The Association between Brain Natriuretic Peptide Level and Short-term Outcomes and Mortality in Patients with Stroke

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Abstract:

Background: Brain natriuretic peptide was first isolated in 1988 from porcine brain, then a similar substance (hormone) was discovered to be secreted by the heart ventricles cardio myocytes in response to stretch. A lot of debate is running for decades regarding its functions as an indicator of the type of pathology or prognostic outcome in strokr patients.

Patients and methods: Twenty four men and twenty four women with admitted at Al Husssieni Teaching hospital within 12 hours of cerebrovascular accidents were investigated to evaluate NT-pro-BNP and troponin levels estimation as indicator for determining pathology type and prognosis in stroke patients.

Results：The maen age mean age of the patients was 50.77 ±12.98 year. Two thirds of the patients had cerebral ischemia, 29% had intracranial hemorrhage and only 6% had sub-arachnoid hemorrhage. There was no significant difference in the mean Pro-BNP level between these three types of stroke and the mean was 29.62±17.10 ng/dl, 143.25±38.29 ng/dl and 179.65±32.27 ng/dl for sub-arachnoid hemorrhage, intra-cranial hemorrhage and cerebral ischemia, respectively. Similarly no significant gender difference was detected (p=.167), nor there was a difference between those who deceased (20.8%) and those who discharged a live (p=.726). The highest fatality rate differ significantly among different types of stroke, and was highest among those with sub-arachnoid hemorrhage (100%), modest anong patients with intra-cranial hemorrhage (50%), while the least was among those with ischemia (no death). The cardiac complications after stroke were explored, but these did not affect NTproBNP level significantly.

Conclusions: brain natriuretic peptide (BNP) level was found not to be significantly different across the thtree main types of stroke. Its level was not affected by gender and it provides no progmostic importance for the fate or oucome after stroke.

Keywords: stroke, NTproBNP, sub-arachnoid hemorrhage, intra-cranial hemorrhage, ischemia, troponin

الملخص:

المقدمةة: تم عزل ، نايتروببتايدات الدماغ في عام 1988 من دماغ الخنزير ، ثم تم اكتشاف مادة مماثلة (هرمون) تفرزها عضلات القلب القلبية البطينية استجابةً لامتدا العضلاتد .ويدور الكثير من النقاش منذ عقود حول وظائفه كمؤشرمرضي أو النتائج التحذيرية له لدى مرضى السكتة الدماغية.

المرضى وطرق البحث: تم فحص أربعة وعشرون رجلاً وأربعة وعشرون امرأة ممن تم ادخالهم في مستشفى الحسيني التعليمي في غضون 12 ساعة من السكتة الوعائية الدماغية لتقييم مستويات نايتروببتايدات الدماغ التروبونين كمؤشر لتحديد نوع المراض والتشخيص لدى مرضى السكتة الدماغية.

النتائج: كان متوسط عمر المريض هو 50.77 ± 12.98 سنة. يعاني ثلثا المرضى من نقص تروية دماغية ، و 29٪ مصابون بنزيف داخل الجمجمة و 6٪ فقط لديهم نزف تحت العنكبوتية. لم يكن هناك اختلاف كبير في مستوى Pro-BNP المتوسط بين هذه الأنواع الثلاثة من السكتة الدماغية وكان متوسط نايتروببتايدات الدماغ 29.62 ± 17.10 نانوغرام / ديسيلتر ، 143.25 ± 38.29 نانوغرام / ديسيلتر و 179.65 ± 32.27 نانوغرام / ديسيلتر للانواع الثلاثة المذكورة اعلاه ، على التوالي. وبالمثل ، لم يتم الكشف عن اختلاف كبير بين الجنسين (ع = .167) ، ولم يكن هناك فرق بين أولئك الذين توفوا (20.8 ٪) وأولئك الذين خرجوا من العيش (ع = 0.726). وظهر اختلاف كبير في معدل الوفاة بين ألانواع المختلفة من السكتة الدماغية ، وكان أعلاها بين المصابين بنزف تحت العنكبوتية (100٪) ، ثم بين المرضى الذين يعانون من نزيف داخل الجمجمة (50٪) ، بينما كان الأقل بين المصابين بنقص التروية الموت). تم استكشاف مضاعفات القلب بعد السكتة الدماغية ، ولكن هذه لم تؤثر على مستوى ، نايتروببتايدات بشكل كبير. الدماغ

الاستنتاجات: تم قياس مستوى نايتروببتايدات الدماغ ووجد انه لا يختلف اختلافًا كبيرًا عبر الأنواع الرئيسية من السكتة الدماغية.وكذلك لم يتأثر مستواه بالجنس ، ولا يقدم أي أهمية استباقية لمصيرالمريض (الوفاة) أو الخروج من الستشفى بعد السكتة الدماغية.

ألمفاتيح: السكتة الدماغية ، نزيف تحت العنكبوتية ، نزف داخل الجمجمة ، نقص تروية ، نايتروببتايدات الدماغ , تروبونين

Introduction

Stroke is a second leading cause of preventable death globally after ischaemic heart diseases (9.7% of all deaths), and will be so till 2030 (1).

A large multinational study in 2009 showed that the risk factors for stroke were similar in developed and the developing countries (2), which include hypertension, dyslipidaemia, current smoking, diabetes, abdominal obesity, poor diet and physical inactivity (3).

Strokes are divided from anatomopathological and physiopathological point of view into two groups: ischemic and hemorrhagic stroke, the majority (87%) are ischemic (4).

It is important to identify the patients with stroke who are at high risk for early and late poor outcome to start more intensive management and rehabilitation and this may improve decision making to improve patient outcome (5). The factors employed as prognostic factors

including risk factors, clinical and radiological features and biochemical factors Of these biochemical factors which may be implicated in prognosis of stroke include BNP, troponin, interleukin, L-arginine and nitric oxide

Natriuretic peptide . There are three types of natriuretic peptides: Beta or Brain natriuretic peptides –BNP-, mainly secreted by the ventricles in the brain, Alphs or Atrial natriuretic peptides –ANP-, secreted in the right atrium, and C type of natriuretic peptide, secreted by the inflammation and lesion of the vascular endothelium (6).
In 1988, brain natriuretic peptide (BNP),also known as B-type natriuretic peptide was first isolated from porcine brain (7), and is a hormone secreted by the heart ventricles cardio myocytes in response to stretch caused by increased ventricular blood volume. BNP had diuretic and vasodilator effect (5). B-type natriuretic peptide is synthesized as an inactive prohormone (pre Pro-BNP). It is cleaved into Pro BNP which is further cleaved into the bioactive hormone BNP and inactive NT-pro-BNP. Pro-BNP, which has an important role in cardiovascular remodeling and volume homeostasis. In healthy individuals Pro-BNP and NT-proBNP are present in almost equal concentrations in the plasma. However, BNP has a half-life of only 20 min, while NT-proBNP 1-2 hour, thus making NT-proBNP more suitable for investigation (8). BNP can be increased in cardiac conditions as heart failure, (even with preserved ejection fraction) (9), myocardial infarction or cardiomyopathies in non cardiac (10, 11).

In addition, BNP acts as neurotransmitters or neuromodulators in the brain, and is released from the hypothalamus and cerebral cortex, and was implicated in neuroprotection following brain injury (12). Pro-BNP and NT pro-BNP testing has a implicated in risk stratification of ischemic stroke and may signal an unfavorable outcome, including the risk of death at admission, short term and long term functional recovery, cardio-embolic etiology of a stroke, the risk of having a new onset AF episode in the setting of an ischemic stroke, identifying those patients likely to require more aggressive treatment and more intensive early rehabilitation.(7,8,10, 13, 14). The relationships between plasma levels of brain natriuretic peptide (BNP) and short term outcome and mortality were investigated in acute ischemic stroke patients who presented within the first 48 hours of stroke.

Patients and methods

This study was conducted in the neurology unit at Al Hussainy Teaching Hospital in Kerbala/ Iraq. Collection of samples was conducted during the period from 1st June 2018 to 31st October 2018. Forty-eight patients admitted with neurological manifestation of stroke were included in this study. Inclusion Criteria were: patients with their first-ever stroke, admitted in the hospital within 48 hours of symptom onset; Age less than 65 years old. Exclusion Criteria: renal dysfunction (serum creatinine >2.5 mg/dL), dialysis dependent renal failure, cardiac dysfunction, chronic obstructive pulmonary disease, and pulmonary embolism. Patients aged > 65 year, morbid obesity BMI>40 and Intensive Care Unit patients were excluded as these groups of patients might exhibit changes affecting the study variable or those who dies before being subjected to the needed study investigations. Ten milliliters of venous blood were drawn from each patient. Aspiration of the blood sample via the needle of syringe done was slowly to prevent hemolysis.

The samples were dropped into clean disposable tubes and were left at the room temperature for 30 minutes for clot formation and then were centrifuged for 20 minutes at 5000 run per minute. The tests were done for the patient NT-pro BNP and high sensitive serum troponine .

Chemical reagents

The chemical reagents and kits that were used in this study (ProBNP & high sensitive serum troponine) were of the highest purity supplied from Biomrieux com- France.

The variables assessed for each patient included age, gender, medical history, smoking and alcohol drinking, body mass inde (BMI), lipid profile, Renal Function test, electrocardiography (ECG), Echocardiography, Carotid Doppler study, brain computerized tomography scan (CT) and brain Magnetic resonance imaging (MRI), in addition serum troponin and serum NT-pro-BNP level were determined for all cases within 48 hours from the start of symptoms of stroke.

The statistical analysis used in this study included descriptive and analytic methods using the Statistical Package for Social Sciences (SPSS-23) through student t-test and chi-square tests at p-value of <0.05. In-hospital death was defined as all causes mortality within 7 days. We divided the patients into two groups: the deceased group, who died during hospitalization; and the survival group. Diagnosis of acute ischemic stroke was made by stroke neurologists, and confirmed by Computerized Tomography (CT) or magnetic resonance imaging (MRI). The value of NT-proBNP is determined as an age-dependent (cut-off value for NT-proBNP are 125 pg/mL for <75 years old and 450 pg/mL for > 75 years old) (13).

Results

The sample consisted of 48 patients with equal gender proportion. The mean age of the patients was 50.77 ±12.98 year with a range between 35 and 65 years, however about one half of the patients aged 60 year or more. No significant gender difference was fond in the mean age (p=.167). The prevalence rates of hypertension, diabetes mellitus, ischemic heart disease, renal impairment, dyslipidemia and obesity were 75%, 35%, 19%, 2.1%, 10% and 4%, respectively. One eighth (12.5%) of the patients were smokers, while none consumed alcohol (table 1).

Table 1: The demographic and other characteristics of str stroke patients admitted at Al-Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

Variable	Group	Frequency	Percentage
Age category	Below 45 year	14	29.2
	45-59 year	12	25.0
	60-65 year	22	45.8
Gender	Male	24	50

	Female	24	50
Hypertension	Negative	12	25.0
	Positive	36	75.0
Diabetes mellitus	Negative	31	64.6
	Positive	17	35.4
Previous Ischemic Heart Disease	Negative	39	81.3
	Positive	9	18.8
Renal Impairment	Negative	47	97.9
	Positive	1	2.1
Obesity (BMI30-40)	Negative	46	95.8
	Positive	2	4.2
Dyslipidemia	Negative	43	89.6
	Positive	5	10.4
Carotid intimal thickening*	Negative	41	85.4
	Positive	7	14.6
Smoking	Negative	42	87.5
	Positive	6	12.5
Alcohol drinking	Negative	48	100
	Positive	0	0.0
Stroke type	Ischemia	31	64.6
	Sub-Arachnoid Hemorrhage	3	6.3
	Intra-Cranial Hemorrhage	14	29.2
Fate	Lived	38	79.2
	Died	10	20.8
Total		48	100

*>70% obstruction

About two thirds of stroke patients in the sample had brain ischemia while more than one quarter had intra-cranial hemorrhage and only a minority (3 patients, 6.3%) had sub-arachnoid hemorrhage (figure 1).

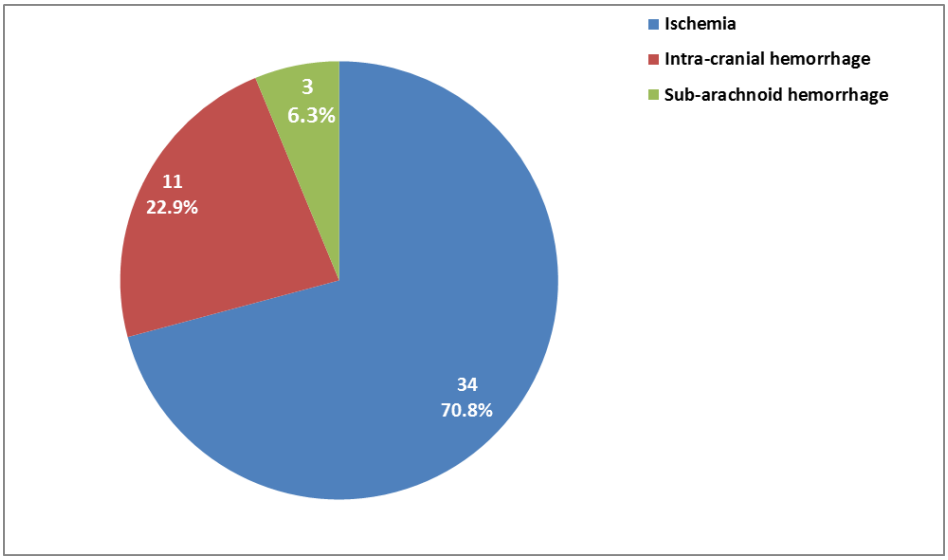

Figure 1: The distribution of the type of stroke patients admitted at Al-Hussein Teaching hospital in Kerbala /Iraq in 2018 (n=48)

Comparison of the positive and negative Pro-BNP level (according to the cut-off point) among patients with different stroke pathology showed no significant difference (p=0.883, table 2).

Table 2: Level of Pro-BNP level among stroke patients admitted at Al- Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

High Pro-BNP level	**Frequency**	**Percentage**
Negative	21	43.7
Positive	27	56.3
Total	100	100.0

The level of serum PRO-BNP ranged between 14.60 ng/dl and 640.20 ng/dl and the mean was 204.23±164.31 pg. A greater majority of patients (56.3%), 27 patient) showed high Pro-BNP level above the cutoff point of 125 ng/dl (table 3). No significant gender difference was fond in the mean Pro-BNP (p=0.604).

Table 3: The distribution of Pro-BNP level by type of stroke pathology among stroke patients admitted at Al-Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

Stroke type	Low Pro-BNP	High Pro-BNP	Total
Ischemia	14 (45.16%)	17 (54.84%)	31 (100.0%)
Intra-Cranial Hemorrhage	5 (35.71%)	9 (64.29%)	14 (100.0%)
Sub-Arachnoid Hemorrhage	2 (66.67%)	1 (33.33%)	3 (100.0%)
Total	21 (43.75%)	27 (56.25%)	48 (100.0%)

p=0.634

The mean Pro-BNP level among patients with different stroke pathology showed that the mean Pro-BNP level was 205.157±172.50043 ng/dl, 228.055±158.165 ng/dl and106.433±29.616 ng/dl for cerebral ischemia, intra-cranial hemorrhage and sub-arachnoid hemorrhage, respectively. Comparison of the mean Pro-BNP level among patients with different stroke pathology showed no significant difference (F=0.278, p=0.759). Comparison of mean Pro-BNP level within groups showed no significant difference between ischemia and subarachnoid hemorrhage (p=0.347), and also between ischemia and intracranial hemorrhage (p=0.824), and subarachnoid hemorrhage and intracranial hemorrhage (p=0.205). The distribution of Pro-BNP level and Troponin was positively skewed (skeweness= and , respectively); so a trial to correct the distribution into logarithmic distribution was conducted, however, no significant difference was found even on comparison of logorythmic vales.

Table 4: The distribution of Pro-BNP level by fate among stroke patients admitted at Al Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

Fate	Low Pro-BNP	High Pro-BNP	Total
Alive	17 (44.74%)	21 (55.26%)	38 (100.0%)
Died	4 (40.00%)	6 (%60.00)	10 (100.0%)
Total	21 (43.75%)	27 (56.25%)	48 (100.0%)

OR=1.21, p=0.539

The mortality rate among the sample was 20.8% (10 deaths), and was significantly different among the different types of stroke with the highest fatality rate among those with sub-arachnoid hemorrhage (100%, 3 deaths), followed by intra-cranial hemorrhage or (50%, 7 deaths), while no death occurred among patients with ischemia.

Similarly, the level of Pro-BNP showed no significant association with the fate of patients (p= 0.726).

Comparison of the mean Pro-BNP level among patients with different cardiac events showed no significant difference (F=0.11, p=0.895, table 5). Similarly, within groups comparisons showed that pro-BNP level was not significantly higher between patient with no cardiac event and patients with ischemia (p=0.654), or with patients with arrhythmia (p=0.989).

No significant difference was found in BNP level between patients with ischemia and patients with arrhythmia (p=0.764).

Table 5: The distribution of Pro-BNP level by the type of cardiac complication among stroke patients admitted at Al Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

Cardiac complications	**Negative Pro-BNP level**	**Positive Pro-BNP level**	**Total**
No Cardiac event	15 (45.45%)	18 (54.55%)	33 (100.0%)
Ischemia	5 (%55.56)	4 (44.44%)	9 (100.0%)
Arrhythmia	1 (%16.67)	5 (83.33%)	6 (100.0%)
Total	21 (43.75%)	27 (56.25%)	48 (100.0%)

p=0.434

On the other hand, comparison between the proportions of positive and negative Pro-BNP patients among the different cardiac event patients also showed no significant differences (p=0.434, table 5).

The serum troponin level ranged between 0.01 and 2.31 ng/dl and the mean was 0.177±0.39545ng/dl and 18 patients (37.5%) had a level above the cut off point of 0.01 ng/dl., and mean Troponin level (p=.474) among the three different types of stroke.

The level of troponin showed no significant association with the fate of patients (p=0.705), although it was higher among those who died in comparison to those who remained alive (0.220±0.326 ng/dl vs. 0.166±0.415 ng/dl).

For the mean level of Troponin, no significant difference was discovered when different types of stroke pathology (F=0.278, p=0.746).

When the mean Troponin level was compared within the groups of patients with different stroke pathology; no significant difference between ischemia and subarachnoid hemorrhage (p=0.510), and also between ischemia and intracranial hemorrhage (p=0.986), and subarachnoid hemorrhage and intracranial hemorrhage (p=0.301).

On the other hand, comparison of the mean level of Troponin among patients with different cardiac events showed no significant difference (F=1.36, p=0.267). Similarly, within groups comparisons showed that the mean level of Troponin was not significantly different between

patient with no cardiac event and patients with arrhythmia (p=0.152), or with patients with ischemia (p=0.805). No significant difference was found in Troponin level between patients with ischemia and patients with arrhythmia (p=0.353).

Comparison of NT-proBNP level between the Troponin positive and negative level among the different cardiac event patients also showed no significant differences (p=0.883, table 6).

Similarly, comparison of Troponin level among patients with different cardiac complications showed no significant difference (p=0.901, table 6).

Table 6: The distribution of Troponin level by the type of cardiac complication among stroke patients admitted at Al Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

Cardiac complications	**Negative Troponin level**	**Positive Troponin level**	**Total**
No Cardiac event	21 (63.64%)	12 (36.36%)	33 (100.0%)
Ischemia	5 (%55.56)	4 (44.44%)	9 (100.0%)
Arrhythmia	4 (%66.67)	2 (33.33%)	6 (100.0%)
Total	30 (62.50%)	18 (37.50%)	48 (100.0%)

p=0.901

Analysis of the simultaneous effect of the predictors of stroke type through Structural Equation Model (SEM) using Amos software showed that the most effective predictor of the type of stroke, where ischemia was the base and subarachnoid hemorrhage was the last and intracranial hemorrhage was in between (has the highest correlation coefficient-r-) was carotid intimal thickening (r=0.43), followed by diabetes mellitus (r=0.31) and then gender (r=0.24, figure 2).

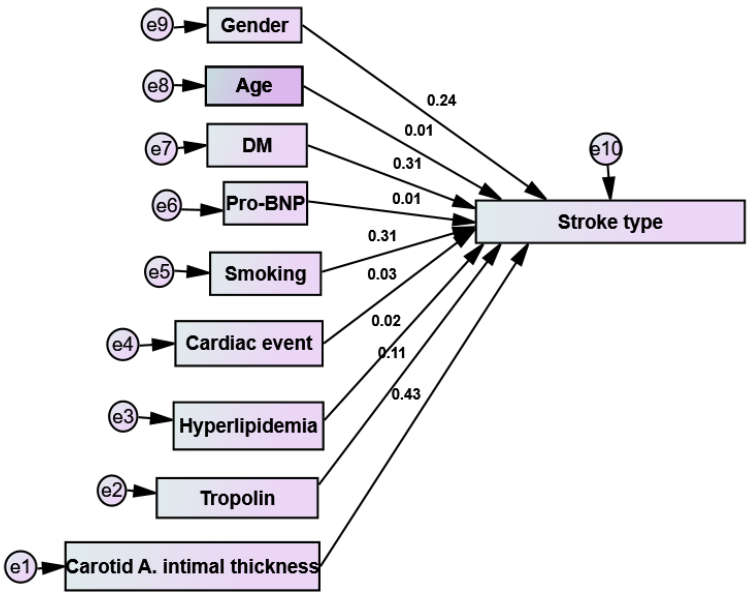

Figure2: The simultaneous effect of the predictors of stroke type through Structural Equation Model among stroke patients admitted at Al Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

While determining the simultaneous effect of the predictors of cardiac complication in stroke patients through SEM showed that the most effective predictor (has the highest correlation coefficient-r-) was smoking (r=0.52), followed by Positive Hyperlipidemia (r=0.50) and then troponin level (r=0.37, figure3).

Figure3: Simultaneous effect of the predictors of cardiac complications through Structural Equation Model among stroke patients admitted at Al Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48).

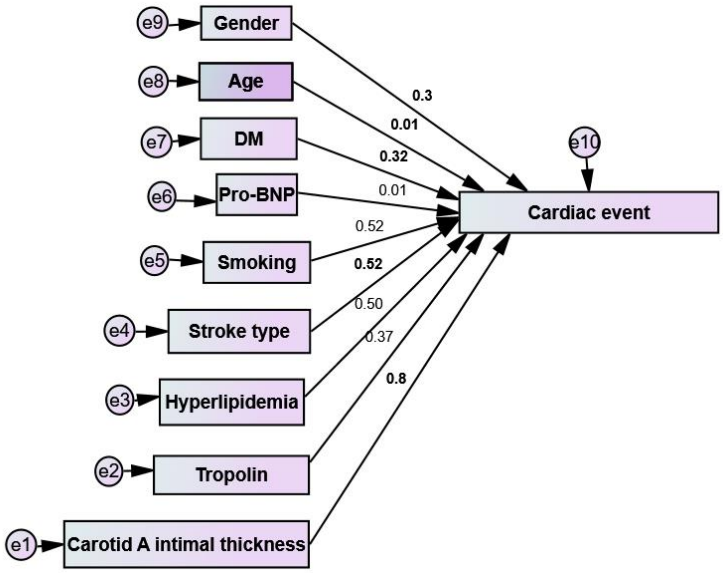

Figure 4: The simultaneous effect of the predictors of cardiac complication through Structural Equation Model among stroke patients admitted at Al Husseini Teaching hospital in Kerbala /Iraq in 2018 (n=48)

Discussion

Since 1981 when BNP discovered a lot of studied done to found the association of BNP with other clinical conditions especially the cardiac and the neurological diseases.

In our study we investigated an association between NTproBNP level and short term outcome post ischemic and non-ischemic stroke.

We found that Pro-BNP level was neither a significant predictor of the fate of the patient (table 4), nor it was related to the pathology type of stroke (table 5) and these is consistet with many previous studies (14, 15).

Etgen and his colleagues found that the prognostic value of cardiac troponins and natriuretic peptide in acute ischemic stroke. In his study nearly two thirds of acute stroke patients have an enelvated level NT-proBNP, whereas elevated cardiac troponins are found only in a small number of acute ischemic stroke patients. He concluded that the clinical outcome not influenced by neither NT-proBNP nor cardiac troponins (16).

While Montaner and his colleagues reported a limited BNP use as a biomarker for prognostic information with acute stroke and suggested that further investigation and systematic reviews should done to clarify the role of natriuretic peptides in stroke outcome (17). While, García-Berrocoso found that BNP/NT-proBNP add only minor predictive value to clinical information (18). While in a further study with meta-analysis of about 3000 patients; cocluded that BNP/NT-proBNP levels were significantly elevated in cardioembolic stroke until 72 hours from symptoms onset (19). Similarly, Etgen show that NT-proBNP is raised in nearly two thirds of acute stroke patients, whereas elevated cardiac troponins are found only in a small number of acute ischemic stroke patients. He concluded Neither NT-proBNP nor cardiac troponins influence clinical outcome if other risk factors are considered (20).

In contrast, Gupta and his colleagues had concluded that Pro-BNP is not independent marker of poor outcome in AIS patients who receive thrombolytic therapy (21).

While there is other studies which are concluded that there is a correlation between the BNP level and the outcome after stoke. Di Angelantonio and Mäkikallio showwd that plasma levels of brain natriuretic peptide (BNP) an independent predictor of mortality after an acute stroke inspite (14, 22). In addition, Shibazaki and his colleagues, investigated the plasma NT-proBNP level acute ischemic stroke. Death was observed in 20 (6.0%) patients and he concluded that the plasma BNP level on admission can predict in-hospital death in patients with acute ischemic stroke.(7) as Llombart and his colleagues found high BNP level in the acute phase increases the risk of worse stroke severity (19).

On the other hand Maruyama and his colleagues found in a recent study that BNP was

a very useful predictor for long-term outcomes of patients with NVAF after AIS apart from NIHSS score (23). Similarly, in Iltumur and his colleagues study among 57 stroke patients who had their first AIS and no history or signs of cardiovascular disease, they found that NT-proBNP plasma levels are significantly elevated in AIS and might be of clinical importance as a supplementary tool for the assessment of cardiovascular function in patients with AIS (24). Additionally, in Sayan and Kotan studied the relationships between plasma (BNP) and severity and location of stroke, prognosis, and infarct volume and concluded that the progression of disease no statistically significant relationship with elevated plasma BNP levels (25). Also, Bunevicius and his colleagues concluded that in acute stroke patients, greater NT-proBNP and hs CRP serum concentrations are independently associated with greater clinical stroke severity (16).

In addition, Pro-BNP level was not significant among patients with different cardiac complications or those with no cardiac complications (table 6).

The possible explanation for this might be related to the small sample size or the high Pro-BNP level found in those without cardiac complications which might be related to their brain pathology as shown in a large bulk of literature (5, 14).

The proportions of subtypes of stroke pathology in the present study were similar to those reported in most published studies where ischemia forms the main bull cases as in this study, while subarachnoid hemorrhage for only a minority of cases (table 3).

In addition, the mortality rate in the present study of about 20% was consistent with many other published studies(7).

The present study found no gender difference in the level of Pro-BNP and this finding was consistent with many other published studies (14).

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