

# The Correlation between Homocysteine Levels and the Incidence of Ischemic Stroke and the Role of Dietary Supplements

Shakhawan Mohammed Hamadameen<sup>1\*</sup>, Azad Anwar Hamad<sup>2</sup>

<sup>1</sup> Higher Diploma student in Neurology, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region–Iraq.

<sup>2</sup> Assistant Professor of Neurology, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region–Iraq.

**\*Corresponding Author**

Email ID : [shakhawan.manmi@gmail.com](mailto:shakhawan.manmi@gmail.com)

## ABSTRACT

**Background and objectives:** Cerebrovascular accident, commonly referred to as stroke, represents a predominant cause of mortality and morbidity globally, thereby imposing a substantial strain on both healthcare infrastructures and individual patients. High levels of homocysteine (Hcy) are considered a risk factor for stroke and its various subtypes. The present study aimed to investigate the association between serum homocysteine concentration and the occurrence of ischemic stroke, as well as the possible effect of dietary supplements.

**Methods:** The study is a cross-sectional study carried out in Rizgary teaching hospital between October 2024 and June 2025 in the Erbil city, Kurdistan Region-Iraq. A sample population of 100 adults aged 35 years and above, diagnosed with acute ischemic stroke, which was confirmed using radiological imaging, was sampled. Stratification of the participants was done in two groups which consisted of normal Hcy level of the serum (NHLG <15 mol/L) and high homocysteine (HHLG  $\geq$ 15  $\mu$ mol/L) level. The data were recorded through a questionnaire developed by a researcher and through the medical record abstraction, which included demographic, clinical, lifestyle, and diet variables. Enzyme immunoassay was conducted on serum Hcy levels within 24–48 hours after the onset of the stroke. Independent t-, chi-square or Fisher, exact tests were used to carry out statistical comparisons and a p-value of  $\leq$ 0.05 was considered statistically significant.

**Results:** The mean Hcy levels had a statistically significant difference between the NHLG ( $10.33 \pm 2.96 \mu\text{mol/L}$ ) and the HHLG ( $21.04 \pm 5.85 \mu\text{mol/L}$ ) ( $P \leq 0.001$ ). The male population was significantly overrepresented within the HHLG (72.2% vs. 42.2%) ( $P \leq 0.004$ ), while lower educational attainment levels were markedly more prevalent in the NHLG ( $P \leq 0.006$ ). There was no significant inter-group difference on hypertension, body mass index, smoking status, diabetes mellitus or severity of stroke using the National Institutes of Health Stroke Scale (NIHSS). Similarly, there was no significant difference between the participants' intaking dietary supplements. However, there was a low and statistically significant negative relationship between history of stroke and previous supplement intake. ( $r = -0.201$ ,  $P = 0.045$ ). In contrast, Hcy levels measured during the acute phase of stroke were not significantly correlated with previous stroke history ( $r = 0.072$ ,  $P = 0.477$ ).

**Conclusion:** The level of serum Hcy in patients with an ischemic stroke was significantly correlated with demographic factors including sex and education level, but no statistically significant relationship was established between the levels of Hcy and known risk factors of a stroke as well as the severity of the disease. Moreover, in spite of the fact that vitamin supplementation had a weak inverse correlation with the presence of a previous stroke, its impact on the levels of Hcy was not obvious at the acute stroke stage.

**KEYWORDS:** Homocysteine, Hyper Homocysteine, Stroke Risk Factors, Vitamin B, Dietary Supplements, Ischemic Stroke, Biomarkers.

**How to Cite:** Shakhawan Mohammed Hamadameen, Azad Anwar Hamad (2025) The Correlation between Homocysteine Levels and the Incidence of Ischemic Stroke and the Role of Dietary Supplements., Vascular and Endovascular Review, Vol.8, No19s, 214-222

## INTRODUCTION

Stroke represents a foremost cause of mortality and disability on a global scale, thereby imposing considerable challenges to healthcare systems and individual patients. Stroke is the third cause of mortality and disability worldwide (1). Despite a notable decline in age-standardized mortality rates associated with strokes in recent years, the reduction in age-standardized incidence rates has been comparatively modest, indicating that preventative strategies have been less efficacious than therapeutic interventions in the context of stroke (2).

Previous studies have shown that about 88% of the disability burden that is caused by ischemic stroke is due to adjustable risk factors, which underscores the need to minimise exposure to these factors to lower the overall disease burden (3). In this regard, it is necessary to explain the entire range of risk factors associated with stroke to develop a set of efficient

preventive and treatment measures (4). The wide-ranging stroke prevention programs are usually focused on hypertension, diabetes mellitus, dyslipidemia, tobacco, mal-adaptive diet, lack of physical exercise, and central obesity (1).

Homocysteine (Hcy) is one of the biochemical indicators that have drawn much academic attention as far as vascular risk is concerned. Hcy is a sulfur based amino acid formed through the process of methionine demethylation, an essential amino acid acquired through the diet (5). Hcy is a naturally occurring sulfur-containing sulphydryl amino acid which is involved in endothelial dysfunction and in proliferative modifications of the extracellular matrix, and thus may contribute to vascular damage (6).

plasma concentrations of Hcy in a fasting state, are usually between 5 and 15  $\mu\text{mol/L}$ . Elevated Hcy or hyperhomocysteinemia is usually classified into three severity levels including moderate (15–30  $\mu\text{mol/L}$ ), intermediate (31–100  $\mu\text{mol/L}$ ), and severe (above 100  $\mu\text{mol/L}$ ) (4). Genetic and environmental factors have a role in inter-individual variability of plasma Hcy. The environmental factors include male sex, old age, smoking, kidney disease and taking of some drugs like corticosteroids or cyclosporine. Classical homocystinuria and homozygous C677T polymorphism of the 5,10 -methylenetetrahydrofolate reductase (MTHFR) gene are two salient genetic factors. Deficiency of nutrients and especially of B6, B12 and folate vitamins has been known to increase the Hcy levels, and vitamin supplementation using these vitamins has been known to reduce such increases (6, 7).

Hcy is involved in important metabolism. High levels can be considered a putative risk factor of stroke and its subtypes (8, 9). Others have observed an association between hyperhomocysteinemia and ischemic stroke (6, 10), but findings have been inconsistent and the actual available mechanism of influence of Hcy on stroke prognosis is still uncertain (6).

Although there is a lot of evidence to support elevated Hcy as a predisposing risk to ischemic stroke, numerous studies have produced contradictive findings, and the effects of dietary supplementation in regulating this biomarker are not fully comprehended. The previous studies have focused more on the overall correlation between Hcy and cardiovascular disease, and relatively less on its particular correlation with ischemic stroke, especially in the indigenous populations, and on the concomitant analysis of nutritional and lifestyle factors. In turn, a case study that would measure the level of Hcy concomitantly with the patient clinical features and the ways of using dietary supplements would contribute to bridging this gap in knowledge and providing new information to construct the preventive approaches. The present study aimed to investigate the association between serum homocysteine concentration and the occurrence of ischemic stroke, as well as the possible effect of dietary supplements.

## METHODS

### Study Design and Setting

This observational cross-sectional study will be carried out with patients who were diagnosed with ischemic stroke and admitted to Rizgary teaching hospital between October 2024 and June 2025 in the Erbil city, Kurdistan Region-Iraq. The present study aimed to determine the relationship between serum Hcy levels and ischemic stroke, taking into account demographic, clinical, lifestyle, and dietary factors.

### Participants

Inclusion criteria included a clinical diagnosis of acute ischemic stroke, age 35 years or older. Diagnosis was confirmed by a thorough clinical evaluation and neuroimaging methods, such as computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria included: presence of hemorrhagic stroke; clinically significant hepatic or renal impairment (eg, estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73  $\text{m}^2$ ), known inherited disorders of homocysteine metabolism (eg, homocystinuria), and unwillingness to participate in the study.

A total of 100 participants were enrolled and retrospectively stratified into two groups based on fasting serum Hcy levels:

Normal Hcy Level Group (NHLG): Hcy  $< 15 \mu\text{mol/L}$

High Hcy Level Group (HHLG): Hcy  $\geq 15 \mu\text{mol/L}$

### Data Collection

Data were gathered using a structured, researcher-administered questionnaire (aligned with the instrument in *questioner.docx*) and through retrospective review of medical records.

The study collected a broad set of variables covering demographic, medical, lifestyle, and clinical aspects.

Demographic information: age, sex, marital status, occupation and education level of the participants.

- Medical history: diabetes mellitus, hypertension, history of previous ischemic stroke, ischemic heart disease, and any

other concurrent conditions.

- Lifestyle variables: physical activity, BMI smoking habits, alcohol use (none, occasional, regular, or alcoholic).
- Clinical assessment: stroke severity analysis at the time of hospital admission using the National Institutes of Health Stroke Scale (NIHSS).

Dietary and supplement intake: participants reported their consumption patterns over the preceding six months for vegetables, fruits, meat, vitamin supplements (particularly B6, B12, and folic acid), and other nutritional products, using a frequency scale (daily, every other day, twice weekly, weekly, monthly, or none).

Medication history: current use of antihypertensives, antiplatelet agents (e.g., acetylsalicylic acid), oral hypoglycemic agents (OHA), cilostazol (“piax”), or other relevant medications.

Venous blood samples were collected in the fasting state and within 24 to 48 hours after stroke onset. Serum homocysteine levels were measured using enzyme immunoassay (EIA). Levels were interpreted as follows: normal (5–15  $\mu\text{mol/L}$ ), moderate hyperhomocysteinemia (15–30  $\mu\text{mol/L}$ ), intermediate (31–100  $\mu\text{mol/L}$ ), and severe ( $>100 \mu\text{mol/L}$ ).

### Statistical Analysis

IBM SPSS Statistics version 26 was used to perform the statistical analysis. The continuous variables were represented using the means and standard deviations (SD) of the variables, and frequencies and percentages were used in summarising the categorical variables.

Group comparisons were performed using:

Independent *t*-tests for normally distributed continuous variables (e.g., age, homocysteine levels, BMI)

Chi-square ( $\chi^2$ ) or Fisher’s exact tests for categorical variables (e.g., sex, smoking, supplement use)

Correlation coefficients spearman for correlation history of previous ischemic stroke with Supplements and Homocysteine level

P-value  $< 0.05$  was considered statistically significant.

### Ethical Considerations

The study protocol underwent scrutiny and received approval from the Ethics Committee of the Kurdistan Higher Council of Specialist Medicine (Ref: ABC). Written informed consent was given to all the participants prior to enrolment. The study was conducted in line with the ethical principles of the Declaration of Helsinki, and confidentiality of patients was strictly observed during the data collection process, analysis and reporting.

## RESULTS

Table 1 presents the demographic characteristics of the participants. Respondents who were located in the normal range of homocysteine level group (NHLG) had the serum level of Hcy of less than 15  $\mu\text{mol/L}$ , and those who were in the high range of homocysteine level group (HHLG) had the serum level of Hcy of 15  $\mu\text{mol/L}$  or above. The mean  $\pm$  standard deviation (SD) of Hcy concentration was  $10.327 \pm 2.963 \mu\text{mol/L}$  in the NHLG and  $21.041 \pm 5.846 \mu\text{mol/L}$  in the HHLG, with a statistically significant difference between the groups ( $P \leq 0.001$ ).

Mean  $\pm$  SD age was  $62.91 \pm 10.818$  years in the NHLG and  $59.44 \pm 12.141$  years in the HHLG; this difference was not statistically significant. Regarding sex distribution, 27 (42.2%) participants in the NHLG were male and 37 (57.8%) were female, compared to 26 (72.2%) males and 10 (27.8%) females in the HHLG, a difference that reached statistical significance ( $P = 0.004$ ). The vast majority of participants in both groups were married: 63 (98.4%) in the NHLG and 35 (97.2%) in the HHLG ( $P = 0.677$ ).

Occupational status varied significantly between the groups ( $P = 0.038$ ). In the NHLG, 32 (50.0%) participants were housewives, whereas in the HHLG, 14 (38.9%) were governmental employees. Educational attainment also differed significantly ( $P = 0.006$ ): in the NHLG, 42 (65.6%) had completed only primary school, 9 (14.1%) secondary school, and 13 (20.3%) held a college degree; in contrast, the HHLG showed a more balanced distribution, with 12 (33.3%) participants at each educational level.

With respect to comorbid conditions, hypertension was reported in 52 (81.3%) NHLG participants and 27 (75.0%) HHLG participants ( $P = 0.610$ ), while diabetes mellitus was present in 15 (23.4%) and 11 (30.6%) individuals in the NHLG and HHLG, respectively ( $P = 0.481$ ). Current smoking was reported by 15 (23.4%) participants in the NHLG and 9 (25.0%) in the HHLG ( $P = 0.861$ ). Alcohol use was uncommon overall but was slightly higher in HHLG (3 cases, 8.3%) than NHLG

(1 case, 1.6%), although this difference was not statistically significant ( $P = 0.132$ ).

**Table .1: Characteristics demographics in two group NHL and HHL**

Characteristics		NHLG (n=64)	HHLG (n=36)	P-value*
Homocysteine level		10.327 ± 2.963	21.041 ± 5.846	0.001
Age		62.91 ± 10.818	59.44 ± 12.141	0.160
Gender	Male	27 (42.2%)	26 (72.2%)	0.004
	Female	37 (57.8%)	10 (27.8%)	
Marital state	Married	63 (98.4%)	35 (97.2%)	0.677
	Single	1 (1.6%)	1 (2.8%)	
Occupation	Farmer	3 (3.1%)	0	0.038
	Governmental employer	14 (21.9%)	14 (38.9%)	
	House wife	32 (50%)	9 (25%)	
	Unemployed	16 (25%)	13 (36.1%)	
Educational level	Primary school	42 (65.6%)	12 (33.3%)	0.006
	Secondary school	9 (14.1%)	12 (33.3%)	
	College	13 (20.3%)	12 (33.3%)	
Hypertension	Yes	52 (81.3%)	27 (75%)	0.610
	No	12 (18.8%)	9 (25%)	
Diabetes	Yes	15 (23.4%)	11 (30.6%)	0.481
	No	49 (76.6%)	25 (69.4%)	
Smoking	Yes	15 (23.4%)	9 (25%)	0.861
	No	49 (76.6%)	27 (75%)	
Alcohol consumption	Yes	1 (1.6%)	3 (8.3%)	0.132
	No	63 (98.4%)	33 (91.7%)	

\*P-value based on chi-square, Fisher exact test and t-test

A history of prior ischemic stroke was reported in 6 (9.4%) participants in the Normal Homocysteine Level Group (NHLG) and 2 (5.6%) in the High Homocysteine Level Group (HHLG); this difference was not statistically significant ( $P = 0.707$ ).

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and was similarly distributed between the two groups. In the NHLG, NIHSS scores were as follows: 2 (3.1%) scored 2, 37 (57.8%) scored 3, 20 (31.3%) scored 4, 4 (6.3%) scored 5, and 1 (1.6%) scored 6. In the HHLG, 20 (55.6%) scored 3, 12 (33.3%) scored 4, and 4 (11.1%) scored 5. No participants in the HHLG had NIHSS scores of 2 or 6. The overall distribution of NIHSS scores did not differ significantly between the two groups ( $P = 0.758$ ).

Regarding other comorbidities, ischemic heart disease was present in 13 (20.3%) individuals in the NHLG and 6 (16.7%)

in the HHLG. This difference was also non-significant ( $P = 0.793$ ). Collectively, history of previous ischemic stroke, NIHSS score distribution, and presence of other comorbidities showed no statistically significant differences between the NHLG and HHLG. (Table 2).

**Table .2: Clinical characteristics demographics in two group NHL and HHL**

Characteristics		NHLG (n=64)	HHLG (n=36)	P-value*
History of previous ischemic stroke	Yes	6 (9.4%)	2 (5.6%)	0.707
	No	58 (90.6%)	34 (94.4%)	
NIHSS	2	2 (3.1%)	0	0.758
	3	37 (57.8%)	20 (55.6%)	
	4	20 (31.3%)	12 (33.3%)	
	5	4 (6.3%)	4 (11.1%)	
	6	1 (1.6%)	0	
Other comorbidity	Ischemic heart disease	13 (20.3%)	6 (16.7%)	0.793
	No	51 (79.7%)	30 (83.3%)	

\*P-value based on chi-square and Fisher exact test

Medication history differed significantly between the two groups ( $P = 0.043$ ). In the Normal Homocysteine Level Group (NHLG), 26 (40.6%) participants reported using anti-hypertensive agents alone; 9 (14.1%) used a combination of anti-hypertensives and acetylsalicylic acid (ASA); 8 (12.6%) used anti-hypertensives, ASA, and oral hypoglycemic agents (OHA); 5 (7.8%) used anti-hypertensives plus OHA; 2 (3.1%) used anti-hypertensives with piex (cilostazol); and 2 (3.1%) used OHA only. Additionally, 14 (21.9%) participants in this group reported no prior medication use.

In the High Homocysteine Level Group (HHLG), 12 (33.4%) participants used anti-hypertensive agents alone; 1 (2.8%) used anti-hypertensives with ASA; 4 (11.1%) used anti-hypertensives, ASA, and OHA; 6 (16.7%) used anti-hypertensives plus OHA; 3 (8.3%) used anti-hypertensives with piex; and 3 (8.3%) used OHA only. Seven (19.4%) participants in this group reported no prior medication use. The overall pattern of drug use showed a statistically significant difference between the 2 groups ( $P < 0.043$ ) (Table 3).

**Table .3: Drug History consumption in two group NHL and HHL**

Characteristics		NHLG (n=64)	HHLG (n=36)	P-value
Drug History	Anti-hypertensive	26 (40.6%)	12 (33.4%)	0.043
	Anti-hypertensive + ASA	9 (14.1%)	1 (2.8%)	
	Anti-hypertensive + ASA + OHA	8 (12.6%)	4 (11.1%)	
	Anti-hypertensive + OHA	5 (7.8%)	6 (16.7%)	
	Anti-hypertensive + piex	0	3 (8.3%)	

	OHA	2 (3.1%)	3 (8.3%)	
	NO	14 (21.9%)	7 (19.4%)	

\*P-value based on chi-square and Fisher exact test

The mean  $\pm$  standard deviation (SD) of body mass index (BMI) was  $23.108 \pm 3.002$  kg/m<sup>2</sup> in the Normal Homocysteine Level Group (NHLG) and  $23.033 \pm 1.825$  kg/m<sup>2</sup> in the High Homocysteine Level Group (HHLG). This difference was not statistically significant ( $P = 0.877$ ).

Regarding diet over the past six months, 10 (15.6%) of NHLG participants reported consuming mainly vegetables, 49 (76.6%) fruits, and 5 (7.8%) meat as the main component of their diet. In the HHLG, 6 (16.7%) reported vegetables, 27 (75.0%) reported fruits, and 3 (8.3%) reported meat. The distribution of dietary patterns did not differ significantly between the two groups ( $P = 1.000$ ).

Supplement use was reported by 10 (15.6%) individuals in the NHLG and 6 (16.7%) in the HHLG, with no statistically significant difference between groups ( $P = 0.892$ ) (Table 4).

**Table .4: BMI, Dietary and Supplements in two group NHL and HHL**

Characteristics		NHLG (n=64)	HHLG (n=36)	P-value*
BMI		$23.108 \pm 3.002$	$23.033 \pm 1.825$	0.877
Dietary intake since last 6 months	Vegetables	10 (15.6%)	6 (16.7%)	1
	Fruits	49 (76.6%)	27 (75%)	
	Meat	5 (7.8%)	3 (8.3%)	
	Vitamins	0	0	
	Others	0	0	
Supplements	Yes	10 (15.6%)	6 (16.7%)	0.892
	No	54 (84.4%)	30 (83.3%)	

\*P-value based on chi-square and Fisher exact test

The correlation between history of previous ischemic stroke and supplements was a weak, direct, and significant correlation ( $r = -0.201$ ,  $P \leq 0.045$ ), such that with increasing supplement consumption, ischemic stroke decreased, while the correlation between history of previous ischemic stroke and homocysteine level was not significant. (Table 5)

**Table.5 Correlation history of previous ischemic stroke with Supplements and Homocysteine level**

Variable	History of previous ischemic stroke
Supplements	$r = -0.201$ , $P^* \leq 0.045$
Homocysteine level	$r = 0.072$ , $P \leq 0.477$

\*P-value based on correlation coefficients spearman

## DISCUSSION

The current study aimed at exploring the association between serum levels of homocysteine (Hcy) and ischemic stroke, as well as to examine the possible effect of an additional diet. The studies involving 100 patient records showed that there was a statistically significant difference between the normal homocysteine level (NHLG) and hyperhomocysteinemia group (HHLG) on the basis of analyses conducted on the 100 patient records. The high average Hcy in the HHLG indicates that a significant number of the patients with ischemic stroke were exposed to moderate to high metabolic risk.

The analysis of demographic characteristics showed that male gender, low level of education and occupation, especially governmental occupation in the HHLG compared to housewife occupation in NHLG had significant association with high levels of Hcy. In contrast, cardiovascular risk factors such as high blood pressure, diabetes mellitus, and BMI did not show significant differences between the two groups. They did not find any significant relation between acute-phase levels of Hcy and antecedent ischemic stroke. However, there was a statistically significant albeit weak inverse relationship between dietary supplement intake and past stroke history, suggesting a possible type of neuroprotective action of supplementation in this group of patients.

The mean Hcy concentration in the HHLG cohort surpassed that of the NHLG cohort, with the observed levels in the HHLG group falling within the spectrum of moderate to severe hyperhomocysteinemia. This finding is consistent with previous research; for instance, a study conducted by HQ Omrani et al. (11) reported similar results among an Iranian population, the mean Hcy level in patients with acute ischemic stroke was comparable to that observed in the HHLG of the present study. This supports the considerable prevalence of this metabolic marker among regional subpopulations.

Increased homocysteine levels can lead to endothelial damage, oxidative stress, and platelet dysfunction, which play a key role in the development of atherosclerosis and vascular thrombosis (12). In a meta-analysis conducted by Srivastava et al. (4) identified elevated Hcy levels as an independent risk factor for all varieties of stroke, especially ischemic stroke, where the relative risk escalated by as much as 25%. The corroboration of these findings with our research underscores the importance of elevated Hcy as a prospective risk indicator. However, a notable difference lies in the intensity of elevation; in the mentioned meta-analysis, moderate levels (15–30  $\mu$ mol/L) were predominant, whereas our study encompassed a range from moderate to moderately high levels, without cases exceeding 100  $\mu$ mol/L. This variation may be attributed to earlier screening in our study population, which primarily included recently diagnosed inpatients.

According to evidence from preceding studies (13, 14), the reduction of Hcy levels has been demonstrated to confer beneficial effects in the prevention and management of neurovascular disorders. Increased plasma Hcy concentration is associated with increased vascular damage and impaired neuronal function, and Hcy can be considered as a significant biomarker and a suitable therapeutic target.

In contrast to the extensive epidemiological evidence and large-scale global meta-analyses identifying elevated Hcy as an independent and strong risk factor for the initial onset of ischemic stroke (15, 16), the present study did not demonstrate a significant correlation between measured Hcy levels and a prior history of stroke. Nonetheless, this absence of correlation does not diminish the pathological significance of Hcy, as the measurements were procured during the acute phase of stroke (within 24–48 hours post-onset), a period characterized by metabolic fluctuations and stress responses that may transiently influence serum Hcy levels.

The gender distribution within this investigation indicated that males comprised the predominant majority of participants in the HHLG group. This finding is in line with previous studies that show that, in relation to women, the physiological levels of homocysteine are higher in the male and that the incidence of hyperhomocysteinemia is still significantly elevated in men despite the possibility of confounding variables (17, 18). The identified sex-based variations are mainly ascribed to an increased muscle mass, high serum creatinine levels and hormonal differences (19). Based on these findings, it is important to note that there is an urgent need to assign males as a high-risk subgroup, which requires specific screening and preventive measures in this group of the population.

Moreover, the current research showed that there is strong correlation between the levels of hyperhomocysteinemia and education attainment as well as occupational status which could be the indirect measure of underlying socioeconomic status (SES). Hyperhomocysteinemia is often associated with the lack of the B-group of vitamins, and educational level and occupation may change the nutritional consciousness and access to the diets containing such micronutrients (20, 21).

Data regarding the dietary supplement use (vitamins B6, B12, and folate) showed no statistically significant difference of the two groups, which is why supplement usage did not seem to have a quantifiable impact on lowering the levels of hyperhomocysteinemia in the participants. Nevertheless, the low but meaningful negative relationship between the intake of the supplements and the history of a previous stroke could be suggestive of a possible long-term protective effect of the supplements, although that was not evident in acute stroke hyperhomocysteinemia levels. The result corresponds to those by S. Gunnala et al. (22) and N. Ahsan et al. (23) in their studies in the United States and Pakistan, respectively, who found that combined supplementation with vitamin B12 and folate could be used as a predictor of the low risk of ischemic stroke.

Lack of the nationwide program of folic acid fortification in the study area makes the local population particularly prone to folate and vitamin B12 deficiencies. Under these circumstances, more significant vascular protective effects would be noted with specifically aimed supplementation interventions than where routine food fortification exists. This noted negative correlation provides ample evidence to support the incorporation of Hcy screening and target-oriented use of B-vitamin supplementation in the secondary prevention of ischemic stroke in this local population.

The main strength of the current study lies in the fact that it receives data regarding a particular local population, and at the same time, it adjusts the clinical, nutritional, and demographic variables. The integrative approach adopted in this study has been utilized immensely to solve the multifactorial interrelationships in the pathogenesis of ischemic stroke. Additionally, the use of the NIHSS scale to assess the severity of the strokes coupled with the accurate classification of the types of ischemic strokes that were assessed by using neuroimaging also increased the validity and reliability of the study results.

The study however is limited in a number of ways. The cross-sectional nature of this study cannot definitively confirm a causal inference between high homocysteine levels and the risk of ischemic stroke. In addition, the small sample size may limit the generalizability of the results. Also, information regarding dietary supplementation and nutrition was based on patient self-report, which added some elements of recall bias.

## CONCLUSION

Finally, the paper shows that there exists a considerable level of correlation between the level of serum homocysteine and demographic indicators (sex and education) and no statistically significant correlations have been observed with the well-established stroke risk factors or clinical severity. Despite the fact that consumption of vitamin supplements showed a small negative relationship with a history of stroke before, the effect that it had on the underlying homocysteine levels at the acute stroke was not observed. The results of such indicate that homocysteine could be a biomarker that will interact with sociocultural and demographic factors but cannot act as a risk factor. In order to further explain the benefits of vitamin supplementation in the prevention of ischemic stroke, longitudinal studies and randomized clinical trials with a long follow-up and more accurate nutritional measures are justified.

**Acknowledgments:** Our sincere gratitude goes out to all those who contributed their time, effort and expertise to make this study a success.

**Conflict of interest:** All authors declare no conflict of interest.

**Data availability:** On demand, the data from the research is made available to the corresponding author.

**Authors' contributions:** Each author contributed equally in this research work.

**Funding:** Not applicable

## REFERENCES

- [1] Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Neurology*. 2021;20(10):795-820. doi: 10.1016/S1474-4422(21)00252-0
- [2] Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: a systematic analysis of the global burden of disease study 2017. *Neuroepidemiology*. 2020;54(2):171-9. doi: 10.1159/000506396.
- [3] Collaborators GS. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2019;18(5):439-58. doi: 10.1016/S1474-4422(19)30034-1.
- [4] Srivastava M, Gulia A, Kumar P. Elevated Homocysteine: A Critical Risk Factor for Stroke Types and Subtypes—A Systematic Review and Meta-Analysis of 96 Studies. *Acta Neurologica Taiwanica*. 2025;34(2):81-92. doi: 10.4103/ant.ANT-D-24-00004.
- [5] Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. *Nutrition & metabolism*. 2017;14(1):78. doi: 10.1186/s12986-017-0233-z.
- [6] Pinzon RT, Wijaya VO, Veronica V. The role of homocysteine levels as a risk factor of ischemic stroke events: a systematic review and meta-analysis. *Frontiers in Neurology*. 2023;14(12):1144584. doi: 10.3389/fneur.2023.1144584.
- [7] Zhou L, Wang J, Wu H, Yu P, He Z, Tan Y, et al. Serum levels of vitamin B12 combined with folate and plasma total homocysteine predict ischemic stroke disease: a retrospective case-control study. *Nutrition*

Journal. 2024;23(1):76. doi: 10.1186/s12937-024-00977-7.

[8] Zhang P, Zhang Y. Association of homocysteine with acute stroke and its subtypes in the chinese population. *Neuropsychiatric Disease and Treatment*. 2023;19:1435-42. doi: 10.2147/NDT.S409591.

[9] Zhang T, Jiang Y, Zhang S, Tie T, Cheng Y, Su X, et al. The association between homocysteine and ischemic stroke subtypes in Chinese: A meta-analysis. *Medicine*. 2020;99(12):e19467. doi: 10.1097/MD.00000000000019467.

[10] Dong W-C, Guo J-L, Xu L, Jiang X-H, Chang C-H, Jiang Y, et al. Impact of homocysteine on acute ischemic stroke severity: possible role of aminothiols redox status. *BMC neurology*. 2024;24(1):175. doi: 10.1186/s12883-024-03681-5.

[11] Omrani HQ, Shandiz EE, Qabai M, Chaman R, Fard HA, Qaffarpoor M. Hyperhomocystinemia, folate and B12 vitamin in Iranian patients with acute ischemic stroke. *ARYA Atheroscler*. 2011;7(3):97-101. doi.

[12] Hurjui LL, Tarniceriu CC, Serban DN, Lozneanu L, Bordeianu G, Nedelcu AH, et al. Homocysteine Attack on Vascular Endothelium—Old and New Features. *International Journal of Molecular Sciences*. 2025;26(13):6298. doi: 10.3390/ijms26136298.

[13] Ortiz-Salguero C, Romero-Bernal M, González-Díaz Á, Doush ES, del Río C, Echevarría M, et al. Hyperhomocystinemia: Underlying Links to Stroke and Hydrocephalus, with a Focus on Polyphenol-Based Therapeutic Approaches. *Nutrients*. 2025;17(1):40. doi: 10.3390/nu17010040.

[14] Wei LK, Menon S, Griffiths LR. Homocysteine and Stroke: A 30-Year Bibliometric Study Uncovering Research Trends and Future Directions. *Journal of Mind and Medical Sciences*. 2025;12(1):8. doi: 10.3390/jmms12010008

[15] Li B, Kou Y, Zhang L, Yi L. Hyperhomocystinemia-Driven Ischemic Stroke: Unraveling Molecular Mechanisms and Therapeutic Horizons. *Food Science & Nutrition*. 2025;13(7):e70517. doi: <https://doi.org/10.1002/fsn3.70517>.

[16] Unadkat SV, Padhi BK, Bhongir AV, Gandhi AP, Shamim MA, Dahiya N, et al. Association between homocysteine and coronary artery disease—trend over time and across the regions: a systematic review and meta-analysis. *The Egyptian Heart Journal*. 2024;76(1):29. doi: 10.1186/s43044-024-00460-y.

[17] Revelli A, Nuzzo AM, Moretti L, Arduino S, Roero S, Scali R, et al. Effects of Homocysteine Circulating Levels on Human Spontaneous Fertility and In Vitro Fertilization Outcomes: A Literature Review. *Nutrients*. 2025;17(20):3211. doi: 10.3390/nu17203211

[18] Sharma DK, Cheok TS, Rogers M, Lu VYZ, Solomon LB, Ramasamy B, et al. Relationship between homocysteine levels and bone quality in healthy adults - A systematic review and meta-analysis. *Clinical Nutrition ESPEN*. 2025;68:790-805. doi: <https://doi.org/10.1016/j.clnesp.2025.06.034>.

[19] Xu R, Huang F, Wang Y, Liu Q, Lv Y, Zhang Q. Gender- and age-related differences in homocysteine concentration: a cross-sectional study of the general population of China. *Scientific Reports*. 2020;10(1):17401. doi: 10.1038/s41598-020-74596-7.

[20] Dahal S, Bhattacharjee D, Kaushik A, Kasaudhan S, Saraswathy KN, Devi NK, et al. Micronutrient Deficiencies and Association With Hypertension: The Role of Folate, Vitamin B12, and Homocysteine. *American Journal of Human Biology*. 2025;37(9):e70143. doi: <https://doi.org/10.1002/ajhb.70143>.

[21] Schauer M, Mair S, Motevalli M, Tanous D, Burtscher M, Wirnitzer K. Health Patterns across Adulthood: An Age-Based Investigation of the Nutritional Status, Homocysteine, and CoQ10 of Bank Staff. *Clin Pract*. 2024;14(2):443-60. Epub 20240314. doi: 10.3390/clinpract14020034.

[22] Gunnala S, Buhlman LM, Jadavji NM. How Increased Dietary Folic Acid Intake Impacts Health Outcomes Through Changes in Inflammation, Angiogenesis, and Neurotoxicity. *Nutrients*. 2025;17(7):1286. doi: 10.3390/nu17071286

[23] Ahsan N, Shahbaz L, Asim S, Erum H, Ansari M, Javaid A. Serum Vitamin B12 as a Risk Factor and Prognostic Indicator in Acute Ischemic Stroke: A Case-Control Study at a Tertiary Care Hospital Mirpurkhas (Sindh): Serum Vitamin B12 as a Risk Factor and Prognostic Indicator in Acute Ischemic Stroke. *Pakistan Journal of Health Sciences*. 2025:331-6. doi: 10.54393/pjhs.v6i1.2430