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Original Article

Internal Medicine Section

N-terminal Pro Brain Natriuretic Peptide (NT-proBNP) as a Marker for Risk Stratification and Prediction of Functional Outcome in Acute Ischaemic Stroke

AG MANOJ[1], K PRABHAKAR[2], KN SHASHIDHAR[3]

ABSTRACT

Introduction: Stroke is the second leading cause of mortality and disability worldwide. A large proportion of stroke survivors are left with significant disability. Assessing stroke severity and predicting morbidity and mortality is essential for treatment decisions and counseling. Traditionally used tools like the National Institutes of Health Stroke Scale (NIHSS) are not reliable in predicting mortality. Studies have shown that B-type Natriuretic Peptide (BNP) and N-terminal pro Brain Natriuretic Peptide (NT-proBNP) are elevated in acute stroke.

Aim: To assess the prognostic importance of NT-proBNP in stroke.

Materials and Methods: A prospective cohort study was conducted at Sri Devaraj URS Medical College (SDUMC), SDUAHER, Kolar, Karnataka, India involving 64 consecutive stroke patients from July 2018 to September 2019. Serum NT-proBNP levels were measured on both the day of admission and on day 7. Stroke severity was assessed using the NIHSS on admission day, and functional disability was determined using the Barthel Index (BI) at the 3-month mark. Data were entered into MS Excel for statistical analysis, where a p-value of <0.05 was considered statistically significant.

Results: The average age of the subjects was 62.36 years with a standard deviation of 12.15 years. The average NIHSS on the day of admission was 12.81 (7), and it was 20.2 (5.882) among deceased patients. The mean NT-proBNP on admission was 776.70 (1023.6) pg/mL, significantly elevated in deceased patients at 2014.65 (1320.546) compared to survivors at 328.94 (239.353). NT-proBNP is strongly associated with stroke severity (NIHSS) (R2=0.522; Spearman's correlation coefficient=0.843, p-value <0.001) and functional outcome (BI) (R2=0.824; Spearman's correlation coefficient -0.923, p-value <0.001) at three months.On Receiver Operating Characteristic (ROC) analysis, a serum NT-proBNP level of 960 pg/mL had a sensitivity and specificity of 94.1% and 97.9% in predicting mortality, and a value of 435.1 pg/mL had a sensitivity and specificity of 90% and 81% in predicting disability.

Conclusion: Serum NT-proBNP was significantly elevated in patients after stroke and was strongly associated with stroke severity and functional outcome at three months. Measuring serum NT-proBNP on the day of admission can predict mortality and functional dependence after acute ischaemic stroke.

Keywords: Barthel index, Disability evaluation, Mortality, National institutes of health stroke scale, Prognosis

INTRODUCTION

Stroke is one of the most common fatal neurological disorders, ranking as the second leading cause of both mortality [1,2] and disability [2] globally. India has one of the highest case fatality rates in the world [3]. Huge proportions of stroke survivors are left with noticeable residual physical, cognitive, and psychological disabilities [1-3]. Prediction of outcome after a stroke is required to administer post-stroke management and to establish an effective continuing care programme to reduce the overall burden of stroke.

Traditionally, the most accepted tool for predicting outcome and severity after an ischaemic stroke is the NIHSS [4]. Even though the NIHSS is designed for clinical trials and is not advised as a bedside tool for clinicians in day-to-day practice [5], it is used worldwide as a prognostic tool and to make treatment decisions. Recent studies have shown that the NIHSS has limited ability to determine the long-term outcome, and a score of 0 on the NIHSS does not rule out a stroke [5-7].

The BI [8] and modified Rankin scale [9] are two well-accepted functional outcome assessment tools used in stroke survivors, but both cannot be used in the acute presentation to predict severity. Computed tomography angiography, which aids in the diagnosis of stroke, is not universally available and requires high cost, infrastructure, and expertise to evaluate patients. This test is not recommended in triaging patients, as it may lead to a doubling of radiation exposure, and the high use of iodinated contrast may lead to contrast-induced nephropathy [10]. For these reasons, there is a need for an inexpensive, widely available, and easily interpreted tool to predict the prognosis following a stroke and to make treatment decisions, and also to counsel the family.

Studies have shown that BNP is elevated in people with a stroke than in normal individuals [11]. The origin of natriuretic peptides in stroke is still unsettled, and there is evidence that suggests BNP is released from the hypothalamus in response to cerebral ischaemia [12,13]. A literature-based meta-analysis study found an association between BNP and NT-proBNP with death after a stroke, independent of the NIHSS score [14]. The proposed mechanisms for elevated NT-proBNP levels in stroke include the neurohormonal and inflammatory response following acute stress reaction due to acute ischaemic stroke [15].

Studies have shown that NT-proBNP can predict poor outcomes following a stroke and they were better predictors of prognosis compared to neurological deficit measurement [11,14,16]. One of the reasons postulated for raised BNP levels in stroke patients is cardiac dysfunction. In present study, patients with past or present cardiac ailments are excluded, and hence a possible cardiac cause was ruled out. There is evidence from an Indian study that plasma log NT-pro-BNP levels appear to be a useful biological marker for predicting in-hospital mortality in patients presenting with acute

ischaemic stroke [17], but they did not assess functional outcome and long-term mortality.

Although there are many studies on stroke severity, its management, and risk factors, very few studies are available for the prediction of outcome following acute ischaemic stroke [4,18,19]. There is a gap in knowledge in the Indian subcontinent. The present study seeks to address a critical gap in knowledge by investigating the prognostic significance of NT-proBNP as a biomarker for risk stratification and the prediction of functional outcomes in acute ischaemic stroke. The research involves measuring NT-proBNP levels at admission and after seven days, alongside assessing stroke severity using the NIHSS at admission and long-term functional outcomes with the BI at the 3-month mark. The objective is to establish correlations between NT-proBNP levels, functional outcomes, and stroke severity, providing valuable insights into potential associations that may inform risk assessment and recovery prediction in acute ischaemic stroke patients.

MATERIALS AND METHODS

It is a prospective cohort study done at Sri Devaraj URS Medical College (SDUMC), SDUAHER, Kolar, Karnataka, India from July 2018 to September 2019. Institutional Ethical Committee approval was taken before the start of the study and for publication (No. SDUMC/KLR/IEC/07/2017-18). Written and informed consent was obtained from all patients or their responsible next of kin.

Inclusion and Exclusion criteria: Patients with acute ischaemic stroke aged 18 years and above, presenting within 24 hours of the onset of symptoms, were included in the study. Patients aged over 80 years, with a previous history of stroke, head injury, intracerebral bleed or haemorrhagic stroke, renal disorders, a history of seizures, anaemia (haemoglobin <10 gm%), severe Chronic Obstructive Pulmonary Disease (COPD) with cor-pulmonale, sepsis, pregnant females, and patients with any evidence of heart failure, left ventricular systolic or diastolic dysfunction, myocardial infarction and acute coronary syndromes, hypertensive heart disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, atrial fibrillation and other arrhythmias, valvular and other structural heart disease were excluded from the study.

Sample size calculation: The estimated average sample size was based on the mean of BI scores reported in Menon B et al.,'s study, with a mean of 57 and a Standard Deviation of 30 [15]. The estimation was conducted aiming for an 8% precision and a 95% confidence interval, resulting in an estimated sample size of 58. Total 300 patients with features suggestive of acute ischaemic stroke were screened between July 2018 and September 2019, and 75 patients who met the inclusion and exclusion criteria were recruited.

Study Procedure

Acute ischaemic stroke (an abrupt onset of neurologic deficit that is attributable to a focal vascular cause) was diagnosed clinically, and a Computed Tomography (CT) brain or Magnetic Resonance Imaging (MRI) brain was done to confirm the diagnosis [20]. The stroke deficit was calculated by the NIHSS on the day of admission, at 7th day, on the day of discharge, and at the end of one and 3rd month. Patients were classified into five groups based on the NIHSS score: No stroke (NIHSS 0), minor stroke (NIHSS 1-4), moderate stroke (NIHSS 5-15), moderate/severe stroke (NIHSS 16-20), severe stroke (NIHSS 21-42) [18].

Stroke disability and functional outcome were measured using BI on the 7th day, at the time of discharge, and at the end of one month and three months following the stroke. BI was classified into three groups based on BI scores: <40 patients are completely dependent, a score >60 indicates the patient is slightly independent for personal care like feeding, bowel and bladder continence but still needs assistance, and a score >85 indicates patients are reasonably independent with minimal aid based on the study by Quinn TJ et al., [21].

About 2 mL of venous blood samples were collected in Ethylenediaminetetraacetic Acid (EDTA) vacutainers from all the patients at the time of presentation and seven days after the stroke. The blood was immediately centrifuged, and the serum sample was stored in EDTA vacutainers at -200 celsius. The serum assay of NT-proBNP was carried out by the NT-proBNP fast test kit using Agappe- Mispa- Revo immunofluorescence quantitative analysis by fluorescence immunochromatography. The test uses anti-human NT-proBNP monoclonal antibody conjugated with fluorescence latex and an anti-human NT-proBNP polyclonal antibody coated on the test line. The total duration of the assay is 10 minutes, and the measuring range is <100-35000 pg/mL. For heart failure, a value of <300 pg/dL is considered normal based on the 97.5th percentile concentration in normal individuals [22].

STATISTICAL ANALYSIS

The data collected on a predesigned proforma was entered into Microsoft Excel software and analysed by Statistical Package for the Social Sciences (SPSS) software version 20.0 Descriptive statistics were performed by computing frequencies, and quantitative variables were expressed as mean ± standard deviation. The correlation of NIHSS, NT-proBNP, and BI was studied using the Spearman's correlation coefficient. Chi-square tests, independent sample t-tests, and one-way Analysis of Variance (ANOVA) were used when necessary. Receiver Operating Characteristic (ROC) analysis was used to obtain optimal cut-off values for NT-proBNP and NIHSS for predicting mortality and functional outcome. A p-value of less than 0.05 was considered significant.

RESULTS

During the study period, 75 patients with acute ischaemic stroke were recruited, and 11 patients were lost to follow-up, resulting in a total of 64 patients being included in the study. The average age of the subjects was 62.36 years with a standard deviation of 12.15 years. Among them, 39 (60.93%) were males, and 25 (39.06%) were females.

The NIHSS scores, which measure stroke severity, BI scores that measure functional independence, and NT-proBNP levels were recorded at various time intervals after admission and tabulated, taking into account the survival status of the patients [Table/Fig-1].

Time point	Day of admission	Day 7	Time of discharge	End of first month	3 months after stroke
NIHSS Score (Mean±SD)	12.81± 7	11.07± 6	10.55± 5.7	8.84± 5.47	7.21± 5.09
BI score (Mean±SD)	19.21± 33.04	29± 33.61	31.78± 322.77	44.80± 33.37	59.68± 28.86
NT-proBNP (pg/mL) (Mean±SD)	776.70± 1023.6	223.53± 268.39			

[Table/Fig-1]: NIHSS scores, Barthel Index (BI) scores, and NT-proBNP levels recorded at various time intervals.

A consistent reduction in NIHSS scores over time was seen, implying improvement in stroke severity. Average scores decreased from the day of admission to three months post-stroke, reflecting a positive outcome. Additionally, the BI exhibited an improvement in scores over the same period, signifying increased functional independence. Furthermore, a paired sample t-test revealed a statistically significant difference in mean NT-proBNP values between admission and day 7 (p-value <0.001), indicating a significant change in NT-proBNP levels over present period.

There were 17 deaths in the study, 12 males and five females. Eight patients died within seven days of hospitalisation, five by the end of one month, and four died by the end of the 3rd month following the stroke. A significant increase in NIHSS scores and NT-proBNP (both at day 0 and day 7) was seen in the deceased when compared to survivors (p<0.001) [Table/Fig-2].

Time point	Variables	Survival status	Number of patients	Average value	Standard deviation	p-value
Day 0	NIHSS	Alive	47	10.11	5.189	<0.001
		Dead	17	20.29	5.882	
Day 0	NT-proBNP	Alive	47	328.94	239.353	<0.001
		Dead	17	2014.65	1320.546	
Day 7	NT-proBNP	Alive	47	287.64	223.5	<0.001
		Dead	9	794.58	852.62	

[Table/Fig-2]: Comparison of NIHSS scores and NT-proBNP between deceased and survived patients.

A total of 34 (53.12%) patients suffered from moderate stroke, and 8 (12.5%) patients suffered from severe stroke. Out of the 57 patients who survived, 13 (27.66%) did not have any dependency, and 10 (21.28%) were completely dependent [Table/Fig-3].

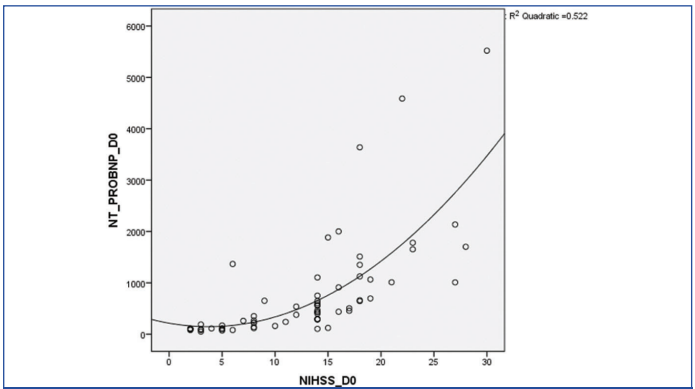
Variables	Number of patients	Percentage
Stroke severity group		
Minor stroke	9	14.06%
Moderate stroke	34	53.12%
Moderate/severe stroke	13	20.3%
Severe stroke	8	12.5%
Independence level		
Completely dependent	10	21.28%
Slightly independent	24	51.06%
Independent	13	27.66%

[Table/Fig-3]: Distribution of patients based-on stroke severity and independence level.
*17 deaths in the study

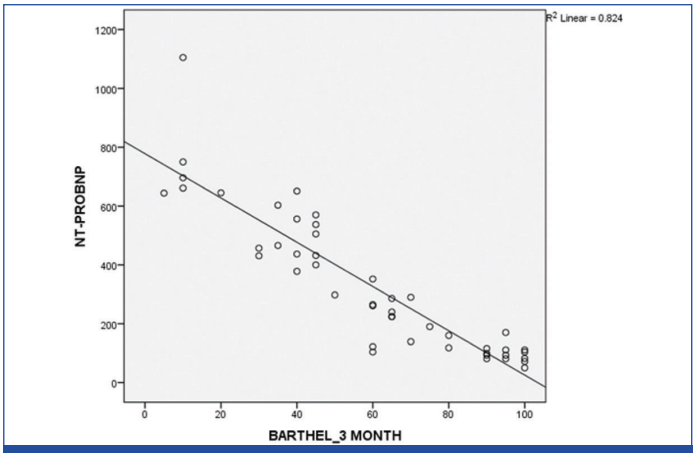
NT-proBNP levels on admission exhibited a strong positive correlation with NIHSS scores on admission (r=0.843, p<0.001). NT-proBNP on admission was inversely correlated with the BI at three months (r=-0.923, p<0.001). NIHSS scores on admission showed a strong negative correlation with the BI at three months (r=-0.86, p<0.001). The positive correlation with stroke severity and negative correlations with functional independence emphasise the potential clinical implications of NT-proBNP as a biomarker in stroke patients [Table/Fig-4-7].

Correlation pair	R^2 (coefficient of determination)	Spearman's correlation coefficient	p-value
NT-proBNP on admission vs. NIHSS on admission	0.522	0.843	<0.001
NT-proBNP on admission vs. Barthel Index (BI) at 3 months	0.824	-0.923	<0.001
NIHSS on admission vs. Barthel Index (BI) at 3 months	0.770	-0.86	<0.001

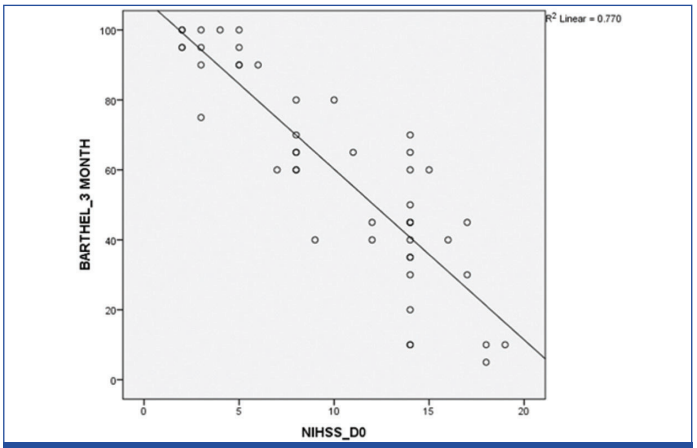
[Table/Fig-4]: Correlation of NT-proBNP, NIHSS, and Barthel Index (BI) in stroke patients.



[Table/Fig-5]: Scatter diagram showing positive correlation between NT-proBNP and NIHSS.



[Table/Fig-6]: Scatter diagram showing negative correlation between NT-proBNP AND BI.



[Table/Fig-7]: Scatter diagram showing negative correlation between BI and NIHSS.

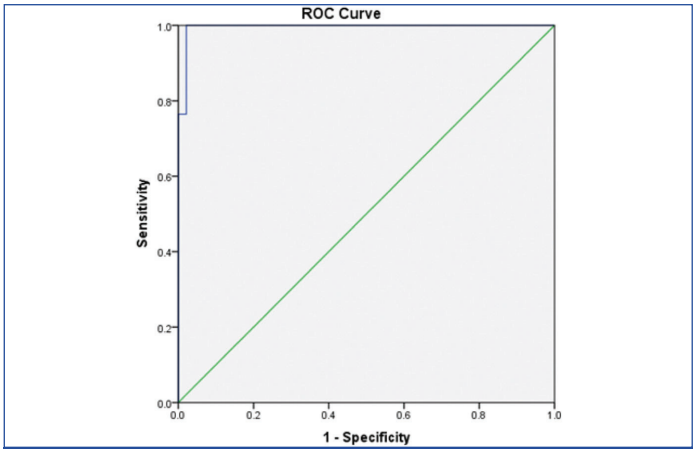
The ROC analysis revealed significant predictive capabilities for NT-proBNP at day 0 in acute ischaemic stroke patients. In predicting death, NT-proBNP demonstrated high accuracy with an Area Under Curve (AUC) of 0.995, a cut-off value of 960 pg/mL, and notable sensitivity (94.1%) and specificity (97.9%). Similarly, in predicting dependency, NT-proBNP exhibited a substantial AUC of 0.946, a cut-off value of 431.5, and a balanced sensitivity (90.0%) and specificity (81%). Comparatively, NIHSS at day 0 also showed significant predictive power for death (AUC: 0.926, cut-off: 14.5, sensitivity: 94.1%, specificity: 86%). These findings underscore the potential of NT-proBNP as a valuable prognostic tool in acute ischaemic stroke, offering precise insights into mortality and functional outcomes [Table/Fig-8-13]. In contrast, NIHSS failed to predict dependency.

Predictor	Area under the curve	Calculated cut-off	Sensitivity	Specificity	p-value
NT-proBNP at day 0 in predicting death	0.995	960 pg/mL	94.1%	97.9%	<0.001
NT-proBNP at day 0 for predicting dependency	0.946	431.5 pg/mL	90.0%	81%	<0.001
NIHSS at day 0 in predicting death	0.926	14.5	94.1%	86%	<0.001

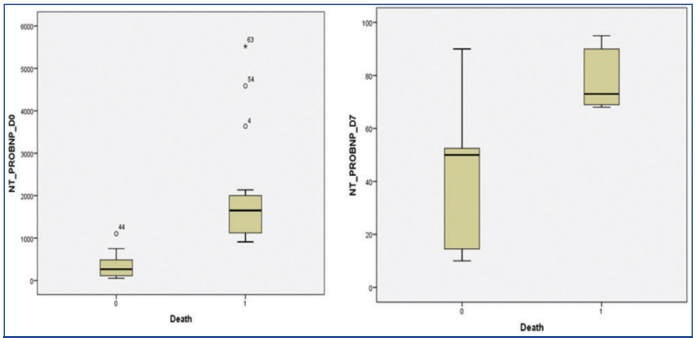
[Table/Fig-8]: Predictive capabilities for NT-proBNP in stroke patients

DISCUSSION

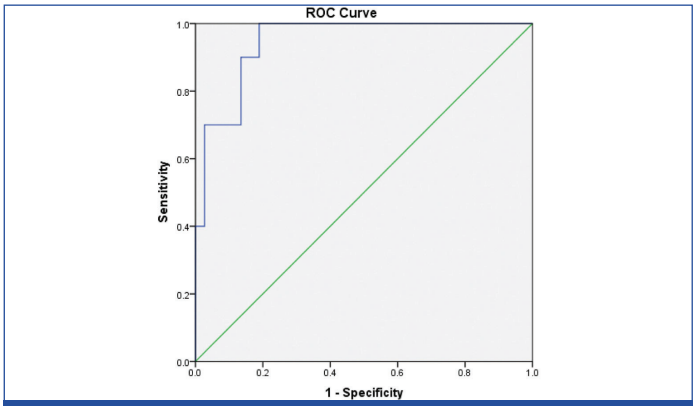
The present study unveils compelling insights into the association between serum NT-proBNP levels, stroke severity, and functional outcomes in patients following acute ischaemic stroke. Elevated serum NT-proBNP levels post-acute ischaemic stroke are not only a notable marker of increased stroke severity but also exhibit a robust correlation with 3-month functional outcomes.



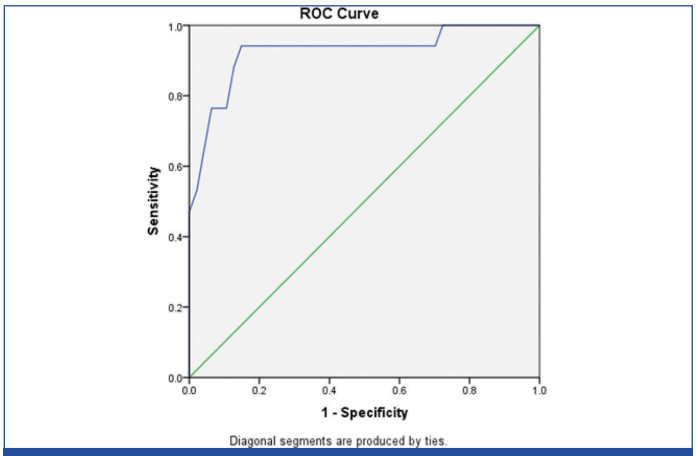
[Table/Fig-9]: ROC curve of NT-proBNP in predicting death.



[Table/Fig-10]: (Death '1' means patient died).
[Table/Fig-11]: (Death '1' means patient died). (Images from left to right)



[Table/Fig-12]: (ROC curve of NT-proBNP in predicting dependency.



[Table/Fig-13]: ROC curve of NIHSS in predicting death.

The present study contributes crucial evidence supporting the utility of NT-proBNP in acute ischaemic stroke management. Beyond its role as a marker of stroke severity, NT-proBNP emerges as a pivotal predictor of both short-term mortality and long-term functional outcomes. These findings could inform early intervention strategies and personalised care plans for stroke patients.

In the present study, NT-proBNP values were elevated on admission, consistent with Zhao YH et al., meta-analysis findings [23]. The average NIHSS score on admission in present study (12.81±7) was higher compared to Menon B et al., (10±7) and Chen X et al., (9.78±5.06) [15,24].

In the study, there were 17 (26.5%) deaths within three months, with 8 (12.5%) patients passing away within seven days of admission. This contrasts with Naveen V et al., 24.3% and Chen X et al., 18.85% hospital mortality rates, showcasing lower mortality rates in present study (17,24). Notably, NIHSS scores differed significantly between survivors (10.11±5.189) and deceased individuals (20.29±5.882) with a p-value <0.001. Similar significant associations between NIHSS scores of survivors (8.69±4.87) and deceased (14.48±2.54) were found by Chen X et al., (p<0.001). However, Naveen V et al., didn't report such an association between NIHSS scores of survivors (10.52±3.3) and deceased (15.8±3.3) with a p-value of 0.661 [17,24].

In the studied group, the mean NT-proBNP at admission stood at 776.70 (1023.6) pg/mL, contrasting Chen X et al., finding of 1,035.50 pg/mL. Jenson JK et al., reported a median NT-proBNP of 147 pg/mL at six months post-stroke, akin to Menon B et al., discovery of NT-proBNP levels at 435 (613) ng/mL [24,25,15]. In the present study, NT-proBNP levels significantly differed between survivors {328.94 (239.353) pg/mL} and deceased individuals {2014.65 (1320.546) pg/mL} with a p-value <0.001. Chen X et al., also observed a significant association between NT-proBNP levels of survivors (926.30 pg/mL) and deceased (3280 pg/mL) with a p-value <0.001, mirroring a similar finding in Naveen V et al., Indian study, where survivors had NT-proBNP levels at 233.5 (145.25-379.5) pg/mL and deceased at 769 (1171-1842) pg/mL (p-value <0.001) [17,24]. Differences in NT-proBNP values between studies may be due to varied considerations, such as short-term in-hospital mortality, the inclusion of cardiac causes of stroke, and diverse methods used to estimate NT-proBNP levels across studies.

In Naveen V et al., study, they found that NT-proBNP levels after seven days were higher in patients who didn't survive (1591 (1171-1842) pg/mL) compared to those who did {78 (60-133.25) pg/mL} [17]. However, in this study, NT-proBNP levels decreased by the end of 7 days, observed both in survivors {287.64 (223.5) pg/mL} and non-survivors {794.58 (852.62) pg/mL}, and this difference was statistically significant (p <0.001). Naveen V et al., suggested that the increased NT-proBNP levels in deceased patients might be due to a potential increase in infarct size, but no such rise in NT-proBNP values was seen in this study [17].

At the 3-month mark, the average BI was 59.68 (28.86), akin to Menon B et al., finding of 57 (30) [15]. Conversely, Jenson JK et al., reported a median BI of 20 at six months post-stroke [25]. In present study, females and non smokers demonstrated higher BI scores at three months compared to males and smokers, suggesting a relationship between gender and functional independence post-stroke.

The NIHSS showed a significant negative correlation with the BI at three months in present study, unlike Menon B et al., findings [15]. Deceased individuals displayed notably higher NIHSS levels than survivors, aligning with Chen X et al., study, whereas Naveen V et al., didn't report such an association [17,24]. For predicting mortality, the optimal NIHSS cut-off determined by ROC analysis was 14.5, boasting a sensitivity of 94.1% and specificity of 86%. This contrasts with Chen X et al., study, which had a cut-off of 12.5 with 82.6% sensitivity and 77.8% specificity [24]. However, NIHSS couldn't predict functional outcomes, echoing Menon B et al., findings [15].

The study revealed a noteworthy positive correlation between NIHSS and NT-proBNP, indicating that higher NT-proBNP levels are linked to increased stroke severity. Conversely, NT-proBNP displayed a negative correlation with the BI, indicating poorer functional

outcomes associated with elevated NT-proBNP levels. Similar trends were identified in Menon B et al., study, demonstrating a positive relation between BNP and NIHSS and a negative correlation between BNP and BI [15]. Correspondingly, Naveen V et al., and Chen X et al., also observed positive correlations between NIHSS and NT-proBNP [17,24].

Using ROC analysis, the study established an optimal NT-proBNP cut-off of 960 pg/mL for predicting death, exhibiting a sensitivity of 94.1% and specificity of 97.9%. This contrasts with Chen X et al., determined cut-off of 1583.50 pg/mL with sensitivity of 82.6% and specificity of 70.7%. Additionally, a cut-off of 431.5 pg/mL for NT-proBNP predicted BI scores <40 and dependency with a sensitivity of 90.0% and specificity of 81%.

The study underscored a robust link between NT-proBNP levels and stroke mortality, positioning NT-proBNP as a superior predictor of death compared to NIHSS. Moreover, it highlighted the association between NT-proBNP and functional outcomes. Admission NT-proBNP levels of 960 pg/mL predicted mortality and 435.1 pg/mL predicted disability. While both NIHSS and NT-proBNP at admission displayed strong predictive abilities for mortality, only NT-proBNP reliably predicted dependency at three months.

Limitation(s)

It is a hospital-based study, where selection bias and variation in medical parameters couldn't be eliminated due to limited resources.

CONCLUSION(S)

Serum NT-proBNP is significantly elevated in patients after acute ischaemic stroke and is strongly associated with stroke severity and functional outcome at three months. Measuring NT-proBNP within 24 hours after acute ischaemic stroke can predict all-cause mortality and functional dependence at three months. Further research could delve into the underlying mechanisms linking NT-proBNP to stroke outcomes, validate findings in larger populations, and explore its potential as a therapeutic target or as a prognostic tool in stroke outcome prediction models.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of General Medicine, ESIC MC PGIMSR, Bengaluru, Karnataka, India.
2. Professor, Department of General Medicine, Sri Devaraj URS Medical College, Kolar, Karnataka, India.
3. Professor, Department of Biochemistry, Sri Devaraj URS Medical College, Kolar, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
AG Manoj,
No. 908, RD Main Road Jnana Ganga Nagar, Jnanabharathi Post,
Bengaluru-560056, Karnataka, India.
E-mail: jonam_ag@yahoo.co.in

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