HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2020.86658
Haydarpasa Numune Med J 2022;62(2):134–139

hnhtipdergisi.com

ORIGINAL ARTICLE

Determination of Pro-BNP and Troponin I Levels for Short-Term Mortality Prediction in Ischemic Stroke Patients who did not Undergo Revascularization

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Abstract

Introduction: Emergency departments (EDs) are the first place to start treatment for most stroke patients. Prognozing patients for planning and proper management of the therapies have an important place in approaching stroke patients. Many studies have been carried out with serum biomarkers especially in terms of prognosis stroke. Our objective, in this study, is to research short-term (14th day) mortality prediction of serum Troponin I (TnI) and pro-brain natriuretic peptide (BNP) levels.

Methods: This was a prospective and observational prognostic test study. All consecutive patients admitted to the ED with the onset of symptoms in the past 24 h and diagnosed with the first episode of acute ischemic stroke were included in the study. A total of 121 subjects were included in the study. On admission, pro-BNP and TnI were collected from all subjects. On the 14th day of admission, patients were checked for mortality.

Results: Of 121 patients, 14 (11.5%) had a mortal outcome at the end of the 14th day. The overall median pro-BNP level of all patients was 799.00 pg/ml (IQR: 220.00–2818.25). The median pro-BNP level of the non-survivor group was significantly higher than that of the survivor group (p:0.030). However, there was no significant difference between the TnI levels of the mortality groups. The optimal cutoff value of serum pro-BNP levels as an indicator of mortality on the 14th day was estimated to be 509 pg/ml (sensitivity: 85.7%, specificity: 49.5%, and AUC: 0.68 [95% CI, 0.59–0.769]).

Discussion and Conclusion: Various biomarkers are investigated for prediction of mortality in ischemic stroke patient. According to our study, elevated pro-BNP values are associated with mortality. Further study with larger patient cohorts can be studied regarding the relationship between these threshold, in terms of predicting the mortality, in a more comprehensive study, as well as using subgroup and underlying conditions.

Keywords: Ischemic stroke; troponin I; pro-BNP; prognosis.

Ischemic stroke is an acute and rapidly progressing event. Common worldwide, it is an important cause of death and major disability. Stroke deaths account for 11.8% of the total deaths worldwide[1]. There are a wide variety of factors that influence stroke prognosis, such as age, stroke severity, stroke mechanism, infarct location, comorbid conditions, clinical findings, and related complications. It is important to predict prognosis to provide a rational approach to stroke patients.

Cerebral ischemia activates a cascade of molecular events that results in a release of several potential biomarkers. Although still in the research phase, there are several

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Submitted Date (Başvuru Tarihi): 30.10.2019 **Accepted Date (Kabul Tarihi):** 30.03.2020

biomarkers being studied to help diagnose and determine the cause of stroke. A biomarker that is both rapidly measurable and accurate to predict prognosis would be very useful.

Laboratory studies have shown that, in stroke, catecholamines are discharged in large quantities, resulting in cardiac dysfunction, reversible cardiac myocyte damage, and cardiac enzyme surges[2].

Elevated levels of cardiac troponin have been reported in 10–35% of patients with acute stroke[3,4]. The etiology of troponin elevation in stroke is not completely understood and is still debated. It has been suggested that it could be related to myocytolysis due to activation of the sympathetic nervous system. Several studies have shown that elevated levels are associated with mortality[5,6].

The brain natriuretic peptide (BNP) is a cardiac hormone released after the stimulation of cardiomyocytes in response to volume or pressure overload[7]. Recent studies have reported that pro-BNP may be elevated in patients with acute ischemic stroke (AIS). Some also suggest that there is a positive association between pro-BNP and stroke severity[8-10]. An increased natriuretic BNP level in acute stroke is a predictor of mortality at presentation, during hospitalization, and after discharge in the long-term[2].

In this study, we aimed to determine whether serum pro-BNP and Troponin I (TnI) levels on admission predict short-term mortality (14 day) after AIS. The secondary aim was to investigate the cutoff values (if present) to predict or exclude mortality.

Materials and Methods

Study Design and Setting

This was a prospective and observational prognostic test study performed in the Marmara University Research and Training Hospital Emergency Department (ED), which has had an annual load of 180,000 between May 2016 and November 2017. The study has been approved by the University Ethics Committee.

Participants

All consecutive patients admitted to the ED with the onset of symptoms in the past 24 h and diagnosed with the first episode of AIS with the criteria explained below were included in the study if they were: 1) Adult (>18 years) and 2) non-pregnant and excluded if they had: 1) A history of CVD (cerebrovascular disease), 2) arrested in the ED, 3) a creatinine level>1.5 mg/dl, 4) ischemic ECG changes or were diagnosed with acute coronary syndrome, or 5) thrombolysis or thrombectomy treatment. Written informed consent was obtained from the patients or their next of kin.

Definitions and Management

All admitted patients included in the study were initially evaluated by the ED physician and the neurology attending physician. AIS was confirmed by neurologic examination and cranial imaging showed ischemic lesions compatible with the clinical findings.

Data Collection and Measurements

On admission, routine blood samples including pro-BNP and TnI were collected from all subjects. Vital signs were electronically measured and recorded. Demographics (age and sex) and properties in the medical history were collected on study data collection forms at the bedside, including positive physical examination findings. Results of the laboratory examinations were collected from the Hospital Information System.

Plasma pro-BNP was measured using an automated electrochemiluminescence immunoassay (sandwich method) with an analytical range of 5–35000 pg/mL (0.6–4130 pmol/L) within 24 h of admission.

The TnI serum analytes were analyzed through chemiluminescent immunoassay. The analysis was performed with Beckman Coulter kits (Cat. No. A78803) on the Beckman Coulter Access 2 Immunoassay System's fully automatized autoanalyzer (Beckman Coulter Inc.), which has an analytical sensitivity of 0.01 µg/L and a 99th percentile of 0.040 µg/L.

Follow-up

The study cohort was prospectively followed up for mortality. On the 14th day of admission, patients were checked for mortality using medical records or telephone interview.

Statistical Methods

Continuous variables were reported with means and standard deviations (95% confidence intervals [CI]) or with medians and interquartile ranges according to their distribution patterns. Categorical variables were reported with counts and percentages. Mann–Whitney U and Chi-squared tests were used to compare independent groups.

The TnI and pro-BNP levels were analyzed by a receiver operating characteristic curve (ROC) to assess their prognostic utility in estimating short-term mortality. Area under the curve (AUC and accuracy), sensitivity, specificity, and likelihood ratios was reported with their 95% CIs. MedCalc

Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; https://www. medcalc.org) was used for all analyzes. The relative risk and odds ratio (OR) of the categorical predictors were also reported.

STARD 2015 guidelines for reporting diagnostic accuracy studies were used as a reference while preparing for this report[11].

Results

During the study period, 251 patients with AIS were screened. Of these, 130 were excluded for various reasons (Fig. 1). A total of 121 subjects (61 females, 50.4%) were included in the analysis. Of 121 patients, 14 (11.5%) had a mortal outcome at the end of the 14th day. The mean age was 73 (62–83) years and there was no statistically significant age difference between mortality groups (p=0.406). The mean age of the non-survivor group was 74.5 (65–85) and the mean age of the 107 patients in survival group was 72 (62–82.75).

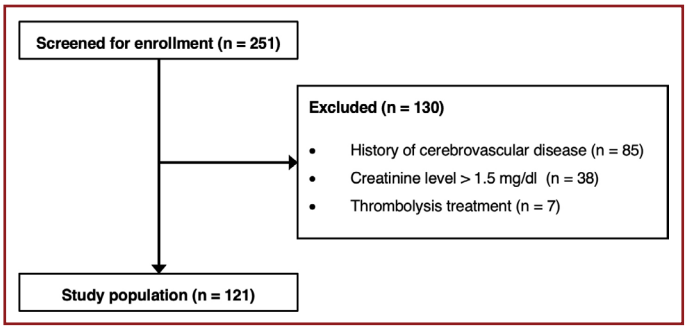

Figure 1. Study flowchart.

The summary of vascular risk factors, vital signs on admission, and the duration of the symptoms are shown in Table 1 for each group and the overall study population. No statistically significant difference among groups of survivors and non-survivors was observed for demographics and vital signs on admission, except history of atrial fibrillation (AF), which was significantly higher in non-survivors (p=0.027).

The primary outcome of the study and the comparison of the median pro-BNP and TnI levels are presented in Table 2. Median pro-BNP levels of the non-survivors was higher and this difference was statistically significant (p=0.030). No significant difference was observed between TnI levels.

The discriminative values of pro-BNP and TnI levels for the prediction of mortality were investigated with the use of ROC curve analysis. Serum pro-BNP levels significantly discriminate the presence of mortality on 14th day with an AUC of 0.68 (95% CI, 0.599–0.769). The criterion value at the highest combined sensitivity (85.7%; 95% CI, 57.2–98.2) and specificity (49.5%; 95% CI, 39.7–59.4) was calculated as 509 pg/ml by the use of Youden J Index (Fig. 2 and Table 3). The positive and negative LRs at this cutoff value were 1.70 (95% CI, 1.30–2.30) and 0.29 (0.08–1.10), respectively.

Discussion

We investigated the short-term (14th-day) mortality prediction role of TnI and pro-BNP levels in AIS patients. The pro-BNP levels in AIS patients at the time of admission were significant in predicting 14th day mortality. However, there was no correlation with the TnI level.

Table 1. Distribution of the patients according to their medical history and vital parameters on admission

	Survival (n=107)	Mortality (n=14)	Total (n=121)	p
Medical history, n (%)*				
DM	33 (30.3)	7 (50.0)	40 (33.1)	0.154
HT	66 (61.7)	12 (85.7)	78 (64.5)	0.079
CAD	31 (29.0)	4 (28.6)	35 (28.9)	0.975
Smoking	28 (26.2)	5 (35.7)	33 (27.3)	0.453
AF	24 (22.4)	7 (50.0)	31 (25.6)	0.027
Vital signs, median (IQA)**				
SBP, mmHg	157 (130–180)	148 (123–177)	157 (130–180)	0.568
DBP, mmHg	93 (80–106)	87 (73–95)	91 (80–104)	0.069
MAP, mmHg	137 (113 –154)	125 (112 –148)	137 (113–154)	0.386
Heart Rate, bpm	86 (77–98)	99 (84–106)	87 (77–100)	0.075
Time of admission (h)	4 (1–10)	3 (1.5–6)	4 (1–10)	0.848

DM: Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease; AF: Atrial fibrillation; IQR: Interquartile range; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial pressure. *Chi-squared test was used for the comparisons. Significant p values were presented in bold. Percentages represent column total. **Mann–Whitney U test was used for group comparisons.

Table 2. Comparison of the median serum pro-BNP and TnI levels among study groups

	Survivors (n=107)	Non-survivors (n=14)	Total (n=121)	p*
Pro-BNP (pg/ml), median (IQR)	690.0 (152.0–2697.0)	1865.5 (745.0–6566.0)	799.0 (220.0–2812.0)	0.0299
TnI (ng/ml), median (IQR)	0.011 (0.010–0.037)	0.028 (0.014–0.031)	0.014 (0.010–0.033)	0.1022

BNP: Brain natriuretic peptide; TnI: Troponin I, IQR: Interquartile range. * Mann–Whitney U test was used for group comparisons. Significant p value was presented in bold.

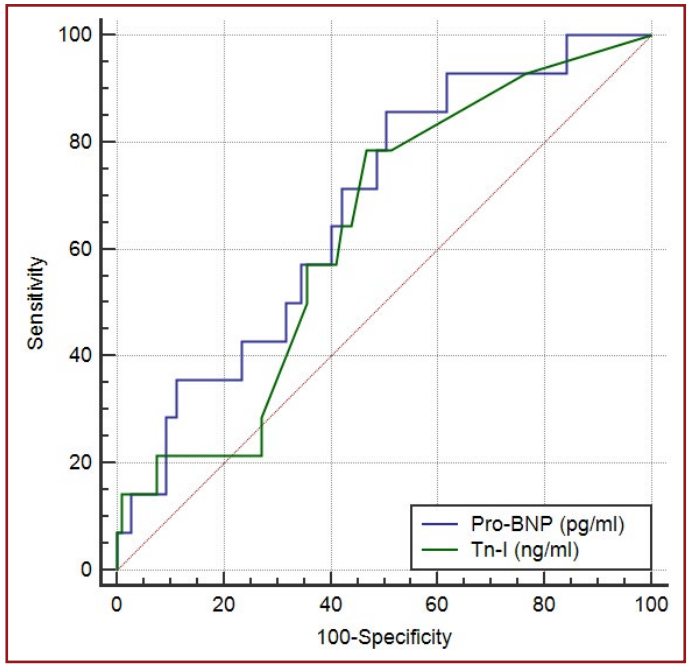

Figure 2. ROC curves of Pro-BNP and Tn-I levels. ROC: Receiver operating characteristic curve, BNP: Brain natriuretic peptide, TnI: Troponin I.

It is seen that advanced age is a negative factor in mortality and morbidity in ischemic stroke. It was found that 75% of all stroke patients were older than 64 years of age, the mean age was 73 in patients with poor outcome, and age was statistically significant in terms of mortality (p<0.05) [12]. In our study, the reason why we did not find age difference between the two groups may be our old patient population.

Women are less likely to have lifelong stroke, but female gender is reported as a negative indicator for prognosis[13]. In our study, 60 (49.6%) of 121 patients in the survivor group had a stroke, and 7 (50%) of 14 patients with mortal outcome were female.

When we examine the relationship between risk factors and mortality in the previous studies, hypertension (HT) is a major risk factor for both cerebral infarction and intracranial hemorrhage[14]. Diabetes mellitus (DM) has been shown to independently increase the risk of ischemic stroke from 1.8 to 6 times[15]. In the study of Jensen et al.,[16] 28 of the patients (11.2%) had DM and 137 (55%) had HT. Fonseca et al.[17] reported that 71 patients (70.3%) had HT and 25 (24.8%) had DM. In our study, 78 (64.5%) of the 121 patients had HT, 40 (33.1%) had DM, and the mean MAP (mean arterial pressure) value was 136.66 mmHg (112.91–153.5). However, no statistically significant difference was found between the survival and non-survival groups on the 14th day in terms of HT or DM history or arrival MAP (p=0.079, p=0.154, and p=0.386).

AF increases the risk of ischemic stroke 4 times even in the absence of cardiac valvular disease, and the mortality and morbidity of AF-induced stroke are also higher[18]. In our study, in 31 (25.6%) of the 121 patients, an AF rhythm was seen. When the incidence of AF in the mortality groups were compared, it was seen that the two groups were statistically different (p=0.027). Similar to our study, in the study of Tu et al.,[19] 14 (56%) of 25 patients with poor outcome had an AF rhythm, and AF in the ECG was significantly higher in the mortality group (p=0.001).

AIS has been shown to cause changes in autonomic functions. After increased sympathetic activity, the heart work-

Table 3. Results of the ROC analyses of serum pro-BNP and TnI levels for the discrimination of mortality

	AUC	SE	95%CI	p	Criterion Value
Pro-BNP (pg/ml), median (IQR)	0.679	0.071	0.599–0.761	0.0122	509
TnI (ng/ml), median (IQR)	0.633	0.073	0.541–0.719	0.0679	-

ROC: Receiver operating characteristic curve; AUC: Area under the curve; SE: Standard error; CI: Confidence interval; BNP: Brain natriuretic peptide; TnI: Troponin I; IQR: Interquartile range. Criterion values were calculated using the Youden J Index analysis. Significant p value, and the corresponding criterion value were presented in bold.

load increases, and this leads to myocardial ischemia. As a result of this temporary myocardial ischemia, BNP production increases due to both increased cardiac arrhythmias and increased left ventricular wall tension[2,7,8].

In the study of Rost et al.,[20] the poor outcome predictions of BNP levels in 569 ischemic stroke patients were investigated over a 6-week period. The serum pro-BNP level was determined as 273 pg/ml, the highest in cardioembolic strokes, and it is mentioned that this could be an independent predictor for mortality (OR 3.05, 95% CI 1.1–8.2) ($p<0.03$), but it was found to be not significant except for in cardioembolic stroke (OR 1.03, 95% CI 0.9–1.1). Tu et al.[19] studied 189 patients with ischemic stroke for 3-month mortality. From all, 25 (13.2%) patients had poor outcome. The median value of pro-BNP was found to be 2680 pg/ml in the poor outcome group and 1262 pg/ml in the good outcome group and a significant difference was observed between these groups (OR 1.75 95% CI 0.75–4.11) ($p=0.000$). Ghabaee et al.[21] investigated pro-BNP values in the prediction of 1-week mortality with 100 ischemic stroke patients and found that the mortality rate was 7%.The mean pro-BNP value of all patients was 1973 pg/ml. A statistically significant difference was detected in the comparison of patients with poor outcomes and patients with good outcomes. The optimal pro-BNP level in predicting mortality was found to be 1330 pg/ml (EAA: 0.83 [95% CI 0.74–0.93]) [21]. We found our pro-BNP median value to be 798.88 pg/ml. The median pro-BNP level of the non-survivor group was significantly higher than that of the survivor group. The threshold value of pro-BNP was as low as 509 pg/ml in our study with an AUC of 0.68. This may be due to the evaluation of pro-BNP levels at admission in our study, whereas Ghabaee et al. collected the blood samples at the 24th h and later.

Several studies have shown that myocardial injury in acute stroke patients causes elevated levels of cardiac markers associated with mortality. Angelantonio et al.[22] conducted a study on 330 patients with acute stroke and analyzed the association of baseline levels of cardiac TnI with all-cause mortality over a 6-month follow-up. They found that TnI levels on admission were an independent predictor of mortality.

In another study that aimed to find the determinants of troponin elevation and its relationship with stroke severity, it was found that Troponin T was elevated in 20 (17.6%) of 114 AIS patients, and troponin levels were higher in patients with more severe stroke, as measured by NIHSS (7.96 [6.49–9.78] vs. 13.59 [10.28–18.00])[23].

Etgen et al.[24] also evaluated the short-term prognostic value of early serial measurements of cTnT, cTnI, and NT-proBNP in the hyperacute phase of ischemic stroke and found that NT-proBNP was raised in nearly two-thirds of AIS patients, whereas elevated cardiac troponins were found only in a small number. Neither NT-proBNP nor cardiac troponins were found to influence clinical outcome in this study. Furthermore, in our study, there was no influence of the admission TnI value on the 14th-day mortality. This may be because of the number of patients, the time of taking the blood sample, or the number of days examined.

There were some drawbacks of our study. There are different reasons that can elevate the troponin levels. We did not exclude the patients who had a history of previous MI or heart disease and diseases which can cause elevation of troponin level such as sepsis, burn, hyperthyroidism, and vasculitis. We did not perform highly sensitive troponin analyzes. Some patient groups (previous CVD, coexisting Coronary artery disease, and renal disease) were not included in our study those might influence the mortality rates. Furthermore, we collected blood samples on admission once.

Conclusion

We investigated the value of TnI and pro-BNP levels in predicting the short-term (14th-day) mortality. Our results demonstrate that ischemic stroke patients with higher levels of pro-BNP at the time of initial presentation to the ED have an increased risk for mortality within 14 days, whereas initial serum TnI levels in the acute period do not predict short-term mortality in patients with acute stroke. The role of biomarkers in ischemic stroke is still unclear, so new studies can be organized in different ways to interpret these biomarkers.

Ethics Committee Approval: Marmara University Ethics Committee , 09.2016.297, 2016.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: N.A., A.D.; Design: N.A., H.A.; Data Collection or Processing: N.A., C.O., O.O.; Analysis or Interpretation: H.A., C.O.; Literature Search: O.O., A.D., N.A.; Writing: C.O., O.O., N.A.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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