TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

# Implications of homocysteine levels and carotid intima-media thickness in Indian stroke patients

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## ABSTRACT

***Background*** The study aimed to evaluate the role of homocysteine (HCY) in modulating various stroke parameters. The primary objective was to study the correlation of HCY levels with carotid intima-media thickness (IMT) in stroke patients and investigate if HCY levels had any predictive value for the National Institutes of Health Stroke Scale (NIHSS) score.

***Material and Methods*** Seventy-eight patients of magnetic resonance imaging or computed tomography scans-confirmed acute ischaemic stroke were recruited for this study, and the NIHSS score was evaluated upon admission. Fasting blood samples were tested for serum HCY, fasting blood glucose (FBG) and lipid profile. Ultrasonography of the neck ascertained IMT of common carotid artery (CCA) and internal carotid artery (ICA).

***Results*** The mean age of male and female subjects was 57.88 ± 13.97 and 59.16 ± 13.62 years, respectively. 71.93% of stroke patients were hyperhomocysteinemic (HHcyc), and 24.36% were hyperlipidemic. Patients with NIHSS ≥ 5 had higher LDL cholesterol than those with NIHSS < 5. Positive correlations were found between FBG and CCA IMT and triglyceride and NIHSS. HCY cut off of ≥ 15 µmol/L had 91.7% sensitivity and 66.7% specificity for predicting NIHSS ≥ 15. HHcyc state was associated with increased ICA IMT. HHcyc state was best predicted by ICA IMT and HCY positively correlated with ICA IMT.

***Conclusions*** HHcyc state holds a good predictive value for the severity of stroke. We also concluded that ICA IMT measurement may reduce the need for a HCY test as it predicts higher HCY levels, reducing the burden on resources. We suggest that evaluating HCY and ICA IMT should be part of the standard cerebrovascular accident management protocol.

*Turk J Int Med 2023;5(3):176-184*
*DOI: 10.46310/tjim.1248356*

***Keywords:*** *Homocysteine, carotid intima-media thickness, stroke.*

***Received:*** *February 6, 2023;* ***Accepted:*** *May 15, 2023;* ***Published Online:*** *July 29, 2023*

***How to cite this article:*** *Jain VN, Rana P, Bhoge KA, Rojekar MV. Implications of homocysteine levels and carotid intima-media thickness in Indian stroke patients Turk J Int Med 2023;5(3):176-184. DOI: 10.46310/tjim.1248356*

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## INTRODUCTION

A cerebrovascular accident (CVA), or stroke, as it is popularly known, is one of the leading causes of mortality and morbidity worldwide[1], with developing countries accounting for 85% of global deaths from stroke.[2] CVA is a medical emergency presenting with an abrupt onset of neurological deficit that can be attributed to a focal vascular cause. Thus, stroke is defined as clinical, and laboratory studies, including brain imaging, are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. The acronym 'FAST' has been popularly used to educate the masses about the sudden-onset symptoms of stroke - Face showing unilateral drooping, Arms with unilateral weakness, Speech impediment, and finally, Timely help required.

Establishing the severity of stroke in a patient helps gauge prognosis and shapes therapeutic approaches. Hence, various scales have been developed to evaluate the clinical severity of stroke. Among these, the National Institutes of Health Stroke Scale (NIHSS) is perhaps the most comprehensive and is easy to perform at the bedside.[3] Muir *et al*.'s study[4] among 373 patients of acute ischaemic stroke showed that at a 3-month follow-up period, the median baseline NIHSS score of patients who were alive at home (good prognosis) was 4, patients alive in care (moderate prognosis) was 14, and dead patients (poor prognosis) was 18. Accordingly, we adopted a general classification criterion wherein we graded the severity of stroke as minor/mild if the NIHSS score lay between 1-4, moderate between 5-14, moderate-to-severe between 15-20, and severe between 21-42.

Measurement of the carotid intima-media thickness (IMT) is an upcoming tool in research methodology. IMT measurement in stroke patients is particularly useful as it gives radiological evidence for atherosclerosis and helps to gauge both - treatment aggressiveness, i.e. dosage of hypolipidaemic drugs, anticoagulants etc., as well as prognosis, such as risk of recurrence - when considered along with traditional risk factors. Since the late 1990s, many factors influencing IMT have been identified. Darabian *et al*.[5] reviewed the significance of carotid IMT in clinical research. Their systematic review found that IMT was affected by most cardiovascular risk factors like age, total cholesterol (TCHOL), high-density-lipoprotein cholesterol (HDLC), smoking, diabetes mellitus, hypertension etc. In addition to traditional cardiovascular risk factors, novel factors such as homocysteine (HCY) are under consideration.

HCY is a four-carbon amino acid with a free thiol group formed by the demethylation of methionine. Plasma HCY levels are affected by both acquired and genetic factors. Acquired factors include ageing, smoking, impaired renal function, and medication with drugs such as corticosteroids and cyclosporine, and the main genetic ones are classical homocystinuria and C677T homozygote mutation of the 5,10 - methylenetetrahydrofolate reductase (MTHFR) gene.[6,7] Normal fasting serum/plasma homocysteine levels remain below 15 µmol/L. We have referred to this state as euhomocysteinemia (EHcy). Hyperhomocysteinemia (HHcy) elevates fasting homocysteine levels beyond 15 µmol/L. High plasma levels of HCY have been implicated in developing vascular diseases, including stroke. Elevated serum HCY is described to have an atherosclerotic and thrombotic effect by various mechanisms such as homocysteinylation, induction of oxidative stress and excitotoxicity.[8] Over the last decade, convincing evidence has been gathered on the relation between elevation of plasma HCY and ischemic stroke. Though HCY has been studied extensively, the evidence supporting its use in practice is conflicted vis-a-vis its prognostic value. The World Health Organization estimates that by 2030, 80% of all strokes will occur in low and middle-income countries.[9] Hence, it is imperative to thoroughly investigate novel risk factors for stroke and their management.

## MATERIAL AND METHODS

A cross-sectional, observational study was conducted in July and August 2022 after obtaining approval from the Institutional Clinical Ethics Committee (approval letter no. IEC/A/264/06/2022 dated 27/06/2022). Good clinical care guidelines and guidelines as per the Helsinki Declaration were followed throughout the process.

Hospitalized patients with radiologically confirmed acute ischaemic stroke showing acute brain infarct(s) on magnetic resonance (MR) or computed tomography (CT) imaging of the brain were approached for the study. The study population consisted of 78 patients with acute ischaemic stroke. Inclusion criteria were adult patients (age > 18 years), radiologically (MR or CT brain imaging) confirmed and hospitalized cases of acute ischaemic stroke, and examination, radiology and blood sampling completed within 24 hours of

hospitalization. Exclusion criteria were pregnant women and minors (age < 18 years).

After taking written informed consent from the guardian and the patient (wherever possible), a neurological examination was done to ascertain the NIHSS score of the patient according to the guide on the National Institutes of Health website. Fasting blood samples were collected and tested for serum HCY, fasting blood glucose (FBG) and lipid profile, which consisted of triglycerides (TG), TCHOL, HDLC and low-density lipoprotein cholesterol (LDLC).

Ultrasonography of the neck was done to ascertain common carotid artery (CCA) IMT and internal carotid artery (ICA) IMT using the colour Doppler method. We also noted the percentage of luminal narrowing (LN%) caused by plaques, if any. Data was recorded using Microsoft Office Excel 2016 spreadsheet software and was further analyzed on IBM SPSS version 26 software.

## RESULTS

Of the 78 stroke patients, 44 were male (M), and 34 were female (F). The $\chi 2$ (chi-square) test to assess the distribution pattern returned a non-significant p-value. Hence, the seemingly unequal distribution of males and females was not statistically significant. The average age of male and female subjects was 57.88 ± 13.97 and 59.16 ± 13.62 years, respectively. The mean NIHSS score of all stroke patients was 10.07 ± 5.95, varying from 1 to 24. Fourteen patients (17.95%) presented with mild CVA, 48 patients (61.54%) with moderate CVA, 12 patients (15.38%) with moderate-to-severe CVA, and four patients (5.13%) with severe CVA (Figure 1). Twenty-two patients (28.07%) were euhomocysteinemic, while 56 patients (71.93%) were hyperhomocysteinemic. 19 out of 78 cases (24.36%; 15 M and 4 F) showed hyperlipidemic lipid profiles. Patients were classified as hyperlipidemic if at least one of these criteria was fulfilled: (i) TCHOL > 240 mg/dL, (ii) TG > 200 mg/dL, (iii) HDLC < 40 mg/dL, (iv) LDLC > 160 mg/dL.

**Grouping by severity of stroke using NIHSS score**

Independent samples t-test was applied to all measured parameters, and patients were grouped separately as minor/mild stroke, moderate, moderate-to-severe and severe cases based on NIHSS scores as described in the introduction. LDLC was significantly higher (t = 2.074, $p$ = 0.043*) in patients with NIHSS score ≥ 5 compared to those with NIHSS score < 5. Receiver-Operator Characteristic (ROC) analysis was performed three times by successively grouping cases as having positive states defined by NIHSS ≥ 5, NIHSS ≥ 15 and NIHSS > 20. The area under the ROC curve (AUC) of HCY increased linearly from 49.0% to 71.6%. Keeping the HCY cut off at 15.00 µmol/L, the sensitivity increased linearly from 74.5% to 100.0% while the specificity increased linearly from 60.0% to 70.4% (Figure 2). HCY cut off of ≥ 15 µmol/L had 91.7% sensitivity and 66.7% specificity

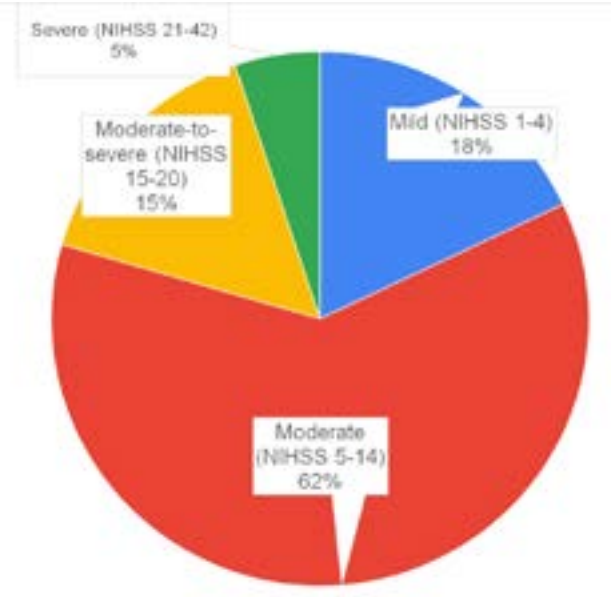


**Figure 1. Proportion of cases graded by stroke severity according to NIHSS score.**

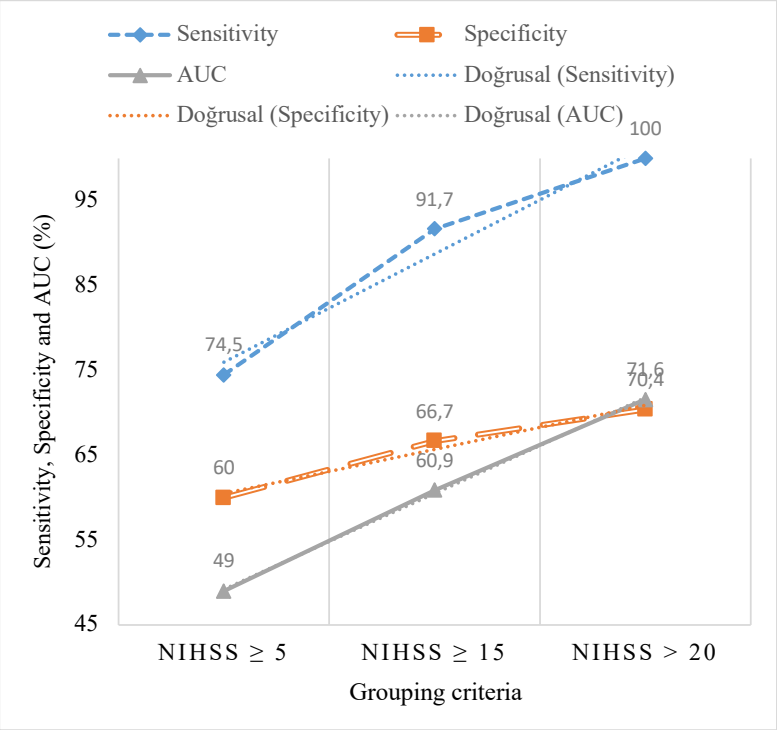


**Figure 2. Predictive value of HCY for NIHSS score via ROC parameters (sensitivity, specificity and AUC).**

for predicting NIHSS ≥ 15. This result confirms that the HHcyc state holds a good predictive value for predicting stroke severity as classified by the NIHSS score and is most valuable for NIHSS ≥ 15 (i.e. moderate-to-severe and severe cases).

## Grouping by serum HCY levels: EHcyc vs HHcyc patients

The data were grouped as either EHcyc patients with HCY < 15 µmol/L or HHcyc subjects with HCY ≥ 15 µmol/L. Independent samples t-tests were run to check differences between EHcyc and HHcyc patients. ICA IMT (t = 2.132, $p$ = 0.039*) was significantly higher in HHcyc patients than EHcyc patients. Other parameters (even NIHSS score, CCA IMT etc.) were not significantly different between the two groups.

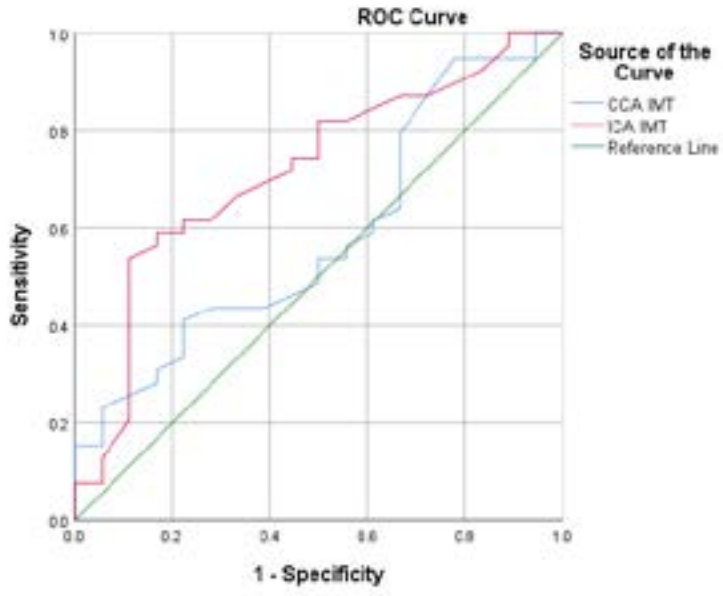


**Figure 3. ROC analysis of HHcyc state with CCA IMT and ICA IMT.**

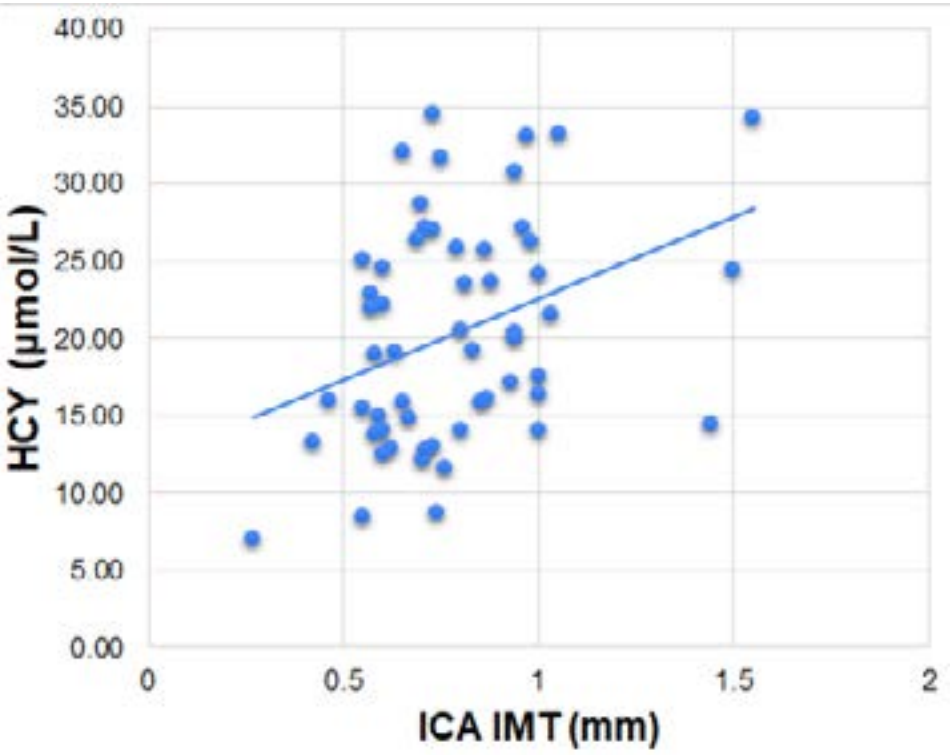


**Figure 4. Scatter plot of ICA IMT against HCY.**

ROC analysis was done to check the predictive value of measured parameters for HHcy. ICA IMT had the highest AUC (> 0.7, $p = 0.002$*), having sensitivity and specificity significant at the 0.01 level. *P* - values of other parameters (including CCA IMT, conventional risk factors such as LDLC, and NIHSS score) were insignificant regardless of their AUC. It is interesting to note here that ICA IMT provides a more sensitive and specific prediction of the HHcyc state than CCA IMT, which is conventionally measured as the carotid IMT (Figure 3).

**Table 1. Pearson correlations for pairs of analytes.**

| Analyte pair | Pearson correlation coefficient | *P* - value |
|---|---|---|
| TCHOL and CCA IMT | 0.296 | 0.026* |
| TCHOL and ICA IMT | 0.320 | 0.015* |
| TCHOL and TG | 0.337 | 0.010* |
| TCHOL and HDLC | 0.666 | < 0.001* |
| TCHOL and LDLC | 0.947 | < 0.001* |
| HCY and ICA IMT | 0.331 | 0.012* |
| TG and LDLC | 0.350 | 0.008* |
| TG and NIHSS | 0.262 | 0.049* |
| FBG and CCA IMT | 0.286 | 0.031* |

TCHOL: total cholesterol, CCA: common carotid artery, IMT: intima-media thickness, ICA: internal carotid artery, TG: triglyceride, HDLC: high-density-lipoprotein cholesterol, LDLC: low-density lipoprotein cholesterol, HCY: homocysteine, NIHSS: National Institutes of Health Stroke Scale, FBG: fasting blood glucose.

**Grouping by ICA IMT > 1.0 mm and ≤ 1.0 mm**

Independent samples t-test was applied to all measured parameters, and cases were grouped as having ICA IMT either > 1.0 mm or ≤ 1.0 mm. Cases with ICA IMT > 1.0 mm had higher HCY ($t = 2.230$, $p = 0.030$*), LDLC ($t = 2.097$, $p = 0.041$*), and CCA IMT ($t = 4.200$, $p < 0.001$*).

**Correlations of blood parameters**

The glycemic marker, FBG, was positively correlated with CCA IMT. Upon analyzing the lipid profile, TCHOL was positively correlated with all other lipid profile parameters (TG, HDLC, LDLC) and CCA IMT and ICA IMT. TG positively correlated with LDLC and NIHSS scores (Table 1). The main analyte, HCY, was positively correlated with ICA IMT (Figure 4, Table 1). Interestingly, it had no other significant correlations, not even with CCA IMT or NIHSS score or any other blood parameters.

## DISCUSSION

Cerebral atherosclerosis is the basic underlying

pathophysiology of ischaemic stroke. Khan *et al.*10 found that hyperlipidemia was present in 16% of stroke patients, while the present study found hyperlipidemia in 24.36% of stroke patients. We report here that patients with NIHSS scores ≥ 5 have higher LDLC than those with NIHSS scores < 5. Affirming our result, Uno *et al.*[11] found that increased levels of oxidised LDLC correlated with a larger extent of ischaemic lesions and could predict enlargement of the lesions. Our study reported that the glycemic marker, FBG, was positively correlated with CCA IMT. FBG has a well-documented incremental effect on the lipid profile. Hyperglycemia is essentially the cause of lipemic and cardiovascular morbidity in diabetes mellitus.[12] Impaired lipemic control, as well as pre-existing cardiovascular damage in diabetes mellitus, contributes to increased carotid IMT. Brohall *et al.*'s systematic review[13], consisting of over 4,000 diabetic patients and reporting higher IMT in people with diabetes than controls, gives excellent insight and evidence-based support to this finding.

Stein *et al.*[14] observed that HHcy was associated with various vascular and haematological abnormalities such as endothelial injury, increased synthesis of thromboxane A2, activation of clotting factors V, X and XII, inhibition of antithrombin III and protein C, promotion of binding of lipoprotein (a) to fibrin, and growth of smooth muscle cells. All of these processes are known to be risk factors in the development and progression of atherosclerosis, leading to coronary artery disease, CVA, and peripheral arterial vascular disease. A prospective population-based cohort study with nearly ten years of follow-up concluded that HCY is an independent risk factor for incident stroke in elderly persons.[15] Several other studies have also postulated that elevated HCY is a strong and independent risk factor for vascular diseases, including ischemic cerebral stroke.[16]

Yang *et al.*[17] aptly noted that other experiments exploring the mechanism of HCY - induced atherosclerosis had used HCY concentrations 100 times higher than human HHcyc concentrations. To overcome this, Yang *et al.*[17] cultured endothelial cells in clinically relevant HHcyc concentrations of 20-50 μmol/L and hypothesized that HCY-induced hypomethylation leads to delayed recovery from endothelial injury. They found that HHcy dramatically inhibited [3H]thymidine incorporation (an indicator of DNA synthesis) and proliferation in endothelial cells. HCY was identified as a unique, cell type-specific growth inhibitory factor at clinically relevant concentrations in endothelial cells. Endothelial cell injury is a hallmark of atherosclerosis. Therefore, growth inhibition of endothelial cells may represent an important mechanism for HCY-induced atherosclerosis.

While some older reviews in the general population[18] found no correlation between HCY levels and IMT, newer studies, specifically in stroke patients[19], have found that HCY levels and IMT are positively correlated. Further, we found that HHcyc state was associated with increased ICA IMT. Our ROC analysis suggested that ICA IMT is the best predictor of the HHcyc state. Dietrich *et al.*'s study[20] ended up with similar results and noted that the ICA/bulb segment is more prone to plaque formation. Hence, correlations with HCY at the proximal ICA or carotid bulb might suggest or confirm the detrimental mechanisms of HHcy. We also found that the HHcyc state holds a good predictive value for stroke severity as graded by the NIHSS score. As it turns out, not only does HCY predict NIHSS at presentation, but it also predicts early neurological deterioration[21] and CVA recurrence[22].

We must correlate two of our results at this point. On the one hand, patients with ICA IMT > 1.0 mm had higher HCY. On the other hand, HHcyc state was associated with higher ICA IMT. These two seemingly overlapping results suggest that ICA IMT > 1.0 mm tends to be associated with HHcy. If carotid Doppler scans reveal ICA IMT > 1.0 mm in a stroke patient, prescribing a homocysteine test may be unnecessary, and physicians could assume HHcy in such a case.

Traditional parameters such as cholesterol levels, vices, i.e. smoking etc., and systemic disorders like diabetes mellitus, hypertension etc., have generally been deemed sufficient to evaluate CVA's risk, severity and prognosis. However, Several newer studies, including the one conducted by Fisher *et al.*[23], have noted that homocysteine-lowering therapy with higher doses of B-complex vitamins had benefits such as reduction of lipoprotein(a) and fibrinogen[24] and halting the progression of carotid plaque in patients whose plaque was progressing despite treatment of traditional risk factors. Spence[25] also suggested that higher doses of vitamin B12 and novel approaches to lowering serum homocysteine besides routine vitamin therapy could reduce the risk of stroke. Pyridoxine, folate and cobalamin, all of which have dietary origins, are three main cofactors

in HCY metabolism. These vitamin deficiencies are rampant in developing countries and may account for many cases of hyperhomocysteinemia and increased risk of stroke.[26] Sainani *et al.*[27] noted that homocysteine-lowering therapy, i.e., vitamins B6, B9 and B12 combined with atorvastatin, completely halved the progression of carotid plaque. In contrast, atorvastatin alone could slow, but not halt, plaque progression. Vitamins are indispensable in treating stroke, as the risk of recurrence can be minimised if plaque progression is arrested early on. We discussed at length the deleterious effects of HHcy and its role in the development and progression of the carotid plaque. However, the rampant prevalence of subclinical vitamin B12 and folate deficiency, especially in Indians, is a major hurdle in overcoming HHcy. Assaying vitamins or HCY is expensive and clinically impractical, as far as the Indian scenario is concerned. Therefore, as ICA IMT seems to predict HHcy, the carotid Doppler protocol should include the same measurement. If it is found to be > 1.0 mm and/or NIHSS ≥ 15, measuring HCY may be unnecessary. Prospective prevention studies have shown that increased IMT is a powerful predictor of stroke complications. However, IMT measurement requires methodological standardisation before routine measurement of IMT can be implemented in clinical practice as a diagnostic tool for assessing cardiovascular risk in primary prevention and gauging treatment decisions' aggressiveness.[28]

## CONCLUSIONS

Our study concluded that HHcyc state holds a reasonably good predictive value for predicting stroke severity. We also found that ICA IMT measurement may reduce the need to run a homocysteine test as it predicts higher HCY levels; this will reduce the burden on resources and time. We suggest that estimating HCY and measuring ICA IMT should be part of the standard protocol for managing CVA, and treatment regimens should plan long-term follow-ups using these parameters as indicators of improvement alongside traditional investigations.

*Conflict of Interest*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

*Funding Sources*

The author(s) received no financial support for the research, authorship, and/or publication of this article.

*Ethical Approval*

The protocol of the study was approved by the Medical Ethics Committee of Chhatrapati Shivaji Maharaj Hospital, Kalwa, Thane, India. (Decision number: RGMC/CSMH/IEC/A/264/06/2023, 27.06.2022).

*Authors' Contribution*

Study Conception: VNJ, KAB, MVR; Study Design: VNJ, KAB, MVR; Literature Review: VNJ, KAB, MVR, PR; Critical Review: PR, MVR; Data Collection and/or Processing: VNJ, KAB, PR; Analysis and/or Data Interpretation: VNJ, KAB, MVR, PR; Manuscript preparing: VNJ, KAB, MVR, PR.

## REFERENCES

1. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Writing Group Members; Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Circulation. 2016 Jan 26;133(4):e38-360. doi: 10.1161/CIR.0000000000000350.

2. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003 Jan;2(1):43-53. doi: 10.1016/s1474-4422(03)00266-7.

3. Instructions scale definition score - National Institutes of Health [Internet]. Oct 07, 2022. National Institute of Neurological Disorders and Stroke. National Institutes of Health. Available at: https://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf. Accessed Jan 01, 2023.

4. Muir KW, Weir CJ, Murray GD, Povey C, Lees

KR. Comparison of neurological scales and scoring systems for acute stroke prognosis. Stroke. 1996 Oct;27(10):1817-20. doi: 10.1161/01.str.27.10.1817.
5. Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. Curr Atheroscler Rep. 2013 Mar;15(3):306. doi: 10.1007/s11883-012-0306-4.
6. Kluijtmans LA, Young IS, Boreham CA, Murray L, McMaster D, McNulty H, Strain JJ, McPartlin J, Scott JM, Whitehead AS. Genetic and nutritional factors contributing to hyperhomocysteinemia in young adults. Blood. 2003 Apr 1;101(7):2483-8. doi: 10.1182/blood.V101.7.2483.
7. Dierkes J, Westphal S. Effect of drugs on homocysteine concentrations. Semin Vasc Med. 2005 May;5(2):124-39. doi: 10.1055/s-2005-872398.
8. Škovierová H, Vidomanová E, Mahmood S, Sopková J, Drgová A, Červeňová T, Halašová E, Lehotský J. The molecular and cellular effect of homocysteine metabolism imbalance on human health. Int J Mol Sci. 2016 Oct 20;17(10):1733. doi: 10.3390/ijms17101733.
9. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006 Nov;3(11):e442. doi: 10.1371/journal.pmed.0030442.
10. Khan H, Afridi AK, Ashraf S. A hospital based study on stratification of risk factors of stroke in Peshawar. Pak J Med Sci. 2006 Jul-Sep;22(3):304-7.
11. Uno M, Harada M, Takimoto O, Kitazato KT, Suzue A, Yoneda K, Morita N, Itabe H, Nagahiro S. Elevation of plasma oxidized LDL in acute stroke patients is associated with ischemic lesions depicted by DWI and predictive of infarct enlargement. Neurol Res. 2005 Jan;27(1):94-102. doi: 10.1179/016164105X18395.
12. Jain VN, Ghangurde S, Carvalho SR, Nirgudkar SS, Rojekar MV. Effect of thyroid hormone levels on glycemic control: The Indian context. Iran J Diabetes Obes. 2022; 14(3):131-7. doi: 10.18502/ijdo.v14i3.10738.
13. Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. Diabet Med. 2006 Jun;23(6):609-16. doi: 10.1111/j.1464-5491.2005.01725.x.
14. Stein JH, McBride PE. Hyperhomocysteinemia and atherosclerotic vascular disease: pathophysiology, screening, and treatment. off. Arch Intern Med. 1998 Jun 22;158(12):1301-6. doi: 10.1001/archinte.158.12.1301.
15. Bostom AG, Rosenberg IH, Silbershatz H, Jacques PF, Selhub J, D'Agostino RB, Wilson PW, Wolf PA. Nonfasting plasma total homocysteine levels and stroke incidence in elderly persons: the Framingham Study. Ann Intern Med. 1999 Sep 7;131(5):352-5. doi: 10.7326/0003-4819-131-5-199909070-00006.
16. Christopher R, Nagaraja D, Shankar SK. Homocysteine and cerebral stroke in developing countries. Curr Med Chem. 2007;14(22):2393-401. doi: 10.2174/092986707781745613.
17. Yang F, Tan HM, Wang H. Hyperhomocysteinemia and atherosclerosis. Sheng Li Xue Bao. 2005 Apr 25;57(2):103-14.
18. Durga J, Verhoef P, Bots ML, Schouten E. Homocysteine and carotid intima-media thickness: a critical appraisal of the evidence. Atherosclerosis. 2004 Sep;176(1):1-19. doi: 10.1016/j.atherosclerosis.2003.11.022.
19. Wu W, Guan Y, Xu K, Fu XJ, Lei XF, Lei LJ, Zhang ZQ, Cheng Y, Li YQ. Plasma homocysteine levels predict the risk of acute cerebral infarction in patients with carotid artery lesions. Mol Neurobiol. 2016 May;53(4):2510-7. doi: 10.1007/s12035-015-9226-y.
20. Dietrich M, Jacques PF, Polak JF, Keyes MJ, Pencina MJ, Evans JC, Wolf PA, Selhub J, Vasan RS, D'Agostino RB. Segment-specific association between plasma homocysteine level and carotid artery intima-media thickness in the Framingham Offspring Study. J Stroke Cerebrovasc Dis. 2011 Mar-Apr;20(2):155-61. doi: 10.1016/j.jstrokecerebrovasdis.2009.10.012.
21. Kwon HM, Lee YS, Bae HJ, Kang DW. Homocysteine as a predictor of early neurological deterioration in acute ischemic stroke. Stroke. 2014 Mar;45(3):871-3. doi: 10.1161/STROKEAHA.113.004099.
22. Wu XQ, Ding J, Ge AY, Liu FF, Wang X, Fan W. Acute phase homocysteine related to severity and outcome of atherothrombotic stroke. Eur J Intern Med. 2013 Jun;24(4):362-7. doi: 10.1016/j.ejim.2013.01.015.
23. Spence JD. Nutrition and stroke prevention. Stroke. 2006 Sep;37(9):2430-5. doi: 10.1161/01.STR.0000236633.40160.ee.
24. Naruszewicz M, Klinke M, Dziewanowski K, Staniewicz A, Bukowska H. Homocysteine, fibrinogen, and lipoprotein(a) levels are simultaneously reduced in patients with chronic renal failure treated with folic acid, pyridoxine, and cyanocobalamin. Metabolism. 2001 Feb;50(2):131-4. doi: 10.1053/meta.2001.20174.
25. Spence JD. Homocysteine-lowering therapy:

a role in stroke prevention? Lancet Neurol. 2007 Sep;6(9):830-8. doi: 10.1016/S1474-4422(07)70219-3.
26. Sánchez-Moreno C, Jiménez-Escrig A, Martín A. Stroke: roles of B vitamins, homocysteine and antioxidants. Nutr Res Rev. 2009 Jun;22(1):49-67. doi: 10.1017/S0954422409990023.
27. Sainani GS, Talwalkar PG, Wadia RS, Keshvani AA. Hyperhomocysteinemia and its implications in atherosclerosis the Indian Scenario. In: Singal RK, ed. Medicine Update. 1st ed. New Delhi, India: Jaypee Brothers Medical Publishers Ltd.; 2007;17:11-20. doi: 10.5005/jp/books/12086_3.
28. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens. 2002 Feb;20(2):159-69. doi: 10.1097/00004872-200202000-00001.