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Original Research Article

Prevalence and Predictors of Hyper-Homocysteinemia among Ischemic Stroke Patients – A Hospital Based Prospective Observational Study

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Abstract:

Objectives: The objectives were to estimate the prevalence of hyper-homocysteinemia in patients with ischemic stroke presenting to a tertiary care hospital in south India; to assess the correlation between levels of hyper-homocysteinemia and carotid intima media thickness in these patients.

Methods: This was a hospital based prospective observational study conducted in the outpatient department and inpatient wards of the Department of General Medicine between January 2021 and December 2021.

Results: The results showed that the levels of homocysteine was raised in 69.0% of the patients – >15µmol/L; however, the levels of ≤15µmol/L, that is normal in 31.0% of the patients with ischaemic stroke. Male gender (72.5% vs 32.3%), smoking (60.9% vs 9.7%), alcohol intake (62.3% vs 9.7%), presence of hemiplegia or hemiparesis (63.8% vs 32.3%), and infarct site being carotid artery (88.4% vs 61.3%) was significantly associated with raised levels of homocysteine is patients with ischemic stroke ($p<0.05$), in comparison with female gender, nonsmokers, patients without alcohol intake, without hemiparesis or hemiplegia and involvement of vertebral artery, respectively. Majority (80.6%) of the patients with homocysteine levels ≤15µmol/L had carotid intimal thickness <0.75; however, among 66.7% patients with homocysteine levels >15µmol/L, the carotid intimal thickness was ≥0.90mm – this difference was found to be statistically significant. The results of correlation analysis showed the Pearson's correlation coefficient to be 0.628 – significant positive moderate correlation ($p<0.05$) between carotid intimal thickness and homocysteine levels.

Conclusion: Monitoring both homocysteine levels and carotid intimal thickness could offer a more comprehensive assessment of vascular risk, allowing for timely and tailored preventive measures.

Keywords: Hyper-homocysteinemia, Carotid intimal thickness, Ischemic stroke, India, Prevalence, Predictors.

Introduction

Ischemic stroke remains a leading cause of morbidity and mortality worldwide, [1] contributing to a significant burden on healthcare systems and necessitating a comprehensive understanding of its underlying risk factors.[2, 3] Hyper-homocysteinemia, an elevated level of homocysteine in the blood, has emerged as a potential contributor to vascular pathology, with implications for ischemic stroke incidence and severity.[4]

This present study aims to shed light on the prevalence of hyper-homocysteinemia in patients presenting with ischemic stroke to a tertiary care hospital in south India and explore its associations with clinical characteristics and carotid intimal thickness.

Homocysteine, a sulphur-containing amino acid derived from methionine metabolism, is intricately linked to cardiovascular health.[5] Elevated levels of homocysteine have been implicated in endothelial dysfunction, oxidative stress, and atherosclerosis, mechanisms that are crucial in the pathogenesis of ischemic stroke.[6] Despite growing evidence of the potential role of hyper-homocysteinemia in cardiovascular diseases, its specific association with ischemic stroke, especially in the context of diverse populations, warrants further investigation. This study unfolds against the backdrop of the unique demographic and lifestyle characteristics of south India, where genetic and environmental factors may influence the prevalence and impact of hyper-homocysteinemia on ischemic stroke risk. South Asian populations, including those in India, have shown distinct patterns of cardiovascular risk factors, highlighting the importance of region-specific research to tailor preventive and

therapeutic strategies.[7-9] Previous studies, including the work by Suleiman et al. have reported varying prevalence rates of hyper-homocysteinemia in ischemic stroke patients, underscoring the need for context-specific investigations.[10] In this pursuit, the primary objective of the present study was to estimate the prevalence of hyper-homocysteinemia in patients with ischemic stroke presenting to a tertiary care hospital in south India. We also assessed the correlation between levels of hyper-homocysteinemia and carotid intima media thickness in these patients.

Materials and methods

This was a hospital based prospective observational study conducted in the outpatient department and inpatient wards of the Department of General Medicine, tertiary healthcare facility in south India between January 2021 and December 2021. The study was approved by the Institute Human Ethics Committee (IHEC). The content of Participant Information Sheet (PIS) in local language was provided to the participants (and their attenders) and contents were read to them in their own language to their satisfaction. The participants were enrolled in the study after obtaining written informed consent. The present study included all the patients presenting to the department of General Medicine with ischemic stroke – verified by computed tomography (CT) brain. However, we excluded patients with haemorrhagic stroke; patients on folic acid supplements, anti-epileptics, oral contraceptive pills, or other drugs causing hyper-homocysteinemia; patients with chronic kidney disease; with pre-existing coronary artery disease; and patients not willing to provide informed written consent.

Suleiman et al. (2019) documented the prevalence of raised homocysteine levels in ischemic stroke patients to be 34.0%.[10] Using this information, considering the type 1 error (alpha error) to be 5.0%, type 2 error (beta error) to be 20.0% (or 80.0% power), 10% absolute precision, and 10.0% non-response rate the minimum estimated sample size was rounded off to 100 with 95% confidence. We used a purpose predesigned, semi structured, pretested questionnaire to collect data on sociodemographic variables, detailed history, general physical examination, and clinical examination findings. All the included patients underwent serum homocysteine measurements and carotid ultrasonography (USG) to measure carotid intima media thickness.

The data obtained was manually entered into Microsoft Excel, coded, and recoded. Analysis was done using Statistical Package for the Social Sciences (SPSS) v23. Descriptive analysis was presented using numbers and percentages for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. To test for association, Chi-square test or Fisher's exact test (two sided) was used for categorical data; independent't' test (two sided) was used for continuous data. To assess the correlation between levels of hyper-homocysteinemia and carotid intima media thickness, we used Pearsons's correlation coefficients. Statistical significance was considered at $p<0.05$.

Results

The present study included a total of 100 patients with ischemic stroke presenting to a tertiary care hospital in south India. More than two third (72.0%) patients were above 30 years of age, with a considerable proportion (33.0%) above 60 years of age. Nearly two third (60.0%) patients were males. The proportion of patients with smoking history was 45.0% and history of alcohol intake was 46.0%. Of the 100 patients included, 26.0% patients had hypertension, 24.0% had diabetes, and 11.0% had dyslipidaemia. The distribution of brain injury based of GCS scores showed that nearly two third patients (64.0%) had mild, 35.0% patients had moderate, and 1.0% patients had severe brain injuries. More than half (54.0%) the patients presented with hemiparesis or hemiplegia, 20.0% had cerebellar symptoms, 15.0% had seizures, and 11.0% patients had encephalopathy. Majority of the included patients (80.0%) had carotid artery involvement, and 20.0% patients had vertebral artery as infarct site.

Prevalence of hyper-homocysteinemia: The results of the present study showed that the levels of homocysteine was raised in 69.0% of the patients – more than 15µmol/L; however, the levels of less than or equal to 15µmol/L, that is normal in 31.0% of the patients with ischaemic stroke.

Factors associated with hyper-homocysteinemia: The results of the tests of association showed that male gender (72.5% vs 32.3%), smoking (60.9% vs 9.7%), alcohol intake (62.3% vs 9.7%), presence of hemiplegia or hemiparesis (63.8% vs 32.3%), and infarct site being carotid artery (88.4% vs 61.3%) was significantly associated with raised levels of homocysteine is patients with ischemic stroke ($p<0.05$), in comparison with female gender, nonsmokers, patients without alcohol intake, without hemiparesis or hemiplegia and involvement of vertebral artery, respectively.

However, we found that age (in years), presence of hypertension, diabetes, dyslipidaemia, and the severity of brain injury were not statistically associated with presence of hyper-homocysteinemia ($p>0.05$).

Association and correlation between carotid intimal thickness and homocysteine levels: The

results of the present study showed that 80.6% patients with homocysteine levels less than or equal to 15µmol/L had carotid intimal thickness less than 0.75; however, among 66.7% patients with homocysteine levels more than 15µmol/L, the carotid intimal thickness was more than or equal to 0.90mm – this difference was found to be statistically significant ($p<0.05$). The results of correlation analysis showed the Pearson's correlation coefficient to be 0.628 – significant positive moderate correlation ($p<0.05$) between carotid intimal thickness and homocysteine levels.

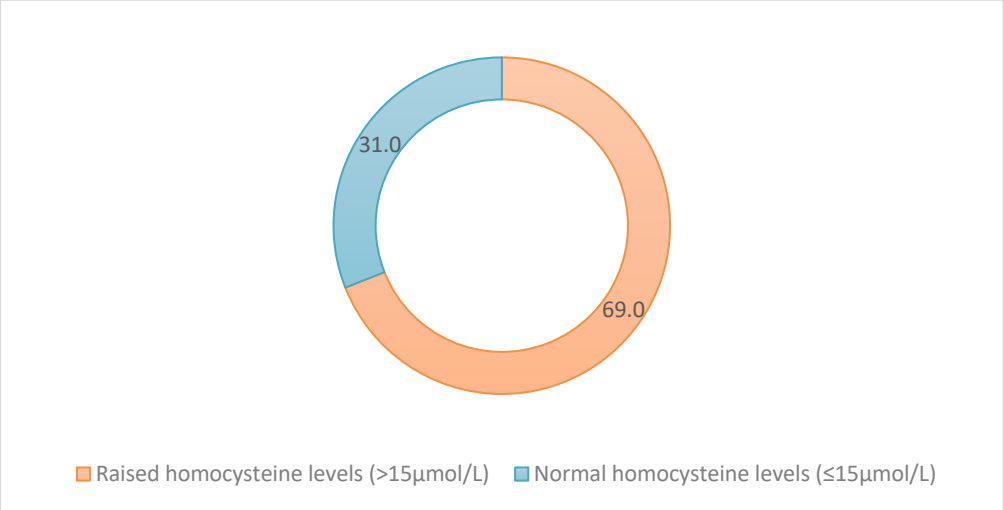

Figure 1: Distribution of ischemic stroke patients, by levels of homocysteine

Table 1: Association between sociodemographic, clinical variables and homocysteine levels

		Homocysteine levels		Total N = 100	p value
		≤15µmol/L N = 31	>15µmol/L N = 69		
Age (in years)	≤30	9 (29.0)	19 (27.6)	28 (28.0)	0.987
	31 to 60	12 (38.7)	27 (39.1)	39 (39.0)	
	>60	10 (32.3)	23 (33.3)	33 (33.0)	
Gender	Male	10 (32.3)	50 (72.5)	60 (60.0)	<0.001*
	Female	21 (67.7)	19 (27.5)	40 (40.0)	
Smoking	Present	3 (9.7)	42 (60.9)	45 (45.0)	<0.001*
	Absent	28 (90.3)	27 (39.1)	55 (55.0)	
Alcohol	Present	3 (9.7)	43 (62.3)	46 (46.0)	<0.001*
	Absent	28 (90.3)	26 (37.7)	54 (54.0)	
Hypertension	Present	7 (22.6)	19 (27.5)	26 (26.0)	0.601
	Absent	24 (77.4)	50 (72.5)	74 (74.0)	
Diabetes	Present	8 (25.8)	16 (23.2)	24 (24.0)	0.776
	Absent	23 (74.2)	53 (76.8)	76 (76.0)	
Dyslipidaemia	Present	2 (6.5)	9 (13.0)	11 (11.0)	0.330
	Absent	29 (93.5)	60 (87.0)	89 (89.0)	
Brain injury^	Severe	0 (0.0)	1 (1.4)	1 (1.0)	0.764
	Moderate	12 (38.7)	23 (34.4)	35 (35.0)	
	Mild	19 (61.3)	45 (65.2)	64 (64.0)	
Clinical profile	Hemiparesis or Hemiplegia	10 (32.3)	44 (63.8)	54 (54.0)	0.035*
	Cerebellar symptoms	9 (29.0)	11 (15.9)	20 (20.0)	
	Seizures	7 (22.6)	8 (11.6)	15 (15.0)	
	Encephalopathy	5 (16.1)	6 (8.7)	11 (11.0)	
Infarct site	Carotid	19 (61.3)	61 (88.4)	80 (80.0)	0.002*
	Vertebral	12 (38.7)	8 (11.6)	20 (20.0)	

^Severe brain injury, as GCS score less than or equal to 8; moderate, GCS between 9 to 12; mild, GCS more than or equal to 13, GCS, Glasgow Coma Scale, *Statistically significant at $p<0.05$

Table 2: Association between carotid intimal thickness and homocysteine levels

		Homocysteine levels		Total N = 100	p value
		≤15µmol/L N = 31	>15µmol/L N = 69		
Carotid Intimal Thickness (in mm)	<0.75	25 (80.6)	8 (11.6)	33 (33.0)	<0.001*
	0.76 to 0.79	1 (3.2)	6 (8.7)	7 (7.0)	
	0.80 to 0.89	3 (9.7)	9 (13.0)	12 (12.0)	
	≥0.90	2 (6.5)	46 (66.7)	48 (48.0)	
*Statistically significant at p<0.05					

Discussion

The demographic profile of the study participants revealed a significant representation of patients above 30 years of age, with a notable portion above 60 years. This aligns with existing literature that highlights the increased susceptibility to ischemic stroke with advancing age.[11] The higher prevalence of males in the study is consistent with some epidemiological trends showing a male predominance in stroke incidence.[12] The observed rates of smoking and alcohol intake among the participants highlight the relevance of lifestyle factors in ischemic stroke, as these habits have been identified as independent risk factors in various studies.[13,14]

The distribution of clinical features among patients, such as hypertension, diabetes, and dyslipidaemia, reinforces the association between traditional cardiovascular risk factors and ischemic stroke.[15] Additionally, the prevalence of hemiparesis or hemiplegia, cerebellar symptoms, seizures, and encephalopathy in the study mirrors the diverse clinical manifestations of ischemic stroke, emphasizing the heterogeneity of the condition.[16] The substantial proportion of patients with carotid artery involvement underscores the significance of extra cranial large vessel disease in ischemic stroke pathology. This finding is consistent with the understanding that atherosclerotic changes in major cervical arteries contribute significantly to cerebrovascular events.[17] Understanding the demographic and clinical characteristics of ischemic stroke patients in a specific region, as demonstrated in the study, is pivotal for tailoring preventive and management strategies. The high prevalence of traditional risk factors emphasizes the need for comprehensive stroke prevention programs targeting these factors.

The finding that 69.0% of the patients with ischemic stroke in the study exhibited elevated levels of homocysteine (more than 15µmol/L) suggests a considerable association between hyper-homocysteinemia and ischemic stroke in the south Indian population. This result aligns with existing literature that has identified hyper-homocysteinemia as a potential risk factor for cardiovascular diseases, including ischemic stroke.[18,19] Comparisons with prior studies, such as the one by Suleiman et al. (2019) that documented a prevalence of 34.0% for raised homocysteine levels in ischemic stroke patients, emphasize the variability in hyper-homocysteinemia prevalence across different populations and settings.[10] This variation may be influenced by genetic, dietary, and regional factors.[20] The high prevalence of hyper-homocysteinemia in the study has important clinical implications. Elevated homocysteine levels have been implicated in endothelial dysfunction, oxidative stress, and atherothrombosis, all of which are factors contributing to the pathogenesis of ischemic stroke.[18,21] As such, identifying and addressing hyper-homocysteinemia could potentially become a target for preventive strategies in ischemic stroke management. The results emphasize the need for integrating homocysteine assessments into routine risk factor evaluations for ischemic stroke. Clinical guidelines may consider including recommendations for screening and managing hyper-homocysteinemia, especially in populations with a higher prevalence.

The significant association between male gender and hyper-homocysteinemia in the study is consistent with existing literature that has reported higher homocysteine levels in men compared to women.[22] The hormonal differences between genders, as well as potential lifestyle variations, may contribute to this observed disparity. The strong association between smoking, alcohol intake, and elevated homocysteine levels aligns with well-established evidence.

Smoking is known to increase homocysteine levels through various mechanisms, including interference with folate metabolism and induction of oxidative stress.[23] Similarly, alcohol consumption has been linked to increased homocysteine, likely due to its impact on folate metabolism and liver function.[24] The emphasis on lifestyle modifications for stroke prevention becomes particularly crucial in light of these associations. The association between the presence of hemiplegia or hemiparesis and hyper-homocysteinemia suggests potential implications for the clinical profile of ischemic stroke patients.

This finding may prompt further investigations into the mechanistic links between hyper-

homocysteinemia and specific stroke phenotypes, contributing to a more nuanced understanding of the disease spectrum. The observed association between carotid artery involvement and elevated homocysteine levels underscores the potential role of large vessel pathology in hyper-homocysteinemia-related ischemic stroke. This aligns with the broader concept of atherosclerosis contributing to vascular events.[25] The association could be influenced by the impact of homocysteine on endothelial function and atherogenesis.

The lack of a statistically significant association between age, hypertension, diabetes, dyslipidaemia, and hyper-homocysteinemia in the study contrasts with some previous findings.

While age is a well-established factor influencing homocysteine levels, the complex interplay with other cardiovascular risk factors may attenuate the direct association.[22] Inconsistencies in findings across studies highlight the multifactorial nature of hyper-homocysteinemia in ischemic stroke. The identified associations have important implications for clinical practice. Recognizing male gender, smoking, alcohol intake, specific clinical presentations, and vascular territories as potential risk factors for hyper-homocysteinemia could inform targeted screening and intervention strategies. Lifestyle modifications, such as smoking cessation and alcohol reduction, may be emphasized in stroke prevention programs.

The observed association between elevated homocysteine levels and increased carotid intimal thickness in the study suggests a potential link between hyper-homocysteinemia and atherosclerosis. A thicker carotid intima-media layer is often indicative of subclinical atherosclerotic changes, and this finding aligns with the notion that homocysteine may contribute to the atherogenic process.[26]

The significant association between carotid intimal thickness and homocysteine levels has clinical implications for risk stratification in patients with ischemic stroke. Monitoring carotid intimal thickness, a surrogate marker for atherosclerosis, alongside homocysteine levels may provide a more comprehensive assessment of vascular risk in these patients.[27] Early identification of individuals with elevated homocysteine levels and increased carotid intimal thickness may guide intensified preventive measures and interventions. The significant positive moderate correlation (Pearson's correlation coefficient of 0.628) between carotid intimal thickness and homocysteine levels further strengthens the evidence for a relationship between these two variables.

The positive correlation suggests that as homocysteine levels increase, there is a corresponding increase in carotid intimal thickness. This reinforces the idea that homocysteine may play a role in the atherosclerotic process, leading to vascular remodelling. Future research could explore these associations in larger and more diverse populations, considering additional variables such as genetic factors, dietary habits, and other cardiovascular risk factors.

Conclusion

Our study provides valuable insights into the prevalence, associated factors, and interplay between hyper-homocysteinemia and carotid intimal thickness in patients with ischemic stroke at a tertiary care hospital in south India. The high prevalence of hyper-homocysteinemia, observed in 69.0% of our study participants, underscores the significance of this condition in the context of ischemic stroke.

The identified associations with male gender, smoking, alcohol intake, specific clinical presentations, and carotid artery involvement highlight the multifactorial nature of hyper-homocysteinemia in this population. These findings contribute to the growing body of evidence emphasizing the need for comprehensive risk stratification in ischemic stroke patients, considering not only traditional cardiovascular risk factors but also lifestyle and clinical parameters. The significant association between hyper-homocysteinemia and increased carotid intimal thickness suggests a potential link between elevated homocysteine levels and early atherosclerotic changes. The positive moderate correlation further supports the notion that homocysteine may play a role in the vascular remodelling process, contributing to the pathogenesis of atherosclerosis in patients with ischemic stroke.

Monitoring both homocysteine levels and carotid intimal thickness could offer a more comprehensive assessment of vascular risk, allowing for timely and tailored preventive measures. In summary, our study adds to the existing knowledge on hyper-homocysteinemia and its associations in patients with ischemic stroke, emphasizing the need for a holistic and personalized approach to stroke risk assessment and management. These findings pave the way for further research and the development of targeted interventions aimed at reducing the burden of hyper-homocysteinemia related vascular complications in clinical practice.

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