Abstract

N-terminal pro-B-type natriuretic peptide, C - reactive protein and albumin as prognostic markers in severe sepsis and septic shock

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Objective: N-terminal pro-BNP (NTproBNP) could be useful to predict outcome in severe sepsis and septic shock. We have conducted a study to evaluate NTproBNP, CRP and serum albumin levels in the setting of severe sepsis or septic shock.

Methodology: Fifty patients with severe sepsis or septic shock were involved in a prospective randomized clinical study (mean age was 49.6 ± 17.7 yrs, 64% female), were divided into 2 groups according to mortality and were subjected to assessment by scoring system (APACHE II & SOFA), laboratory measurement of the mentioned sepsis biomarkers (NT-proBNP, CRP & serum albumin) on day of ICU admission & two-dimensional transthoracic echocardiography (TTE).

Results: Mortality rate was 38%, SOFA score in non survivors was significantly elevated (9.7±2.8 vs 6.5±2.6, p value: <0.001). APACHEII score in non survivors was significantly elevated (26.3±6.0 vs 17.9±4.5 .p value: <0.001). Sepsis biomarkers (NT-proBNP, CRP and Albumin levels) were found to be elevated on ICU admission. NTBNP level had a mean value of 3798.9 ± 2347.5 pg/ml, serum CRP had a mean value of 53.2 ± 33.2 mg/dl and serum albumin had a mean value of 2.7 ± 0.6 g/dl. NT-proBNP level in non survivors was significantly elevated (4619.6 ± 2118.1 vs 2328.2 ± 2061.0 pg/ml, p value: <0.001), CRP level in non survivors was significantly elevated (67.3±32.0 vs 44.5±31.3 mg/dl, p value: 0.02) and serum level of albumin in non survivors was significantly elevated (2.4±0.5 vs 2.9±0.6 g/dl, p value: 0.002). There were significant strong positive correlations between serum NTPNB levels with both APACHEII score (r. 0.74 & p. <0.001) and SOFA score (r. 0.62 & p. 0.00).There were significant strong positive correlation between serum NTPNB levels with serum CRP levels (r. 0.52 & p.

<0.001) and significant weak negative correlation with albumin level (r. -0.28 & p. 0.05). NTproBNP had a cutoff point of 3045.0 pg/ml where AUC was 0.85, P; <0.001, sensitivity 89.5 %, specificity 77.4 %. CRP had a cutoff point of 36.0 mg/dl where AUC was 0.69, P; 0.027, sensitivity 78.9 % & specificity 48.4 %. Albumin had a cutoff point 2.85 mg/dl where AUC was 0.73, P; 0.007, sensitivity 73.7% & specificity 51.6 %.

Conclusions: NT-proBNP values are frequently increased in severe sepsis and septic shock. Values are significantly higher in nonsurvivors than survivors. NT-proBNP on admission day in the intensive care unit is an independent prognostic marker of mortality in severe sepsis.

Key words: severe sepsis, septic shock, mortality, NT-proBNP, CRP, Albumin

Introduction:

The diagnosis of sepsis and evaluation of its severity are complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis. (1) However, the early diagnosis and stratification of the severity of sepsis are very important, increasing the possibility of starting timely and specific treatment. Biomarkers can have an important place in this process and their use in the intensive care setting is gaining increasing popularity. (2) Amino-terminal pro-BNP (NT-proBNP) is a promising cardiac biomarker that has recently been shown to be of diagnostic value in decompensated heart failure, acute coronary syndromes and other conditions resulting in myocardial stretch and volume overload. The diagnostic and prognostic use of natriuretic peptides in the intensive care setting for patients with various forms of shock could be an attractive alternative as noninvasive markers of cardiac dysfunction that could obviate the need for invasive monitoring such as pulmonary artery catheterization in some patients. (3) C-reactive protein is thought to represent a measure of cytokine-induced protein synthesis. The relatively short half-life of approximately 19 hours makes it a useful monitor for follow-up of inflammatory response, infection and antibiotic treatment. In addition, laboratory tests for CRP are easily available and less costly than cytokine tests. (4) Low

serum albumin levels have been correlated with increased mortality and poor clinical outcomes in hospitalized patients. [5] The test is intended to be simple, cheap and applicable to all critically ill patients. [6]

Methods:

We have studied 50 patients who had severe sepsis or septic shock prospectively over a period of 1 1/2 year. Patients' data was collected from the Critical Care Unit at Kasr El-Aini Hospital, Cairo University and from intensive care unit, New General Hospital, Ministry Of Health, Mansoura. We included in our study patients who were admitted to the ICU for at least 24 hours with APACHE II score more than 12 calculated on admission, had presumptive source of infection suspected by the treating clinician with at least 2 of 4 criteria for the systemic inflammatory response syndrome (temperature > 38^{o}C or < 36^{o} C, HR> 90 bpm, RR > 20/min with PaCo2 < 32 mmHg, TLC > 12000/dL or < 4000 /dL or > 10% staff cells), and with either hypotension (a decrease in systolic blood pressure <90 mm Hg, a mean arterial pressure <60 mm Hg, or a reduction of >40 mm Hg from baseline) or a lactate level of at least 4 mmol/L. We excluded from our study, all patients with acute coronary syndrome, acute pulmonary edema at admission, chronic hemodialysis, pregnancy, cardiac dysrhythmia (as a primary diagnosis) or congestive heart failure. All patients were subjected to history taking and clinical examination, vital signs and hemodynamics,Laboratory investigations including routine laboratory tests and Labs specific for our study on ICU admission (NT-ProBNP, CRP& Albumin) , assessment of disease severity by APACHEII and SOFA scores. Two-dimensional transthoracic echocardiography was done and the following parameters were measured: LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), LV ejection fraction (LVEF) & fraction shortening (FS). The patients were divided to 2 groups according to the mortality outcome, Group I (survivors, 31 patients) and group II (non survivors, 19 patients).

Biochemical assay:

1. NTProBNP: freshly collected heparinated blood sample was centrifuged within one hour& stored at -70^{o}. NTproBNP assay was done using Biomedica Slovakia kits. The procedure was done by ELISA technique. N=99±20 fmol/l (1 fmol/l =8.475 pg/ml).

2. CRP: freshly collected blood sample was centrifuged within one hour & stored at – 70^{o} (serum sample). The procedure was done by ELISA technique. N <1.0 mg/l.

Statistical Methods:

The data were coded & entered using the statistical package SPSS 15. The data were tabulated then analyzed using descriptive statistics: mean, standard deviation, minimal and maximum values for quantitative variables and number and percentage for qualitative values. Statistical differences between groups were tested using Chi Square test for qualitative variables, independent sample t test for quantitative normally distributed variables while Nonparametric Mann Whitney test was used for quantitative variables which aren't normally distributed. Correlations were done to test for linear relations between variables. Discrimination between hospital survivors and non-survivors was evaluated by receiver operating characteristic (ROC) curve analysis. Kaplan-Meier survival analysis was done and Log Rank test was used to test for equality of survival distributions among different levels of independent variables. P. values less than or equal to 0.05 were considered statistically significant.

Results:

Mortality rate was 38%. SOFA score in non survivors was significantly elevated (9.7±2.8 vs 6.5±2.6, p value: <0.001). APACHEII score in non survivors was significantly elevated (26.3±6.0 vs 17.9±4.5 .p value: <0.001). Sepsis biomarkers (NT-proBNP, CRP and Albumin levels) were found to be elevated on ICU admission. NTBNP level had a mean value of 3798.9 ± 2347.5 pg/ml, serum CRP had a mean value of 53.2 ± 33.2 mg/dl and serum albumin had a mean value of 2.7 ± 0.6 g/dl. NT-proBNP level in

non survivors was significantly elevated (4619.6 ± 2118.1 vs 2328.2 ± 2061.0 pg/ml, p value: <0.001), CRP level in non survivors was significantly elevated (67.3±32.0 vs 44.5±31.3 mg/dl, p value: 0.02) and serum level of albumin in non survivors was significantly elevated (2.4±0.5 vs 2.9±0.6 g/dl, p value: 0.002). There were significant strong positive correlation between serum NTPNB levels with both APACHEII score (r. 0.74 & p. <0.001) and SOFA score (r. 0.62 & p. 0.00).There were significant strong positive correlation between serum NTPNB levels with serum CRP levels (r. 0.52 & p. <0.001) and significant weak negative correlation with albumin level (r. -0.28 & p. 0.05). NTproBNP had a cutoff point of 3045.0 pg/ml where AUC was 0.85, P; <0.001, sensitivity 89.5 %, specificity 77.4 %. CRP had a cutoff point of 36.0 mg/dl where AUC was 0.69, P; 0.027, sensitivity 78.9 % & specificity 48.4 %. Albumin had a cutoff point 2.85 mg/dl where AUC was 0.73, P; 0.007, sensitivity 73.7% & specificity 51.6 %. LVEDD was more dilated in nonsurvivors but no statistically significant difference (5.2 ± 0.9 &4.9 ± 0.8 cm with a P value of 0.3) while there were statistically significant increased LVESD (3.8 ± 0.9 & 3.2 ± 0.8 cm with a P value of <0.001). EF was significantly depressed (47.2 ± 12.2 & 59.3 ± 10.2 % with a P value of <0.001). FS was depressed in nonsurvivors (24.4+7.5%) compared with survivors (31.2+7.1%) with statistically significant difference (P Value <0.001). NTproBNP level on admission was not correlated to LV diameters, LVEF or FS. Correlation coefficient factor between NTproBNP and each of EF was (r. -0.259 & p. 0.07), FS (r. -0.231 & p. 0.107), LVEDD (r. 0.148 & p. 0.303) and LVESD (r. 0.124 & p. 0.39)

Discussion:

The main focus of our study was to prove if N-terminal pro-BNP (NTproBNP) could be useful to predict outcome in severe sepsis and septic shock. Our study, also aimed at evaluating CRP and serum albumin levels as useful prognostic markers in the setting of severe sepsis or septic shock.

During our study, we had found that serum NT pro-BNP levels at admission were elevated in patients with severe sepsis and septic shock (3798.9 $\pm$ 2347.5 pg/ml). Even there was significant higher level of NTproBNP in nonsurvivors (4619.6 ± 2118.1 pg/ml)

compared to survivors (2328.2 ± 2061.0 pg/ml) (p value <0.001) indicating that elevated serum NT pro-BNP at admission was an independent predictor of mortality (AUC 0.85, cutoff point 3045.0 pg/ml, P; <0.001, sensitivity 89.5 %, specificity 77.4 %).

In agreement with our finding, a metaanalysis of 12 studies on adult septic patients found that elevated NT-proBNP was significantly associated with increased risk of mortality (P < 0.0001). The pooled sensitivity and specificity were 79% and 60% respectively. Their results suggested that elevated NT-proBNP level might prove to be a powerful predictor of mortality in septic patients. [7]

Ruiz-Vera et al (2011) [8] showed that in 51 patients with severe abdominal sepsis or septic shock, values of NT-proBNP were significantly higher in nonsurvivors (4,090.50 [3,064 to 32,147.75] vs. 2,256.50 [1,071 to 2,832]pg/mL, *P* < 0.05) from the first day of the study and NT-proBNP could be useful to discriminate patients with worse outcome.

In disagreement with our findings, **Maroto et al (2008)** [9] analyzed the behavior of NT proBNP and its prognostic value in a cohort of 98 septic patients admitted to the ICU. The admission values for NTproBNP of septic patients in the ICU did not add significant information for prognosis, but were indicators of cardiovascular and renal dysfunction.

In our study, there was significant strong positive correlation between serum NTPNB levels with serum CRP levels (r. 0.52 & p. <0.001) and weak negative correlation with albumin level (r. -0.28 & p. 0.05).

In patients with acute heart failure and septic shock, **Rudiger et al (2008)** [10] found changes in NT-pro-BNP levels correlated significantly (p<0.01) with those in C-reactive protein values. In contrast to our finding, **Cubrilo-Turek et al (2012)** [11] results showed that NT-proBNP had no correlation for C-reactive protein or lactates.

In addition, we found that elevated serum NT pro-BNP levels on admission were associated with increased severity of sepsis associated organ dysfunction as there were strong positive correlations between NT proBNP levels and APACHEII score (r. 0.74 &

p. <0.001), as well as to SOFA score on admission (r. 0.62 & p. 0.00).

Piechota et al (2006) found NT pro-BNP levels correlated with the severity of organ dysfunction as assessed by the SOFA score in his 20 septic patients (r=0.5164, p<0.05) [12], as well as, **Brueckmann et al (2005)** [13] in his 57 patients with severe sepsis found NT-pro BNP correlated with APACHE II score (r=0.42, P<0.05).

Contradictory to our results, **Withhaut et al (2003)** [14] who found APACHE II score not correlated with BNP. Also, **Kadaj et al (2007)** [15] showed that APACHE II scores were superior to BNP alone in predicting mortality in ICU patients.

Regarding CRP value as a prognostic marker, septic patients in our study showed elevated CRP levels on ICU admission (53.2±33.2 mg/dl). In addition, that elevation was significantly marked in nonsurvivors (67.3±32.0 mg/dl) than survivors (44.5±31.3 mg/dl).

In **Su et al (2012)** [16] reported that CRP levels of the nonsurvivors were higher than those of the survivors in ICU patients with sepsis. Also in **Zaki et al (2012)** [17] study, high CRP had a significant prognostic value for predicting mortality as there were a statistically significant higher values in the non-survivor group 133.0 ± 43.698 vs 70.18 ± 40.167 mg/ L in the survivor group (P = 0.00). The optimum cutoff limit was 92.5 mg/ L achieving a sensitivity of 91.3% and a specificity of 76.5%.

This is not in line with **Dahaba etal (2006)** [18] study, there was no significant difference in the mean CRP level between ICU survivors [18.9±24.1 mg/ dl] and non-survivors [22.9 ±11.3 mg /dl]. Also, **Hillas et al (2010)** [19] found neither CRP threshold values nor its kinetics could predict VAP survival or septic shock development. No difference was found in CRP levels between survivors and nonsurvivors [19.0 (13.9–28.5) vs 16.50 (6.3–23.7), p 0.088].

With regard to the effect of admission albumin level on sepsis outcome in the present study, we had found that sepsis was associated with hypoalbuminemia (2.7±0.6 g/dl). Moreover the degree of hypoalbuminemia significantly affected sepsis severity and

mortality. Serum albumin level on admission was significantly (p value 0.002) lower in nonsurvivors (2.4±0.5 g/dl) compared to survivors (2.9±0.6 g/dl).

In agreement with our results, **Seligman et al (2006)** [20] found that albumin level was decreased significantly in non-survivors on admission day (2.5 ± 0.5vs. 2.8 ± 0.6 mg/dl, $P = 0.02$).

Qian and Liu (2012) [21] found that hypoalbuminemia < 35 g/L was common in septic patients and serum albumin level was closely related to prognosis. The rates of hypoalbuminemia of the survived cases were significantly lower than that of the non-survived cases ($P < 0.001$). Besides, serum albumin concentration was negatively correlated with the mortality ($P < 0.05$).

While **Yap et al (2002)** [22] found that albumin concentrations poorly differentiated survivors from non-survivors groups. Their data showed that serum albumin had low sensitivity and specificity for predicting hospital mortality; even combining APACHE II score with serum albumin concentrations did not improve the accuracy of outcome prediction over that of APACHE II alone.

Conclusion:

NT-proBNP on admission day in the intensive care unit is an independent prognostic marker of mortality in severe sepsis. Sepsis biomarkers (NTPNB, CRP and Albumin levels) evaluated in our study on ICU admission were found to have significant correlation with sepsis severity assessed with both APACHEII score and SOFA score.

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