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# N-Terminal B Natriuretic Peptide as a Prognostic Marker in Sepsis Induced Myocardial Dysfunction

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## Abstract

**BACKGROUND:** Sepsis-induced myocardial dysfunction (SIMD) is an increasingly recognized form of transient cardiac dysfunction in sepsis patients.

**AIM:** The aim of the study was to evaluation of N-terminal pro brain natriuretic peptide (NT-pro BNP) as a predictor of SIMD and poor outcome in patients with sepsis or septic shock.

**METHODS:** Forty patients were enrolled and divided into: Group 1 with sepsis; Group 2 with septic shock. Each group was subdivided according to the presence or absence of cardiomyopathy. Echocardiography, NT-pro BNP - assay on the 1st and 2nd days of admission - were performed.

**RESULTS:** NT-pro BNP level was significant predictor for cardiomyopathy in all case group with 75% sensitivity, 70% specificity (cutoff level >334 pg/ml) on 1st day of admission and 65% sensitivity, and 80% specificity (cutoff level >325 pg/ml) on 2nd day. On subgroup analysis, pro-BNP had 70% sensitivity, 90% specificity; cutoff level >334 pg/ml for prediction of cardiomyopathy in sepsis group and 70% sensitivity and 80% specificity; cutoff level >357pg/ml in septic shock group. Pro-BNP on 2nd day was excellent predictor of mortality in septic shock group with 100% sensitivity and specificity; cutoff level >350 pg/ml.

**CONCLUSION:** N terminal pro-BNP is a good diagnostic and prognostic indicator for cardiomyopathy and mortality in septic patients.

## Introduction

Sepsis, being defined as life threatening organ dysfunction caused by altered host response to infection, is considered one of the preponderant causes of morbidity and mortality worldwide. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction [1]. Patients are at increased risk for irreversible organ failure and a lethal outcome. Sepsis entails a substantial economic burden to the society; hence, early and comprehensive management may significantly improve the outcome [2]. Sepsis induced myocardial dysfunction is a multifaceted pathological condition frequently characterizing severe sepsis and septic shock and incorporates the coexistence of various pathophysiologic alterations such as decreased myocardial contractility; altered myocardial relaxation ability as well as ventriculo-arterial uncoupling [3]. Several studies have reported an average incidence of 40–50% for sepsis induced myocardial dysfunction [4]. Different molecular pathways are possibly implicated in the development of sepsis induced myocardial dysfunction and have been comprehensively investigated including nitric oxide, calcium trafficking, and Toll-like receptor pathways [5]. Circulating cardiac biomarkers have emerged as simple tools for triage, diagnosis, and prognosis of cardiovascular diseases such as acute coronary syndrome and congestive heart failure [6]. Cardiac troponin indicates cardiac myocyte injury and natriuretic peptides are indicators of ventricular wall stress and fluid homeostasis [7]. Plasma levels of cardiac markers commonly reach a peak within 1–2 days post-intensive care admission in survivors with severe sepsis or septic shock [8] and therefore are now increasingly employed in the risk prediction and assessment of outcomes in patients with sepsis. N-terminal of the pro-hormone brain natriuretic peptide (NT-pro BNP) is a marker of myocardial injury. Several studies have confirmed that the level of NT-pro BNP is liable to increase in patients with sepsis [9], [10], [11], [12] and hence alterations in plasma NT-pro BNP levels in patients with sepsis may influence the prognosis of the disease [13], [14]. Moreover, it has been observed that N-terminal pro brain natriuretic peptide (NT-pro) BNP is associated with the left ventricular systolic and diastolic dysfunction together with the right ventricular dysfunction in patients with sepsis induced cardiomyopathy [15]. Many factors, other than impaired myocardial function, have been

implicated for the increased NT-pro BNP levels during sepsis. These include enhanced secretion or decreased inactivation of NT-pro BNP due to the inflammatory response [16], [17], [18], [19]. There has been many conflicting reports regarding the role of NT-pro BNP in determining prognosis and mortality outcomes in patients with sepsis or septic shock and hence further studies are warranted [15].

The aim of the present study was to evaluate the role of NT-pro BNP in diagnosis of sepsis-induced myocardial dysfunction (SIMD) and as a predictor factor for cardiac dysfunction and poor outcome in patients with sepsis or septic shock.

## Methods

This prospective study was conducted on forty patients with a primary diagnosis of sepsis or septic shock, who were admitted to the Intensive Care Units of Kasr El-Ainy Hospital, Faculty of Medicine, Cairo University between the period from June 2019 to June 2020. Patients were randomly recruited after approval by the Research Ethics Committee of Cairo University and an informed consent from the patients or their relatives was attained before enrolment after explaining to them the value of the study. The diagnosis of sepsis was based on suspected or documented infection together with an acute increase in Sequential Organ Failure Assessment (SOFA) score ≥2 according to the International Consensus definitions for sepsis and septic shock (Sepsis-3) [20]. The diagnosis of septic shock was based on the presence of severe sepsis with persisting hypotension (with mean arterial pressure (MAP) of <65 mm Hg) or requiring vasopressor agents after appropriate fluid resuscitation and blood lactate ≥2 mmol/L [20]. Inclusion criteria included age above 18 years, both gender, a presentation of sepsis or septic shock and any source of sepsis (urinary tract infection, chest infection, abdominal sepsis, and wound infection). Patients were excluded if: They were younger than 18 years; pregnant females; known to have cardiac dysfunction whether ischemic or valvular; any regional wall abnormalities on echocardiography; acute pulmonary embolism; chronic renal failure; liver failure; patients referred from other intensive care units with history of any interventional procedure; and patients who were discharged or died before fulfilling all the required investigations for the study.

All the patients were subjected to detailed history and full physical examination including MAP measurement, Glasgow Coma Scale and measurement of daily urine output. Laboratory investigations included kidney function tests (urea, creatinine), serum transaminases, serum albumin, serum bilirubin (total and direct), coagulation profile, complete blood count, arterial blood gases, C-reactive protein, as well as plasma cardiac troponin I were measured.

A bed-side chest X-ray and a base line 12-leads electrocardiogram was performed for all patients. The severity of sepsis was assessed using the SOFA score that allows for calculation of both the number and the severity of organ dysfunction and includes six components (respiratory, nervous, cardiovascular, liver, coagulation, and renal) and assigns a score of 0–4 to each system [21]. Total SOFA Score ranges from 0 to 24. Criteria for sepsis includes a SOFA Score ≥2 (or change in SOFA Score by ≥2 points) where a two point increase is associated with an increased mortality by 20%. Maximum SOFA score: The maximum SOFA score defines the highest daily SOFA score over the period of the study [22]. Regarding mortality rate, according to maximal SOFA score: Score 0–6: mortality <10%; Score 7–9: mortality 15–20%; Score 10–12: Mortality 40–50%; Score 13–14: Mortality 50–60%: Score 15: Mortality >80%; and Score 15–24: Mortality >90% [23].

### *Echocardiography*

Was performed for evaluation of the cardiac condition using two-dimensional and pulsed Doppler echocardiograms at rest with the patient positioned in the left lateral position, to evaluate left ventricular size and left ventricular systolic function. Echo parameters measured included the following: Left ventricular end diastolic diameter, left ventricular end systolic diameter, Ejection fraction (EF%), and Tricuspid annular plane systolic excursion (TAPSE) for evaluation of the right ventricular function. Sepsis-induced cardiomyopathy was considered in sepsis and septic shock patients with left ventricular EF <50% in the absence of regional wall motion abnormalities or valvular lesions. The echocardiographic examination was performed by a single operator with high expertise in this field (greater than 10 years of experience), to avoid inter-observer variability.

### *Cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-pro BNP)*

Was measured by Enzyme–Linked Immunosorbent Assay (Sandwich-ELISA technique) using Human NT-pro BNP kit; Cat no: EL-01129 hu).

### *Sample collection and storage*

Venous blood samples (3 ml) were collected from patients on the 1$^{st}$ and 2$^{nd}$ days of admission using EDTA or heparin containing tubes as an anticoagulant. The samples were centrifuged for 30 min at 2–8°C within 30 min of collection and then stored at –20°C.

### *Assay procedure*

Standard wells and testing sample wells were set and 50 μL standard was added to each standard well. 10 μL of test sample was then added to the testing sample well followed by 40 μL of a sample diluent. 100 μL of HRP-conjugate reagent was added to each well, covered with an adhesive tape and incubated for an hour at a temperature of 37°C. Afterward, the wells were aspirated and washed for a total of 5 washes. Any remaining Wash Solution was removed after the last wash. The plate was then inverted and blotted by a clean paper towel.

An equivalent amount of 50 μL of chromogen solutions A and B were then added to each well, carefully mixed, followed by incubation for quarter an hour at 37°C. 50 μL of a Stop Solution was added to each well. The color change from blue to yellow and the optical density were measured at 450 nm by spectrophotometry within 15 min. Standard curves were plotted and the results calculated.

### *Statistical analysis*

Recorded data were analyzed using the Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-square (x2) test of significance was used to compare proportions between qualitative parameters. The receiver operating characteristic (ROC) curve was used for assessing the predictive value of NT-pro BNP in discriminating between septic patients with and without septic-induced cardiomyopathy and to provide optimum cutoff values. It was also used to determine predictive value of NT-pro BNP for mortality in patients with and without cardiomyopathy. The confidence interval was set to 95% and the margin of error accepted was set to 5%. $p < 0.05$ were considered significant; $p < 0.001$ was considered as highly significant.

## Results

A total of forty patients were enrolled (19% were males and 21% were females). with a mean age of 51.05 ± 14.96 years.

In all, 50% of patients had cardiomyopathy (EF <50%); 60% were mechanically ventilated; 15% had positive troponin; 95% of patients had TAPSE >1.7 cm denoting normal right ventricular function and mortality occurred in 27.5% of patients (non-survivors). The clinical, demographic, and laboratory parameters of all patients are summarized in Table 1.

**Table 1: Demographic and clinical parameters in all-cases group**

| Parameter | All cases (n = 40) n(%) | p value |
|---|---|---|
| Age (Mean ± SD) (years) | 51.05 ± 14.96 | |
| Gender n (%) | | |
| Males | 19 (47.5) | |
| Females | 21 (52.5) | |
| Cardiomyopathy | | |
| Yes | 20 (50) | 1 |
| No | 20 (50) | |
| Troponin | | |
| Positive | 6 (15) | <0.0001* |
| Negative | 34 (85) | |
| TAPSE | | |
| >1.7 cm | 38 (95) | <0.0001* |
| <1.7 cm | 2 (5) | |
| Mechanical Ventilation | | |
| Yes | 24 (60) | 0.2059 |
| No | 16 (40) | |
| Mortality | | |
| Non-Survivors | 11 (27.5) | 0.0044* |
| Survivors | 29 (72.5) | |

TAPSE: Tricuspid annular plane systolic excursion, Cardiomyopathy (was considered when Ejection Fraction <50%); N=Number of patients, %: Percentage; SD: Standard deviation; *p < 0.05 was considered statistically significant.

Patients were divided into two groups: Group 1 patients with sepsis (50%) and Group 2 patients with septic shock (50%). Each group was further subdivided according to presence or absence of cardiomyopathy. Patients with cardiomyopathy exhibited significantly increased mean SOFA scores ($p = 0.006$), increased mean NT-pro BNP levels on first ($p = 0.005$) and 2nd days ($p = 0.037$) of admission as well as increased mean left ventricular end-systolic diameter (LVESD) (<0.001) compared to those without cardiomyopathy (Table 2).

**Table 2: Association between prognostic factors and the presence or absence of cardiomyopathy in all- cases group (n = 40)**

| Prognostic parameter | With cardiomyopathy (n = 20) | Without cardiomyopathy (n = 20) | p value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| NT-pro BNP (1st day) (pg/ml)† | 374.5 ± 69.88 | 312.15 ± 61.43 | 0.005* |
| NT-pro BNP (2nd day)(pg/ml)† | 359.15 ± 112.17 | 285.70 ± 102.54 | 0.037* |
| LVED (mmHg)† | 5.25 ± 0.33 | 5.09 ± 0.30 | 0.115 |
| LVESD (cm)† | 3.99 ± 0.31 | 3.17 ± 0.28 | <0.001* |
| SOFA score† | 8.35 ± 1.34 | 6.85 ± 1.87 | 0.006* |
| ICU stay (days)† | 9.95 ± 4.04 | 9.30 ± 5.38 | 0.668 |

*p < 0.05 is considered statistically significant; Cardiomyopathy (was considered when Ejection Fraction < 50%) LVED: Left ventricular end-diastolic pressure, LVESD: Left ventricular end-systolic diameter, SOFA: Sequential Organ Failure Assessment score, N=Number of patients .Comparison between patients with sepsis-induced cardiomyopathy and those without, was performed by t-test†.

Using the $\chi^2$ test no significant association was found between incidence of cardiomyopathy and the source of sepsis within the studied groups. Furthermore, no statistically significant relation was observed between the mean ICU stay and the NT-pro BNP levels.

### *In all cases group*

When evaluating the relationship between the prognostic parameters and the incidence of mortality, non-survivors showed a significantly greater mean SOFA score compared to survivors (9.27 vs. 6.97 respectively $p < 0.001$) as well as higher mean NT-pro BNP levels on the 1st day (387.73 pg/ml vs. 326.48 pg/ml; $p = 0.015$), higher NT-pro BNP levels on 2nd day of admission(450.64 vs. 273.79 pg/ml,

respectively; p < 0.001) and greater LVESD (3.88 cm vs. 3.47 cm respectively; p = 0.021) (Table 3). Moreover, there was a statistically significant association between the incidence of cardiomyopathy and mortality as 81.8% of non-survivors had cardiomyopathy while 37.9% of survived patients had cardiomyopathy (p = 0.014). There was also a significant association between a TAPSE <1.7 cm and incidence of mortality (Table 3).

**Table 3: Association between prognostic factors and mortality outcome in all – cases group (n = 40)**

| Prognostic parameter | Non-survivors (n = 11/40) | Survivors (n = 29/40) | p value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| NT-pro BNP (1st day) (pg/ml)† | 387.73 ± 80.66 | 326.48 ± 62.22 | 0.015* |
| NT-pro BNP (2nd day) (pg/ml)† | 450.64 ± 103.50 | 273.79 ± 69.75 | <0.001* |
| LVED (mmHg)† | 5.24 ± 0.32 | 5.14 ± 0.33 | 0.423 |
| LVESD (cm)† | 3.88 ± 0.57 | 3.47 ± 0.44 | 0.021* |
| SOFA score† | 9.27 ± 1.79 | 6.97 ± 1.32 | <0.001* |
| ICU stay (days)† | 9 ± 4.87 | 9.86 ± 4.71 | 0.612 |
| Cardiomyopathy (EF <50%)** | 9 (81.8%) | 11 (37.9%) | 0.0144* |
| TAPSE <1.7 cm** | 2 (18.2%) | 0 (0%) | 0.020* |

*p < 0.05 is considered statistically significant, N=Number of patients, LVED: Left ventricular end-diastolic pressure, LVESD: Left ventricular end-systolic diameter, SOFA: Sequential Organ Failure Assessment score, TAPSE: Tricuspid annular plane systolic excursion, Cardiomyopathy and TAPSE values were expressed in number and percentage and comparison of those two parameters between the two groups was done using Fisher's exact test*; Comparison between survivors and non-survivors regarding the other parameters was performed by t-test†.

NT-pro BNP levels performed on the 1st day of admission was a significant predictor for cardiomyopathy on ROC curve analysis with a sensitivity of 75%, specificity of 70% with a cutoff level >334 pg/ml (AUC = 0.755; p < 0.05). NT-pro BNP done on the 2nd day was also a significant predictor for cardiomyopathy with a sensitivity of 65%, specificity 80% and a cutoff level >325 pg/ml (AUC = 0.708; p < 0.05) (Figure 1).

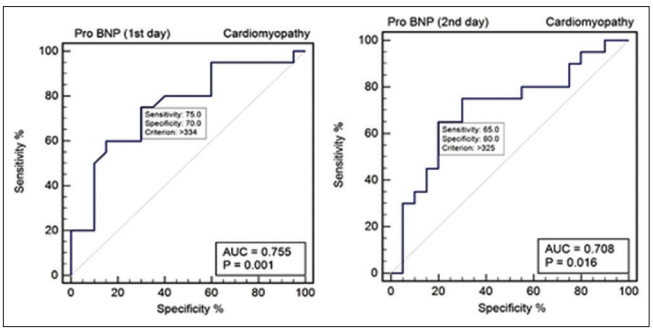


*Figure 1: ROC curve analysis to determine the predictive value of mean NT-pro BNP for cardiomyopathy on the first and second days of admission in all-cases group*

Furthermore, NT-pro BNP on the 1st day was a significant predictor for mortality with a sensitivity of 63.64%, specificity 82.76% and a cutoff level >370pg/ml (AUC = 0.727; p < 0.030). NT-pro BNP on the 2nd day showed a greater sensitivity and specificity (90.91% and 89.66%, respectively) for prediction of mortality within all the studied groups with a cutoff level >350pg/ml (AUC = 0.931; p < 0.001) (Figure 2).

### *Sepsis group*

There was a significant association between the mean age of patients (56.2 ± 10.33 years) as well as the mean NT-pro BNP levels on the 1st day (354.60 ± 65.34 pg/ml) and the presence of cardiomyopathy in

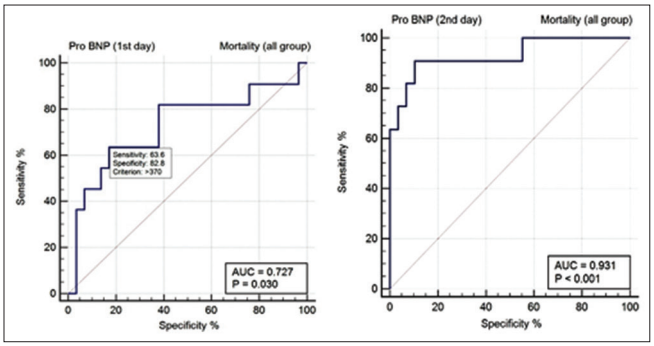


*Figure 2: ROC curve analysis to determine the value of mean NT-pro BNP on the first (left image) and second days (right image) of admission in predicting mortality in all-cases group*

the sepsis group (p < 0.05). However, the mean NT-pro BNP levels on the 2nd day did not differ significantly between patients with sepsis who had cardiomyopathy and those without cardiomyopathy.

Among patients in the sepsis group, the mean NT-pro BNP levels decreased on the 2nd day of admission in survivors (272.75 ± 78.35 pg/ml) but increased significantly in non-survivors (407.50 ± 113.54 pg/ml) and these changes were statistically significant (p = 0.011). Moreover, non-survivors showed a significantly greater mean LVESD compared to survivors (4.07 ± 0.37 cm vs. 3.46 ± 0.47 cm respectively, p = 0.029).

The mean NT-pro BNP level on the 1st day was a significant predictor for cardiomyopathy in the sepsis group on ROC curve analysis with a sensitivity of 70% and a specificity of 90%, with a cutoff level >334 pg/ml (AUC = 0.785; p = 0.014) (Figure 3). Conversely, the mean NT-pro BNP level on the 2nd day was a non-significant predictor for incidence of cardiomyopathy in the sepsis group (p = 0.092) (Figure 3), yet was found to be a significant predictor for mortality in the sepsis group on ROC curve analysis with a sensitivity and a specificity of 75% and 93.75%, respectively, with a cutoff level >380 pg/ml (AUC 0.875; p < 0.001).

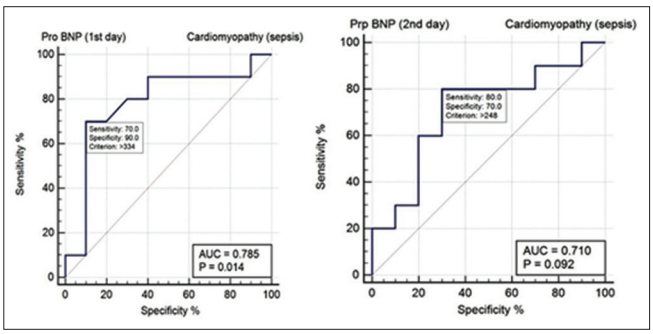


*Figure 3: ROC curve analysis to determine the predictive value of mean NT-pro BNP for cardiomyopathy on the first (left image) and second days (right image) of admission in the Sepsis group*

When considering the prognostic factors in the sepsis group, patients with cardiomyopathy exhibited a significantly greater mean SOFA score compared to patients without cardiomyopathy (9.90 vs. 4.91, respectively; p < 0.001) as well as an increased mean

LVESD (3.99 vs. 3.18 cm, respectively; p < 0.001) (Table 4). There was non-significant association between incidence of cardiomyopathy and source of sepsis or troponin levels in the sepsis group (p > 0.05). There was, however, a significantly greater need for mechanical ventilation (p = 0.0076) and increased mortality in patients with cardiomyopathy in the sepsis group (p = 0.029) (Table 4).

Evaluation of changes in NT–pro BNP levels according to cardiomyopathy in sepsis group, revealed that 7/20 sepsis patients experienced a rise in NT-pro BNP levels on 2nd day of admission whereas 13/20 patients showing a decline in plasma levels on the 2nd day. These alterations in the NT-pro BNP levels on the 2nd day were not statistically significant between patients with cardiomyopathy and those without cardiomyopathy within the sepsis group.

### *Septic shock group*

The mean NT-pro BNP level on the 1st day of admission was significantly higher in septic shock patients with cardiomyopathy as compared to patients without cardiomyopathy (396.40 ± 71.84 pg/ml vs. 338.10 ± 48.47 pg/ml, respectively; p = 0.045). On the 2nd day of admission, patients with cardiomyopathy showed higher mean NT-pro BNP level compared to those without cardiomyopathy; however, these differences were not statistically significant (380.10 ± 119.14 pg/ml vs. 310.20 ± 120.68 pg/ml; p = 0.209) (Table 4).

Comparison between patients with and without cardiomyopathy in the septic shock group revealed no significant differences in the mean age, SOFA score, mean LVED or ICU stay, but patients with cardiomyopathy demonstrated a significant increase in LVESD compared to those without cardiomyopathy (4 ± 0.30 cm vs. 3.17 ± 0.30 cm, respectively; p < 0.001) (Table 4). No significant association was found between the incidence of cardiomyopathy and prognostic factors in septic shock group such as source of sepsis, troponin levels, TAPSE, need for mechanical ventilation or mortality (Table 4).

Plasma NT-pro BNP levels on 1st day of admission were non-significantly higher in non-survivors of septic shock compared to survivors. On the 2nd day of admission, the BNP levels increased in non-survivors (475.29 ± 97.26 pg/ml), whereas decreased in survivors (275.08 ± 60.63 pg/ml) of septic shock but mean NT-pro BNP level still remained higher among non-survivors and this difference was statistically significant(p < 0.001). The mean SOFA score was also significantly greater among non-survivors of septic shock compared to survivors (11.4 ± 1.82 vs. 7.38 ± 1.19, respectively; p = 0.001).

On ROC curve analysis, NT- pro BNP on the 1st day was found to be a significant predictor for cardiomyopathy in the septic shock group with a sensitivity and specificity of 70% and 80%, respectively, and a cutoff level >357pg/ml (AUC = 0.745; p = 0.04) (Figure 4).

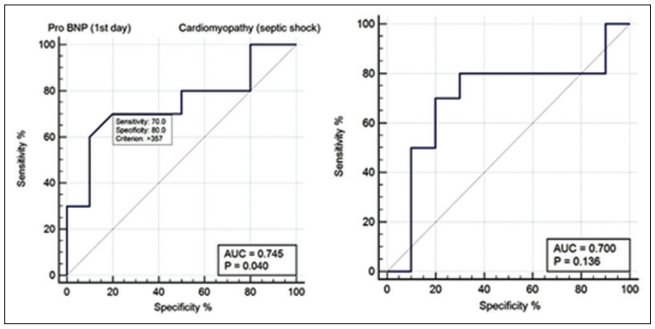


*Figure 4: ROC curve analysis to determine the predictive value of mean NT-pro BNP for cardiomyopathy on the first (left image) and second days (right image) of admission in septic shock group*

Pro-BNP on the 2nd day was an excellent predictor for mortality in septic shock group on ROC

**Table 4: Comparison of clinical, laboratory and prognostic parameters between Sepsis group and Septic shock group**

| Parameter | Sepsis group (n = 20) | | p value | Septic shock group (n = 20) | | p value |
|---|---|---|---|---|---|---|
| | With cardiomyopathy | Without cardiomyopathy | | With cardiomyopathy | Without cardiomyopathy | |
| | Mean ± SD | Mean ± SD | | Mean ± SD | Mean ± SD | |
| Age (years) | 56.2 ± 10.33 | 45.6 ± 19.21 | 0.001* | 56.70 ± 14.32 | 45.70 ± 12.63 | 0.085 |
| NT-pro BNP (1st day) (pg/ml) | 354.60 ± 65.34 | 286.20 ± 64.20 | 0.030* | 396.40 ± 71.84 | 338.10 ± 48.47 | 0.045* |
| NT-proBNP (2nd day) (pg/ml) | 338.20 ± 106.73 | 261.20 ± 79.37 | 0.084 | 380.10 ± 119.14 | 310.20 ± 120.68 | 0.209 |
| SOFA score | 9.90 ± 0.73 | 4.91 ± 1.10 | <0.001* | 10.8 ± 1.68 | 9.80 ± 2.04 | 0.248 |
| LVED (mmHg) | 5.23 ± 0.14 | 5.01 ± 0.37 | 0.102 | 5.27 ± 0.46 | 5.16 ± 0.21 | 0.508 |
| LVESD (cm) | 3.99 ± 0.33 | 3.18 ± 0.28 | <0.001* | 4 ± 0.30 | 3.17 ± 0.30 | <0.001* |
| Troponin | | | | | | |
| Positive (%) | 30% | 0% | 0.0671 | 20% | 10% | 0.5416 |
| Negative (%) | 70% | 100% | | 80% | 90% | |
| ICU stay (days) | 10.50 ± 3.77 | 7.30 ± 3.36 | 0.061 | 9.40 ± 4.42 | 11.30 ± 6.39 | 0.450 |
| Mechanical ventilation | | | | | | |
| Yes (%) | 30% | 90% | 0.0076 | 90% | 70% | 0.2758 |
| No (%) | 70% | 10% | | 10% | 30% | |
| Mortality | | | | | | |
| Non-survivors (%) | 40% | 0% | 0.0293* | 50% | 20% | 0.1704 |
| Survivors (%) | 60% | 100% | | 50% | 80% | |
| Source of sepsis | | | | | | |
| Abdominal abscess (%) | 40% | 30% | 0.9241 | 40% | 70% | 0.3065 |
| Diabetic foot (%) | 10% | 20% | | 0% | 10% | |
| Pneumonia (%) | 40% | 40% | | 30% | 10% | |
| UTI (%) | 10% | 10% | | 20% | 0% | |
| CNS infection (%) | 0% | 0% | | 10% | 10% | |

*p < 0.05 is considered statistically significant; LVED: Left ventricular end-diastolic pressure; LVESD: Left ventricular end-systolic diameter; SOFA: Sequential Organ Failure Assessment score. N=Number of patients; %:percentage; SD: standard deviation. Comparison between patients with sepsis-induced cardiomyopathy and those without, was performed by t-test.

curve analysis with sensitivity and specificity of 100% and a cutoff level >350 pg/ml (AUC = 1; p < 0.0001). However, the NT pro-BNP on 1st day of admission was a non-significant predictor of mortality.

## Discussion

Previous studies have demonstrated that plasma BNP and NT-pro BNP levels are commonly raised in patients with sepsis and septic shock and can dependably distinguish patients developing sepsis-induced cardiac dysfunction [24], [25]. The rise in BNP levels in patients with sepsis may be attributable to various factors including ventricular dilatation induced by sepsis, augmented release of pro-inflammatory cytokines [26], increased lipopolysaccharides, acute renal insufficiency and decreased clearance [27], sepsis-induced acute lung injury [28], and the consumption of vasopressor agents and fluid resuscitation [29].

The role of BNP and NT-pro BNP as a predictor for mortality in patients with sepsis has been analyzed in various prospective studies and meta-analyses with marked heterogeneity in sensitivity, specificity, and cutoff values. Despite that BNP has been considered as a prognostic marker and has been integrated in the risk assessment of patients with congestive heart failure, pulmonary embolism, and coronary syndromes, the role of BNP and NT-pro-BNP as a tool for prognosis and risk-stratification of patients with sepsis and septic shock is still a matter of debate. In the present study, patients with cardiomyopathy exhibited significantly increased mean NT-pro BNP levels on the 1st and 2nd days of admission (p values 0.005 and 0.037, respectively). On subgroup analysis, patients in the sepsis group and septic shock group showed a significant association between the mean NT-pro BNP levels on the 1st day (354.60 ± 65.34 pg/ml and 396.40 ± 71.84 pg/ml, respectively) and the presence of cardiomyopathy (p < 0.05). Conversely, the mean NT-pro BNP levels on the 2nd day did not differ significantly between patients with cardiomyopathy and those without cardiomyopathy in the sepsis and septic shock groups, although levels were higher in those with cardiomyopathy.

This agrees with a study by Charpentier *et al*. [16] that evaluated the relation between plasma BNP levels and left ventricular dysfunction in patients with severe sepsis and septic shock. It revealed that patients with the left ventricular EF <50% and higher end-systolic left ventricular diameter had higher BNP levels on the 2nd day of ICU admission compared to those without cardiac dysfunction. Another study by Post *et al*. [30]. demonstrated an increase in plasma BNP levels in patients with sepsis particularly at days 3 and 5 of ICU admission and this was accompanied with worsening of the left ventricular EF while declining levels correlated with its improvement. A study by Klouche *et al*. [8] similarly showed that from the time of admission to day 5, patients with sepsis and septic shock who had septic-induced myocardial dysfunction displayed higher BNP levels compared to those without and the differences were particularly significant on days 3 and 4. SIMD is probably linked to the combined effect of circulating factors - causing myocardial depression - like tumor necrosis factor - $\alpha$ and interleukin- 1$\beta$, which may be mediated by mechanisms involving the release of cyclic GMP and nitric oxide [31]. The exact cause of cardiac dysfunction with severe sepsis and septic shock, however, still remains to be elucidated.

Groeneveld and Trof [32] also reported that elevated NT-pro BNP levels in septic shock patients reflected left ventricular systolic dysfunction and were linked to poor outcomes. They also affirmed the potential role of NT-pro-BNP in the early recognition and management of cardiac dysfunction induced by shock particularly when invasive hemodynamic monitoring is deferred. A cohort study on 51 cancer patients with septic shock also found a significant correlation between NT-pro BNP levels on day 2 of admission and the development of left ventricular systolic dysfunction demonstrable on echocardiography [33].

A study by Jeong *et al*. [34] conducted on 25 patients with sepsis or septic shock with SIMD and 27 patients with stress-induced cardiac dysfunction, revealed that NT-pro BNP levels were significantly more elevated in SIMD group. Furthermore, a study by Hartemink *et al*. [35] evaluating the role of NT-pro-BNP as a marker of cardiac load in septic and non-septic critically ill patients, established that increased plasma NT-pro BNP level is an independent indicator of pronounced cardiac systolic dysfunction irrespective of filling status in patients with sepsis.

On the contrary, other studies demonstrated elevations in BNP levels occurred in patients with severe sepsis and septic shock irrespective of the presence or absence of the left ventricular systolic dysfunction [27], [36], [37], [38], [39], [40].

In the present study, patients in the sepsis group with cardiomyopathy exhibited a significantly greater mean SOFA score (p < 0.001), an increased mean LVESD (p < 0.001), a significantly greater need for mechanical ventilation (p = 0.0076) and increased mortality (p = 0.029) compared to those without cardiomyopathy. When considering the septic shock group, mortality was higher among patients with cardiomyopathy compared to those without (71.5% vs. 28.6%, respectively) but these differences were not significant (p = 0.1704). This is in accordance with the study by Klouche *et al*. [8] that showed a non-significant higher mortality among patients with sepsis and septic shock who had cardiac dysfunction compared to those without (p = 0.7). Another study evaluating left ventricular function in fifty patients with sepsis or septic shock using the systolic excursion (Mitral annular

plane systolic excursion) and correlating it to SOFA severity score showed that combining both parameters provided a better predictive value for mortality [41]. One of the important findings in the current study is that NT-pro BNP level performed on the first and 2nd days of admission in all patients had a significant predictive value for sepsis-induced cardiomyopathy on ROC curve analysis with a sensitivity of 75%, specificity of 70% and a cutoff level >334 pg/ml (AUC = 0.755; $p < 0.05$). On the 1st day and a sensitivity 65%, specificity 80% with a cutoff level >325 pg/ml (AUC = 0.708; $p < 0.05$) on the 2nd day.

On subgroup analysis, however, NT - pro BNP on the 1st day only was found to be a significant predictor for cardiomyopathy in the sepsis group and septic shock group with a 70% sensitivity and 90% specificity (AUC = 0.785; p = 0.014) and best cutoff level >334 pg/ml for the sepsis group and a sensitivity and specificity of 70% and 80%, respectively, for septic shock group with a cutoff level >357pg/ml (AUC = 0.745; p = 0.04). Our results were in concordance with a study by Ikonommidis *et al*. [42] evaluating the diagnostic utility of pro-BNP in discriminating between septic patients with the left ventricular diastolic dysfunction and those without cardiac dysfunction and revealed a best cutoff value >941 pg/ml for pro-BNP with a comparable sensitivity of 73%, but reported a lower specificity of 70%. On the contrary, a study by Fayed *et al.* [43] demonstrated that pro-BNP with a cutoff level >2900 pg/ml had a poor diagnostic accuracy on ROC curve analysis (AUC:0.563; p: 0.603) in differentiating between patients with severe sepsis and septic shock who had cardiac dysfunction and those with normal cardiac function. Regarding the relation between NT-pro BNP and mortality in septic patients in the present study, NT-pro BNP level on the 2nd day of admission was found to be a significant predictor for mortality in the sepsis group on ROC curve analysis with sensitivity and specificity of 75% and 93.75%, respectively and a cutoff level >380 pg/ml (AUC 0.875; $p < 0.001$). Moreover, pro-BNP on the 2nd day was an excellent predictor for mortality in septic shock group with sensitivity and specificity of 100% and cutoff level >350 pg/ml (AUC = 1; $p < 0.0001$). However, the NT pro-BNP on 1st day of admission was a non-significant predictor of mortality.

The results of our study are in accordance with a study by Cheng *et al*. [44] who confirmed the association between elevated NT-pro BNP levels and disease severity in patients with severe sepsis or septic shock, with more elevated levels being observed in non-survivors compared to survivors. A study by Wang *et al*. [12] performed on 38 patients with sepsis also revealed significantly higher NT-pro BNP levels in the non-survival group compared with the survival group on days 1, 3, and 7 of admission ($p < 0.05$). In addition, a multi-center observational study by Masson *et al*. [45] studied 995 patients with severe sepsis or septic shock and demonstrated that plasma level of NT-pro BNP performed on day 1, 2 and day 7 had a prognostic value in predicting in-hospital and 90-day mortality. The previous studies have evaluated the prognostic role of BNP and NT-pro BNP in patients with severe sepsis and septic shock and attempted to determine optimum cutoff values, sensitivity and specificity in predicting mortality but results have been conflicting. In a study by Charpentier *et al*. [16] patients with sepsis and septic shock who had plasma BNP levels greater than 190 pg/ml had a five-fold increased risk of death within 30 days of ICU admission. Chen and Li [46] established that BNP with a cutoff level 113 pg/ml was an independent predictor for mortality in patients with sepsis. Likewise, a study by Varpula *et al*. [47] confirmed that NT-pro BNP measured at admission and at day 3 (72 h from admission) was an independent marker of mortality with higher median levels reported among non-survivors compared to survivors. Furthermore, a study conducted on 52 patients with severe sepsis reported that a cut-off value for NT-pro BNP as high as 1400 pg/ml on day 2 of admission was accompanied with a 3.9 times greater risk of mortality [48]. A higher NT-pro BNP cutoff value >6624 pg/ml was, however, reported in a study by Mokart *et al*. [31] to be a good predictor of mortality on day 2 of admission in cancer patients developing sepsis.

A meta-analysis of 35 observational studies [49] that included 3508 patients reported elevated BNP and NT-pro BNP in patients with sepsis and septic shock and confirmed its prognostic value with optimum cutoff values of 622 pg/ml (AUC: 0.766; 95% CI: 0.734–0.797; 69.5% sensitivity and 90.7% specificity) and 4000 pg/ml (AUC: 0.787; 95% CI: 0.766–0.809; 72.8% sensitivity and 78.9% specificity), respectively, for predicting short-term in-hospital mortality. The importance of timing of BNP measurement was also emphasized in the latter meta-analysis, as on subgroup analyses, the BNP and NT-pro BNP level had a better discriminating ability for mortality if the measurements were made within 24 h of admission [49]. The prognostic utility of serial measurement of BNP and NT-pro BNP in prediction of mortality in patients with severe sepsis and septic shock has been highlighted in the study by Papanikolou *et al*. [40] who affirmed that a persistent elevation of BNP >500 pg/ml provided better prediction of 28-day mortality when compared to a single time measurement (AUC:0.704; 95% CI:0.55–0.93;p = 0.03). Likewise, studies by Klouche *et al*. [8] and Guarrici *et al*. [50] established that alteration in BNP levels between baseline and at 72 h of admission significantly correlated with 28-day mortality and that improvement in plasma levels of BNP on serial monitoring during hospital stay was associated with improved survival.

It is worthy of mention that sepsis-induced left ventricular dysfunction as shown by a reduction in EF in the first 3 days (72 h) of admission may be unmasked by appropriate fluid replacement and restoration

of hemodynamics and hence necessitating serial monitoring of NT-pro BNP levels for better prediction of mortality [51]. Moreover, a study by Khoury *et al*. [52] reported that plasma BNP level assessed at admission was a better predictor of short-term in-hospital mortality compared to SOFA severity score in patients with sepsis. On the other hand, the previous studies suggested that BNP combined with the SOFA severity score allowed better risk stratification and prediction of in-hospital mortality in patients with sepsis and septic shock, rather than employing either method on its own [30], [46], [53]. On the contrary, a number of studies did not reveal a correlation between raised circulating BNP levels and mortality in patients with sepsis. Mclean *et al*. [38] concluded that BNP levels at ICU admission and changes during hospital stay did not have predictive value for in-hospital mortality in patients with sepsis and septic shock. Likewise, a study by Cuthbertson *et al*. [36] demonstrated that BNP levels had no prognostic significance regarding mortality outcome, although levels were significantly elevated in patients with sepsis and septic shock. The discrepancy in results among studies may be attributed to various factors including: different clinical settings of sepsis, sample size, type of assay employed, the timing and frequency of BNP measurement as well as confounding factors such as volume status, timing of fluid resuscitation, use of vasopressors, and pre-existing renal or cardiac disease which may have varied significantly among the different studies. Regarding the association of cardiac troponin to sepsis-induced cardiac dysfunction, no association was observed in the present study as there was a statistically insignificant elevation in cardiac troponin level in sepsis and septic shock patients with cardiomyopathy as compared to those without cardiomyopathy. The elevation in troponin levels with sepsis could be probably explained by the disturbance in the microcirculation induced by sepsis and direct effect of inflammatory cytokines, bacterial endotoxins, and reactive oxygen radicals resulting in myocardial cell injury and a consequent release of cardiac troponin into the circulation [12], [16]. The exact mechanism, however, is not yet fully elucidated. Various studies have evaluated the correlation between cardiac troponin levels and sepsis-induced cardiac dysfunction but the results have been conflicting. A cohort study on sepsis patients by Rosjo *et al*. [54] demonstrated that highly sensitive cardiac troponin levels were indicative of myocardial cell injury but were not reliable predictors of SIMD or mortality outcome. Likewise, a study by Klouche *et al*. [8] reported only a transient and significant elevation in cardiac troponin levels on admission in non-survivors of sepsis; however, there was a comparable decline in troponin levels between non-survivors and survivors of sepsis. On the other hand, Wang *et al*. [12] confirmed a significant association between cardiac troponin levels and prognosis in patients with sepsis, as levels was significantly greater in non-survivors compared to survivors.

Some of the limitations of our study were: The relatively small sample size and hence larger prospective studies are required to validate our results; secondly, coronary angiography was not performed to exclude coronary artery disease or stenosis which may have contributed to elevation in cardiac troponin levels in patients with sepsis. Furthermore, the echocardiographic parameters employed in the present study to diagnose right or left ventricular dysfunction were quite limited, so in future more parameters could be included for better diagnostic yield and accuracy.

## Conclusion

N terminal pro-BNP is readily available, non-expensive and has the potential to identify septic patients with imminent cardiovascular compromise and those at high risk for mortality and hence may assist in the clinical management of cardiac dysfunction or failure in patients with sepsis or septic shock. Further studies integrating these cardiac biomarkers and other clinical data into a structured assessment of myocardial dysfunction are needed to better define the role of BNP and NT pro-BNP in sepsis.

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