Assessment of Plasma N-Terminal Pro-Brain Natriuretic Peptide and CRP in Patients with Severe Sepsis, Septic Shock and Acute Heart Failure

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Abstracts: Background: Increased plasma levels of brain natriuretic peptide (BNP) have been identified as predictors of cardiac dysfunction and prognosis in congestive heart failure and ischemic heart disease. In severe sepsis patients, however, no information is available yet about the prognostic value of natriuretic peptides in Egyptian patients. Aim: The aim of the present work is to study the relationship between amino-terminal pro-BNP, C-reactive protein in one hand and the severity of organ dysfunction and mortality on admission in the other in patient with severe sepsis and septic shock.Patients and methods: This study population consisted of ninety patients aged >18 years, who were admitted to the internal medicine department ICU, Kasr El-Aini Hospitals, Cairo University and enrolled within 24 hours of admission to the ICU with severe sepsis, patients with septic shock, patients with acute decompensated heart failure and patients who developed severe sepsis while in the ICU. The patients were divided to 3 groups, Group I (septic shock), group II (severe sepsis) and group III (heart failure). Plasma N-Terminal Pro-Brain Natriuretic Peptide and CRP were measured.Results: There was higher CRP level in group I (69.56 ± 38.01) compared to group II (41.70 ± 25.34) with a significant p value (0.002). There was higher level of NTproBNP in group I (2809.73 ± 2362.32 pg/ml) compared to group II (2595.13 1968.39 pg/ml) and group III (789.37 ± 348.01pg/ml) with a statistically significant p valueConclusion: NT-pro BNP values are increased in severe sepsis and septic shock. Values are significantly higher in non survivors than survivors. Elevated concentrations of serum CRP on admission are indicators of an increased risk of severe sepsis, septic shock and death.

Keywords: CRP, INT ProBNP, sepsis, septic shock, heart failure.

1. 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).

Sepsis is defined as the presence or presumed presence of an infection accompanied by evidence of a systemic response called the systemic inflammatory response syndrome which is defined as the presence of 2 or more of the following: temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F); pulse rate greater than 90 beats/min; respiratory rate greater than 20 breaths/min (or PaCO2 less than 32 tor); and WBC count greater than 12,000/mm or less than 4,000/mm , or greater than 10% immature band forms (3).

Severe sepsis is defined as the presence of sepsis and 1 or more organ dysfunctions. Organ dysfunction can be defined as acute lung injury; coagulation abnormalities; thrombocytopenia; altered mental status; renal, liver, or cardiac failure; or hypoperfusion with lactic acidosis. Septic shock is defined as the presence of sepsis and refractory hypotension, ie, systolic blood pressure less than 90 mm Hg, mean arterial pressure less than 65 mm Hg, or a decrease of 40 mm Hg in systolic blood pressure compared to baseline unresponsive to a crystalloid fluid challenge of 20 to 40 ml/kg (3).

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 (4). 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 (5).

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 (6).

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 (7).

Patients & Methods:

This study population consisted of ninety patients aged >18 years, who were admitted to the internal medicine department ICU, Kasr El-Aini Hospitals, Cairo University, August 2017 to May 2018. Written informed consent from each patient or an authorized relative was taken.

Eligible patients were enrolled within 24 hours of admission to the ICU with severe sepsis, patients with septic shock, patients with Acute decompensated heart failure and patients who developed severe sepsis while in the ICU.

The patients were divided to 3 groups, Group I (septic shock, 30 patients), group II (severe sepsis, 30 patients) and group III (heart failure, 30 patients) the following variables were described then analyzed between the three groups.

Patients included in the study were fulfilling the following criteria on admission: patients who were admitted to the ICU in 1st 24 hours, a presumptive source of infection suspected by the treating clinician, at least 2 of 4 criteria for the systemic inflammatory response syndrome (temperature > 38oC or < 36o C, HR> 90 bpm, RR > 30/min with PaCo2 < 32 mmHg and TLC > 12000/dL or < 4000 /dL or > 10% staff cells) and 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.

Patients with age less than 18 years, patients with an acute coronary syndrome, patients on chronic hemodialysis, pregnancy, cardiac dysrhythmia (as a primary diagnosis) were excluded from the study.

All patients were subjected to full history taking, clinical examination, vital signs and hemodynamics (data of discharge were collected daily based on the average of last 24 hrs before ICU discharge or death) including temperature, heart rate, mean arterial pressure, diastolic pressure, pulse pressure, respiratory rate and CVP, routine laboratory investigations, N-Terminal Pro-Brain Natriuretic Peptide, CRP and culture and sensitivity, ECG, two-dimensional transthoracic echocardiography with assessment of LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) and LV ejection fraction (LVEF). Acute Physiology and Chronic Health Evaluation (APACHE) II score were assessed for each patient once on admission. It is made of three components: Acute Physiology Score, age adjustment and chronic health evaluation.

Statistical Methods

Statistical Package for Social Sciences (SPSS) computer program (version 19 windows) was used for data analysis. Chi square test. Fisher exact test, ANOVA test, Mann Whitney test, Kruskal-Wallis, receiver operating curve (ROC), Spreaman Rank correlation coefficient test. were used. P value ≤ 0.05 was considered significant.

2. RESULTS

Table 1: Sex distribution in the three groups

	Septic shock (n= 30)	Sepsis (n= 30)	HF (n= 30)	P value
Age	45.97 ± 16.78	42.13 ± 16.32	50.93 ± 14.88	0.109
Gender				
Female	18 (60.0%)	17 (56.7%)	17 (56.7%)	0.955
Male	12 (40.0%)	13 (43.3%)	13 (43.3%)	

Although there were more females in all Groups, there was no statistically significant difference between groups regarding age, sex as shown in table (1).

Table 2: Mortality rate in all studied population

	Septic shock (n= 30)	Sepsis (n= 30)	HF (n= 30)	P value
Survivors	18 (60.0%)	21 (70.0%)	24 (80.0%)	0.240
Non survivors	12 (40.0%)	9 (30.0%)	6 (20.0%)	

Mortality rate in our study in all studied groups ranged 20% -40% which was more in septic shock than severe sepsis and heart failure (Table 2).

Table 3: Source of sepsis and Causative organisms in sepsis and septic shock population

	Septic shock (n= 30)	Sepsis (n= 30)	P value
Identified source of sepsis			
Respiratory	10 (33.3%)	10 (33.3%)	0.930
Genitourinary tract	4 (13.3%)	3 (10.0%)	
Intraabdominal	10 (33.3%)	9 (30.0%)	
IV line	2 (6.7%)	4 (13.3%)	
Soft tissue	4 (13.3%)	4 (13.3%)	
Causative organisms			
E. coli	3 (10.0%)	2 (6.7%)	0.201
No growth	3 (10.0%)	0 (0.0%)	
Acinetobacter	2 (6.7%)	5 (16.7%)	
Klebsilla	6 (20.0%)	5 (16.7%)	
Pseudomonas	8 (26.7%)	12 (40.0%)	
Staph	3 (10.0%)	5 (16.7%)	
Strept. pneumoniae	5 (16.7%)	1 (3.3%)	

There was no statistically significant difference between both groups as regard the identited source of infection and causative organism as shown in table (3).

Table 4: Use of vasopressors or mechanical ventilator

	Septic shock (n= 30)	Severe Sepsis (n= 30)	HF (n= 30)	P value
Need of vassopressors (yes)	30 (100.0%)	19 (63.3%)	27 (90.0%)	0.001*
Need for mechanical ventilation (yes)	20 (66.7%)	13 (43.3%)	11 (36.7%)	0.051
Duration of ICU stay	6.63 ± 2.53	6.73 ± 2.16	6.87 ± 2.36	0.929

The need for the use of vasopressors (Dopamin,noradrenalin) was significantly higher in septic shock (30 cases, 100%) than heart failure (27 cases, 90%) and severe sepsis (19 cases, 63.3%) (P value <0.001). But no significantly different was found between the three groups in need for mechanical ventilator or duration of ICU stay as shown in table (4).

Table 5: CVP (cmH2o) in all studied population.

	Septic shock (n= 30)	Sepsis (n= 30)	HF (n= 30)
CVP admission	5.60 ± 1.52	7.37 ± 1.10	20.27 ± 5.27
CVP discharge	10.33 ± 1.03	10.19 ± 0.98	10.92 ± 1.41

The CVP of the studied septic shock patients on admission ranged from 2.0 to 8 cmH2o with mean of 5.6 ± 1.52 cmH2o , while on discharge it ranged from 9 to 12 cmH2o with mean of 10.33 ± 1.03 cmH2o as shown in table , The CVP of the studied sepsis patients on admission ranged from 5.0 to 9 cmH2o with mean of 7.37 ± 1.10 cmH2o , while on discharge it ranged from 9 to 12 cmH2o with mean of 10.19 ± 0.98 cmH2o as shown in table, the CVP of the studied heart failure patients on admission ranged from 8.0 to 30 cmH2o with mean of 20.27 ± 5.27 cmH2o , while on discharge it ranged from 9 to 13 cmH2o with mean of 10.92 ± 1.41 cmH2o as shown in table 5.

Table 6: Arterial blood gas parameters of the studied population.

	Septic shock (n= 30)	Sepsis (n= 30)	HF (n= 30)
PH	7.25 ± 0.16	7.31 ± 0.10	7.33 ± 0.06
PACO2	29.67 ± 9.49	36.93 ± 6.83	35.67 ± 5.50
PAO2	86.03 ± 8.56	89.73 ± 5.23	89.43 ± 5.70
Sat*	93.83 ± 3.44	99.43 ± 20.03	104.13 ± 21.48
HCO3	21.37 ± 5.35	23.80 ± 3.66	23.37 ± 3.43

The range and mean values of arterial blood gases parameters (PH, PaCO2, PaO2, HCO3, SaO2) of the studied septic shock patients, sepsis patients and heart failure patients on admission) (Table 6)

Table 7: Laboratory investigations of the three studied groups.

		Septic shock (n= 30)	Sepsis (n= 30)	HF (n= 30)
Na	mg/dl	136.37 ± 8.56	138.10 ± 6.46	134.03 ± 8.08
K	mg/dl	3.77 ± 1.02	3.76 ± 0.92	4.11 ± 0.85
Hb	g/dl	8.77 ± 2.14	8.80 ± 2.86	9.37 ± 2.16
WBC thousands/cmm		19.56 ± 5.93	16.99 ± 4.74	7.02 ± 2.01
Plt thousands/cmm		232.53 ± 139.87	189.37 ± 126.53	170.77 ± 99.12
BUN	mg/dl	107.20 ± 94.98	77.70 ± 83.80	52.70 ± 26.10
Cr	mg/dl	1.59 ± 0.61	1.28 ± 0.62	1.23 ± 0.52
Pt	seconds	19.07 ± 6.16	19.27 ± 7.44	24.70 ± 11.82
INR		1.57 ± 0.61	1.47 ± 0.65	2.06 ± 0.96
AST	U/L	470.36± 296.97	253.55± 197.60	357.50± 250.57
ALT	U/L	460.77±309.20	267.30± 209.83	363.01± 260.73
T bilirubin	mg/dl	3.82± 2.757	4.18± 3.31	2.35 ± 1.64
D bilirubin	mg/dl	1.42 ± 2.20	1.46 ± 2.30	0.97 ± 0.63
Albumin	g/dl	3.06 ± 0.70	2.92 ± 0.54	3.39 ± 0.49

Laboratory investigations of the three studied groups are shown in (Table 7)

Table 8: Lactate level (mmol/L) of all studied population

	Septic shock (n= 30)	Sepsis (n= 30)
Lactate	4.46 ± 1.84	4.31 ± 1.99
Lactate after 24 hrs.	5.24 ± 1.65	4.02 ± 1.72
Lactate after 72 hrs.	5.12 ± 2.02	4.29 ± 2.40

In all studied septic patients, serum lactate on ICU admission ranged from 3 to 9 mmol/L as shown in table (8).

Table 9:Comparison between mean values of ….. (CRP, SOFA and APACHII scores) in patients with sepsis and septic shock groups.

	Septic shock (n= 30)	Sepsis (n= 30)	P value
CRP	69.56 ± 38.01	41.70 ± 25.34	0.002*
SOFA score	8.93 ± 3.42	7.63 ± 3.21	0.135
APACHII score	18.30 ± 6.73	13.27 ± 6.97	0.006*

There was higher CRP level in group I (69.56 ± 38.01) compared to group II (41.70 ± 25.34) with a significant p value (0.002) as shown in table (25). There was higher APACH II score in group I (18.30 ± 6.73) compared to group II (13.27 ± 6.97) with a significant p value (0.006) as shown in table (9).

Table 10: Comparison between mean values of INT ProBNP of the three studied groups.

Septic shock (n= 30)	Sepsis (n= 30)	HF (n= 30)	P value
2809.73 ± 2362.32	2595.13 ± 1968.39	789.37 ± 348.01 ab	0.001*

There was higher level of NTproBNP in group I (2809.73 ± 2362.32 pg/ml) compared to group II (2595.13 ± 1968.39 pg/ml) and group III (789.37 ± 348.01pg/ml) with a statistically significant p value (<0.001) as shown in table (10).

Table (11): ROC curve of INT ProBNP in all septic patients [(septic shock and sepsis (n= 60)].

	AUC	Cut off value	Sensitivity	Specificity	PPV	NPV	P value
INT ProBNP	0.899	> 980	80.0%	86.67%	92.3%	68.4%	0.001

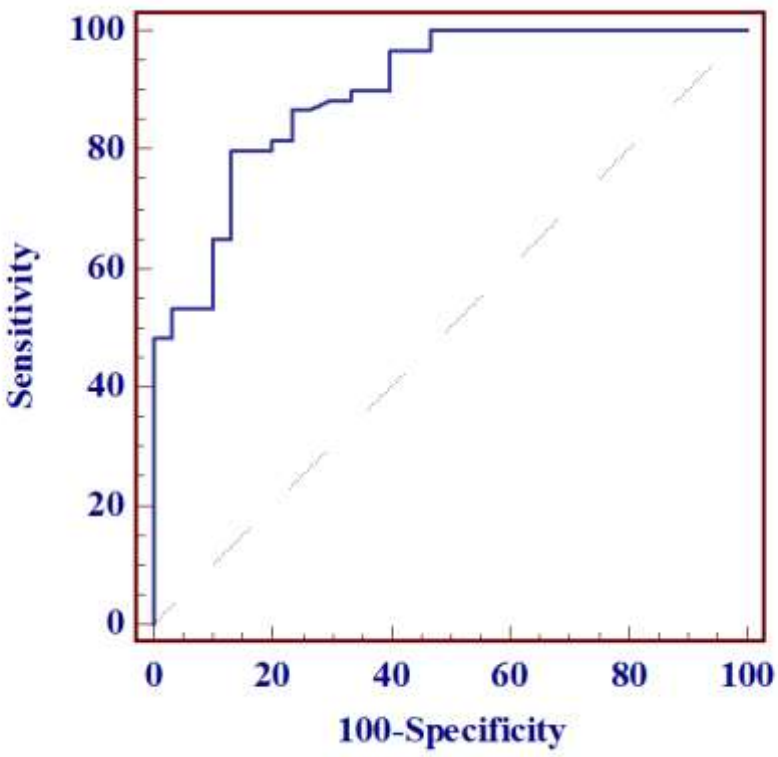

Fig.1: ROC curve of INT ProBNP in all septic patients classified according diagnosis.

Table 12: SOFA score in both groups.

	Group I	Group II	P value
	Mean ±SD	Mean ± SD	
SOFA score	8.93 ± 3.42	7.63 ± 3.21	0.135

The mean SOFA score in group I was 8.93 ± 3.42 while in group II, it was7.63 ± 3.21, p value: 0.135 as shown in table (12) & Fig (1).

Table 13: APACHEII score in both groups.

	Group I	Group II	P value
	Mean ±SD	Mean ± SD	
APACHEII score	18.30 ± 6.73	13.27 ± 6.97	<0.006

APACHEII score on the first 24hr in group I showed statistically significant difference than group II. The mean APACHEII score in group I was 18.30 ± 6.73while in group II, it was 13.27 ± 6.97 (p value: <0.006) as shown in table

(13).

Table (14): Comparison between values of CRP, SoFA and APACHII scores of non-survivor and survivor groups of septic patients

	Non survivor (n= 21)	Survivor (n= 39)	P value
CRP	94.53 ± 26.98	34.68 ± 15.12	0.001*
SOFA score	11.90 ± 2.39	6.33 ± 1.83	0.001*
APACHII score	23.81 ± 4.18	11.46 ± 4.20	0.001*

There was higher CRP level in non survivor (94.53 ± 26.98) compared to survivor (34.68 ± 15.12) with a significant p value (0.001). APACHEII score on the first 24hr in group I showed statistically significant higher values than group II. The mean APACHEII score in group I was 23.81 ± 4.18 while in group II, it was 11.46 ± 4.20 (p value: <0.001). SOFA score on the first 24hr in group I showed statistically significant higher values than group II. The mean SOFA score in group I was 11.90 ± 2.39 while in group II, it was 6.33 ± 1.83, p value: 0.001 as shown in table (14).

Table (15): Comparison between values of NT ProBNP of non-survivor and survivor groups

	Non survivor (n= 21)	Survivor (n= 39)	P value
Mean ± SD	4826.52 ± 2212.89	1558.69 ± 905.94	0.001*

NT ProBNP in group I (Non survivor) showed statistically significant higher values than group II (survivor). The mean NT ProBNP in group I was 4826.52 ± 2212.89 while in group II, it was 1558.69 ± 905.94 (p value: <0.001) as shown in table (15).

Table 16: ROC curve of INT ProBNP in all septic patients classified according diagnosis.

	AUC	Cut off value	Sensitivity	Specificity	PPV	NPV	P value
INT ProBNP	0.916	> 2457	85.71%	87.18%	78.3	91.9	0.001*
CRP	0.617	≤ 71	85.71%	42.11%	45.0%	84.2%	0.119

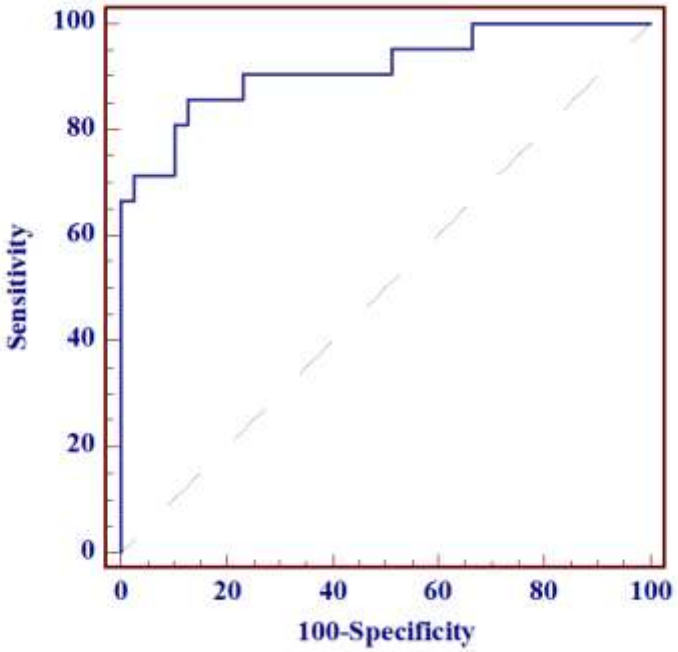

Fig.2: ROC curve of INT ProBNP in all septic patients classified according diagnosis.

Table 17: Correlation between INT ProBNP and CRP, SOFA and APACHII scores in SEPSIS and septic shock patient.

	INT ProBNP			
	Septic shock		Sepsis	
	r value	p value	r value	p value
CRP	0.588	0.001*	0.563	0.001*
SOFA score	0.407	0.025*	0.556	0.001*
APACHII score	0.430	0.018*	0.705	0.001*

Sepsis biomarkers (NTproBNP, CRP 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 as shown in table (17).

3. DISCUSSION

In the current study, there was no statistically significant difference between groups regarding sex with(p value 0.955). Mortality rate during our study reached 35% in all studied septic patients. In patients with septic shock, mortality rate was 40% while it was 30% in patients with severe sepsis but without statistically significant difference between both groups (P value 0.240).

Mahavanakul et al (8) reported that mortality rate in patients with sepsis was 53%. The mortality for patients with septic shock was 60% versus 38% for that not in septic shock. Also, Laudari et al (9) found that the mortality rate increased with the severity of sepsis. It was 19.9% in sepsis without organ failure, 44.4% in severe sepsis, and 58.6% in septic shock. Also Ismaeil et al (10) found 40% mortality rate in their study.

We observed that the source of infection in our studied patients with severe sepsis and septic shock were the respiratory tract (33,3%) followed by intra-abdominal (31.6%), soft tissue (13.3%), urinary (11.6%) and central line

infections (10%).

This went with Park et al (11) who observed that pneumonia was the most common cause of septic shock (45%), followed by gastrointestinal tract infection (26%) and urinary tract infection (11%). Also, Que et al (12) reported that over 75% of patients had pulmonary or abdominal infections.

Regarding the causative pathogen of sepsis in our patients, 5% of them showed negative cultures. In patients who had positive culture (95%), Gram –ve organisms were the most frequent (71.6%) including, E. coli, Klebsiella, Pseudomonas & Enterobacter followed by gram +ve organisms (23.3%) including Staph. Aureus & S. pneumonia .

This is matched with Lueangarun and Leelarasamee (13) who reported that the most commonly identified pathogens were Gram-negative bacteria (72.5%) as follows: Escherichia coli (28.2%), Klebsiella pneumoniae (12.7%), and Acinetobacter spp. (12.2%). Gram-positive bacteria were found in 27.5% of cases, including methicillin-susceptible S. aureus (8.7%), methicillin-resistant S. aureus (MRSA) (4.8%), and Streptococcus group D (3.5%).

In Que et al (12) study on patients with severe sepsis and septic shock, high percentages were infected with Streptococcus pneumoniae (18.7%) or Escherichia coli (21.5%).

The number of patients who needed to be treated with vasopressor medications (dopamine, epinephrine, nor epinephrine, dobutamine) was 76 cases (84.4%). The need for the use of vasopressors was significantly higher in septic shock (30 cases, 100%) than heart failure (27 cases, 90%) and sepsis (19 cases, 63.3%) (P value <0.001). No significant difference was found between the three groups in the need for mechanical ventilator or duration of ICU stay.

Pisarchik et al (14) 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.

Post et al (15) found that non survivors 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). Hunter et al (16) study demonstrated that significant predictors of mortality were use of vasopressors 16.4 (95% CI, 1.80-149.2) and mechanical ventilation 16.4 (95% CI, 3.13-85.9).

On assessment of disease severity, we observed that both SOFA and APACHEII scores were significantly related to mortality in patients admitted to ICU with severe sepsis and septic shock. The mean SOFA and APACHE II scores were elevated (8.93 ± 3.42 and 18.30 ± 6.73 respectively) in septic shock patients. There were significant higher SOFA and APACHEII score values on the first 24hr in non survivors compared with survivors. The mean SOFA score in survivors group was 6.33 ± 1.83 while in non-survivors group was 11.90 ± 2.39 ($p < 0.001$), and the mean APACHEII score in survivors group was 11.46 ± 4.20 while in non-survivors group was 23.81 ± 4.18 ($p < 0.001$).

In the Min-jie et al (17) study, on ICU admission, the mean APACHE II and SOFA scores were elevated (17.83 ± 6.51 & 7.85 ± 4.35 respectively). Moreover, they were positively related to each other ($r=0.514$, $P <0.001$). Ruiz-Vera et al (18) showed that in severe abdominal sepsis or septic shock, the mean APACHE II score at admission was 20.52 ± 5.07. This value was found to be significantly higher in non survivors (24.00 ± 4.03 vs. 18.38 ± 4.56, $P < 0.05$).

Juneja et al (19) assessed the performance of various ICU scoring systems in septic patients admitted to a medical ICU. SOFA performed the best (AUC 0.889, cut off >5.5, sensitivity 86.9% & specificity 79.2%) followed closely by APACHE II score (AUC 0.880, cut off >18.5, sensitivity 86.9% & specificity 75.8 %). However, all the scores tested had good efficacy and the difference in efficacy was not significant. (422)

In our study, we found that serum NT pro-BNP levels at admission were elevated in patients with severe sepsis and septic shock (2595.13 ± 1968.39 pg/ml, 2809.73 ± 2362.32 pg/ ml). Even there was significant higher level of NTproBNP in non survivors (4826.52 ± 2212.89 pg/ml) compared to survivors (1558.69 ± 905.94 pg/ml) (p value

<0.001) indicating that elevated serum NT pro-BNP at admission was an independent predictor of mortality (AUC 0.916, cutoff point < 2457.0 pg/ml, P; <0.001, sensitivity 85.71 %, specificity 87.18 %).

A prognostic impact of NT-proBNP with respect to mortality was also found by Zhao et al (20) 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 than13.30 µg/L was an independent indicator of mortality (sensitivity 80.6% & specificity 70.2%).

Samransamruajkit et al (21) 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 between survival & non survival groups (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.

The result of Rezaie-Majd et al (22) study showed that NT-proBNP levels were significantly higher in patients after undergoing major surgery at risk of developing SIRS/sepsis. NT-proBNP may therefore be an appropriate prognostic marker indicating the early development of postoperative severe sepsis after major surgery.

Ruiz-Vera et al (18) showed that in 51 patients with severe abdominal sepsis or septic shock, values of NT-proBNP were significantly higher in non survivors (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 more useful than PCT to discriminate patients with worse outcome. (453)

In our study, there was significant strong positive correlation between serum NTPNB levels with serum CRP levels (r. 0.563 & p. <0.018). Sensitivity and specificity of NTproBNP in predicting ICU mortality were 85.71 % and 87.18 % respectively while they were85.71 % & 42.11 % for CRP.

In patients with acute heart failure and septic shock, Rudiger et al (23) found that changes in NT-pro-BNP levels correlated significantly (p<0.01) with those in C-reactive protein values. Their results added further evidence to the hypothesis that there was an interaction between the systemic inflammatory response and the natriuretic peptides.

Wang et al (24) reported that, in the cardiac subgroup, NT-proBNP but not CRP independently predicted ICU mortality while in the non-cardiac group, CRP rather than NT-proBNP was an independent predictor of ICU mortality. Although the predictive ability was lower as compared with the APACHE II score, the addition of CRP or NT-proBNP or both to the APACHE II score could significantly improve the ability to predict ICU mortality.

In addition, we found that elevated serum NT pro-BNP levels on admission was associated with increased severity of sepsis associated organ dysfunction as there was strong positive correlations between NT proBNP levels and APACHEII score in septic shock (r. 0.430 & p. <0.018) and (r. 0.705 & p. <0.001) in sepsis, as well as to SOFA score on admission in septic shock (r. 0.407 & p. 0.025) and (r. 0.556 & p. <0.001) in sepsis.

Piechota et al (25) found that 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) , as well as, Brueckmann et al (26) in his 57 patients with severe sepsis found NT-pro BNP correlated with APACHE II score (r=0.42, P<0.05).

In the Min-jie etal (17) study, they found that both DNT-proBNP (NT-proBNP on day 3 minus NT-proBNP on day 1) (P <0.001) and admission SOFA (P <0.001) were independent predictors for in-hospital mortality and they positively related to each other (r=0.245, P=0.014). They also found that their combination was a more robust predictor for in-hospital mortality than either of them alone.

Januzzi and coworkers (27) found higher values of NT-proBNP were strongly associated with death and were even

stronger predictors of death than APACHE II scores , as well as, Yan and Li (28) concluded that nautriuretic peptide was better than APACHE II score in predicting mortality in non-cardiogenic critically ill patients in emergency department.

Regarding CRP value as a prognostic marker, septic shock patients in our study showed elevated CRP levels on ICU admission (69.56 ± 38.01mg/dl)and patient with sepsis (41.70 ± 25.34 mg/dl) . In addition, that elevation was significantly marked in non survivors (94.53 ± 26.98 mg/dl) than survivors (34.68 ± 15.12mg/dl). CRP levels predicted ICU mortality at cutoff point of 36.0 mg/dl, where AUC was 0.617, P; 0.119, sensitivity 85 % & specificity 42.11 % but CRP levels predicted ICU mortality in our study was higher with cut off 71 mg/dl.

In agreement with our work, a case-control study by Mamani et al (29) for evaluation of fibronectin and CRP plasma levels in 180 patients with sepsis and without sepsis concluded that decreased levels of fibronectin and increased levels of CRP might be considered as reliable diagnostic markers for sepsis. Also, CRP could be a better predictive factor for sepsis than fibronectin.

Gradel et al (30) concluded that thirty-day mortality increased with higher CRP level in adult bacteraemic patients and a high magnitude of bacteraemia strengthened the association between high CRP level and 30-day mortality (p <0.0001). Also Su et al (31) reported that CRP levels of the non survivors were higher than those of the survivors in ICU patients with sepsis.

In Zaki et al (32) 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%. Deballon et al (33) showed similar results with optimum cutoff limit of >125 mg/L. but CRP levels predicted ICU mortality in our study was lower with cut off 71 mg/dl.

This is not in line with other studies demonstrating that CRP does not allow early discrimination of survivors from non survivors in septic patients. In Dahaba et al (33) 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]. In addition, area under ROC curves on day 3 of CRP (0.61) was non-predictive and remained non-predictive over the duration of ICU stay. Jensen and coworkers (34) showed that CRP level was not an early independent predictor of all-cause 90-day mortality after ICU admission.

Serum level CRP had significantly correlation to other biomarkers of sepsis (NT-proBNP) in our study. There were significant strong positive correlation between serum (NT-proBNP) level with serum CRP levels (r. 0.588 & p. <0.001) in septic shock and (r. 0.563 & p. <0.001) in sepsis.

Lee et al (35) concluded that for predicting secondary outcome of community-acquired pneumonia regarding vasopressor use or the need for mechanical ventilation, only albumin had an additive role when combined with pneumonia severity index (PSI) but CRP did not.

Yucel et al (36) showed that BNP was the most powerful diagnostic parameter for the prediction of non survivors on admission while CRP did not in patients with sepsis.

In our study, we found that CRP value correlated significantly with sepsis severity assessed by SOFA (r. 0.56 & p. <0.001) and APACHII scores (r. 0.57 & p. <0.001) indicating the ability of admission CRP level to detect outcome and severity of sepsis.

In their study, Coelho et al (37) showed a good correlation between CRP ratio course and organ failure evolution measured by the SOFA score, either improving or not as well as the rate of improvement. In fact, the decrease of CRP ratio by day 3 anticipates the decrease in SOFA score, and this could suggest that CRP is a better marker of resolution of severe CAP. Additionally, the clinical application of the SOFA score is not as easy and straightforward as CRP interpretation, since SOFA score calculation implies the collection of data of several clinical and laboratorial

parameters. So SOFA score determination is more time-consuming and difficult to perform routinely at the bedside.

In Zaki et al (32) study, they found that both APACHE II (P = 0.00) and SOFA (P = 0.00) scores showed significant correlation with high CRP values. Also, Lobo et al in a study on 313 ICU patients; found that CRP levels were correlated to higher SOFA scores ($p < 0.05$) which was similar to our results.

4. CONCLUSION:

NT-pro BNP values are increased in severe sepsis and septic shock. Values are significantly higher in non survivors than survivors. Elevated concentrations of serum CRP on admission are indicators of an increased risk of severe sepsis, septic shock and death.

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