Original Article

Prognostic role of N-terminal prohormone of brain natriuretic peptide for patients in the medical intensive care unit with severe sepsis

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ABSTRACT

Background: Sepsis is an important cause of mortality in intensive care units worldwide. The increased levels of N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) are related with dysfunction of the cardiovascular system and systemic inflammation. It is uncertain whether this increase reflects sepsis-related cardiac dysfunction that translates to poorer outcomes. **Aims and Objectives:** The primary aim of this study was to evaluate the prognostic role of NT-pro BNP on the outcome and duration of hospital stay of patients admitted with sepsis. The secondary objective was to identify other associated risk factors for mortality in sepsis. **Patients and Methods:** The patients who presented to emergency room with diagnosis of suspected sepsis were studied. Risk factors associated with outcome were studied by univariate analysis. The variables having statistical significance were further included in multivariate analysis to identify the independent predictors of mortality. **Results:** A total of 215 patients with sepsis were included in this study. In univariate analyses, NT-pro BNP, procalcitonin, need of mechanical ventilation (MV), blood culture positivity, chronic kidney disease-chronic liver disease CKD-CLD, and diabetes mellitus were predictors of prolonged hospital stay, and it was same for multivariate analysis excluding procalcitonin. In univariate analysis, NT-pro BNP, MV, and DM were risk factors associated with mortality but in multivariate analysis showed significance only with MV and DM. **Conclusion:** There was a statistically significant correlation between NT-pro BNP levels and mortality. The other factors associated with increased mortality were diabetes mellitus and need of MV. In addition to the above factors, the presence of CKD and CLD was associated with increased duration of hospital stay. There was concordance between increased NT-pro BNP and elevated trop I, s creatinine, need of MV, and CKD.

KEY WORDS: Mortality, N-terminal prohormone of brain natriuretic peptide, sepsis

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INTRODUCTION

The 108-amino acid prohormone B-type natriuretic peptide (BNP) and its product 76-amino acid N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) are secreted in response to atrial or ventricular wall stretch or myocardial ischemia by cardiomyocytes into the blood.[1,2] BNP is cleared through internalization by cells that express BNP receptors, while renal clearance is the main mechanism for NT-pro BNP. This difference accounts for the difference in plasma concentration half-lives and is likely to be responsible, in part, for delayed clearance in patients with sepsis. That is why, the half-life of BNP is 20 min and that of NT-pro BNP is 1–2 h.[3]

BNP is considered a marker of left ventricular end-diastolic pressure[4] 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.[5,6] 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.[7]

Sepsis is defined as life-threatening organ dysfunction caused by dysregulated host response to infection.[8] 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.[8] The finding of elevated plasma levels of BNP or NT-pro BNP in sepsis over a decade ago has resulted in an ongoing search for a meaningful role of the hormone in clinical practice. BNP has been shown to be a useful cardiac biomarker for the identification of patients with suspected heart failure.[2] In the presence or absence of cardiac dysfunction, the concentrations of BNP increase in patients with severe sepsis or septic shock. In a recently published studies, BNP was found to be significantly elevated in patients with septic shock in comparison with controls.[9-12] There are not many studies from India. The present study was aimed to find out the relationship between elevated NT-pro BNP and mortality among patients who presented to ER with suspected sepsis. The secondary objective of the study was to find out correlation of NT-pro BNP with other laboratory and clinical parameters.

PATIENTS AND METHODS

All the patients who presented to the emergency department with suspected sepsis were included in the study after taking informed consent. Sepsis and septic shock were defined in accordance with the criteria of the consensus conference of the American College of Chest Physicians and Society of Critical Care Medicine.[7]

Blood sampling and determination of N-terminal prohormone of brain natriuretic peptide levels

All patients had blood samples taken for serum NT-pro BNP measurement within 6 h of admission. Serum NT-pro BNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany).

Ethics

Approval was obtained from our hospital's Institutional Review Board.

Statistical analysis

Results are expressed as mean ± standard deviation (SD). The statistical analyses were done by SPSS version 17 (SPSS Statistics for Windows, SPSS Inc., Chicago). 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. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 215 patients with sepsis were included in this study. The mean age of the cohort was 66.9 ± 12.72 years. There were 151 (69.3%) males and 63 (28.9%) females. The median NT-pro BNP was 2546 ng/ml 28–162150). Other laboratory parameters with mean and SD are shown in Table 1. In univariate analysis, [Table 2] NT-pro BNP, mechanical ventilation (MV,) and DM were risk factors associated with mortality but in multivariate analysis [Table 3] showed significance only with MV and DM. In univariate analyses, NT-pro BNP, MV, blood culture positivity, chronic kidney disease-chronic liver disease (CKD-CLD,) and diabetes mellitus were predictors of prolonged hospital stay, and it was same for multivariate analysis except for procalcitonin.

Table 1: Study population characteristics

Characteristics	*n* (%)	Mean±SD
Age (years)	215	66.9023±12.72442
Mortality	19 (8.8)	NA
Duration of hospital stay	215	13.4605±9.17723
NT-pro BNP	215	7056.0657±16,122.51608
CRP (g/dl)	204	83.1555±79.01202
Procalcitonin	131	20.9827±68.29153
WBC count/ml^3	212	12.8172±5.79570
Platelet/ml^3	212	486.8738±3970.75258
Hb (gm/dl)	212	10.6381±1.97162
Creatinine (mg/dL)	208	3.5394±8.64248
Urea	207	69.3271±50.98353
Troponin I	185	17.8018±51.61299
CKMB	164	22.6835±82.01054
Serum bilirubin (mg/dL)	192	1.2471±2.75848
Need of MV	22 (10.2)	NA

NT-pro BNP: N-terminal prohormone of brain natriuretic peptide, CRP: C-reactive protein, WBC: White blood cell, Hb: Hemoglobin, NA: Not applicable, MV: Mechanical ventilation, CKMB: Creatinine kinase-MB

Spearman's correlation was done for checking the relation between BNP and other laboratory parameters. Values are shown in Table 4. The need of MV was the only clinical factor with a significant positive correlation associated with increased NT-pro BNP. There was no significant correlation between BNP and age, creatinine kinase-MB, urea, pyruvic transaminase, prothrombin time, blood culture, presence of DM, CLD, or CKD, and death.

Table 2: Univariate analysis of risk factors and duration of hospital stay (*t*-test) and outcome

Risk factors	Duration of hospital stay		Outcome		
	χ^2	*P*	OR	χ^2	*P*
Gender	64.5	0.38		0.19	0.907
NT-pro BNP (>2546)	67.5	<0.001	0.343	4.23	0.040
Blood culture	48.6	0.017	1.585	0.34	0.55
Procalcitonin			1.829	0.48	0.489
Mechanical ventilation	53.5	<0.001	0.266	5.869	0.031
Abnormal ECHO findings	40.8	0.11	1.329	0.33	0.56
DM	58.0	<0.001	8.19	20.7	<0.001
CLD/CKD	57.1	<0.001	0.93	0.01	0.89

NT-pro BNP: N-terminal prohormone of brain natriuretic peptide, OR: Odds ratio, ECHO: Echocardiography, DM: Diabetes mellitus, CLD: Chronic liver disease, CKD: Chronic kidney disease

Table 3: Multivariate analysis for the variables for DHS and outcome

Risk factors	Duration of hospital stay *P*	Outcome		
		OR	χ^2	*P*
NT-pro BNP	<0.0001	0.343	4.23	0.031
Blood culture	0.600	1.585	NA	NA
Procalcitonin	0.129	1.829	NA	NA
Mechanical ventilation	<0.001	0.251	42.2	0.012
DM	0.025	8.19	20.7	<0.001
CLD/CKD	<.001	0.93	NA	NA

NT-pro BNP: N-terminal prohormone of brain natriuretic peptide, OR: Odds ratio, DM: Diabetes mellitus, CLD: Chronic liver disease, CKD: Chronic kidney disease, NA: Not applicable

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

Parameters	Correlation coefficient	*P*
Age	−0.021	0.765
Duration of hospital stay	0.043	0.534
Trop I	0.340	<0.001 (S)
CKMB	−0.181	0.018 (NS)
Procalcitonin	0.108	0.202
Serum creatinine	0.240	<0.001 (S)
Mechanical ventilation	0.317	<0.001 (S)
ECHO	0.084	0.222
Blood culture	−0.046	0.560
DM	−0.051	0.458
CLD/CKD	0.157	0.005 (S)
Outcome	−0.140	0.040 (NS)
CRP	0.013	0.786
Albumin	−0.002	0.970
LV systolic dysfunction	0.049	0.384
Blood culture	0.022	0.731

S: Significant, NS: Nonsignificant, ECHO: Echocardiography, DM: Diabetes mellitus, CLD: Chronic liver disease, CKD: Chronic kidney disease, CRP: C-reactive protein, LV: Left ventricular, CKMB: Creatinine kinase-MB

DISCUSSION

BNP or NT-pro BNP 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.[13] BNP increase in patients with sepsis can be considerably high, even in the absence of cardiac pathology,[14] but normal BNP levels can be used to rule out cardiac disorders.[15] High plasma levels of BNPs are associated with poor outcomes of sepsis.[12] As well as, despite initial recovery from critical illness requiring intensive care unit (ICU) admission, many patients remain at risk of subsequent deterioration and death.[16]

Our study was aimed at estimating the role of BNP as a marker of sepsis among adult patients admitted with sepsis and to identify the risk factors which are predictors of short-term mortality as well as duration of hospital stay. The mortality rate was found to be 8.8% in the present study. The present study showed a significant correlation between elevated BNP and sepsis-related mortality ($P = 0.031$). These data are in agreement with those of Baptista *et al*.[17]

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*.[13] The patient population varied across studies: three studies included patients with sepsis and nine studies included patients with severe sepsis or septic shock.[18] These studies were carried out in various departments including the emergency department, medical ICU, surgical ICU, and general ICU.

Spearman's correlation showed concordance between BNP levels and trop I and serum creatinine. However, there was no significant association between BNP levels and CK Mb, urea, albumin, procalcitonin, or CRP [Table 4]. These data are in agreement with those of Baptista *et al*.[17]

Diabetes mellitus, need of MV, NT-pro BNP (>2546), and chronic respiratory disorders were found to be associated with mortality, an observation similar to the Outcomerea study.[19] Neither blood culture positivity nor elevated procalcitonin was found to be significantly related to mortality.

MV was required in 22 (10.2%) of the 215 patients treated for severe sepsis as most of the patients had respiratory failure. Out of 22 ventilated patients, five (22.72%) patients succumbed despite the interventions. The MV was associated with higher mortality as seen in study by Vincent *et al*.[20] This observation was statistically significant implying that undergoing invasive MV could be a predictor of mortality in sepsis. On multivariate logistic regression analysis, invasive MV in patients with severe

sepsis was identified to be an independent predictor of mortality.

In this study, the mean platelet count, CRP, serum bilirubin, or urea were not identified as an independent predictor of mortality. This observation was in discordance with other studies.[7,8] The reason may be lower mortality and low number of patients with severe sepsis in the present study. There was a significant difference in the mean values of serum creatinine among the survivors and nonsurvivors. This was in similar to a study by Oppert e*t al*., who had found renal failure a significant independent risk factor for mortality in patients with sepsis and septic shock.[21]

The secondary outcome of the study was duration of hospital stay. Study showed that elevated NT-pro BNP, need of MV, comorbidities such as DM, CKD, or CLD had a significant correlation with increased duration of hospital stay. This finding was similar to other studies.[11-18]

SUMMARY AND CONCLUSION

There was a statistically significant correlation between NT-pro BNP levels and mortality. The other factors associated with increased mortality were diabetes mellitus and need of MV. In addition to the above factors, the presence of CKD and CLD was associated with increased duration of hospital stay. There was concordance between increased NT-pro BNP and elevated trop I, serum creatinine, need of MV, and CKD.

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Conflicts of interest
There are no conflicts of interest.

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