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Role of plasma N-terminal proB-type natriuretic peptide (NT-proBNP) level in differentiating cardioembolic stroke from other stroke subtypes

Neurology

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ABSTRACT

BACKGROUND:
NT-proBNP is a well-recognized biochemical marker of congestive heart failure. Recent studies suggested that NT-proBNP may be used as a marker of cardioembolic stroke.

OBEJECTIVE:
To study the value of N-terminal proB-type natriuretic peptide in differentiating cardioembolic stroke from other subtypes of stroke.

MATERIAL & METHODS:
A total of 108 consecutive patients presenting with acute ischemic stroke within 72 hours of onset of stroke were studied. They were classified in to four groups: Cardioembolic (CE), Large artery atherosclerosis (LAA), Small-vessel disease (SVD) and other subtypes. Serum NT-proBNP levels were assessed.

RESULTS:
Out of 108 patients, 28(25.9%) were cardioembolic whereas 74.1% patients were in non-cardioembolic (NCE) group. The levels of NT-proBNP were significantly high in CE group (839.2±491.6 pg/ml) vs NCE group (153.96±144.25pg/ml) (p value<0.001).

CONCLUSION:
Our results showed that NT-proBNP level estimation as a biomarker has an acceptable diagnostic value in distinguishing cardioembolic stroke from other subtypes.

KEYWORDS

NT-proBNP, TOAST criteria, electrochemi-luminescence immunoassay, cardioembolic stroke.

INTRODUCTION:

Brain natriuretic peptide (BNP) is a neurohormone that is synthesized and released primarily from the cardiac ventricles in response to increased wall tension.[1,2] BNP is produced as a prohormone (pro-BNP) comprising of 108 amino acids and is enzymatically cleaved into physiologically active BNP (77-108 amino acids) and the amino-terminal portion of the prohormone NT-proBNP (1-76 amino acids).[2,3]

Ischemic stroke is classified as large-vessel disease, cardioembolic, small-vessel disease or other stroke with undetermined or unknown cause according to the (TOAST) Trial of Org 10172 in acute stroke treatment classification.[4] It is important to differentiate the stroke subtypes particularly cardioembolic (CE) stroke from non-cardioembolic (NCE) stroke (atherothrombotic stroke and lacunar stroke), since acute treatment, secondary prevention, outcome as well as prognosis differ in these case. Cardioembloic (CE) stroke accounts for 20% of all cerebral infractions and it is the most common subtype among all strokes with an identifiable cause.[5-7]

At present accurate determination of the stroke subtype immediately after admission requires magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), electrocardiography, and transthoracic echocardiography. The development of a method to predict stroke subtype only by drawing blood would be an examination superior to all others. Several investigators have tried various markers such as the D-dimer and high sensitive C reactive protein (CRP) to differentiate the stroke subtypes, however the diagnostic accuracy of these tests has been low.[8,9]

It has been shown that BNP is frequently increased after an acute ischemic stroke (AIS) and it can be used a marker to distinguish CE origin of ischemic stroke from other subtypes.[10-13] It can also serve as a potential marker of left atrial thrombus in transient ischemic attack (TIA) and AIS in patients with atrial fibrillation (AF), and has been shown to be a predictor of mortality, myocardial infraction, delayed AF, and recurrence in ischemic stroke patients. However, few studies have reported using NT-proBNP as a differentiation in ischemic stroke.[14-19]

In this study, we measured the level of plasma NT pro-brain natriuretic peptide in acute ischemic stroke patients and investigate whether we could differentiate between cardioembolic stroke and non-cardioembolic stroke on the basis of plasma NT pro-brain natriuretic peptide level.

METHODS:

A total of 108 consecutive patients presenting with acute ischemic stroke within 72 hours of onset of stroke in the emergency department or neurology OPD were enrolled in the study. Prior approval from the institutional ethic committee / research review board and informed consent from the patients/legal guardian has been taken.

All patients underwent thorough evaluation including clinical history, general physical examination including vitals and systemic examination of respiratory, cardiovascular and neurological system. Demographic characteristics along with risk factor vascular disease like age, gender, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, prior history of stroke and coronary artery disease, history of smoking and alcohol intake were assessed.

The diagnosis of acute ischemic stroke was established both clinically and radiologically computed tomography (CT) or magnetic resonance imaging (MRI). All magnetic resonance images were performed with 3-T system (Achieva 3T, Philips Medical Systems) Sequences included diffusion-weighted images (DWIs) obtained by multi-slice spin echo planar imaging (slice thickness, 4.5mm; slice gap, 1.0 mm; field of view, 23X23 cm; repetition time (TR), 2000-3000 ms; echo time (TE), 65-75ms. B values were 0 and 1000 s/mm^2. For the acquisition of the apparent diffusion coefficient, the images were applied in the x, y, and z directions. Fluid attenuated inversion recovery images (slice thickness, 5 mm; slice gap, 0.5 mm; field of view, 19.9 x 22 cm; TR, 5000-6000; TE, 92-96 ms; inversion time, 2000-2600 ms) and T2 weighted images (slice thickness, 5mm; slice gap, 0.5mm; field of view, 19.9 x 22 cm; TR, 3200-3400 ms, TE 100-105 ms). For the acquisition of the apparent diffusion coefficient, the images were applied in the x, y, and z directions. Acute cerebral infraction was defined as an area of high signal intensity on the DWI. Complete two-

dimensional (2D) echocardiography including transthoracic as well as trans-esophageal echocardiography and carotid Doppler study were performed using Philips i E33 system with probe S5-1. Serum NT-proBNP levels were measured by electrochemi-luminescence immunoassay (ECLIA) using cobas e immunoassay analyzers, Roche Diagnostics. Measuring range of this assay was 5-35000 pg/ml.

Stroke Subtype Classification was done using TOAST criteria.[4] According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, stroke subtype were classified as large artery atherosclerosis (LAA), Cardioembolic (CE), small-vessel disease (SVD) and other subtypes.

Patients were evaluated for etiology of stroke using brain CT or MRI, carotid Doppler study or magnetic resonance angiography (MRA) or cerebral angiography, transthoracic echocardiography (TTE) or trans-esophageal echocardiography (TEE) or Holter monitoring depending upon clinical indications.

Statistical analysis was performed with SPSS software (version 18.0; SPSS Inc., Chicago, IL). Continuous data were presented as mean (SD) or median. Difference in the clinical characteristics, including BNP level between stroke subtypes was analyzed by one-way ANOVA for quantitative variables and the Pearson chi-square test for qualitative variables. Multivariate analysis was performed using logistic regression. A receiver operating characteristic (ROC) curve was plotted to estimate the diagnostic performance of NT-proBNP levels and to calculate the optimum cutoff levels that predicted the cardioembolic origin of stroke, sensitivity and specificity of that cutoff level.

RESULTS:

The present study was conducted on 108 acute ischemic stroke patients presenting within 72 hours of onset of stroke. Mean age of patients was 58.99± 11.92 years ranged from 19 to 89 years, majority of the patients 88(81.48%) were more the 50 years of age group. 72(66.7%) were males and 36(33.3%) were females, male female ratio was 2:1 (Table 1). 28(25.9%) were cardioembolic, 31(28.7%) were large artery atherosclerosis, 28(25.9%) were small-vessel disease and 21(19.4%) were classified as others subtypes (Table 2, Figure 1).

Age group(years)	CE n(%)	NCE n(%)	Total n(%)
<40	1(3.6%)	5(6.3%)	6(5.6%)
41-50	3(10.7%)	11(13.8%)	14(13.0%)
51-60	12(42.9%	34(42.5%)	46(42.6%)
61-70	7(25.0.%)	17(21.3%)	24(22.2%)
>70	5(17.9%)	13(16.3%)	18(16.7%)
Total	28(100%)	80(100%)	108(100%)
Age in years (Mean±SD)	60.54±11.37)	58.45±12.14	58.99±11.92

Table 1: Age distribution of CE and NCE groups (CE: Cardioembolic, NCE: Non-cardioembolic)

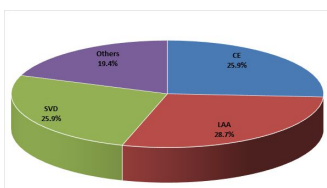


Figure 1: Classification of stroke (CE: Cardioembolic, LAA: Large artery atherosclerosis, SVD: Small vessel disease)

Type of stroke	Frequency	Percentage (%)
CE	28	25.9%
LAA	31	28.7%
SVD	28	25.9%
Others	21	19.4%
Total	108	100%

Table 2: Classification of stroke (CE: Cardioembolic, LAA: Large artery atherosclerosis, SVD: Small vessel disease)

In our study population, 28(25.9%) patients were in cardioembolic group whereas 80(74.1%) patients were in non-cardioembolic group (Table 3, Figure 2).

Type of stroke	Frequency	Percentage (%)
CE	28	25.9%
NCE	80	74.1%

Table 3: Classification in to CE and NCE (CE: Cardioembolic, NCE: Non-cardioembolic)

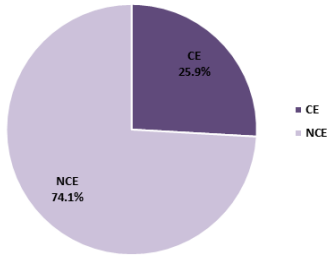


Figure 2: Classification in to CE and NCE groups.

While comparing various risk factors in cardioembolic and non-cardioembolic group, we found that most significant risk factor associated with cardioembolic stroke in our study was atrial fibrillation which was found in 17(60.7%) patients in CE groups as compared to 1(1.3%) patients in NCE group (p value<0.001). History of previous coronary artery disease was found in 42(38.9%) patients. It was significantly higher in patients with CE group as compared to NCE group (p value 0.006). Rest all factors including diabetes mellitus, hypertension, previous history of stroke, dyslipidemia, smoking and alcohol were not significantly different in cardioembolic and non-cardioembolic group.

To determine the variables associated with stroke subtype and remove the effect of confounding variables, we performed multivariate analysis using logistic regression backward stepwise elimination (likelihood ratio) and found that atrial fibrillation and NT-proBNP levels were independent predicators of CE stroke.

In our study, the mean NT-proBNP levels were 331.6±409.1 pg/ml and ranged from 30 to 2148 pg/ml and the median was 148 pg/ml. Patients with previous CAD had higher levels of NT-proBNP (463.10±517.90 pg/ml) as compared to patients with no history of CAD (248.0±296.7 pg/ml) and the difference was statistically significant (p value<0.01) NT-proBNP levels were significantly higher in patients with AF (812.67±520.69 pg/ml) as compared to patients without AF (235.41±305.41 pg/ml) and the difference was highly significant (p value <0.001) NT-proBNP levels in all other factors including diabetes mellitus, hypertension, previous history of stroke, dyslipidemia, smoking and alcohol were not significantly different (Table 4, Figure 3).

Risk factor	Yes	No	p-value		
	n	NT-proBNP(pg/ml) Mean±SD	n	NT-proBNP (pg/ml)Mean±SD	
Previous stroke	43	385.26±446.32	65	296.14±381.95	0.27
Previous CAD	42	463.10±517.90	66	248.0±296.7	0.01
DM	57	349.89±432.08	51	311.2±385.06	0.63
HTN	72	377.51±466.59	36	239.83±238.83	0.10
Dyslipidemia	54	272.93±334.01	54	390.31±468.31	0.14
Smoking	54	322.87±362.39	54	340.37±454.33	0.83
Alcohol	13	341.54±387.22	95	330.26±413.96	0.93
AF	18	812.67±520.69	90	235.41±305.41	0.001

Table 4: Various risk factors affecting NT-proBNP levels (CAD: Coronary artery disease, DM: Diabetes mellitus, HTN: Hypertension, AF: Atrial fibrillation)

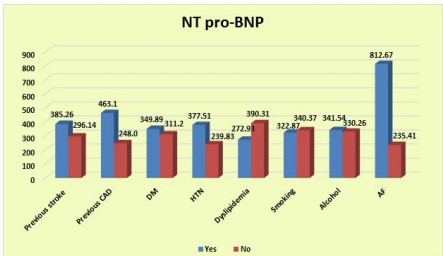


Figure 3: Various risk factors affecting NT-proBNP levels (CAD: Coronary artery disease, DM: Diabetes mellitus, HTN: Hypertension, AF: Atrial fibrillation)

The mean NT-proBNP levels were highest in CE group (839.2±491.6 pg/ml) followed by LAA group (191.9±217.9 pg/ml) followed by others group (142.7±48.5 pg/ml) and were lowest in SVD group (120.4±48.5 pg/ml) (Table 5, Figure 4). While comparing NT-proBNP levels in CE group (839.2±491.6 pg/ml) vs NCE group (153.96±144.25 pg/ml), the levels of NT-proBNP were significantly high in CE group (p value<0.001) (Table 5 & 6, Figure 4 &5).

Type of stroke	n	NT-proBNP(pg/ml)Mean±SD
CE	28	839.2±491.62
LAA	31	191.9±217.90
SVD	28	120.4±48.5
Others	21	142.7±48.5
Total	108	331.6±409.1

Table 5: NT-proBNP levels in different types of stroke. (NT-proBNP: N-terminal pro-brain natriuretic peptide)

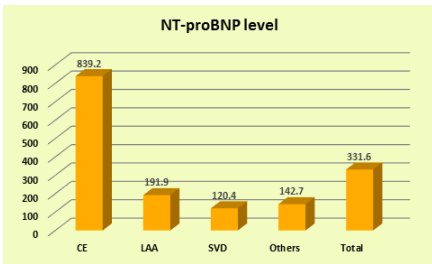


Figure 4: NT-proBNP levels in different types of stroke (NT-proBNP: N-terminal pro-brain natriuretic peptide)

Type of stroke	n	NT-proBNP(pg/ml) Mean±SD	p-value
CE	28	839.2±491.62	<0.001
NCE	80	153.96±144.25	

Table 6:NT-proBNP levels in CE and NCE groups (CE: Cardioembolic, NCE: Non-cardioembolic)

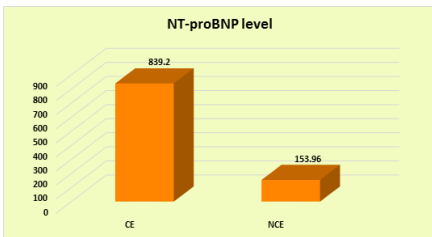


Figure 5: NT-proBNP levels in CE and NCE groups (CE: Cardioembolic, NCE: Non-cardioembolic)

In our study, A receiver operating characteristic (ROC) curve was plotted which revealed that the diagnostic performance of NT-proBNP levels as measured by area under the curve was 0.948±0.029 pg/ml and the optimum cutoff levels that predicted the cardioembolic origin of stroke was 255 pg/ml with its sensitivity and specificity being 92.9%, and 93.8% respectively (Table 7, Figure 6).

ROC Curve				
Area under the curve	Std. Error	Optimum level (pg/ml)	Sensitivity	Specificity
0.948	0.029	255	0.929	0.062

Table 7: Receiver operating characteristic (ROC) curve analysis

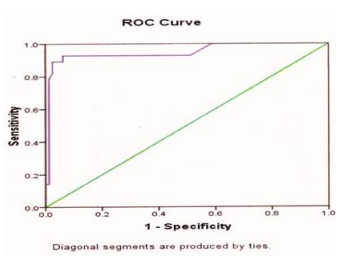


Figure 6: Receiver operating characteristic (ROC) curve analysis

DISCUSSION:

The Present study was conducted on 108 acute ischemic stroke patients presenting within 72 hours of onset of stroke to the department of neurology, Indraprastha Apollo Hospital, New Delhi.

Out of 108 patients, 28(25.9%) were cardioembolic, 31(28.7%) were large artery atherosclerosis, 28(25.9%) were small-vessel disease and 21(19.4%) were classified as other subtypes. 25.9% patients were cardioembolic whereas 74.1% patients were non cardioembolic. This Proportion was in concordance with various previous studies, reported cardioembolic stroke (25-35%) and non-cardioembolic stroke (65-75%).[20-23]

In our study population, mean age of patient was 58.99±11.92 years. Maximum number of patients, 88(81.48%) were in >50 years age group. The mean age of patients in various stroke groups was very much similar and the difference between the groups was statistically not significant (p value >0.05). 72(66.7%) patients were male and 36(33.3%) were female; the male female ratio was 2:1.

History of previous coronary artery disease was found in 42(38.9%) patients. It was significantly higher in patients with CE group as compared to NCE group (p value <0.001). Most significant risk factor associated with cardioembolic stroke in our study was atrial fibrillation which was found in 17 (60.7%) patients in CE group as compared to 1(1.3%) patients in NCE group (p value<0.001). Various studies have reported the higher incidence of CE stroke in patients with atrial fibrillation, coronary artery disease and mitral regurgitation, our results are similar to these studies.[12,21,24,25]

In our study, the mean NT-proBNP levels were 331.6±409.1 pg/ml and ranged from 30 to 2148pg/ml and the median was 148 pg/ml. The mean NT pro-BNP levels in age groups 51-70 year as compared to < 50 year and females as compared to males were higher, but the difference was insignificant (p value >0.05). Similar findings were observed in certain previous studies.[12, 26] However Hajsadeghi S et al reported significant difference in NT pro-BNP levels between sexes (1502.4±579.1 for females vs. 986.1±1775.7pg/ml for males) which is in contrast to our findings.[21]

The mean NT-proBNP levels in hypertensives, diabetics, dyslipidemics, smokers, alcoholics and patients with previous history of stroke was almost similar and the difference was not statistically significant(p value= > 0.05). Patients with previous CAD had higher levels of NT-proBNP (463.10±517.90pg/ml) as compared to patients with no history of CAD (248.0±296.7pg/ml) and the difference was statistically significant (p value <0.01). In our study also, NT-proBNP levels were significantly higher in patients with AF (812.67± 520.69pg/ml) as compared to patient without AF (235.41± 305.41pg/ml) and the difference was highly significant (p value <0.001). In various studies atrial fibrillation was recognized as most significant factor associated with raised BNP/NT-proBNP levels.[12,21,26,27] While comparing NT-proBNP levels in CE group (839.2±491.6pg/ml) vs. NCE group (153.96±144.25pg/ml) the levels of NT-proBNP were significantly high in CE group (p value <0.001). Our observation was consistent findings in previous studies.[20,21,23,24,27]

In our study , A receiver operating characteristic (ROC) curve was plotted which revealed that the diagnostic performance of NT-proBNP levels (area under the curve) was 0.948± 0.029 pg/ml and the optimum cut off levels that predicated the cardioembolic origin of stoke was 255pg/mL with its sensitivity and specificity being 92.9% and 93.8% respectively. Our result were similar to those published in earlier studies.[22,24,27]

Each year, 5 million individuals die as a consequence of stroke and CE stroke is associated with the highest mortality and highest recurrence rate, with 15% patients experiencing recurrence within 5 years. Because cardioembolism is the most amenable to anti-coagulation prevention, early identification of cardioembolism among patients with ischemic stroke is important.[28,29]

The use of plasma biomarkers in the diagnosis and differentiation of diseases is becoming increasingly popular in almost all medical specialties, i.e., D-dimer in pulmonary thromboembolism, troponin I and T for acute cardiovascular syndromes, hemoglobin A1c in

monitoring diabetic patients etc. rapid, accurate and almost harmless assays are the reason for popularity listed most often by physicians.[29]

Neurobiomarkers are difficult to determine because of multiple molecular pathway of neuro-degeneration and neuro-regeneration and the existence of the blood-brain barrier in stroke pathophysiology. Hirano et al[30] evaluated 69 acute patients in the emergency setting and shown that fibrin complex, soluble fibrin, and D-dimer levels are useful for differentiating CE stroke during the early stages. Becker et al[31] have also shown that C-reactive protein, D-dimer, fibrinopeptide-A, interleukin-6, platelet factor IV, tissue factor, and tumor necrosis factor-alpha are elevated in patients with CE stroke in contrast to non-CE stroke. All of these studies have linked vascular damage, inflammation, and especially AF and its embolus formation as the cause of this phenomenon.[24,30,31]

Diagnosis of CE stroke is based on the presence of a potential major cardiac source of embolism after the exclusion of severe arterial disease, such as arteritis, arterial dissection, or venous occlusion. Left atrial appendage in patient with atrial fibrillation (AF) is a major source of cardioembolism.[32] However, even after extensive investigation, the cause of stroke remains undetermined in approximately 30%-40% patients.[33,34]

High level of NT pro-BNP have also been associated with atrial abnormalities in patients with ischemic stroke, such as atrial dilatation, low flow velocity, spontaneous echo contrast or intra-ventricular thrombus, and atrial fibrillation. The majority of cardioembolic strokes are due to atrial fibrillation. Paroxysmal atrial fibrillation is an under diagnosed arrhythmia associated with an increased risk of ischemic stroke comparable to that of chronic atrial fibrillation. Patients with paroxysmal atrial fibrillation show also higher levels of BNP, so these high level in patients with stroke of undetermined origin might reflect the presence of paroxysmal atrial fibrillation or of any other atrial abnormality as potential cardioembolic source.[2,13-19]

The exact mechanism of elevated NT pro-BNP level in acute cerebral infraction is unknown, but there are several hypothesis. First, elevated NT pro-BNP in acute cerebral infraction may be related to cardiac disorders, which may be a cause of the infraction, a co-existing condition, or a result of the infarction. Second, NT pro-BNP production may be stimulated by changes in catecholamine in acute cerebral infarction, regardless of cardiac dysfunction. Third, inflammatory markers or hypoxia-inducible factor that is induced in acute cerebral infarction may stimulate NT pro-BNP production. However, we cannot ignore the theory of NT pro-BNP secretion from the brain because of the neurodegenerative process.[4,35-38]

Our study result showed that NT-proBNP levels were significantly higher in CE compared to other stroke subtypes. Moreover, NT-proBNP levels >255pg/ml could differentiate the CE group from others with high sensitivity and specificity. The NT-proBNP test is sensitive, specific, can be performed quickly and is also easier than routine workups, such as echocardiography or Holter monitoring. It therefore costs less and both intra- and inter-observer variability may be prevented. In addition, NT-proBNP measurement is more practical than some cardiac imaging modalities, including TEE and cardiac MRI.

Our study had some limitations. First, the classification of stroke subtype according to the TOAST criteria does not have a gold standard, for example, pathologic examination, for confirmation of the exact etiology. Second, the sample size was small to generalize, and further research with a larger population would be needed. Third, our study was bases on a single test and repeated tests during cerebral infarction would be more informative.

CONCLUSION:

Our results showed that NT-proBNP level estimation as a biomarker has an acceptable diagnostic value in distinguishing cardioembolic stroke from other subtypes.

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