

## Hyperhomocysteinemia in Patients of Essential Hypertension Presenting with Acute Ischemic Stroke

Ayaz Aslam, Abdul Latif Khattak\*, Syed Karamat Hussain Shah Bukhari\*\*, Ali Yousaf, Babar Rafique\*\*\*, Mohammad Khalid Azam Khan\*

Department of Medicine, Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan, \*Department of Medicine, Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, \*\*Department of Medicine, Pak Emirate Military Hospital Sargodha/National University of Medical Sciences (NUMS) Pakistan, \*\*\*Department of Medicine, Combined Military Hospital Badin/National University of Medical Sciences (NUMS) Pakistan

### ABSTRACT

**Objective:** To determine the frequency of Hyperhomocysteinemia in patients of essential hypertension presenting with acute ischemic stroke.

**Study Design:** Cross-sectional analytical study.

**Place and Duration of Study:** Department of Internal Medicine, Combined Military Hospital, Quetta Pakistan, from Feb 2018 to Jan 2019.

**Methodology:** The patients of essential hypertension presenting with acute ischemic stroke between 20-70 years of age of either gender were evaluated for the serum homocysteine level.

**Results:** A total 195 patients of essential hypertension presenting with acute ischemic stroke for  $\geq 24$  hours duration, of age between 20-70 years, of both genders were included in the study by non-probability consecutive sampling. Majority of patients were between 50-59 year of age (34.3%) with majority of them were male (66.4%). Out of 195, 70.3% were smokers, 56.4% were diabetics, 60.5% were obese and 71.7% had hyperhomocysteinemia respectively. The statistical significance was also observed for hyperhomocysteinemia in accordance with age ( $p=0.04$ ), gender ( $p=0.02$ ), obesity ( $p=0.03$ ) smoking ( $p=0.01$ ) and diabetes mellitus ( $p=0.03$ ).

**Conclusion:** Hyperhomocysteinemia is more prevalent in patients of essential hypertension with acute ischemic stroke.

**Keywords:** Acute ischemic stroke, Essential hypertension, Hyperhomocysteinemia.

**How to Cite This Article:** Aslam A, Khattak AL, Bukhari SKHS, Yousaf A, Rafique B, Khan MKA. Hyperhomocysteinemia in Patients of Essential Hypertension Presenting with Acute Ischemic Stroke. *Pak Armed Forces Med J* 2023; 73(Suppl-1): S144-147. DOI: <https://doi.org/10.51253/pafmj.v73iSUPPL-1.4645>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### INTRODUCTION

Cardiovascular and cerebrovascular diseases are the leading causes of death accounting for over 40% of all deaths worldwide and have been observed a positive association between serum homocysteine (Hcy) and risk of hypertension, ischemic stroke (IS) and coronary heart disease (CHD).<sup>1</sup> Hypertension increases the risk for development of systemic adverse events and the majority of these patients have essential hypertension that can be defined as a rise in blood pressure due to unknown cause.<sup>2</sup> The prevalence of hypertension has been increased since last decades from 2% to 25% among urban residents and from 2% to 15% among the rural residents of India, while the National Health Survey of Pakistan estimated that hypertension affects 18% of adults and 33% of adults above 45 years old.<sup>3</sup> The Seventh Report of the Joint National Committee (JNC-7) identifies that left ventricular hypertrophy, angina/previous myocardial infarction, stroke or transient ischemic attack as end organ damage due to

long standing hypertension.<sup>4</sup> A reduction of 5mmHg in diastolic BP results in decrease risk of coronary heart disease by 6% and stroke by 15%.<sup>5</sup> An increase in body mass index (BMI) is associated with an increased risk of developing conditions such as hypertension, it is recommended to take Diet low in salt, total fat, and cholesterol.<sup>6</sup> C.T scan brain is the most accurate method to differentiate between hemorrhage and ischemic stroke and also rule out many other brain diseases.<sup>7</sup> No consensus exists on the timing of the blood test of homocysteinemia with respect to an acute event.<sup>8</sup>

The homocysteine is a homologue of cysteine and has an additional methylene group, biosynthesized by the removal of terminal methyl group from methionine and can be recycled into methionine or into cysteine with the help of vitamin-B.<sup>9</sup> Increase in plasma concentration of homocysteine is reported in patients with stroke, peripheral vascular disease & coronary disease and confer an independent risk of atherosclerosis.<sup>10</sup>

Therefore, the present study was conducted to evaluate the hyperhomocysteinemia in essential hypertensives presenting with acute ischemic stroke in our

**Correspondence:** Dr Ayaz Aslam, Department of Medicine, Combined Military Hospital, Quetta-Pakistan  
Received: 27 Jun 2020; revision received: 21 Apr 2021; accepted: 26 Apr 2021

population because the literature on the relations of serum homocysteine to raised blood pressure and stroke had been scarce and the adverse events might be mediated in part by its relationship with hyperhomocysteinemia. The study would be helpful for physicians, who should consider screening for serum homocysteine in hypertensive individuals because early screening and treatment can reduce life threatening events such as acute ischemic stroke and on the basis of the observations of present study the early management strategies can be planned to save the patients from hypertensive adverse events as far as acute ischemic stroke is concerned.

## METHODOLOGY

The cross sectional analytical study was carried out From February 2018 to January 2019 in the Department of internal Medicine, Combined Military Hospital, Quetta Pakistan. A total of 195 patients were selected by taking the prevalence of hyperhomocysteinemia in essential hypertension with acute ischemic stroke 46%, 12d=7% , n=195 patients of essential hypertension by non-probability consecutive sampling.

**Inclusion Criteria:** Patients of age between 20-70 years of both genders who had essential hypertension for  $\geq 6$  months and presented with acute ischemic stroke persist beyond 24 hours duration documented by a brain CT that showed hypodense area and evident for the presence of infarction, were included.

**Exclusion Criteria:** Patients with hemorrhagic stroke and already on folic acid, steroids, immunosuppressive, pyridoxine and vitamin B12 therapy were excluded from the study along with diagnosed cases of chronic kidney disease, hyperthyroidism, coarctation of the aorta, hyperaldosteronism, Cushing syndrome, pheochromocytoma and pregnant and lactating ladies.

The serum homocysteine level  $\geq 15 \mu\text{mol/L}$  was considered as hyperhomocysteinemia. This study was conducted after taking the consent from patients and permission by ERC (Ltr no. CMH Quetta/027) on the patients with essential hypertension for more than six months duration presented with acute ischemic stroke in the department of Medicine, Combined Military Hospital, Quetta. All relevant participants and the blood pressure was measured by sphygmomanometer (apparatus/instrument) and the acute ischemic stroke was evaluated by clinical examination and CT scan film. For serum homocysteine level, after all aseptic measures 2ml venous blood sample were taken in a disposable 5ml syringe from all the relevant (essential

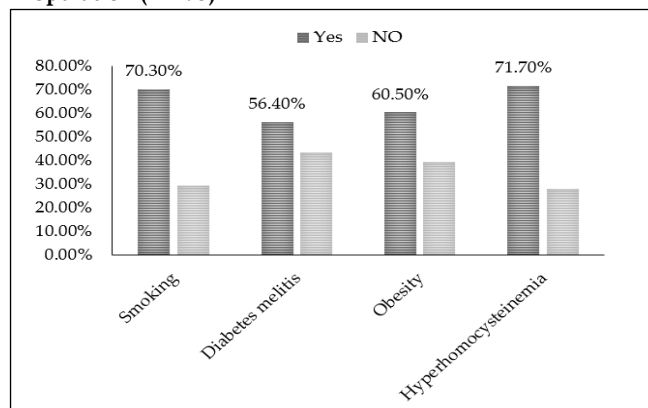
hypertensive) patients and then sent to laboratory for analysis.

The SPSS version 17.00 was used for the analysis of data. The variables such as frequency, percentage (%) and *p*-value was derived for hyperhomocysteinemia in essential hypertension presenting with acute ischemic stroke as well as for smoking, D.M and gender distribution. The mean and standard deviation (SD) was calculated for age, BMI, duration of hypertension, systolic and diastolic blood pressures. The stratification was done for age, gender, obesity, smoking, duration of hypertension, and diabetes mellitus accordingly to see the effect on outcome and to control the effect modifiers. The chi-square test was used on categorical variables at 95% confidence interval and the *p*-value  $\leq 0.05$  was considered as statistically significant.

## RESULTS

A total 195 patients of essential hypertension for  $\geq 6$  months with acute ischemic stroke for  $\geq 24$  hour duration of 20-70 year of age either gender were recruited. The demographical and clinical parameters of study population is shown in Figure.

**Figure: The Demographic and Clinical Parameters of Study Population (n=195)**



While the Mean $\pm$ SD for age, duration of hypertension (yrs), duration of acute ischemic stroke (hrs), body mass index-BMI (kg/m<sup>2</sup>), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and homocysteine level ( $\mu\text{mol/L}$ ) is shown in Table-I. The stratification for hyperhomocysteinemia according to age, gender, smoking and diabetes Mellitus is shown in Table-II, statistical significance was also observed for hyperhomocysteinemia in accordance with gender (*p*=0.02) smoking (*p*=0.01) and obesity (*p*=0.03).

## Hyperhomocysteinemia in Patients

**Table-I: Descriptive Statistics (n=195)**

Quantitative variables	Mean±SD
Age (yrs)	61.83±7.93
Duration of hypertension (yrs)	7.83±3.86
Duration of acute ischemic stroke (hrs)	37.92±7.51
Body mass index-BMI (kg/m <sup>2</sup> )	30.21±3.32
Systolic blood pressure (mmHg)	175.72±12.8
Diastolic blood pressure (mmHg)	100.83±8.75
Homocysteine level (μmol/L)	32.72±7.42

**Table-II: The Hyperhomocysteinemia in Accordance with Gender, Smoking and Obesity (n=195)**

		Hyperhomocysteinemia n(%)		p-value
		Yes	No	
Gender	Male	93	28	0.02
		66.4%	50.9%	
	Female	47	27	
		33.6%	49.1%	
Smoking	yes	106(75.7%)	31(56.4%)	0.01
	No	34(24.3%)	24(43.6%)	
Obesity	yes	91(65.0%)	27(49.1%)	0.03
	No	49(35.0%)	28(50.9%)	

## DISCUSSION

The present cross sectional analytic study has shown a firm association of hyperhomocysteinemia with acute ischemic stroke in older as well as younger age groups. The vascular damage due to hyperhomocysteinemia in hypertensive population is more as compare to normotensive.<sup>11</sup> While the prevalence for hyperhomocysteinemia in essential hypertension with ischemic stroke was reported as 46%.<sup>12</sup>

This present study results are comparable with many former studies.<sup>13-15</sup> how ever there are few studies which could not ascertain any relationship between hyperhomocysteinemia and stroke.<sup>16</sup> the exact threshold level for homocysteine associated with increased risk of vascular events has not been established in any study. The association between homocysteine (Hcy) and Atherosclerotic vascular disease (ASVD) appears to be directly proportional, as increasing cholesterol and blood pressure are directly proportional to vascular disease.<sup>17</sup> it has been postulated that normal range for homocysteine lie between 5 and 15 mmol/l, whereas a number of studies,<sup>18</sup> have shown increased risk of vascular disease within this range. There are multiple factors which are responsible for Hyperhomocysteinemia like nutritional, genetic, pathological and pharmacological factors.<sup>19</sup> The Lindgren,<sup>20</sup> did not find any association between infarct subtype (lacunar vs cortical) and plasma homocysteine concentration.

However the Eikelboom conducted a large study,<sup>21</sup> which revealed that association was higher in patients of large artery disease as compared to those with small artery disease. The noxious effect of hyperhomocysteinemia is primarily mediated by a pro-atherogenic effect as compare to prothrombotic effect, which might be contributory in the large vessel disease. Evers *et al*,<sup>22</sup> also compared elevated homocysteine levels and revealed that these are associated with cerebral microangiopathy and not with cardio embolic associated ischemic stroke. it is postulated that hyperhomocysteinemia is both atherogenic and prothrombotic, which includes different types of mechanisms including direct endothelial injury, proliferation of smooth muscle cells, ineffective endogenous fibrinolysis and alteration in arachidonic acid metabolism. It has been also observed in few studies that cigarette smoking was associated with high homocysteine levels.<sup>23</sup> This study also showed that patients with stroke, who are smokers have high levels of homocysteine as compared to non-smokers.

## CONCLUSIONS

Hyperhomocysteinemia is more prevalent (71.7%) in patients of essential hypertension presenting with acute ischemic stroke with male gender predominance (62.1%). Thus, raised level of homocysteine is a strong risk factor for hypertensive population with acute ischemic stroke. A larger Pakistani population with and without hypertension should be screened to ascertain a definite threshold level of homocysteine as it will play a pivotal role to consider treatment of hyperhomocysteinemia in hypertensive patients presenting with ischemic stroke. In order to reduce the risk of damage due to hyperhomocysteinemia measures need to be taken at the level of primary and secondary prevention with use of vitamin B complexes and folate.

**Conflict of Interest:** None.

### Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AA: & ALK: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

SKHSB: & AY: Study design, data interpretation, critical review, approval of the final version to be published.

BR: & AKAK: Concept, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## REFERENCES

- Blacher J, Halimi JM, Hanon O, Mourad JJ, Pathak A, Schnebert B, et al. Management of hypertension in adults: the 2013 French

## Hyperhomocysteinemia in Patients

- Society of Hypertension guidelines. *Fundam Clin Pharmacol* 2014; 28(1): 1-9.
- 2 Saleem F, Hassali AA, Shafie AA. Hypertension in Pakistan: time to take some serious action. *Br J Gen Pract* 2010; 60(575): 449-50.
  - 3 Saleem F. Hypertension in Pakistan: time to take some serious action. *Br J Gen Pract* 2010; 60(575): 449-50.
  - 4 Boer IH, Bangalore S. Diabetes and hyper-tension: a position statement by the American Diabetes Association. *Diabetes Care* 2017; 40(9): 1273-1284. <https://doi.org/10.2337/dci17-0026>
  - 5 Alam T, Khan S, Gaba B. Nanocarriers as treatment modalities for hypertension. *Drug Deliv* 2017; 24(1): 358-69. <https://doi.org/10.1080/10717544.2016.1255999>
  - 6 Osborn JW, Banek CT. Catheter-based renal nerve ablation as a novel hypertension therapy: lost, and then found, in translation. *Hypertension* 2018; 71(3): 383-88. <https://doi.org/10.1161/hypertensionaha.117.08928>
  - 7 Fukuoka T, Nakazato Y, Kawasaki H. The clinical features of ischemic stroke patients for whom smoking was considered the sole risk factor for ischemic stroke. *Intern Med* 2018; 57(12): 1703-1706. <https://doi.org/10.2169/2018.57.1703>
  - 8 Cheng D, Kong H, Pang W. B vitamin supplementation improves cognitive function in the middle aged and elderly with hyperhomocysteinemia. *Nutr Neurosci* 2016; 19(10): 461-466.
  - 9 Gopinath B, Flood VM, Rochtchina E, Wang JJ. Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration. *Am J Clin Nutr* 2013; 98(1): 129-135.
  - 10 Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J* 2015; 14(1): 6-11
  - 11 Sen U, Mishra PK, Tyagi N. Homocysteine to Hydrogen Sulfide or Hypertension. *Cell Biochem Biophys* 2010; 57(2-3): 49-58.
  - 12 Hashmi SF, Dasti MA. Serum homocysteine in hypertensive patients. *Professional Med J* 2013; 20(6): 932-937.
  - 13 Zhao M, Wang X. Homocysteine and stroke risk: modifying effect of methylenetetra-hydrofolate reductase C677T polymorphism and folic acid intervention. *Stroke* 2017; 48(5): 1183-1190.
  - 14 Zhou Z, Liang Y, Qu H, Zhao M, Guo F, Zhao C, et al. Plasma homocysteine concentrations and risk of intracerebral hemorrhage: a systematic review and meta-analysis. *Sci Rep* 2018; 8(1): 2568-2570.
  - 15 Shi Z, Liu S, Guan Y, Zhang M, Lu H, Yue W, et al. Changes in total homocysteine levels after acute stroke and recurrence of stroke. *Sci Rep* 2018; 8(1): 6993.
  - 16 Wang W, Gao C, Yu C, Liu S, Hou D, Wang Y, et al. No association between elevated total homocysteine levels and functional outcome in elderly patients with acute cerebral infarction. *Front Aging Neurosci* 2017; 9(1): 70-72.
  - 17 Lehotsky J, Tothova B, Kovalska M, Dobrota D, Benova A, Kalenska D, et al. Role of homocysteine in the ischemic stroke and development of ischemic tolerance. *Front Neurosci* 2016; 10(1): 538.
  - 18 Yao ES, Tang Y, Xie MJ, Wang MH, Wang H, Luo X. Elevated homocysteine level related to poor outcome after thrombolysis in acute ischemic stroke. *Med Sci Monit* 2016; 22(1): 3268-3273.
  - 19 Devasia AJ, Joy B, Tarey SD. Serum homocysteine as a risk factor for carotid intimal thickening in acute stroke: A cross sectional observational study. *Ann Indian Acad Neurol* 2016; 19(1): 48-51.
  - 20 Lindgren A, Brattstrom L, Norrving B, Hultberg B, Anderson A. Plasma homocysteine in acute and convalescent phases after stroke. *Stroke* 1995; 26(1): 795-800.
  - 21 Eikelboom JW, Hankey GJ, Anand SS, Lofthouse E, Staples N, Baker RI. Association between high homocysteine and ischemic stroke due to large and small artery disease but not other etiologic subtypes of ischemic stroke. *Stroke* 2000; 31(2): 1069-1075.
  - 22 Evers S, Koch HG, Grotemeyer KH. Features, symptoms and neurophysiological findings in stroke associated with hyperhomocysteinemia. *Arch Neurol* 1997; 54(1): 1276-1282.
  - 23 Stein JH, McBride PE. Hyperhomocysteinemia and atherosclerotic vascular disease. Pathophysiology, screening and treatment. *Arch Intern Med* 1998; 158(1): 1301-1306.
- .....