e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com doi: 10.25258/ijpqa.16.3.6

International Journal of Pharmaceutical Quality Assurance 2025; 16(3); 31-38

Original Research Article

Assessment of NT Pro-BNP Levels in Different Ischemic Cerebrovascular Stroke Subtypes

Chirag Contractor[1], Amita Dabhi[2], Param Patel[3], Kartikeya Parmar[4]

[1]Senior Resident, Department of Medicine, GMERS Medical College Dharpur, Patan, Gujarat, India
[2]Senior Resident, Department of Microbiology, GMERS Medical College Dharpur, Patan, Gujarat, India
[3]3rd Year Resident, Department of Medicine, B.J. Medical College Ahmedabad, Gujarat, India
[4]Associate Professor and Head of Unit, Department of Medicine, B.J. Medical College Ahmedabad, Gujarat, India

Received: 08-01-2025 / Revised: 06-02-2025 / Accepted: 08-03-2025
Corresponding Author: Chirag Contractor
Conflict of interest: Nil

Abstract:

Introduction: Cerebrovascular stroke is a leading cause of morbidity and mortality worldwide. It is clinically defined as an abrupt onset of neurological deficit due to a focal vascular cause. Symptoms include loss of sensory and/or motor function, change of gait, change of vision or inability to speak or understand spoken words, headache, nausea, vomiting, giddiness, convulsions, loss of consciousness etc. There are few studies which have proven the association between elevated levels of NT Pro-BNP and cardioembolic cerebrovascular stroke as well as post-stroke outcomes. Some studies have shown a positive association between elevated plasma NT Pro-BNP levels in Acute Ischemic Stroke with atrial fibrillation. Hence this study aims to find the association of elevated levels of NT Pro-BNP in cardioembolic ischemic cerebrovascular stroke.

Materials and Methods: This is a cross sectional type of study, conducted in the department of medicine at B.J Medical college Ahmedabad during the time period of October 2020 to December 2022. We included a total of 40 patients with ischemic cerebrovascular stroke for study. Patients with hemorrhagic stroke and those with stroke recurrence were excluded from the study. All the details were recorded in standard case record form and all these data were entered in Microsoft Excel sheet. Results were presented as mean $\pm$ standard deviation (SD) or percentages. Continuous variables were analysed for normalization and compared using the student t test. Inter group comparisons were made using chi-square test. A cut-off value of $p<0.05$ was considered statistically significant.

Results: In this study we tested 40 patients with ischemic stroke of different etiologies for elevated NT Pro-BNP levels. Among these 40 patients, 55% stroke were of cardioembolic origin (n=22), 32% were having large artery thrombosis as a cause of cerebral ischemia (n-13), 5% with lacunar stroke (n=2) and 8% were of undetermined etiology (n=3). A cut-off value of 125pg/mL for age for NT Pro BNP levels was selected based on previous studies and the diagnostic kit used. We found that 53% (n=21) of patients with ischemic stroke were tested positive for elevated levels of NT Pro-BNP. Of those 21 patients who tested positive for elevated NT Pro BNP levels, 90% (n=19) were having cardio-embolic origin of stroke whereas only 10% (n=2) were having large artery thrombosis, a value that has a high statistical significance with a *p* value of 0.000034. Out of 22 patients with cardio-embolic origin of stroke 86% (n=19) patients had an elevated level of plasma NT Pro BNP, a value that is statistically significant with a *p* value of <0.05(p = 0.000034.).

Conclusion: It is important to diagnose and classify stroke in its acute phase as it is associated with majority of adverse outcomes. NT Pro-BNP can be used as a biomarker for identifying cardioembolic origin of stroke. Also, it is useful for ruling out thrombotic stroke. It can be useful for differentiation of cardioembolic from other stroke subtypes for initiating proper treatment.

Keywords: Ischemic, Cardioembolic, Thrombotic.

Introduction

A Cerebrovascular stroke is defined clinically as an abrupt onset of a neurological deficit due to a FOCAL vascular cause [1]. Cerebrovascular stroke can lead to Hypoxia-Ischemia which can further lead to Hypoxic-Ischemic Encephalopathy. The symptoms may vary in view of complex anatomy of Human Brain and its vasculature.

Symptoms of a CV stroke include Loss of sensory and/or motor function, change of Gait, change of vision or ability to speak or understand, Headache

etc. Stroke subtypes are classified as large artery thrombosis, cardioembolic, lacunar and undetermined according to the TOAST criteria.

Ischemic CV stroke manifests in two phases: Acute and Convalescent. After symptom onset, first two weeks are called Acute phase [2]. Acute phase of Acute Ischemic Stroke (AIS) is associated with obvious physiological and pathological changes and is associated with majority of unstable outcomes. It is necessary to diagnose and manage the patient in acute phase of AIS.

NT Pro-BNP [N Terminal Pro B type-Natriuretic Peptide] is released after cleavage of BNP from its precursor Pro-BNP which is released from cardiac myocytes after inflammation, volume or pressure overload. Measurements of plasma NT Pro-BNP have increased the diagnostic accuracy of acute heart failure [3]. Elevated levels of NT Pro-BNP in plasma have been associated with Myocardial Infarction, Atrial fibrillation and essential Hypertension. Hence NT Pro-BNP has emerged as an important biomarker in development of prognostic and diagnostic tool for cardiovascular diseases [3].

Very less is known about the relation between NT Pro-BNP and Cerebrovascular diseases. It is stated that BNP is released by Brain tissue, the organ where BNP was first identified. There are only few studies which have proved the association between elevated levels of NT Pro-BNP and Cardioembolic origin of CV Stroke and post-stroke outcomes [4]. Some studies have shown a positive association between elevated plasma NT Pro-BNP levels in AIS with Atrial Fibrillation [5].

This study aims to find the association of elevated levels of NT Pro-BNP in Cardioembolic Ischemic Cerebrovascular Stroke.

Materials and Methods

Study design and setting: The present study is a cross sectional type of study which was carried in the department of General Medicine, Civil Hospital Ahmedabad - A tertiary health care hospital in Gujarat, India for a period of 26 months.

Study population: This study included Patients admitted in Civil Hospital Ahmedabad with symptoms suggestive of cerebrovascular stroke. For example: limb weakness, facial deviation, speech disturbances, giddiness/nausea/vomiting, loss of consciousness, convulsion etc. admitted within first 48 hours of symptom onset. Those with hemorrhagic stroke and stroke recurrence were excluded from the study.

Sample size: we included 40 patients meeting the inclusion criteria.

Data collection: During the study period of 26 months, among the patients admitted in Civil Hospital Ahmedabad with symptoms suggestive of Cerebrovascular Stroke [limb weakness, facial deviation, speech disturbances, giddiness/nausea/vomiting, loss of consciousness, convulsion etc.], information pertaining to age, sex, associated co-morbid conditions, habits and drug therapy were obtained and detailed clinical examination of the central nervous system and other systems was done.

After thorough examination NCCT brain was done in suspected Cerebrovascular Stroke patients to rule out Intracranial Hemorrhage [ICH]. After ruling out ICH in these patients, samples for NT Pro-BNP were taken and sent for testing. 1 ml of patient's plasma was sent for testing for NT Pro-BNP levels. Age standardized cut-offs for NT Pro BNP values were selected. A cut-off value of 125pg/mL was set based of age and laboratory standardization.

After stabilization MRI Brain with Angiography was done to confirm the vascular territory involved in brain. Carotid arterial Doppler was done to look carotid artery thrombus as a source of ischemia. ECG, 2D Echo and Fundus examination were done to look for Risk factors and End Organ Damage. Patients were screened for renal dysfunction with the help of Renal Ultrasound. After thorough workup patients were classified into the following stroke subtypes as per the TOAST criteria: large artery thrombosis, cardioembolic, small artery occlusion or lacunar and stroke of undetermined etiology.

In the "atherothrombotic subtype," a stenosis of 50% of an appropriate intracranial or extracranial artery should be demonstrated. In the "cardioembolic subtype," the presence of a high- or medium-risk cardiac source of embolism is necessary. "Lacunar subtype" requires a traditional clinical lacunar syndrome without evidence of cerebral cortical dysfunction and normal computed tomography or magnetic resonance imaging findings or a relevant brain stem or sub cortical hemispheric lesion with a diameter of 1.5 cm. Strokes of "undetermined etiology" include patients with 2 or more causes identified, those patients with a negative evaluation, and patients with incomplete evaluation [6].

Data Analysis: All the details were recorded in standard case record form and all these data were entered in Microsoft Excel sheet. Results were presented as mean $\pm$ standard deviation (SD) or percentages. Continuous variables were analysed for normalization and compared using the student t test. Inter group comparisons were made using chi-square test. A cut-off value of $p<0.05$ was considered statistically significant.

Results

Out of 40 patients selected for the study who matched the inclusion criteria, correlation between the below mentioned parameters was assessed among different types of Stroke: Age distribution, Gender distribution, Clinical presentation, ECG findings, 2d Echo findings, Arterial territory involved in various stroke types, NT-Pro BNP levels.

Table 1: Demographic characteristics of study participants

		No. of patients
Age group (years)	20-40	5
	40-60	21
	>60	14
Gender	Male	26
	Female	14
Addiction	Alcohol	6
	Tobacco chewing	7
	Smoking	7
	None	24
Co-morbidity	Diabetes mellitus	13
	Hypertension	22
	Rheumatic heart disease	1
	Ischemic heart disease	9
	None	13

Table 2: Clinical and Laboratory investigations of study participants

Clinical and laboratory investigations of the study participants			
		No of patients	**Percentage (%)**
Time of Symptom Onset	early morning	5	12.5
	Daytime	19	47.5
	night time	16	40
		40	**100**
Arterial Territory Involved	A2 segment ACA	2	5
	M1 segment MCA	12	30
	M2 segment MCA	10	25
	P2 segment PCA	1	2.5
	Basilar artery	7	17.5
	ACA+ MCA	2	5
	MCA + PCA	6	15
		40	**100**
SBP (mmHg)	<120	8	20
	120-129	2	5
	130-139	7	17.5
	>140	23	57.5
		40	**100**
DBP (mmHg)	<80	8	20
	80-89	13	32.5
	>90	19	47.5
		40	**100**
ECG Findings	normal sinus rhythm	24	60
	AF present	9	22.5
	LVH	2	5
	Ischemic changes	5	12.5
		40	**100**
2D ECHO Findings	Normal	12	30
	LVD	20	50
	LA/LV Dilatation	1	2.5
	RHD	6	15
	Prosthetic Heart Valve	1	2.5
		40	**100**
Type of Stroke	Cardioembolic	22	55

	Large artery thrombosis	13	32
	Lacunar	2	5
	Undetermined	3	8

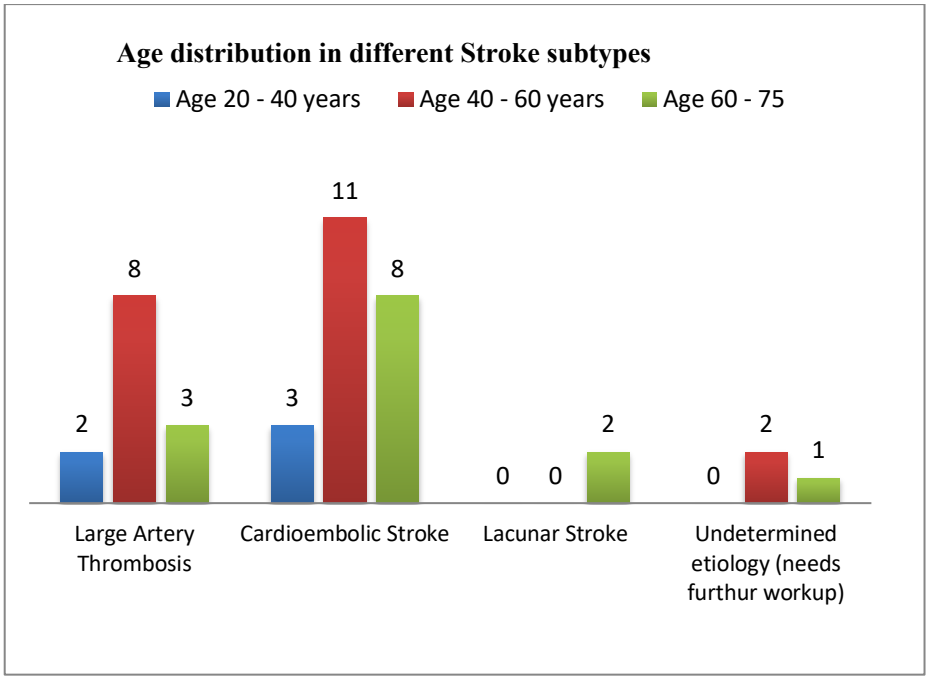

Figure 1: Age distribution in different Stroke subtypes

Figure 1: Age distribution of different stroke subtypes. Majority of patients with cardioembolic stroke as well as thrombotic stroke were falling under 40-60 years age group. The difference was not statistically significant.

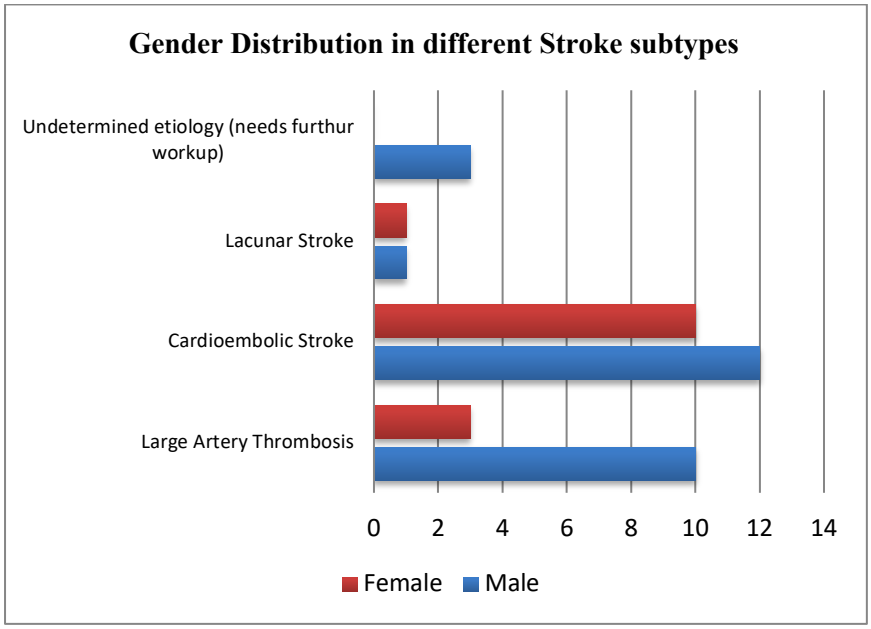

Figure 2: Gender Distribution in different Stroke subtypes

Figure 2: gender distribution of patients with different stroke subtypes. Patients with cardioembolic stroke had equal gender distribution but those with thrombotic stroke had a male preponderance.

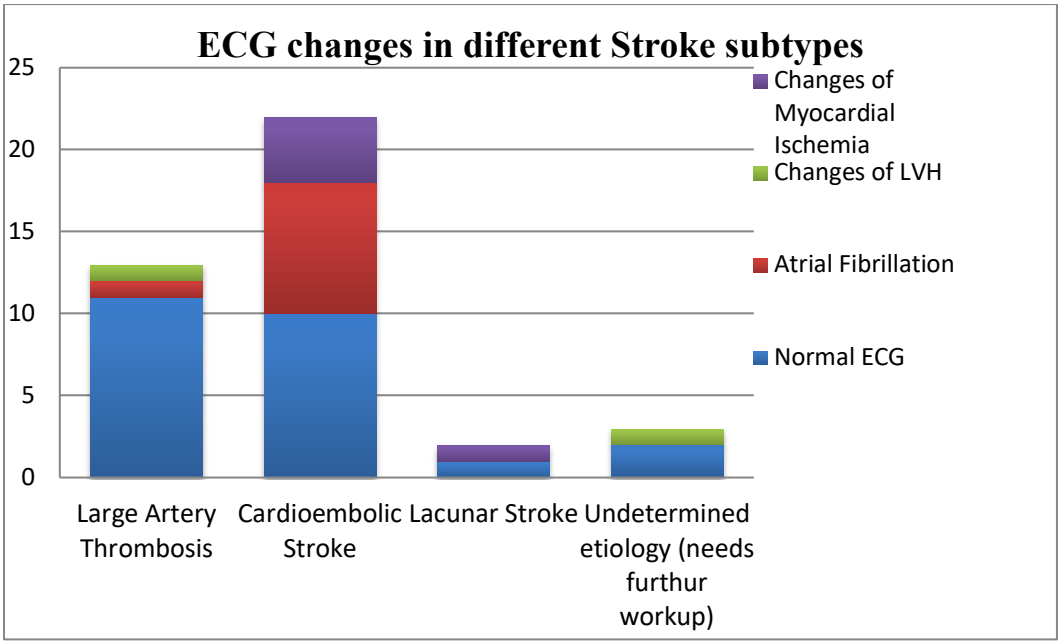

Figure 3: ECG changes in different Stroke subtypes

Figure 3: ECG changes in different stroke subtypes. Majority of the patients with thrombotic stroke had normal ECG. The test is statistically significant. (The chi-square statistic is 5.2214. The *p*-value is 0.02231. The result is significant at $p < 0.05$)

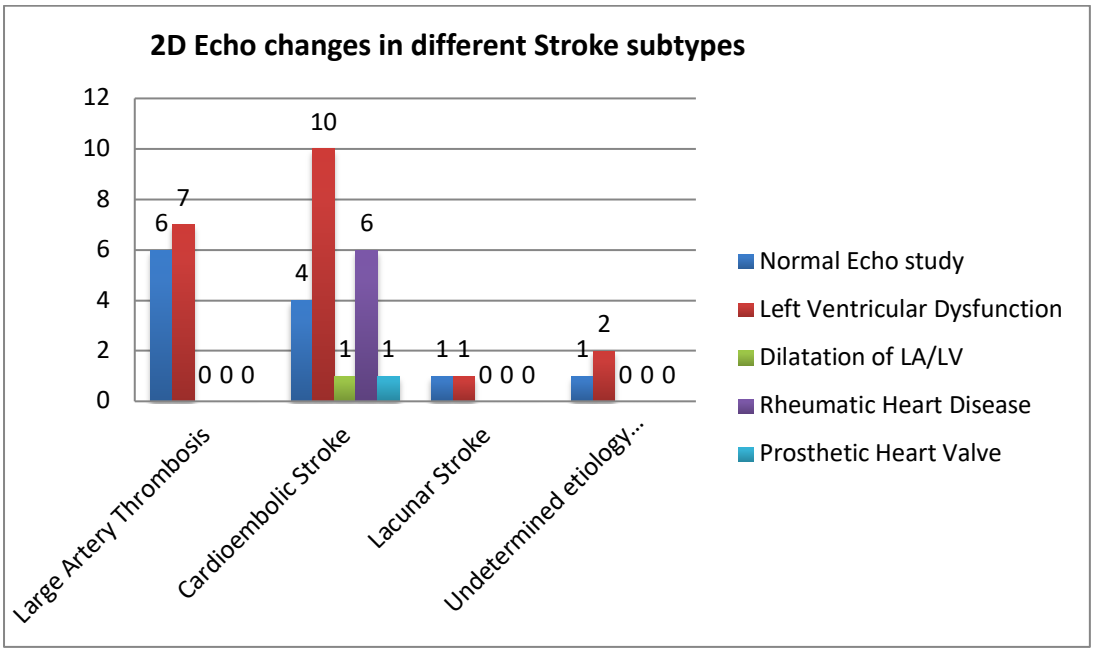

Figure 4: 2D Echo changes in different Stroke subtypes

Figure 4: 2D Echo findings in different stroke subtypes. Majority of patients with cardioembolic stroke had shown abnormal 2D Echo findings. The test was not statistically significant. (The chi-square statistic is 3.1329. The *p*-value is .076729).

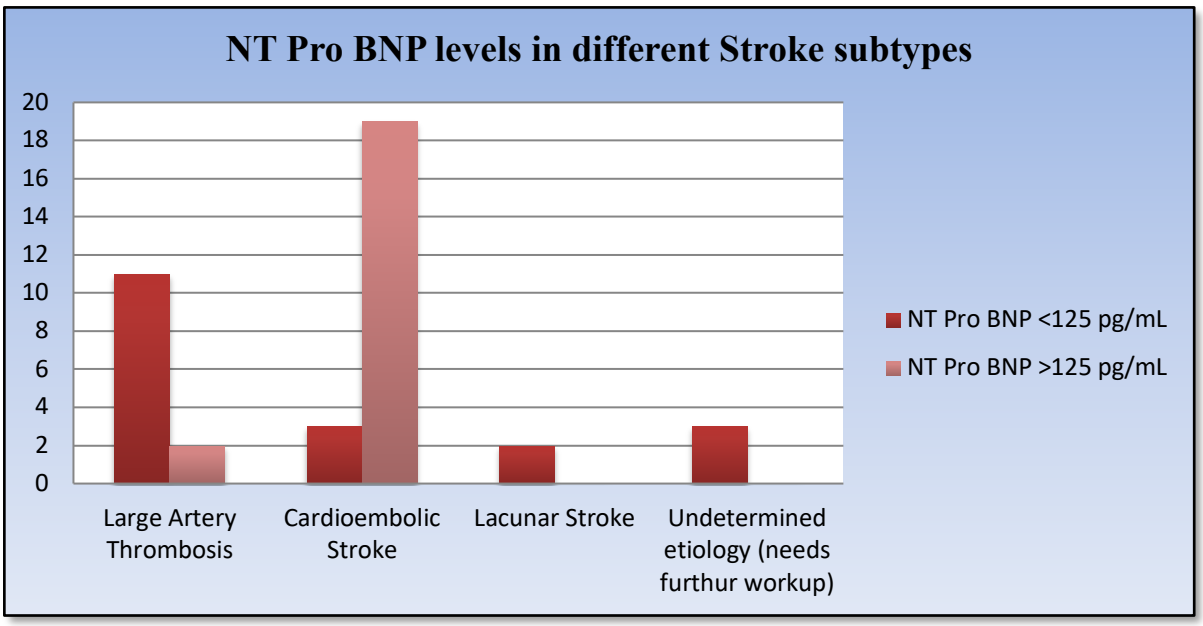

Figure 5: NT Pro BNP levels in different Stroke subtypes

Figure 5: NT Pro-BNP levels in different stroke subtypes. 19 patients with cardioembolic stroke (n = 22) had a raised NT Pro-BNP levels above the age standardized cut-off values. 11 patients with thrombotic stroke (n = 13) had a normal NT Pro-BNP levels. The test was statistically significant (chi-square statistic is 17.1533. The *p*-value is .000034. The result is significant at $p < 0.05$).

Discussion

Cerebrovascular stroke is a devastating neurological disorder with an estimated lifetime global risk of 25% from age 25 years onwards. It is important to diagnose and categorize the stroke type in its acute phase especially during the first 48 hours as acute phase of ischemic stroke is associated with worst prognostic outcomes.

BNP is a neurohormone synthesized and released from cardiac myocytes in response to increased ventricular wall tension. Blood levels of both BNP and its metabolically active form NT Pro BNP are raised in heart failure [7]. NT Pro-BNP is preferred for analysis due to its longer half-life (70 minutes).

In this study we tested 40 patients with ischemic stroke of different etiologies for elevated NT Pro-BNP levels. Among these 40 patients, 55% stroke were of cardioembolic origin (n=22), 32% were having large artery thrombosis as a cause of cerebral ischemia (n-13), 5% with lacunar stroke (n=2) and 8% were of undetermined etiology (n=3).

A cut-off value of 125pg/mL for NT Pro BNP levels was selected based on previous studies and the diagnostic kit used. We found that 53% (n=21) of patients with ischemic stroke were tested positive for elevated levels of NT Pro-BNP. Of those 21 patients who tested positive for elevated NT Pro BNP levels, 90% (n=19) were having cardio-embolic origin of stroke whereas only 10% (n=2) were having large artery thrombosis, a value that has a high statistical significance with a *p* value of 0.000034.

Out of 22 patients with cardio-embolic origin of stroke 86% (n=19) patients had an elevated level of plasma NT Pro BNP, a value that is statistically significant with a *p* value of <0.05($p = 0.000034$.).

Among patients with Large artery thrombosis as a cause of ischemic stroke (n=13), 85% patients (n=11) had a NT Pro BNP value <125pg/mL. Out of those two patients with large artery thrombosis who tested positive for elevated NT Pro BNP levels, one patient had hypertension with left ventricular hypertrophy and other has hypertension with moderate left ventricular dysfunction as a confounding factor for elevation in NT Pro BNP levels. As increased plasma NT Pro-BNP concentrations may serve as a part of compensatory mechanisms in response to the cardiac overload associated with hypertension [6].

We also compared different stroke subtypes with ECG changes in the form of either atrial fibrillation or changes of myocardial ischemia. Out of 13 patients with large artery thrombosis 11 patients had a normal ECG whereas 12 patients out of 22 with Cardioembolic stroke had ECG changes either in the form of atrial fibrillation or myocardial ischemia which was statistically significant with a *p* value of 0.02231.

We also compared effect of addiction on stroke subtypes. We found that patients with thrombotic stroke were having some addiction in the form of alcohol consumption, smoking or tobacco chewing.

Smoking and tobacco are associated with an increased risk of atherosclerosis [8]. Whereas majority of patients with cardioembolic stroke did not have any addiction (n=17). The difference was statistically significant with a *p* value of 0.0216.

Joan Montaner et al in a prospective study examined 707 patients with ischemic stroke and classified stroke subtypes according to TOAST classification and compared with 10 different biomarkers including BNP. They found that BNP as a biomarker, best differentiated cardioembolic stroke from other stroke subtypes (*p* value <0.001). BNP (>76pg.mL) and D-dimer were labeled as independent predictors of cardioembolic stroke [9]. However, in our study we used NT Pro-BNP as a biomarker for identification of cardioembolic stroke. Due to its longer half-life (70 minutes compared to 20 minutes of BNP) and high sensitivity, NT Pro-BNP was preferred over BNP [10]. NT Pro-BNP came out as a good predictor of cardioembolic stroke as well as a great negative predictor in thrombotic stroke.

Mary Cushman et al in a case cohort study evaluated the association of cardiac biomarker NT Pro-BNP with stroke risk and etiologic stroke subtypes. They found increase in NT Pro-BNP values >125pg/mL as a major risk factor for cardioembolic stroke. There was also presence of positive association between elevated NT Pro-BNP levels and thrombotic stroke [11]. In our study we have proved a significant association between elevated levels of NT Pro-BNP and cardioembolic stroke as well as a significant negative predictive value of elevated NT Pro-BNP levels in thrombotic stroke. Cushman et al also studied association between NT Pro-BNP and albuminuria and GFR. However, our study did not take such factors into consideration as there are separate causal pathways of elevation of NT Pro-BNP levels in chronic kidney disease patients.

Jia Li et al also compared acute ischemic stroke with elevated levels of NT Pro-BNP and D dimer [10]. They proved a positive correlation between occurrence of atherosclerosis and elevated NT Pro-BNP levels. They also stated that thrombosis can accelerate NT Pro-BNP secretion. Whereas in our study there is a clearcut negative correlation between stroke due to large artery thrombosis and elevated levels of NT Pro-BNP (*p* value of 0.000034).

Manuel Rodr´ıguez-Y´a˜nez et al proved a positive association between elevated Pro BNP levels and cardioembolic origin of stroke with a cut-off value 360 pg/mL for Pro-BNP [12]. In our study even at a lower cutoff value for NT Pro-BNP i.e. 125 pg/mL we were able to prove a statistical significance difference between cardioembolic and thrombotic stroke.

References

1. Harrison, chapter 426, introduction to cerebrovascular diseases, page 3324
2. Jurgen A. H. R. Claassen,1 Dick H. J. Thijssen,2,3 Ronney B. Panerai,4,5 and Frank M. Faraci6. Regulation of cerebral blood flow in Humans: physiology and clinical Implications of autoregulation. Physiol Rev 101: 1487–1559, 2021
3. Joseph Donnelly1, Karol P. Budohoski1, Peter Smielewski1 and Marek Czosnyka1,2*. Regulation of the cerebral circulation: bedside assessment and clinical implications. Donnelly et al. Critical Care (2016) 20:129 DOI 10.1186/s13054-016-1293-6
4. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. Anesthesiology. 2015;123:1198–208.
5. Lingzhong Meng, M.D., Wugang Hou, M.D., Ph.D., Jason Chui, M.B.Ch.B., Ruquan Han, M.D., Adrian W. Gelb, M.B.Ch.B. Cardiac Output and Cerebral Blood Flow. The Integrated Regulation of Brain Perfusion in Adult Humans. Anesthesiology 2015; 123:1198-208
6. Naruse M, Takeyama Y, Tanabe A, Hiroshige J, Naruse K, Yoshimoto T, Tanaka M, Katagiri T, Demura H. Atrial and brain natriuretic peptides in cardiovascular diseases. Hypertension. 1994 Jan;23(1 Suppl):I231-4. doi: 10.1161/01.hyp.23.1_suppl.i231. PMID: 8282365
7. https://www.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.119.006541
8. Centner AM, Bhide PG, Salazar G. Nicotine in Senescence and Atherosclerosis. Cells. 2020 Apr 22;9(4):1035. doi: 10.3390/cells9041035. PMID: 32331221; PMCID: PMC7226537.
9. Montaner J, Perea-Gainza M, Delgado P, Ribó M, Chacón P, Rosell A, Quintana M, Palacios ME, Molina CA, Alvarez-Sabín J. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. Stroke. 2008 Aug;39(8):2280-7. doi: 10.1161/STROKEAHA.107.505354. Epub 2008 Jun 5. PMID: 18535284.
10. Li J, Gu C, Li D, Chen L, Lu Z, Zhu L, Huang H. Effects of serum N-terminal pro B-type natriuretic peptide and D-dimer levels on patients with acute ischemic stroke. Pak J Med Sci. 2018 Jul-Aug;34(4):994-998. doi: 10.12669/pjms.344.15432. PMID: 30190768; PMCID: PMC6115578.
11. Cushman M, Judd SE, Howard VJ, Kissela B, Gutiérrez OM, Jenny NS, Ahmed A, Thacker EL, Zakai NA. N-terminal pro-B-type natriuretic peptide and stroke risk: the reasons for geographic and racial differences in stroke cohort. Stroke. 2014 Jun;45(6):1646-50. doi: 10.1161/STROKEAHA.114.004712. Epub

2014 Apr 22. PMID: 24757103; PMCID: PMC4142424.
12. Rodríguez-Yáñez M, Sobrino T, Blanco M, de la Ossa NP, Brea D, Rodríguez-González R, Leira R, Dávalos A, Castillo J. High serum levels of pro-brain natriuretic peptide (pro BNP) identify cardioembolic origin in undetermined stroke. Dis Markers. 2009;26(4):189-95. doi: 10.3233/DMA-2009-0630. PMID: 19729800; PMCID: PMC3833699.