Brain natriuretic peptide for prediction of mortality in patients with sepsis

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Introduction Worldwide, sepsis is one of the leading causes of morbidity and mortality. Patients are at high risk for irreversible organ failure and a lethal course. About 60 000 individuals die from sepsis annually, and survivors have a reduced quality of life. In addition, sepsis places a considerable economic burden on the society. Early and comprehensive treatment improves outcome significantly. Brain natriuretic peptides (BNPs) are powerful predictors of death and major events in patients with stable coronary disease and pulmonary embolism. Several prospective studies have been carried out to investigate the potential role of BNPs in predicting mortality in septic patients in ICUs. The aim of this prospective study was to evaluate BNP for the prediction of mortality and myocardial dysfunction in severe sepsis and septic shock.

Patients and methods This prospective study was carried out on 50 patients including group I, patients with sepsis, group (II), patients with severe sepsis, and group III, patients with septic shock. This study was carried out in the ICU of the Internal Medicine Department, Al-Zahraa University Hospital, in the period between January 2013 and March 2014 with written consents from our patients according to the ethical committee of the university. BNPs were determined by enzyme-linked immunosorbent assay.

Results There was a highly statistical difference in the mean ±SD of the BNP levels in group III (901.77±259.6) compared with group II (610.84±102.46), *P* value less than 0.01; also, there was a statistical difference in the BNP levels in group III (901.77±259.6) compared with group I (217.4±81.16), *P* value less than 0.01, whereas there was a statistically significant difference in group II (610.84±102.46) compared with group I (217.4±81.16), *P* value less than 0.05. In terms of the correlation between the BNP levels and other parameters of the patient groups, there was a highly positive significant correlation between BNP levels and the acute physiology and chronic health evaluation (APACHE II) score, the Sequential Organ Failure Assessment score, and white blood cells count. A significant positive correlation was found between BNP levels and prothrombin concentration (PC). There was a nonsignificant correlation between BNP and age, creatine phosphokinase, creatine kinase-MB, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, prothrombin time, international normalized ratio, and length of stay.

Conclusion Our results suggested that an elevated BNP level may prove to be a powerful predictor of mortality in patients with sepsis. Future larger and more adequately powered prospective studies are warranted to clarify the prognostic value of BNPs in conjunction with other biomarkers.

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Introduction

Brain natriuretic peptide (BNP) and its product N-terminal fragment (NT-proBNP) are secreted into the blood in response to atrial or ventricular wall stretch [1] or myocardial ischemia [2] by cardiomyocytes. The half-life of BNP is ~20 min and that of NT-proBNP is 1–2 h [3]. Natriuretic peptides play an important role in the regulation of cardiovascular homeostasis and fluid volume. They natriuresis and diuresis, by acting as vasodilators, and also exert antimitogenic effects on cardiovascular tissues [4,5]. They also play a role as counter-regulatory hormones in heart failure [6]. BNP is synthesized as a 134-amino acid preprohormone; the 25-residue N-terminal signal peptide generates the prohormone, proBNP, which is stored intracellularly as an O-linked glycoprotein [7]. Its cleavage at other sites produces shorter BNP peptides with unknown biological activity [8]. Processing of proBNP may be regulated by O-glycosylation of residues near the cleavage sites [9]. In the presence or absence of cardiac dysfunction, the concentrations of BNP increase in patients with severe sepsis or septic shock. Neither the BNP levels for the first 3 days nor the daily changes in BNP are considered to be of prognostic value for length of stay in-hospital and mortality of patients, including patients with chronic cardiac dysfunction [10]. B-type natriuretic peptide (BNP) is considered a marker of left ventricular

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end-diastolic pressure [11], and has been proven to be a useful diagnostic tool to differentiate dyspnea caused by congestive heart failure (CHF) from noncardiac dyspnea in patients presenting at the emergency room [12,13]. It has been shown that a normal BNP level (<80–100 pg/ml) has a high negative predictive value to exclude CHF, whereas a markedly elevated BNP has a high positive predictive value for CHF [14].

Sepsis is defined as life-threatening organ dysfunction caused by dysregulated host response to infection [15]. Severe sepsis is defined as sepsis that is complicated by end-organ dysfunction, as signaled by altered mental status, an episode of hypotension, elevated creatinine concentration, or evidence of disseminated intravascular coagulopathy [16]. Septic shock is a subset of sepsis in which underlying circulatory and cellular or metabolic abnormalities are severe enough to markedly increase mortality [17].

Patients and methods

This prospective study was carried out on 50 patients with sepsis. This study was carried out in the ICU of Internal Medicine Department, Al-Zahraa University Hospitals, in the period between January 2013 and March 2014 with written consents from our patients according to the ethical committee of the university.

The age of the patients with sepsis ranged from 25 to 75 years; there were 24 women and 26 men.

Patients were divided into three groups as follows:

(1) Group I: included 10 patients with sepsis, three men and seven women, ranging in age ranged from35 to 65 years, mean±SD 53.5±11.3.
(2) Group II: included 15 patients with severe sepsis, six men and nine women, ranging in age from 28 to 60 years, with mean±SD 49.7±9.4.
(3) Group III: included 25 patients with septic shock, 17 men and eight women, ranging in age from 25 to 75 years, with mean±SD 56.8±13.3.

Exclusion criteria

Patients with renal failure, heart failure, and pregnancy were excluded.

All patients were subjected to the following:

(1) Full assessment of history and full clinical examination, complete blood count with differential count, fasting blood glucose, kidney function tests (urea, creatinine), liver function tests (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and serum bilirubin), lipid profile (cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein), cardiac enzymes (creatine phosphokinase, creatine kinase-MB, and troponin I), coagulation profile (prothrombin time, activated partial thromboplastin time, fibrinogen level).
(2) BNP in blood by enzyme-linked immunosorbent assay.
Seven milliliters of fasting venous blood samples (6–8 h) were obtained from each patient in the study and divided into aliquots: the first aliquot was 2 ml on EDTA for complete blood count determination. The second aliquot was 1.6 ml of venous blood, which was added to a tube containing 0.4 citrate for prothrombin time and the concentration was determined using the tissue thromboplastin method on an automated blood coagulation analyzer (Siemens AG, Erlangen, Germany). The third aliquot was 1.6 ml of blood on 0.4 ml citrate for erythrocyte sedimentation rate determination using Westergren's method. The fourth aliquot was the rest of the blood, which was allowed to clot for 30 min before centrifugation for 15 min at ~1000*g*.

The serum was removed and assayed immediately or aliquoted, and the samples were stored at −20°C or −80°C.
BNP concentrations in serum were determined using the enzyme-linked immunosorbent assay kit supplied by EIAab (Wuhan EIAab Science Co. Ltd, Wuhan, China) [18]. Normal BNP values range from 0 to 99 pg/ml.
(3) Echocardiography.
(4) APACHE II score:
Acute physiological assessment and chronic health evaluation are widely used methods for assessing the severity of illness in acutely ill patients in ICUs, taking into account a variety of routine physiological parameters. The acute physiology and chronic health evaluation (APACHE II) scoring system was developed by Knaus *et al.* [19].
(5) The Sequential Organ Failure Assessment (SOFA) score:
The SOFA score was developed in 1994 during a Consensus Conference organized by the European Society of Intensive Care and Emergency Medicine in an attempt to provide a means to describe the degree of organ failure over time in individuals and groups of patients with sepsis[20].

Statistical analysis

Data were analyzed using Microsoft Office 2003 (excel) and statistical package for the social science , version 16 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Parametric data were expressed as mean±SD and nonparametric data were expressed as number. Comparison between the different groups studied was performed using analysis of variance and the relations between the groups were determined using the post-hoc correction for analysis of variance. Measurement of the mutual correspondence between two values was performed using the Spearman correlation coefficient. A *P* value more than 0.05 was considered nonsignificant and a *P* value less than 0.01 was considered highly significant.

Results

Tables 1–3 shows the demographic data of patients included in the study; their age ranged from 25 to 75 years, with mean±SD 53.5±11.3 years in group I, mean ±SD 49.7±9.4 years in group II, and mean±SD 56.8 ±13.3 years in group III.

Table 4 There was a highly significant positive correlation between BNP levels and the APACHE II score (r=0.904, P<0.01), the SOFA score (r=0.647, P<0.01), and the white blood cells count (r=0.511, P<0.01) (Figs 1–3).

There was a significant positive correlation between BNP levels and systolic blood pressure (r=–0.296, P<0.05), mean blood pressure (r=–0.330, P<0.05), prothrombin concentration (PC) (r=–0.330, P<0.05), albumin (r=–0.296, P<0.05), erythrocyte sedimentation rate (r=0.342, P<0.05), total bilirubin (r=0.342, P<0.05), and direct bilirubin (r=0.371, P<0.05).

There was no significant correlation between BNP and age, creatine kinase-T, creatine kinase-MB, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, prothrombin time, international normalized ratio and length of stay, and ejection fraction (Fig. 4).

Table 1 Demographic data of all the groups studied

Variables	Group I	Group II	Group III
Male	3	6	17
Female	7	9	8
Age (mean ±SD)	53.5±11.3	49.7±9.4	56.8±13.3
Source of infection	5 patients: urinary tract 2 patients: skin infection 3 patients: pneumonia	2 patients: undefined infection 5 patients: pneumonia 8 patients: blood stream infection	1 patient: CNS infection 5 patients: undefined infection 5 patients: intra-abdominal infection 5 patients: pneumonia 9 patients: blood stream infection
Mechanical ventilator	–	–	10

CNS, central nervous system.

Discussion

BNPs increase in patients with sepsis can be considerably high, even though cardiac problem not present [21], but normal BNPs levels could be used to rule out cardiac disorders [22]. BNPs level is related to APACHE II and SOFA scores [23]; high plasma levels of BNPs are associated with poor outcomes of sepsis [24]. Despite initial recovery from critical illness requiring ICU admission, many patients remain at risk of subsequent deterioration and death [25].

Table 2 Comparison study of all three studied groups

Variables	Group I	Group II	Group III
Length of stay (days)	5–21	4–20	4–21
APACHE II scores	10–20	10–27	13–41
SOFA scores	2–5	2–9	2–17
BNP level (pg/ml)	80.9–283.2	410–723.7	391.8–1492
Patients outcome	Survival patients	Survival patients	Nonsurvival patients
Mortality scores (%)	11.30–35.50	11.30–60–50	16.50–92.20

APACHE II, acute physiology and chronic health evaluation; BNP, brain natriuretic peptide; SOFA, Sequential Organ Failure Assessment.

Table 3 Comparison of brain natriuretic peptide, APACHE II, and Sequential Organ Failure Assessment among the three groups studied

Variables	Group I	Group II	Group III	*P*I	*P*II	*P*III	*P* value
BNP (pg/ml)	217.4±81.16	610.84±102.46	901.772±259.6	<0.01	<0.01	<0.05	<**0.001** HS
APACHE II	15.7±3.4	17.2±4.27	24.3±7.82	<0.01	<0.05	<0.01	<0.01 HS
SOFA	3.6±1.34	5.0±1.85	8.6±4.92	>0.05	<0.01	<0.05	<0.01 HS

APACHE II, acute physiology and chronic health evaluation; BNP, brain natriuretic peptide; HS, highly significant; SOFA, Sequential Organ Failure Assessment. *P*I, group I versus group II. *P*II, group I versus group III. *P*III, group II versus group III.

There was a highly significant increase in BNP levels among the septic shock patients in comparison with severe sepsis patients and this was in agreement with Wang *et al.* [26]. The patient population varied across studies: three studies included patients with sepsis [27] and nine studies included patients with severe sepsis or septic shock. These studies were carried out in various departments, including the emergency department, medical ICU, surgical ICU, and general ICU.

Table 4 Correlation between brain natriuretic peptide levels and the studied parameters of all groups

Parameters	BNP (*R* value)	*P* value	Significance
Age	0.236	>0.05	NS
APACHE II	0.904	<0.01	HS
SOFA	0.647	<0.01	HS
CK-T	0.198	>0.05	NS
CKMB	–0.071	>0.05	NS
SGOT	0.021	>0.05	NS
SGPT	0.021	>0.05	NS
PT	0.173	>0.05	NS
PC	–0.330	>0.05	NS
INR	0.065	>0.05	NS
WBCs	0.511	<0.01	HS
LOS	–0.007	>0.05	NS
ALB	–0.296	<0.05	S
ESR	0.342	<0.05	S
T.BIL.	0.342	<0.05	S
MBP	–0.330	<0.05	S
SBP	–0.296	<0.05	S
EF	–0.159	>0.05	NS

ALB, albumin; BNP, brain natriuretic peptide; APACHE II, acute physiology and chronic health evaluation ; CKMB, creatine kinase-MB; D.BIL., direct bilirubin; EF, ejection fraction; ESR, erythrocyte sedimentation rate; HS, highly significant; INR, international normalized ratio; LOS, length of stay; MBP, mean blood pressure; PC, prothrombin concentration; PT, prothrombin time; S, significant; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SOFA, Sequential Organ Failure Assessment; T. BIL., total bilirubin; WBC, white blood cell.

Patients with pre-existing conditions known to increase BNPs levels were excluded from the study [28]. The cardiovascular response to septic shock is peripheral vasodilatation resulting in systemic hypotension, hyporesponsiveness to vasopressors, and reduced systemic vascular resistance. Cytokines and endotoxins from Gram-negative microorganisms may lead to myocardial depression, ventricular dilatation, and wall stretch, leading to an increase in the levels of BNP because of myocardial cell damage [29].

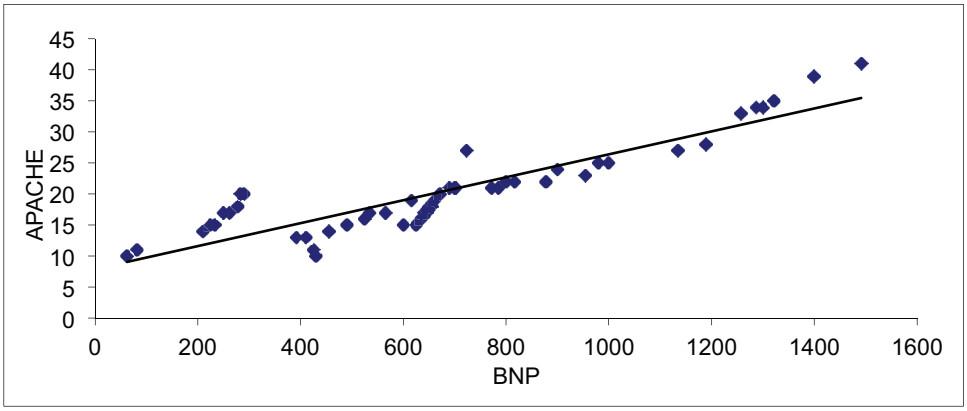
BNP or NT-proBNP levels may be a powerful predictor of mortality in patients with sepsis. This test appears to represent a rapid and relatively inexpensive method to enhance mortality prediction in sepsis and elevated natriuretic peptides are associated significantly with an increased risk of mortality [26].

There was a highly significant increase in BNP levels among septic shock patients in comparison with sepsis patients and this was in agreement with Witthaut *et al.* [30].

There was a highly significant increase in BNP levels among severe sepsis patients in comparison with sepsis patients and this was in agreement with Kada *et al.* [31].

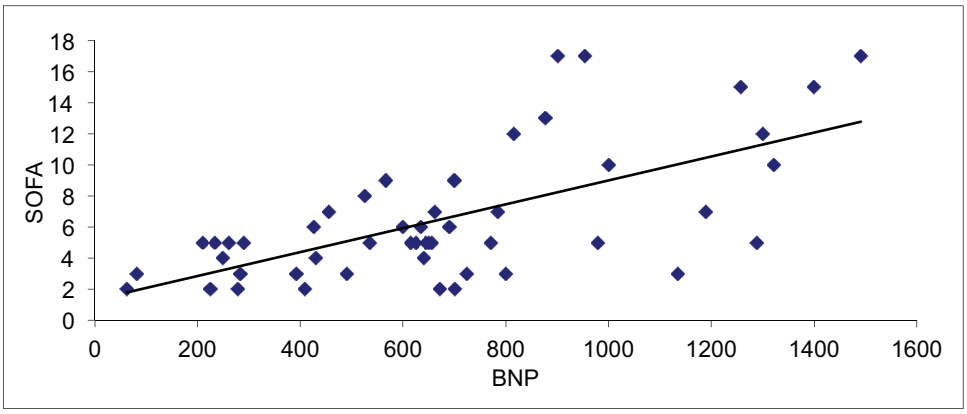
There was a highly significant increase in the APACHE II score among severe sepsis patients in comparison with sepsis patients; also, there was a highly significant increase in the APACHE II score among septic shock patients in comparison with severe sepsis patients. Meanwhile, there was a significant increase in the APACHE II score among septic shock patients in comparison with

Figure 1



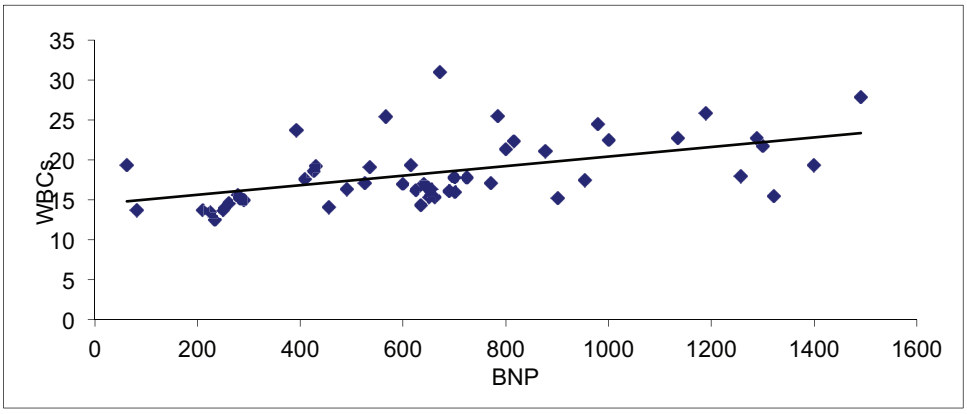
Positive correlation between BNP and APACHII score. BNP, brain natriuretic peptide.

Figure 2



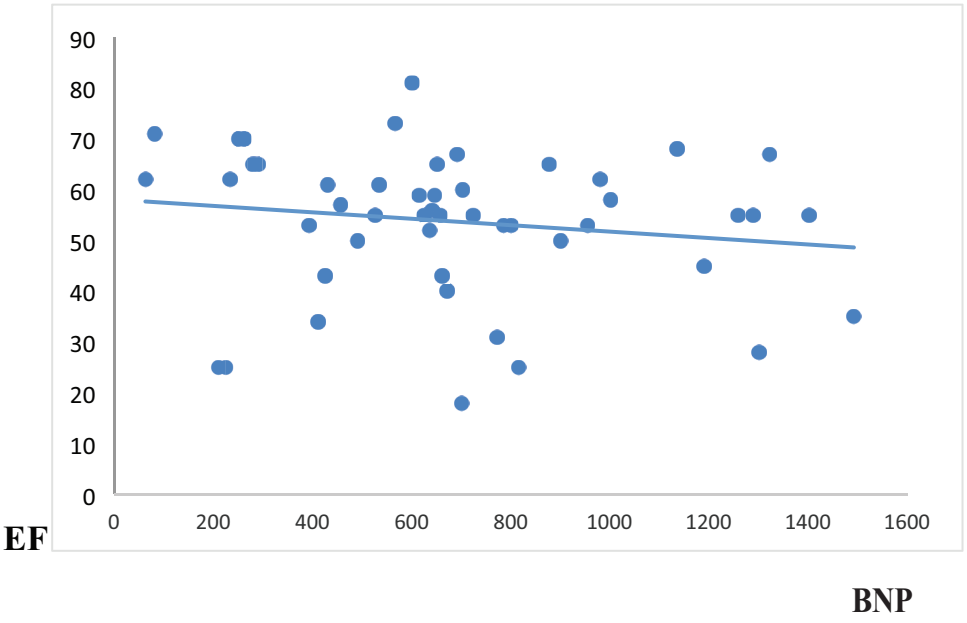
Positive correlation between BNP and SOFA score. BNP, brain natriuretic peptide; SOFA, Sequential Organ Failure Assessment.

Figure 3



Positive correlation between BNP and WBCs count. BNP, brain natriuretic peptide; WBC, white blood cell.

Figure 4



Negative correlation between BNP and ejection fraction. BNP, brain natriuretic peptide.

sepsis patients and this was in agreement with Pratikaki *et al.* [32].

There was a highly significant increase in the SOFA score among septic shock patients in comparison with sepsis patients; also, there was a significant increase in the SOFA score among septic shock patients in comparison with severe sepsis patients and this was in agreement with Trzeciak and Rivers [33]. Meanwhile, there was a nonsignificant increase in the SOFA score among severe sepsis patients in comparison with sepsis patients.Myocardial insufficiency is more frequently encountered in patients with sepsis mainly in the form of left ventricular diastolic dysfunction (LVDD). Two out of 10 patients had LVDD in group I (20%), three out of 10 patients had LVDD in group II (30%), whereas 15 out of 25 patients had LVDD in group III (60%). These data are in agreement with Omar *et al.* [34]. Reversible diastolic and systolic myocardial dysfunction has been documented in human septic shock, with a different rate of recovery for survivors and nonsurvivors [35]. Patients with severe sepsis or septic shock and echocardiographically preserved left ventricular ejection function can show a significant increase in plasma BNP levels as high as that in CHF [36].

There was a highly significant positive correlation between BNP levels and APACHE II score. These data are in agreement with those of Rui *et al.* [37].

Also, there was a highly significant positive correlation between BNP levels and the SOFA score. These data are in agreement with Kandil *et al.* [22].

Summary and conclusion

Sepsis is the presence of the systemic inflammatory response syndrome in response to infection. Sepsis is acause of death at high risk patients in ICUs despite antimicrobial therapy and supportive care more better than before. In the presence or absence of cardiac dysfunction, the concentrations of BNP increase in patients with severe sepsis or septic shock. In this study, we found that patients with septic shock showed higher levels of BNP than patients with sepsis or severe sepsis; also, BNP is a predictor of mortality in septic patients and is considered to be of powerful prognostic value of BNPs along with other biomarkers.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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