemic stroke in young adults.[5] Ohya et al. also demonstrated that the etiological profile of young adults differs from that of older adults, while conventional vascular mechanisms become increasingly relevant with advancing age within the young-adult population.[4] More recent data from Schneider et al. further emphasize age- and sex-related heterogeneity in stroke mechanisms among young adults.[10] Thus, the concentration of patients in the 40–49-year age group in the present cohort may partly explain the relatively substantial representation of atherosclerotic stroke.

The distribution of TOAST subtypes in the present study further highlights the heterogeneous nature of young-adult ischemic stroke. Small-vessel occlusion was the most frequent subtype (26.7%), followed by undetermined etiology (23.3%), large-artery atherosclerosis (20.0%), cardioembolism (18.0%), and other determined etiologies (12.0%). This pattern is broadly compatible with contemporary studies showing that young-adult stroke cannot be attributed to a single dominant mechanism. Ekker et al. described considerable etiological diversity in a large multicenter cohort of young adults.[7] while Tan et al. reported heterogeneous mechanisms in an Asian young-stroke population.[8] Huang et al. similarly demonstrated variation in etiological patterns according to age and sex.[9] The present findings therefore reinforce the importance of evaluating metabolic and vascular factors within a detailed etiological framework rather than considering young stroke as predominantly cryptogenic or cardioembolic.

The principal finding of this study was the higher homocysteine burden among patients with large-artery atherosclerosis. Mean homocysteine was 23.4 ± 10.2 μmol/L in the large-artery atherosclerosis group compared with 18.7 ± 7.9 μmol/L in small-vessel occlusion, 17.6 ± 8.6 μmol/L in undetermined stroke, 14.9 ± 6.3 μmol/L in cardioembolism, and 13.8 ± 5.7 μmol/L in other determined etiologies. Hyperhomocysteinemia was present in 60.0% of patients with large-artery atherosclerosis compared with 40.0% of those with small-vessel occlusion and undetermined stroke. This observation extends previous evidence linking homocysteine with ischemic stroke by suggesting that its association may be particularly evident in an atherosclerotic stroke phenotype. A previous study of young ischemic stroke patients reported that large-artery atherosclerosis accounted for the greatest proportion of patients with elevated homocysteine, although the difference across TOAST subtypes did not reach statistical significance.[3] The stronger association observed in the present study may reflect differences in sample size, age distribution, population characteristics, homocysteine categorization, and adjustment for potential confounders.

The association between homocysteine and cerebrovascular disease is biologically plausible. Elevated homocysteine has been implicated in endothelial dysfunction, oxidative injury, vascular smooth-muscle proliferation, altered nitric-oxide signaling, and prothrombotic pathways. Wu et al., in a dose-response meta-analysis of prospective cohort studies, demonstrated a graded association between circulating homocysteine and subsequent stroke risk.[12] Holmen et al. similarly reported evidence supporting a dose-response relationship between hyperhomocysteinemia and ischemic stroke.[14] More recently, Srivastava et al. synthesized evidence across 96 studies and reported associations between elevated homocysteine and different stroke phenotypes and subtypes.[22] Although these studies establish an epidemiological relationship, the present findings provide additional subtype-specific evidence by demonstrating a stronger association with large-artery atherosclerosis among young adults.

The dose-response analysis in the present study is particularly relevant. Each 5-μmol/L increase in homocysteine was associated with an adjusted OR of 1.31 for large-artery atherosclerosis, while concentrations >20 μmol/L were associated with more than threefold higher adjusted odds compared with concentrations ≤10 μmol/L. This concentration-dependent pattern is directionally consistent with the dose-response relationship described by Wu et al,[12] and Holmen et al,[14] However, the present analysis differs from those studies because the outcome was not ischemic stroke occurrence itself but a specific etiological subtype among individuals who had already experienced ischemic stroke. Accordingly, the finding should be interpreted as evidence of an association between greater homocysteine exposure and the large-artery atherosclerotic phenotype rather than evidence that increasing homocysteine directly causes atherosclerotic stroke.

The observed relationship between hyperhomocysteinemia and vitamin status provides additional biological context. Patients

with hyperhomocysteinemia had lower mean vitamin B12 and folate concentrations than those with normal homocysteine, while creatinine was higher and eGFR was lower. This is consistent with the central role of B-vitamin-dependent metabolic pathways in homocysteine handling. Ghose et al. demonstrated associations among homocysteine, vitamin B6, vitamin B12, folate, and ischemic stroke in an Indian case-control population.[17] Zhou et al. further reported that the combined profile of vitamin B12, folate, and total homocysteine could contribute to identification of ischemic stroke.[18] Jin et al. also demonstrated an association among MTHFR C677T genotype, homocysteine concentrations, and ischemic stroke in a large Han Chinese population.[16] supporting the possibility that nutritional and genetic determinants of homocysteine metabolism may contribute to interindividual differences in vascular risk. Importantly, the present association between hyperhomocysteinemia and large-artery atherosclerosis persisted after adjustment for vitamin B12, folate, and renal function, suggesting that the observed relationship was not explained solely by these measurable metabolic determinants.

Renal function also deserves consideration because impaired renal clearance can increase circulating homocysteine concentrations. In the present cohort, patients with hyperhomocysteinemia had modestly higher serum creatinine and lower eGFR. Adjustment for renal function attenuated potential confounding without eliminating the association between hyperhomocysteinemia and large-artery atherosclerosis. This strengthens the interpretation that renal impairment alone was unlikely to account for the observed relationship. Nevertheless, residual confounding by nutritional status, genetic variation, medication exposure, or unmeasured metabolic factors cannot be excluded.

The relationship between homocysteine and stroke may also extend beyond conventional atherosclerotic mechanisms. Lin et al. recently reported an association between slightly increased homocysteine and ischemic stroke caused by spontaneous cervical artery dissection in young Asian adults.[21] emphasizing that homocysteine may interact with multiple vascular pathways rather than exclusively with atherosclerosis. Similarly, the contemporary literature recognizes hyperhomocysteinemia as one of several potentially relevant prothrombotic or vascular factors in young stroke populations. The comparatively lower homocysteine concentrations observed in the cardioembolic and other determined groups in the present cohort suggest that the biological relevance of homocysteine may vary according to stroke mechanism.

Hypertension was the other factor independently associated with large-artery atherosclerosis in the adjusted model. This finding is biologically and epidemiologically coherent because prolonged blood-pressure elevation can promote endothelial injury and arterial remodeling. The association also illustrates why homocysteine should not be interpreted in isolation. Earlier work in young adults demonstrated interaction between homocysteine and conventional vascular risk factors, particularly hypertension and smoking, in relation to ischemic stroke risk.[1] Contemporary young-stroke studies likewise demonstrate that traditional vascular risk factors remain important despite the broader etiological spectrum in younger patients.[5,7] The present findings therefore support a multifactorial interpretation in which elevated homocysteine may coexist with, and potentially contribute to, a broader vascular-risk phenotype.

The clinical significance of these findings lies primarily in etiological characterization. A high homocysteine concentration in a young patient with ischemic stroke should not be regarded as diagnostic of a particular stroke mechanism, because elevated homocysteine was also observed in small-vessel and undetermined stroke. Rather, the present results suggest that substantially elevated homocysteine may provide additional metabolic information when interpreted alongside vascular imaging, conventional risk factors, vitamin status, renal function, and the complete etiological evaluation. This is particularly relevant because young-adult stroke requires a broad diagnostic approach encompassing vascular, cardiac, hematological, metabolic, genetic, and other less common causes.[1,2,11]

Limitations: This study has several limitations. First, its prospective observational design permits identification of associations but does not establish causality between hyperhomocysteinemia and large-artery atherosclerosis. Second, the study was conducted in a single cohort of 150 patients, and the relatively small number of large-artery atherosclerosis events limits the precision and stability of multivariable estimates. Third, homocysteine was measured during the acute stroke period, and acute illness may influence metabolic biomarkers. Fourth, genetic determinants such as MTHFR polymorphisms, dietary intake, vitamin B6 status, and medication-related effects were not comprehensively assessed. Finally, residual confounding and limited generalizability to other ethnic or geographic populations cannot be excluded.

Overall Interpretation: In young adults with first-ever ischemic stroke, hyperhomocysteinemia was frequent and showed a graded association with large-artery atherosclerosis after adjustment for conventional vascular and metabolic factors. The findings are consistent with the broader literature linking elevated homocysteine to ischemic stroke risk.[12,14,21,22] and extend that evidence by examining etiological heterogeneity within a young-stroke population. However, these results should be interpreted as evidence of an etiology-specific association rather than proof of a causal role, and larger multicenter studies incorporating nutritional, genetic, and longitudinal assessments are warranted to determine whether the observed association is reproducible and clinically useful.

Conclusion

In this prospective cohort of young adults with first-ever ischemic stroke, hyperhomocysteinemia was frequent and showed a distinct association with the large-artery atherosclerotic stroke phenotype. Patients with large-artery atherosclerosis had the highest homocysteine concentrations and the greatest prevalence of hyperhomocysteinemia, and the association remained evident after adjustment for conventional vascular risk factors, vitamin B12, folate, and renal function. The observed concentration-dependent relationship further

supports the potential relevance of homocysteine as a metabolic marker of atherosclerotic stroke mechanisms in young adults. These findings do not establish causality but indicate that homocysteine may provide complementary information during etiological characterization and justify prospective multicenter studies investigating its biological determinants and clinical significance across distinct young-stroke phenotypes.

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Conflicts of interest
There are no conflicts of interest.

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