A Prospective Study of Brain Natriuretic Peptide as a Marker for Prediction of Severity in Patients with Sepsis

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Abstract: Background: Sepsis is a major cause of morbidity and mortality in intensive care units (ICU) worldwide. The incidence of sepsis is increasing and it is as high as the incidence of myocardial infarctions. The mortality rate has been reported at 20 to 50 per cent, most of which are attributed to cardiovascular collapse. Several studies have been performed to identify biomarkers for use in the early identification of patients at risk. **Objectives:** This study was done to estimate and evaluate the plasma levels of BNP in patients with sepsis and to study the association of BNP levels with severity of disease progression and prognosis of those patients. **Patients and Methods:** This prospective cohort study was conducted on 30 patients admitted to intensive care unit at October 6 university hospital in the period from June 2018 to January 2019 with diagnosis of sepsis. **Results:** There was significant decrease in serum sodium in those who did not survive. Serum lactate and CRP were significantly high in those who did not survive. As regard BNP, it was significantly higher in the non-survivor group, Also it correlated with prolonged length of stay in ICU, progressing to septic shock and need of mechanical ventilation. **Conclusion:** Laboratory and clinical medicine groups should actively collaborate and optimize their individual expertise to potentially prove standardized biomarkers assays that will optimize patient care.
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1. Introduction

Sepsis is a leading cause of death in critically ill patients despite improvements in antimicrobial therapy and supportive care ***(Angus et al., 2001)***. The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, hormonal and cellular reactions, and circulatory abnormalities ***(Gullo et al., 2006).*** Early identification of patients at high risk of dying after intensive care unit (ICU) admission may help to determine therapeutic interventions, such as changes in therapeutic protocols or further diagnostic procedures aiming at preventing shock and multiple organ failure with all their sequels that could have an impact on patients' outcome ***(Zambon et al., 2008).*** Therefore, there is a need for a fast simple and cost-effective method to enhance risk stratification in septic patients.

Brian natriuretic peptide (BNP) and its inactive cleavage product N-terminal fragment (NT-proBNP) (108 amino acids prohormone made when 32-amino acid polypeptide BNP is attached to a 76–amino acid N-terminal fragment). were secreted into the blood in response to atrial or ventricular wall stretch, or myocardial ischemia by cardiomyocytes. The half-life of BNP is approximately 20 minutes, and that of NT-proBNP is 1-2 hours ***(Vanderheyden et al., 2004).***

Brain naturietic peptides have been found to be useful markers in the diagnosis, management and prognosis of patients with congestive heart failure. In addition, BNPs are powerful predictors of death and major adverse cardiovascular events in patients with stable coronary disease, acute coronary syndromes and pulmonary embolism, and pulmonary hypertension, and COPD with corpulmonale, and those who undergo noncardiac surgery ***(Karthikeyan et al., 2009).***

Aim of the Work

The aim of this study is to investigate the plasma level of BNP in patients with sepsis and to study the association of BNP level with severity of disease progression and prognosis of those patients.

2. Patients and Methods

This prospective cohort study included 30 patients diagnosed to have sepsis admitted to the Intensive care unit at October six University hospital and Ain Shams university hospital during period between June 2018 and January 2019.

After approval of the local ethical committee in October 6 university hospital and Ain Shams

university hospital, A consent was obtained from the patient or first kin for participation.

Included patients fulfilled the following criteria on admission: -

1- Age 18-80 years old

2- Sepsis: Two or more of the following variables of SIRS with suspected site of infection:

- Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or Arterial carbon dioxide tension ($PaCO_2$) of less than 32 mm Hg
- Abnormal white blood cell count (>12,000/µL or <4,000/µL or >10% immature [band] forms)

We excluded from our study any patient with any of the following criteria.

- Congestive heart failure
- Chronic renal disease or End stage renal disease (ESRD) on regular dialysis
- Ischemic heart disease
- Acute coronary syndrome
- Terminal malignancy patients
- Polytrauma patients

As the above conditions may be associated with an elevation of BNP.

Methodology

After the study explanation to all patients or first kin.

Patients were subjected to the following:

1- Complete medical history taking

2- Hemodynamic monitoring

3- Duration of ICU stay

4- Need of mechanical ventilation

5- Sepsis: Two or more of SIRS variables with suspected site of infection:

6- Laboratory Investigations: CBC, ESR, CRP, S. lactate, KFT, LFT, INR and BNP level was done by the use of the Triage BNP Test

Test device contains:

- Murine monoclonal and polyclonal antibodies against BNP
- Fluorescent Dye
- Stabilizers

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median with inter-quartile range (IQR) when non parametric. Also qualitative variables were presented as number and percentages. So, the p-value was considered significant as the following: P-value > 0.05: Non significant (NS), P-value < 0.05: Significant (S), P-value < 0.01: Highly significant (HS).

3. Results

Table 1: Shows relation between mortality and demographic data, risk factors and clinical data of the studied cases:

		Total cases	Alive	Died	Test value	P-value	Sig.
		No. = 30	No. = 15	No. = 15			
Age (years)	Mean ± SD	54.70 ± 18.01	47.20 ± 18.31	62.20 ± 14.69	-2.474•	0.020	S
Sex	Male	13 (43.3%)	8 (53.3%)	5 (33.3%)	1.222*	0.269	NS
	Female	17 (56.7%)	7 (46.7%)	10 (66.7%)			
HTN	Positive	16 (53.3%)	5 (33.3%)	11 (73.3%)	4.821	0.028	S
	Negative	14 (46.7%)	10 (66.7%)	4 (26.7%)			
DM	Positive	14 (46.7%)	4 (26.7%)	10 (66.7%)	4.821	0.028	S
	Negative	16 (53.3%)	11 (73.3%)	5 (33.3%)			
COPD	Positive	7 (23.3%)	3 (20.0%)	4 (26.7%)	0.186	0.666	NS
	Negative	23 (76.7%)	12 (80.0%)	11 (73.3%)			
Hepatic	Positive	8 (26.7%)	3 (20.0%)	5 (33.3%)	0.682	0.409	NS
	Negative	22 (73.3%)	12 (80.0%)	10 (66.7%)			
Site of sepsis	Pneumonia	20 (66.7%)	9 (60.0%)	11 (73.3%)	5.200	0.158	NS
	UTI	4 (13.3%)	4 (26.7%)	0 (0.0%)			
	Wound infection	4 (13.3%)	1 (6.7%)	3 (20.0%)			
	Intraabdominal sepsis	2 (6.7%)	1 (6.7%)	1 (6.7%)			
SBP (mmHg)	Mean ± SD	115.83±28.23	124.67±21.00	107.00±32.28	1.777	0.086	NS
DBP (mmHg)	Mean ± SD	73.50 ± 14.33	78.67 ± 11.87	68.33 ± 15.08	2.085	0.046	S
Temp ©	Mean ± SD	38.80 ± 0.96	38.53 ± 0.55	39.07 ± 1.20	-1.586	0.124	NS
HR (beat/min)	Mean ± SD	110.33±18.91	110.33±21.50	110.33±16.69	0.000	1.000	NS
RR (breath/min)	Mean ± SD	28.83 ± 5.89	25.93 ± 3.77	31.73 ± 6.30	-3.061	0.005	HS
SPO2 (%)	Mean ± SD	92.77 ± 5.82	94.73 ± 5.47	90.80 ± 5.66	1.935	0.063	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test; •: Independent t-test Data expressed as Mean ± SD / percentage

DM: diabetes mellitus, HTN: hypertension, COPD: chronic obstructive pulmonary disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, spo2: oxygen saturation, RR: respiratory rate

The previous table shows that there was statistically significant relation found between mortality and older age, hypertension, Diabetes mellitus, low diastolic blood pressure and high respiratory rate among the studied cases with p-values = 0.020, 0.028, 0.028, 0.046 and 0.005 respectively, while no statistically significant relation found between mortality and gender or other risk factors and clinical data.

Table 2: Showed relation between mortality and laboratory data on admission

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: Independent t-test; ≠: Mann-Whitney test Data expressed as Mean ± SD / Median (IQR)

The previous table showed that there was statistically significant relation found between mortality and high CRP, high serum Lactate, low Hemoglobin, low sodium and high BNP of the studied cases with p-values = 0.031, 0.020, 0.022, 0.042 and 0.014 respectively, while no statistically significant relation found with the other laboratory data.

Table 3: Shows relation between mortality and outcome variables.

		Total cases	**Alive**	**Died**	**Test value**	**P-value**	**Sig.**
		No. = 30	**No. = 15**	**No. = 15**			
Length of ICU stay in days	Mean ± SD Range	10.67 ± 6.39 2 – 23	6.20 ± 3.95 2 – 14	15.13 ± 5.11 5 – 23	-5.356•	0.000	HS
MV	Yes No	14 (46.7%) 16 (53.3%)	1 (6.7%) 14 (93.3%)	13 (86.7%) 2 (13.3%)	19.286*	0.000	HS
Progressing to septic shock	Yes No	11 (36.7%) 19 (63.3%)	2 (13.3%) 13 (86.7%)	9 (60.0%) 6 (40.0%)	7.033*	0.008	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test; •: Independent t-test Data expressed as Mean ± SD / percentage ICU: intensive care unit, MV: mechanical ventilation

The previous table showed statistically significant relation between mortality and length of ICU stay, mechanical ventilation and progression to septic shock with p values = 0.000, 0.000 and 0.08 respectively.

Table 4: Shows relation between BNP and the other studied parameters

		BNP (pg/ml)	**Test value**	**P-value**	**Sig.**
		Median (IQR)			
Sex	Male Female	100 (61.8 – 418) 90 (58 – 428)	-0.314≠	0.754	NS
HTN	Positive Negative	239 (49.5 – 459) 89.3 (61.8 – 300)	-0.416≠	0.678	NS
DM	Positive Negative	239.0 (57.2 – 428) 89.5 (63.65 – 400)	-0.042≠	0.967	NS
COPD	Positive Negative	100 (58 – 493) 81 (57.2 – 418)	-0.466≠	0.641	NS
Hepatic	Positive Negative	61.75 (40.55 – 234.5) 130.5 (78 – 493)	-1.688≠	0.091	NS
Site of sepsis	Pneumonia UTI Wound infection Intra-abdominal sepsis	84.3 (57.6 – 459) 81.4 (29.4 – 590.5) 249.5 (80 – 760) 254.5 (100 – 409)	1.488≠≠	0.685	NS
Blood culture	Negative Positive	90 (58 – 418) 500 (500 – 500)	-1.213≠	0.225	NS
Urinal culture	Negative Positive	81 (58 – 388) 500 (41.8 – 1040)	-1.741≠≠	0.082	NS
Sputum culture	Negative Positive	90.5 (78 – 418) 115 (57.6 – 495)	-0.125≠	0.901	NS
MV	Yes No	423 (90 – 500) 71.75 (31.1 – 110.5)	-3.035≠	0.002	HS
Progressing to septic shock	Yes No	409 (100 – 500) 78 (38.3 – 140)	-2.518≠	0.012	S
Lactate	< 2 ≥ 2	78.3 (49.5 – 130.5) 398.5 (81 – 493)	1.995	0.046	S

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

≠: Mann-Whitney test; ≠≠: Kruskal-Wallis test Data expressed as Mean ± SD MV: mechanical ventilation

The previous table shows that there was statistically significant relation found between BNP level and mechanical ventilation, serum lactate and progressing to septic shock with p-value 0.002, 0.046 and 0.012 respectively while no statistically significant relation found with the other parameters.

4. Discussion

Although sepsis is one of the leading causes of mortality in hospitalized patients, information regarding early predictive factors for mortality and morbidity is limited. Early identification of septic patients at high risk of dying remains a challenge. The prognostic role of brain natriuretic peptide (BNP) in septic patients remains controversial. Therefore, there is a need for a fast simple and cost-effective method to enhance risk stratification in septic patients ***(Wang et al., 2012; Aziz et al., 2017).***

Brain natriuretic peptide has been found to be useful markers in the diagnosis, management and prognosis of patients with congestive heart failure. Also, BNP is a powerful predictor of death and major adverse cardiovascular events in patients ***(Tang et al., 2007).***

Given that BNP levels has been linked with hemodynamics and cardiovascular functions which are both affected in sepsis, we suggest that BNP can be a prognostic indicator for prediction of sepsis severity ***(Ahmed et al., 2011).***

During the period from June 2018 to January 2019, thirty patients were registered in our study from those who were admitted to Intensive care unit of October 6 university hospital and Ain shams university hospital.

We studied 30 patients with sepsis with age ranged from 19 to 80 years and with mean age of 54.70±18.01, 13 males (43.3%) and 17 females (56.7%). while, ***Omar et al. (2013)*** studied 30 patients divided into two groups 20 patients with sepsis and 10 patients with septic shock with age range of 19-72 years with mean age of 49.8±16.7 years, 18 males (60%) and 12 females (40%), ***Ahmed et al. (2011)*** studied 30patients divided into three groups group 1was 10 patients with sepsis, group 2 was 10 patients with septic shock and group 3 was 10 controls with a mean age of 45.33±5.22years, 18 males (60%) and 12 females (40%), ***Singh et al. (2017)***, studied 505 patients admitted with sepsis or severe sepsis or septic shock with age more than 18 and they were 220 males (43.5%) and 285 females (56.5%).

Eighty percent of patients in our study were admitted with sepsis due to medical cause versus twenty percent with surgical cause.

Thirty three percent of our studied patients showed negative cultures while, ***Ahmed et al. (2011)*** study showed 20% negative cultures, ***Cohen et al. (1999)*** study reported that negative cultures was found in 39% of his patients, also ***Kieft et al. (1993)*** showed that 20-30% of his patients who presented with sepsis were never identified infection sites and both imaging studies and blood culture analysis did not rule out presence of infection in these study groups.

Chest infection was predominant in 20 out of 30 patients (66.7%) in our study and that matches with ***Ahmed et al. (2011)*** study who reported that 13 out of 20 patients of his patients with sepsis and septic shock due to chest Infection, also ***Tang et al. (2007)*** showed that respiratory infection is the most common cause of sepsis in his study results.

In our study, 15 patients died out of 30 patients (50%) with hospital stay = 15.13 ± 5.11, these results matches with ***Fleischmann et al. (2016)*** study who recorded sepsis motality of 41% in his study patients, Also ***Alberti et al. (2003)*** study that documented hospital mortality from 25-60% according to sepsis stage, ***Ahmed et al. (2011)*** that reported 40% mortality in his study subjects, while ***Vieillard-Baron et al. (2003)*** that showed 60% mortality in his study.

In the current study we correlated BNP level on admission with mortalities and it was observed that BNP level was significantly higher in those who did not survive (15 out of 30 patients) (Median 418pg/ml) than in those who survived (15 out of 30 patients) (median 78 pg/ml) and it was statistically significant with p value <0.014 and the cut off point for BNP level to predict mortality was recorded > 300 (pg/ml) with sensitivity of 66.67%, specificity of 93.3%. These results matched with ***Singh et al. (2017)*** study who found that that sepsis mortality was associated with an average of 300 higher BNP units. Also ***Wang et al. (2012)*** in a meta-analysis involving a total of 1,865 patients, both inactive and active forms of natriuretic peptide were elevated and significantly associated with increased risk of mortality, with a sensitivity and specificity of 79% and 60%, respectively.

During monitoring of the results we have found that higher BNP level on admission correlated to the progression to septic shock with cut off point for BNP level to predict progressing to septic shock was found > 200 (pg/ml) with sensitivity of 72.73%, specificity of 78.95%. This results matched ***Guaricci et al. (2015)*** study that showed that BNP changes within 72 h could predict mortality at 28 days in patients with septic shock. This study also found that levels greater than 1,000 pg/mL at 72 h were associated with an adverse outcome, sensitivity and specificity of 95.5% and 94.4%, respectively. Also ***Bar et al. (2006)*** study documented that BNP was higher in those patients who progressed to septic shock.

We also observed that higher BNP levels predicted high length of stay in ICU, there was highly

significant correlation with p value= 0.0001, these results matched ***Zhang et al. (2012)***, reported that a BNP greater than 100 pg/mL was predictive of Intensive care unit length of stay (ICULOS) > 7 days, and hospital length of stay (HLOS) > 12 days. ***Zhao et al. (2009)***, also showed that the Intensive care unit length of stay (ICULOS) was significantly higher in the BNP elevated cohort compared to the BNP normal group (23.7 ± 7.5 days vs. 14.9 ± 5.1 days, P < 0.05) also ***Singh et al. (2017)*** study recorded that patients with a high BNP had 1.18 times longer average hospital stay.

Also our study showed that higher plasma BNP levels correlated with the need of mechanical ventilation with best cut off point for BNP level to predict MV was found > 300 (pg/ml) with sensitivity of 71.43%, specificity of 93.75% this results was correlated to ***Vander et al. (2010)*** study that BNP at the first 24 hours correlated with the number of days on mechanical ventilation. Also ***Farghaly et al. (2015)*** study documented that BNP can be used as a predictor for underlying need of further mechanical ventilation of already ventilated patients or failure of weaning of ventilation also there was some trials suggesting the use of BNP in predicting spontaneous breathing trial outcome however, No studies directly stated whether BNP can predict the need of mechanical ventilation in patients with sepsis.

Conclusion

Laboratory and clinical medicine groups should actively collaborate and optimize their individual expertise to potentially prove standardized biomarkers assays that will optimize patient care.

From the present study we could conclude that:

1. BNP level on admission was higher in non-survivors that has statistical significance.
2. BNP level on admission was higher in those who stayed longer in ICU that has statistical significance.
3. BNP level on admission was higher in those who progressed to septic shock that has statistical significance.
4. BNP level on admission was higher in those who required mechanical ventilation that has statistical significance.
5. BNP has a diagnostic and prognostic role in patients with sepsis.

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