N-Terminal Pro-B-Type Natriuretic Peptide, C-Reactive Protein and Albumin as Prognostic Markers in Severe Sepsis and Septic Shock

SHERIF SABRI, M.D. 1; SOUZI FAWZI, M.D. 2; HATEM EL-ATROUSH, M.D. 2; ABEER MOABAH, M.D. 4 and NESREEN FARAHAT, M.Sc. 3

The Department of Critical Care, Faculty of Medicine, Beni-Suif 1, Cairo 2 and Mansoura 3 Universities and The Department of Clinical Pathology, Faculty of Medicine, Mansoura University 4

Abstract

Introduction: There is growing evidence supports the hypothesis that BNP could be an early predictor of mortality in septic shock.

Aim of the Work: Study the relationship between amino-terminal pro-BNP levels and the severity of organ dysfunction and mortality on admission in severe sepsis and septic shock and correlate its level with CRP and albumin.

Patients and Methods: This study population consisted of fifty patients aged >18 years, who were admitted to critical care department. Eligible patients were enrolled within 24 hours of admission to the ICU with severe sepsis and/or septic shock. Laboratory work up specific for our study (on ICU admission) was BNP through collected heparinated blood sample, CRP and albumin. Also all laboratory study and clinical assessment needed to calculate APACHE II and SOFA score were done beside imaging investigations (if needed).

Results: The patients were divided to 2 groups according to the mortality outcome, Group I (survivors, 31 patients) and Group II (non survivors, 19 patients) there was higher level of NT proBNP in Group II (4619.6 ± 2118.1 pg/ml) compared to Group I (2328.2 ± 2061.0 pg/ml) with a statistically significant p-value (<0.001). There were significant strong positive correlation between serum NT proBNP levels with serum CRP levels (r=−0.28 and p<0.05) there were significant strong positive correlations between serum NT proBNP levels with both APACHE II score (r=0.74 and p<0.001) and SOFA score (r=0.62 and p<0.00). The APACHE II score were done beside imaging investigations (if needed).

Conclusion: BNP levels in patients with severe sepsis and septic shock have a beneficial rule in (ICU) for high risk stratification of critically ill patients, as it is an independent prognostic marker of mortality in severe sepsis.

Key Words: BNP – CRP – Albumin – APACHE II – SOFA.

Introduction

SEPSIS is a leading cause of death in critically ill patients despite the use of modern antibiotics and resuscitation therapies [1]. The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, humeral and cellular reactions and circulatory abnormalities [2]. The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis [3]. However, the early diagnosis and stratification of the severity of sepsis is 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 [4]. 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 [5]. Increased release of BNP into the circulation may be a general feature of cardiac inflammation or injury. Inflammatory process can produce specific cytokines leading to the dysregulation of cardiac BNP production observed during myocardial inflammation and this process might be angiotensin receptor 1-dependent [6]. BNP level are increased in some patients with acute perimyocarditis. It is probably associated with hemodynamical stress caused by transient contractility.
abnormalities [7]. At present a relationship between BNP with myocardial dysfunction in septic shock has not been evaluated. However, growing evidence supports the hypothesis that BNP could be an early predictor of mortality in septic shock. If proven, the hypothesis would have important clinical and public health implications.

**Aim of the work:**

Aim of the present work is to study the relationship between amino-terminal pro-BNP levels and the severity of organ dysfunction and mortality on admission in severe sepsis and septic shock and correlate its level with CRP and albumin.

**Patients and Methods**

This study population consisted of fifty patients aged >18 years, with severe sepsis and septic shock or patients who developed severe sepsis while in the ICU, who were admitted to the Critical Care Department, Kasr El-Aini Hospitals, Cairo University and Intensive Care Unit, New General Hospital, Ministry Of Health, Mansoura from August 2010 to March 2012.

Eligible patients were enrolled within 24 hours of admission to the ICU with severe sepsis and patients with septic shock or patients who developed severe sepsis while in the ICU. Written informed consent from each patient or an authorized relative was taken. Patients included in the study were fulfilling the following criteria on admission, patients who were admitted to the ICU for at least 24 hours and APACHE II score more than 12 calculated on admission and at least 2 of 4 criteria for the systemic inflammatory response syndrome, in addition to a presumptive source of infection suspected by the treating clinician. Patients were excluded if had an acute coronary syndrome based on the presence of a myocardial infarction or unstable angina. The diagnosis of myocardial infarction was based on serum troponin concentrations and clinical judgment of the ICU physician. Acute pulmonary edema at admission and cardiac dysrhythmia (as a primary diagnosis), patients on chronic hemodialysis and pregnancy were also excluded. Complete history taking from patients or relatives besides general examination including assessment of vital signs, Glasgow Coma Score (GCS), MAP, mean arterial pressure, SaO2, PaO2/FIO2 ratio was used preferentially if not available, the SaO2/FIO2 ratio was used; vasoactive medications administered for at least 1hr (dopamine and norepinephrine ug/kg/min), also all laboratory study needed to calculate APACHE II and SOFA score. Imaging investigations (if needed) as chest X-ray, CT brain or abdominal sonography and transthoracic echocardiography were done to each patient on admission or when needed.

Laboratory study specific for our study (on ICU admission) was BNP through collected heparinated blood sample was centrifuged within one hour and stored at –70º thin analyzed by ELISA. Also CRP and microbiological studies including Pan Cultures (sputum, blood, urine or biological fluid according to clinical suspicion) prior to antibiotic administration or after discontinuation of antibiotic for 48hrs.

The data were coded and entered using the statistical package SPSS 15 and 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. p-values less than or equal to 0.05 were considered statistically significant.

**Results**

The study was conducted on 50 patients with severe sepsis and septic shock. The patients were divided to 2 groups according to the mortality outcome, Group I (survivors, 31 patients) and Group II (non survivors, 19 patients) and the following variables were described then analyzed between both groups.

**A- Demographic characteristics:**

Fifty patients had enrolled to our study, they included 18 males (36%) and 32 females (64%), there was no statistically significant difference between both groups regarding sex whereas the age ranged from 19 to 87 years old with mean of 49.6±17.7 years old. Group I was significantly younger compared with Group II (43.5±16.2 versus 59.6±15.5 years old respectively). Of the studied 50 patients; 22 (44%) patients had septic shock and 28 (56%) patients had severe sepsis. The most common source of sepsis in Group I was chest infection (14 cases) followed by soft tissue infection...
(8 cases) and abdominal infection (6 cases) while in Group II it was chest infection (7 cases) followed by abdominal sepsis (5 cases) and urinary tract infection (5 cases). There was no statistically significant difference (p-value 0.2) between both groups as regard the source of sepsis or the type of organism. Regarding the causative organisms of sepsis in all patients, there were 22 cases (44%) stained gram negative (E. coli, Klebsiella, Pseudomonas and Enterobacter), 10 cases (20%) stained gram positive (Staphylococcus Aureus and Streptococcus pneumonia), 6 cases fungal (12%) while in 12 cases (24%), there was no identified growth.

The need for the use of vasopressors was significantly higher in non-survivors (16 cases, 61.5%) than survivors (10 cases, 38.5%) (p-value <0.001), also the need for the use of MV was significantly higher in non-survivors (16 cases, 80.0%) than survivors (4 cases, 20.0%) (p-value <0.001) which was ranged from 3 to 18 days with mean of 7.1 ±3.7 day, however did not reach a statistically significant value (p-value 0.7).

The duration of ICU stay was significantly longer in survivors (15.5±9.8 days) than non-survivors (9.3±4.7 days) (p-value 0.01).

SOFa score of the studied septic patients ranged from 2 to 15 with a mean of 7.7±3.1, it showed statistically significant higher values in Group II (p-value: <0.001). Whereas APACHEII score of the studied septic patients ranged from ranged from 11 to 38 with a mean of 21.1±6.6 and showed statistically significant higher values in Group II (p-value: <0.001).

B- The hemodynamic parameters of the studied population:

On admission, there were no significant differences in nonsurvivors compared with survivors (all p-values 0.9), while on discharge, there were significant decrease in systolic, diastolic, mean blood pressure in nonsurvivors compared with survivors (all p-values <0.001).

C- The laboratory parameters of the studied population:

On admission, there were no significant differences regarding arterial blood gas parameters between survivors and non-survivors while on discharge, there were significant differences between them in all parameters. There were no significant differences regarding serum electrolytes (Na, K) between survivors and non-survivors on ICU admission or discharge (p-value 0.8, 0.9 and 0.3 respectively) except for discharge where hyperkalemia was significant in non-survivors (p-value <0.001. Only WBCs were significantly higher in non-survivors on ICU admission (p-value 0.04), while there were significant lower HB (p-value 0.006), platelet count (p-value <0.001). Kidney functions (BUN, Cr) were significantly impaired in non-survivors than survivors (p-value <0.001). Serum lactate on ICU admission was significantly higher in non-survivors (7.7±3.2mmol/L) compared to survivors (5.8±1.9mmol/L) (p.0.03).

Sepsis biomarkers (NTproBNP, Albumin, CRP levels) on admission:

In the studied population, serum albumin ranged from 2 to 4g/dl with a mean value of 2.7±0.6g/dl, serum CRP ranged from 12 to 96mg/dl with a mean value of 53.2±33.2mg/dl and serum NTproBNP ranged from 372.2 to 10766.0pg/ml with a mean value of 3798.9±2347.5pg/ml.**

I- NT pro BNP level (pg/ml):

There was higher level of NTproBNP in Group II (4619.6±2118.1pg/ml) compared to Group I (2328.2±2061.0pg/ml) with a statistically significant p-value (<0.001) as shown in Fig. (2).

II- CRP level (mg/dl):

There was higher CRP level in Group II (67.3 ±32.0) compared to Group I (44.5 ±31.3) with a significant p-value (0.02) as shown in Fig. (3).

III- Serum albumin level (g/dl):

There was lower serum albumin level on admission in Group II (2.4±0.5g/dl) compared to Group I (2.9±0.6g/dl) with a significant p-value (0.002).

**Correlation among APACHEII score, SOFA score, NT pro BNP, CRP and Albumin levels on ICU admission:

Sepsis biomarkers (NTproBNP, 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.

There were significant strong positive correlations between serum NTproBNP levels with both APACHEII score (r.0.74 and p.<0.001) Fig. (4) and SOFA score (r.0.62 and p .00) Fig. (5).

There were significant strong positive correlation between serum NTproBNP levels with serum CRP levels (r.0.52 and p .001) Fig. (6) and
significant weak negative correlation with albumin level \( (r \approx 0.28 \text{ and } p < 0.05) \) Fig. (7).

Fig. (8): Showed that elevated serum NT pro-BNP at admission was an independent predictor of mortality (AUC 0.85, cutoff point 3045.0pg/ml, \( p < 0.001 \), sensitivity 89.5%, specificity 77.4%).

Also CRP, SOFA and APACHEII scores were good tools for prediction of mortality in septic shock patients as shown in Fig. (8).
Discussion

Sepsis is a leading cause of death in critically ill patients despite improvements in antimicrobial therapy and supportive care [8,9]. Early identification of patients at high risk of dying after ICU admission may help determine therapeutic interventions, such as changes in therapeutic protocols or further diagnostic procedure [10,11].

A rapidly available biochemical test that provides similar or better prognostic information could therefore be useful, e.g. to help discussions about prognosis with patients’ relatives and decisions regarding earlier interventions [12]. Although some prognostic factors had been identified in septic patients, they provided few survival benefits during clinical practice [13].

NT-pro BNP 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 [14]. The aim of the present work was to evaluate serum level of NT-proBNP, C-reactive protein and albumin on ICU admission and their relation to the mortality and severity of organ dysfunction assessed by SOFA and APACHEII. The impact of gender on severe infections is in highly controversial discussion, however the experimental data showed a natural survival advantage after polymicrobial sepsis for females, [15] on the other hand human studies gave inconsistent results showing a lower, equal or higher mortality rate. Mahavanakul et al., reported that mortality rate in patients with sepsis was 53%. [13] whereas Ismaeil et al., (2009) found 40% mortality rate in their study [14]. We had observed that the mortality rate in our study was 38% and the source of infection were respiratory tract (42%) followed by intra-abdominal (22%), soft tissue (20%), urinary (14%) and IV line infections (2%).

Also, Pisarchik found that the mortality rate increased with the severity of sepsis, it was 19.9% in sepsis and 58.6% in septic shock [18], which goes with Park et al., (2012) who observed that pneumonia was the most common cause of septic shock (45%), followed by gastrointestinal tract infection (26%) and urinary tract infection (11%) [16]. In our study, the need for the use of vasopressors and MV were significantly higher in non-survivors than survivors (61.5% vs. 38.5%, p value <0.001 and 80.0% vs. 20.0%, p-value <0.001 respectively). The duration of MV need was longer in survivors (8.3±6.6 days) than non-survivors (6.8±2.8 days) but that difference did not reach a statistically significant value (p-value 0.7) while the duration of ICU stay was significantly longer in survivors (15.5±9.8 days) than non-survivors (9.3±4.7 days) (p-value 0.01).

Pisarchik et al., reported that in sepsis patients, survivors had prolonged ICU stay [22.8 (21-31) vs. 14.5 (12-27) days, p<0.05] and needed less MV (75.1% vs. 100%, p<0.05) than nonsurvivors [18]. Brunbuisson et al., found that nonsurvivors needed more vasopressor (<0.001) than survivors while there were no significant differences between length of ICU stay (16.9±27.6 vs. 19.1±25.6 days, p 0.485) or mechanical ventilation need between nonsurvivors and survivors (70% vs. 55%, p 0.165).

In our septic patients, serum lactate on ICU admission had a level of 6.5±2.6mmol/L and was significantly higher in non-survivors (7.7±3.2 mmol/L) compared to survivors (5.8±1.9mmol/L) (p,0.03), this was comparable with that mentioned by Mackay et al., [18].

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
NT-proBNP, CRP & Albumin as Prognostic Markers in Severe Sepsis & Septic Shock

+2347.5 pg/ml). Even there was significant higher level of NT pro-BNP 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 meta analysis of 12 studies on adult septic patients found that elevated NT pro-BNP 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 [17].

A prognostic impact of NT pro-BNP with respect to mortality was also found by Zhao et al., evaluating patients with severe sepsis and septic shock, NT-proBNP levels (µg/L) at admission to ICU [20.86 (14.28-23.92)] were significantly higher in non-survival group compared with survival group [10.02 (5.58-16.41)], p <0.01, and the difference persisted to 72 hours. In the ROC curves for NT-proBNP at admission, the Area Under the Curve (AUC) for hospital mortality was 0.842 and p <0.01. NT-proBNP at admission greater than 13.30 µg/L was an independent indicator of mortality (sensitivity 80.6% and specificity 70.2%) [20]. Samran-samruajkit et al., (2012) showed that initial Plasma NT-proBNP level was a valuable prognostic factor for children with severe sepsis and septic shock even it was a better prognostic factor compared to procalcitonin level. Their results showed that the mean initial NT-proBNP was at 9780.5 ±12531 ng/L). There was significant difference of NT-proBNP level compared between survival and non survival (6280.3±9597, p <0.001). In the ROC curve for NT-proBNP, the area under the curve for ICU mortality was 0.93, p=0.001 [21]. The same was reported by Liu et al., who studied 72 ICU patients with severe sepsis and septic shock and found the level of NT-proBNP in nonsurvivors was higher than that of survivors. They concluded NT-proBNP level on day 3 and APACHE II Score were independent prognostic marker of hospital mortality in severe sepsis and septic shock [22].

The result of Rezaie-Majd et al., study showed that NT-proBNP levels were significantly higher in patients after undergoing major surgery at risk or developing SIRS/sepsis [23]. NT-proBNP may therefore be an appropriate prognostic marker indicating the early development of postoperative severe sepsis after major surgery. Varpula et al., study for evaluation of the predictive value of NT-proBNP on mortality in 254 patients with severe sepsis and septic shock in 24 intensive care units in Finland, they ended their work concluding that NT-proBNP values were frequently increased in severe sepsis and septic shock. Values were significantly higher in nonsurvivors than survivors. NT-proBNP on day 3 in the Intensive Care Unit was an independent prognostic marker of mortality in severe sepsis (AUC 0.831, cutoff point 7090 pg/ml, sensitivity 58% and specificity 66%) [24]. Roch et al., found that NT-proBNP seemed to be an early factor of prognosis and myocardial dysfunction in 39 patients with septic shock. An NT-proBNP of > 13,600pg/mL predicted ICU mortality with AUC 0.8, sensitivity of 73% and specificity of 83%. NT-proBNP values were significantly higher in nonsurvivors at each time between inclusion and day 7 [25]. Cubrilo-Turek et al., showed that admission NT-proBNP levels could be elevated in critically ill patients and might also serve as markers of severity and prognosis for survival. The median NT-proBNP (pg/ml) was 2.485.1 pg/ml (range 31.5 to 12,041 pg/ml) (log NT-proBNP mean 3.34 ± 0.71 pg/ml). Mean log NT-proBNP levels were higher at admission to the hospital in nonsurvivors (3.73±0.67 pg/ml) compared with survivors (3.12 ± 0.65 pg/ml), which was statistically significant (p <0.0001). Mean baseline levels of NT-proBNP were higher in patients with proved bacteriological infection than without proven infection. The use of ROC curve analysis reveals for serum NT-proBNP high sensitivity (75%), low specificity (57.9%) for discriminating survivors from nonsurvivors [26]. In disagreement with our findings, Cepkova et al., found that in patients with acute lung injury, the level of natriuretic peptides were increased, but were not predictive of mortality in their population [27]. In a narrative review of evidence identified searching Medline, Christenson general findings were that the performance of NT-proBNP was unimpressive among ICU patients [28]. Also, Maroto et al., (2008) 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 NT proBNP of septic patients in the ICU did not add significant information for prognosis, but were indicators of cardiovascular and renal dysfunction [29].

Conclusion:

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.
References


يعتبر الإنتن الشديد والصدمة الإنتانية من أهم مسببات الوفاة في مرضى العناية المركزة وذلك بالرغم من استخدام الأدوية والمضادات الحيوية الحديثة ويرجع ذلك إلى التعقيد الشديد في سلسلة التفاعلات الحيوية بالجسم والتي تشمل التفاعلات المناعية والالتهابية وتك الخاصة بالجهاز الدوائي.

وفي نفس الوقت يستمر البحث بذيل شديد عن اختبارات عملية لمحددات حيوية أكثر دقة وسرعة في تشخيص المرض والذي يعتبر ناجحاً في الوصول إليها بمثابة المفتاح الحقيقي في التعامل مع هذا المرض.

ونظرًا كون البحوث الجديرة في مدارس الصيدليات بالإضافة إلى البوتيتين SI التفاعلي والألبومين في خمسين مريضاً بالآنتن الشديد وللصحة الإنتانية عند وقت الدخول للعناية المركزة، وتحديد مدى العلاقة مع معدلات الوفاة والتغير الشديد للأجهزة الحيوية بواسطة نظام APACHE II (SOFA II) والصحة المزمنة الثانية.

قياس تقييم وظائف الأعضاء الحاد (SOFA II) والصحة المزمنة الثانية.

وعلى ذلك فقد تم عمل الأكثري لحالات البحوث:

* بين وجود علاقة قوية إيجابية بين متوسط قياس الهرمون المخی المدر للصواديوم ونظام الصحة المزمن الثاني (r=0.74) (SOFA II score p<0.001) وكذلك مع نظام تقييم وظائف الأعضاء الحاد (SOFA II score (p<0.001, r=0.57). ولذلك مع نظام تقييم وظائف الأعضاء الحاد (SOFA II score) (p<0.001, r=0.36) APACHE II score.

* بين وجود علاقة قوية إيجابية بين متوسط قياس البوتيتين SI التفاعلي ونظام الصحة المزمن الثاني (r=0.01) APACHE II score (p<0.003, r=0.37). ولذلك مع نظام تقييم وظائف الأعضاء الحاد (SOFA II score (p<0.001, r=0.7).

* بين وجود علاقة قوية إيجابية بين متوسط قياس الهرمون المخی المدر للصواديوم والبوتيتين SI التفاعلي (r=0.052) APACHE II score (p<0.001, r=0.37). وكما تبين أيضاً وجود علاقة سلبية متوسطة القوة بين الألبومين والبوتيتين SI التفاعلي (r=0.01).

* بين وجود علاقة قوية إيجابية بين نظام الصحة المزمن الثاني APACHE II score (r<0.001, r=0.7) ونظام تقييم وظائف الأعضاء الحاد.

وتتضح مما سبق التالي:

* الهورمون المخی المدر للصواديوم والبوتيتين SI التفاعلي والألبومين عادة ما يترافقون في مرضى الانتن والصدمة الإنتانية خاصة في عدم الناتج.

* الهورمون المخی المدر للصواديوم أكثر حساسية وخصوصية لتوقع الوفاة من التفاعلي والألبومين.

* APACHE II score يعتبر كلاً من الهورمون المخی المدر للصواديوم والبوتيتين SI التفاعلي والألبومين مقارنة بنظام تقييم وظائف الأعضاء الحاد 

* والصحة المزمنة آدنو عظيمة الفائدة في توقع أمكانيات حدوث في مرضى الصحة الإنتانية.