Septic Cardiomyopathy: Role of Echocardiography and Brain Natriuretic Peptide

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Abstract: Introduction: Myocardial dysfunction occurs in about 40% of patients presenting with sepsis and septic shock. The most important hypothesis to explain it is based on a circulating myocardial depressant substance. Hypothesis: To evaluate the possibility of early diagnosis of myocardial dysfunction in patients in sepsis or septic shock using the transthoracic echocardiography or the brain Natriuretic peptide (BNP). Methods: 46 patients presented with severe sepsis or septic shock according to the criteria of the 2001 SCCM/ESICM/ACCP/ATS/SIS sepsis definition were included in the study. The patients undergone serial transthoracic Echocardiographic examinations, Sequential Organ Failure Assessment (SOFA score) and BNP measurements on admission to the ICU and till death or discharge. The patients were retrospectively divided into survivors and non survivors for statistical analysis of the sensitivity and specificity of the Echocardiographic data and the BNP in correlation to the SOFA score and the prognosis. Results: The mortality of patients with systolic left ventricular failure (LVEF < 55%) was 82.4%, in contrast to 51.7% in patients with normal systolic function. (p=0.037) Patients who had diastolic dysfunction on admission represented 39.1%. In the non survivors group 44.8% of them had diastolic dysfunction in comparison to 29.4% in the survivor group. The BNP in the survivor group ranged from 345.01±222.10 pg/ml on admission and increased till it reached a mean of 406.2±295.39 pg/ml at day 3 before decreasing to 163.69±134.39 pg/ml at discharge. The non-survivors had a higher mean which ranged from 708.62±305.17 pg/ml on admission to 1022.11±363.41 pg/ml at the third day. The BNP had a significant correlation with both the SOFA score (p=0.037) and delta SOFA score (p=0,025). A BNP level of 250.5 has a sensitivity of 82.8% and a specificity of 64.7% in predicting the mortality of patients in our study. Conclusion: BNP is sensitive but not specific for the diagnosis of heart failure and is correlated to the prognosis and SOFA score in patients admitted to the ICU with severe sepsis and septic shock. A cut off value of 250 pg/ml has a sensitivity of 82.8% and specificity of 64.7% in detecting the mortality of such patients.

1. Introduction

Sepsis is defined as "the systemic inflammatory response syndrome (SIRS) that occurs during infection". [1] Sepsis is estimated to account for 1% of all hospital admissions in the U.S.A.[1] The total national hospital cost invoked by severe sepsis in the U.S.A. was estimated at approximately $16.7 billion on the basis of an estimated severe sepsis rate of 751 000 cases per year with 215 000 associated deaths annually. [2]

The cardiovascular system and its dysfunction during sepsis have been studied for more than 5 decades. In 1951, Waisbren described cardiovascular dysfunction due to sepsis for the first time. [3] As early as the 1980s, significant reductions in both stroke volume and ejection fraction in septic patients were described despite normal total cardiac output. [4] Importantly, the presence of cardiovascular dysfunction in sepsis is associated with a significantly increased mortality rate of 70% to 90% compared with 20% in septic patients without such cardiovascular impairment. [5]

In studies of septic shock lasting $\geq$ 48 hours, 24% to 44% had systolic LV dysfunction (6-8) while 44% showed features of diastolic dysfunction. [7] Myocardial depression is a reversible phenomenon that subsided in 7 – 10 days if the patient survived. [9] The characteristics of myocardial depression in septic shock are reduced ventricular ejection fraction and biventricular dilatation, although the marked dilatation has not been confirmed in some studies. [7,10,11]

Diastolic dysfunction is not as clearly defined. [9] Poelart et al. [7] demonstrated that cardiac dysfunction in septic shock is a continuum from isolated diastolic dysfunction to both diastolic and systolic ventricular failure.

The impact of septic myocardial dysfunction on the outcome has been controversial. Some studies have found an initially lower LVEF and more dilated LV in patients who survived,[4,11] while some have noticed decreased cardiac function in non-survivors.[7,12] Different mechanisms in evaluation of

cardiac function and fluctuation of the loading conditions probably explain these differences.

Mechanisms Underlying Myocardial Dysfunction in Sepsis

1. Global Ischemia

An early hypothesis of septic cardiomyopathy was based on the theory of global myocardial ischemia; however, septic patients have been shown to have high coronary blood flow and diminished coronary artery– coronary sinus oxygen difference. [13]

2. Myocardial Depressant Substance

Parrillo et al [14] quantitatively linked the clinical degree of septic myocardial dysfunction with the effect the serum had on rat cardiac myocytes, with clinical severity correlating well with the decrease in the velocity of myocyte shortening. These effects were not observed when serum from convalescent patients whose cardiac function had returned to normal was applied.

The myocardial depressant substances studied in previous studies include:

a) Cytokines
• Tumor necrosis factor-α (TNF-α) [15]
• IL-1[16]

They result in the induction or release of additional factors that in turn alter myocardial function, such as prostanoids or NO. [17]

b) Prostanoids
Such as thromboxane and prostacyclin. [18]

c) Endothelin-1
Endothelin-1 (ET-1) up regulation has been demonstrated within 6 hours of LPS-induced septic shock. [19]

d) Nitric Oxide
Sepsis leads to the expression of inducible NOS (iNOS) in the myocardium, [20] followed by high-level NO production, which in turn importantly contributes to myocardial dysfunction, in part through the generation of cytotoxic peroxynitrite, a product of NO and superoxide.[21]

e) Adhesion Molecules
Such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. [22]

3. Autonomic Dysregulation

Heart rate on presentation predicted survival in septic shock patients. [23]

4. Metabolic Changes

5. Mitochondrial Dysfunction

Cardiomyocytes demonstrate mitochondrial ultrastructural damage in both septic animals [24] and patients.[25] Decreased activities of mitochondrial electron transport chain enzyme complexes, [26] endotoxin-induced mitochondrial DNA damage [27] and increased expression of mitochondrial uncoupling proteins [28] are examples mitochondrial dysfunction in sepsis. Finally, the mitochondrial permeability transition pore may also play a role in the development of mitochondrial dysfunction. [29]

6. Cell Death

Cellular hypoxia and dysoxia may both place the Cardiomyocytes at risk of energy depletion and cell death if energy demands are not met by supply. [30]

Elevated circulating concentrations of Natriuretic peptides are clinical hallmarks of cardiac dysfunction. The serum levels of BNP are elevated in heart failure. Therefore, plasma BNP concentrations are a good diagnostic indicator of congestive heart failure. [31]

The role of neurohormonal markers of myocardial dysfunction in sepsis has been reported in both animal and human models. Hartemink et al. [32] found that right and left systolic dysfunction correlated with an increase in plasma levels of atrial Natriuretic peptide (ANP) during the first 72 hours after the diagnosis of septic shock.

Echocardiography is unique as it offers an instantaneous, bedside, comprehensive assessment of cardiac function in septic patients. Echocardiography allows qualitative and quantitative assessment of global and regional left and right ventricular systolic function, diastolic function, left and right ventricular preload, regional wall motion abnormalities, and cardiac output. [33]

Although the clinical utility of echocardiography was apparent, imaging quality was reduced by technological limitations in at least a third of ventilated ICU patients. Advances in ultrasound technology have improved the imaging quality obtained by the TTE in the ventilated critically ill patient. TTE can now be considered the Echocardiographic modality of first choice for imaging in most ICU patients, including those with sepsis. [34] It is possible and often relatively easy to derive or estimate standard hemodynamic data using the echocardiography. [35] Although the information obtained is not continuous, repeating a TTE study is relatively easy as long as an experienced operator is available.

The aim of the current study is to determine the role of Brain Natriuretic Peptide versus left ventricular ejection fraction measured by echocardiography in defining patient with left ventricular systolic dysfunction in patients presenting with severe sepsis and septic shock in the intensive care unit. Also we aimed to evaluate the role of the brain Natriuretic peptide (BNP) as a diagnostic factor of new onset heart failure in critically ill patients presenting with severe sepsis and septic shock (sepsis

induced cardiomyopathy) or as a prognostic factor of survival in the studied patients.

2. Material and Methods

The present study was conducted on forty six patients admitted to the intensive care units in Alexandria main University hospital (AMUH).

Inclusion criteria:

Forty six consecutive patients presenting with severe sepsis or septic shock as defined according to the criteria of the 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference was selected for this study [36]

An informed consent was obtained from every patient or his next to kin if he is unable to give the consent before being included in the study. The study was approved by the ethical committee of the faculty of medicine of Alexandria University.

Exclusion criteria:
1- Patients refusing being included in the study.
2- Patients less than18 years.
3- Patients with atrial fibrillation.
4- Patients with known heart failure before the admission to the ICU.
5- Patients presenting with acute myocardial infarction within 72 hours.
6- Patients with mitral insufficiency as diagnosed by the echocardiography.

The study is a comparative prospective cohort study.
The included patients were subjected to the following:
1- **The Sequential Organ Failure Assessment (SOFA score) determination:** was done for every patient daily. (39)
   a- Laboratory investigation for
      • Arterial blood gases. (ABG)
      • Serum Bilirubin. (mg/dL)
      • Serum Creatinine. (mg/dL)
      • Complete blood count.
   b- Glasgow coma scale (daily)
   c- Urine output (daily over 24 hours)
2- **Brain Natriuretic Peptide (BNP):** was measured within 12 hours of diagnosis in the ICU unit, and then daily for three days or on discharge (if discharged after less than 72 hours).

The arterial blood gases (ABG) was done using the radiometer pH gas analyzer type 248 or 348 (Chiron diagnostic, England). Other laboratory investigations included: complete blood count (CBC) done by SYSMEX- KX21N. The Creatinine (mg/dL) and serum bilirubin was done by Hitachi 902. BNP

was measured in a venous blood sample (10 ml of venous blood) from a peripheral vein. It was analyzed used the Peptide Enzyme Immunoassay (EIA) method. The used kits are that of Peninsula laboratories, LLC (Member of the Bachem group).

The reference values for ABG parameters are as follows: pH (7.35-7.45), PaCO2 (35-45), PaO2 (70-100) HCO3 (22-26), SaO2 (90-95). The reference values for the CBC were: Hemoglobin (12-17 g/dL), Leukocytic count (4-10.5 k/µL) and platelet count (150 – 450 k/µL). The reference value for the lab tests is as following: Creatinine (0.5-1.4 mg/dL) and total bilirubin (0.3 to 1.9 mg/dL).

3- **Transthorathic Echocardiography:** was done daily after patient admission to the ICU and for three consecutive days (unless if the duration of stay is less than the study period) and on discharge from the ICU. The following measurements were done using echocardiography (The General Electric Vivid 3 pro apparatus, General Electric (GE), USA).

The following data was measured by the echocardiography:

1- The left ventricular systolic function:

The Ejection fraction (LVEF) through determination of the left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) in the long axis left parasternal view.

An ejection fraction of less than 55% is used as a threshold of heart failure according to the American Society of Echocardiography committee Recommendations for Chamber Quantification. [37]

2- The left ventricular diastolic function:

The E/A ratio (early to atrial mitral inflow waves by pulsed wave Doppler in the apical four chamber view), the deceleration time (DT) and the left atrial diameter (LA) in the left parasternal long axis view.

To differentiate between the normal and the pseudonormal pattern of mitral inflow the tissue Doppler were used. The sample volume should be positioned at or 1 cm within the lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5-10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Patients with e' (lateral) <8.5 cm/s will be considered to have impaired myocardial relaxation. [38].

The patient management was according to the management protocol of severe sepsis and septic shock in the critical care department of Alexandria University. The treatment decision was made by the intensivist working in the service blind to the current study.
The end point:

The patients were followed till discharge or death.

Statistical Analysis:

Data into the computer was done followed by tabulation and analysis. Analysis was done using SPSS-15 (Statistical package for Social Sciences version 15).

Correlation was done between:

The Echocardiographic data and the BNP.

The SOFA score and the BNP.

3. Results

Characteristics of patients: The current study included 46 patients who suffered from severe sepsis or septic shock. Of the 46 enrolled patients 23 were males (50%) and 23 were females (50%). The age ranged from 26 to 79 years with a mean of 60.1 ± 10.3 years. Table (1) shows the baseline characteristics of the enrolled patients. Patients are then retrospectively categorized under two groups: survivors and non-survivors.

Table (1): Characteristic features of all patients

Age (years):		
Range	26 – 79	
Mean± S.D.	60.1±10.3	
Sex: number (%)		
Male	23	(50.0%)
Female	23	(50.0%)
Duration of stay (years):		
Range	3 – 18	
Mean± S.D.	7.62±3.68	
Sepsis state number (%):		
Septic shock	16	(32.7%)
Severe sepsis	30	(61.2%)
Mechanical ventilation number (%):	32	(65.3%)
Yes	14	(28.6%)
No		
Categories number (%):		
Survivors	17	(36.9%)
Non-survivors	29	(63%)

P is significant if ≤ 0.05

Table (2): Comparison between the survivors and non survivors regarding the age, sex, cause of sepsis, and heart rate on admission.

	Survivors "n=17"		Non-survivors "n=29"		p
Age (years):					
Range	43-74		26-79		0.369
Mean±SD	60.53±7.53		59.34±10.29		
Gender: number (%)					
Male	9	(52.94%)	14	(48.28%)	0.760
Female	8	47.06%)	15	(51.72%)	
Cause of sepsis:					
Abdominal	2	(11.76%)	6	(20.69%)	0.123
Urinary	5	(29.41%)	3	(10.3%)	0.036*
Respiratory	7	(41.18%)	11	(37.9%)	0.541
Others	3	(17.6%)	9	(31.0%)	0.032*
Heart rate (beats/minute):					
Range	54-132		88-124		0.019*
Mean±SD	99.07±17.58		108.76±8.25		

P is significant if ≤ 0.05

Table (3): Comparison between the survivors and non-survivors regarding the duration of stay, shock state and the mechanical ventilation

	Survivors "n=17"	Non-survivors "n=29"	p
Duration of stay (days):			
Range	3-18	3-15	0.092
Mean±SD	6.82±3.73	8.31±3.54	
Shock state: (number (%)):			
Septic shock	2 (11.8%)	14 (48.3%)	0.012*
Severe sepsis	15 (88.2%)	15 (51.7%)	
Invasive MV (number (%)):			
Yes	8 (47.06%)	24 (82.76%)	0.011*
No	9 (52.94%)	5 (17.24%)	

P is significant if ≤ 0.05

Table (4): Comparison between the mean value of LVEF (%) in survivors and non-survivors at different time intervals

	Admission	Day 1	Day 2	Day 3	Discharge
LVEF: (%)					
Survivors:					
Range	29.3-82.2	25 – 79.2	24 – 73.5	24-71.1	49.5-75
Mean±SD	57.03±12.54	54.2±10.6	52.1±11.25	51.80±12.32	61.49±6.31
P1		0.103	0.068	0.03*	0.01*
Non-Survivors:					
Range	47.4-78.4	45.5-77.9	47.6-79.5	45.9-73.4	-
Mean±SD	65.19±9.20	61.2±10.22	60.2±10.3	59.54±8.31	
P1		0.103	0.098	0.06	
P2	0.012*	0.021*	0.033*	0.013*	-

P is significant if ≤ 0.05

Age& gender: The mean age was 60.53±7.53 and 59.34±13.29 years for survivors and non-survivors respectively. Survivors included 9 males and 8 females while non survivors included 14 males and 15 females. Both survivors & non-survivors were comparable in age & sex distribution (table 2).

Causes of sepsis: the most important cause was the respiratory system in 41.18% in survivors group and 37.93% in non-survivors. The other sources included the urinary as the second most common in the survivors group (29.41%) while the abdominal source was the second and represented 20.69% of patients in the non-survivors group (table 2).

Heart rate on admission: The heart rate in non-survivors group was statistically higher than survivors group.

Hospital stay and fate: There were no statistical significant differences between the two groups regarding the hospital stay (table 3). Fourteen out of the sixteen (87.5%) shocked patients died. The mortality among the patients with severe sepsis was 50%. The rate of survival in patients with septic shock was significantly lower than those with severe sepsis, (table 3).

Mechanical ventilation: The percentage of patients on invasive mechanical ventilation who died (82.8%) was significantly higher than those who were not ventilated (table 3).

Left ventricular ejection fraction (LVEF): The LVEF in survivors remained stable during day 1 & 2 but decreased significantly by day 3 & on discharge. In non-survivors the LVEF ranged between 47.4% and 78.4% on admission and remained unchanged thorough days 1, 2, 3 till death. When the two groups were compared to each other, survivors had a significantly lower LVEF than non-survivors on admission and at all three intervals (table 5).

Seventeen patients (37%) had an ejection fraction of less than 55% on admission while 29 patients had an ejection fraction of more than 55%. Fourteen patients

(82.4%) out of the 17 patients who had an ejection fraction less than 55% died. On the other side 15 patients out of 29 patients (51.7%) who had an ejection fraction of more than 55% died. The probability test was significant for the last data.

Table (5): Comparison between the mortality and the left ventricular ejection fraction on admission in survivors and non survivors.

	LVEF category on admission		Total
	< 55%	> 55%	
Non-survivors	14	15	29
	48.2%	51.7%	100.0%
Survivors	3	14	17
	17.6%	82.3%	100.0%
Total	17	29	46
	36.9%	63.0%	100.0%
X2	4.35		
P	0.037*		

P is significant if ≤ 0.05

Left ventricular and atrial diameters: The left ventricular end systolic diameter (LVESD) in survivors on admission and remained stable during day 1, 2 and 3 but decreased significantly on discharge. In non-survivors the LVESD remained unchanged thorough days 1, 2, 3 till death. Survivors had a significantly higher LVESD than the non survivors on admission and at all three intervals (table 6).

The left ventricular end diastolic dimension (LVEDD) in survivors remained stable during days 1, 2, 3 and discharge. In non-survivors LVEDD remained unchanged thorough days 1, 2, 3 till death. When the two groups were compared to each other, there was no significant difference between survivors and non survivors except on day 3 when survivors had a significant higher mean of LVEDD than non-survivors (table 6). There was no significant difference between survivors and non survivors concerning the left atrial diameter (table 6).

Incidence of diastolic dysfunction on admission: 39.1% of our studied patients (n=18) had diastolic dysfunction. In non survivors group 13 patients out of 29 had diastolic dysfunction (44.8% of the group) in comparison to 5 out of 17 patients in the survivor group (29.4% of the group). There was a significant difference between the two groups.

Table (6): Comparison between survivors and non-survivors regarding the mean values of LVESD, LVEDD & LA in at different periods

	Admission	Day 1	Day 2	Day 3	Discharge
LVESD (mm)					
Survivors					
Range	27-50	28-50	30-51	37-52	32-43
Mean±SD	41.28±6.32	42.65±7.1	43.2±6.6	44.10±3.89	37.65±2.83
P1		0.352	0.41	0.33	0.44
Non-Survivors					
Range	29-46	30-45	31-44	32-44	-
Mean±SD	37.41±6.03	36.8±7.1	37.9±3.98	38.12±2.87	
P1		0.123	0.22	0.02	-
P2	0.024	0.013*	0.003*	0.001	-
LVEDD (mm)					
Survivors					
Range	48-63	47-62	48-65	48-65	47-58
Mean±SD	55.17±3.61	54.6±4.01	55.9±3.98	56.79±4.13	52.06±3.21
P1		0.42	0.52	0.10	0.16
Non-Survivors					
Range	45-59	46-60	45-59	48-56	-
Mean±SD	53.41±4.37	52.65±5.12	53.2±4.2	51.82±2.35	
P1		0.33	0.42	0.06	
P2	0.073	0.321	0.285	0.001	-
LA (mm)					
Survivors					
Range	28-42	29-45	28-43	30-42	31-43
Mean±SD	36.18±3.63	37.2±4.01	36.2±3.65	36.2±3.11	36.29±3.06

P is significant if ≤ 0.05

Table (7): Incidence of diastolic dysfunction on admission.

	Diastolic dysfunction		No diastolic dysfunction		Total
	No.	%	No.	%	
Survivors	5	29.4	12	70.6	17
Non survivors	13	44.8%	16	55.2	29
Total	18		28		46
p	0.036*				

P is significant if ≤ 0.05

Table (8): Comparison between survivors and non-survivors regarding BNP (pg/ml) and SOFA score at different periods

	Admission	Day 1	Day 2	Day 3	Discharge
BNP (pg/ml):					
Survivors					
Range	80-936	67-1071	74-1420	62-954	45-521
Mean±SD	345.01±222.10	415.22±271.63	431.2±269.11	406.2±295.39	163.69±134.39
P1		0.34	0.33	0.46	0.001*
Non-Survivors					
Range	145-1210	175-1345	312-1343	331-1478	-
Mean±SD	708.62±305.17	661.11±365.45	921.23±304.99	1022.11±363.41	
P1		0.02*	0.001*	0.001*	-
P2	0.001*	0.004*	0.001*	0.001*	-
SOFA:					
Survivors					
Range	3-10	3 – 11	4-12	4-12	0 – 1
Mean±SD	6.35 ±2.01	5.65±1.95	5.24±1.05	5.16±1.09	0.68±0.11
P1		0.098	0.088	0.08	0.0001*
Non-Survivors					
Range	4-12	5 – 13	7-15	8 – 15	-
Mean±SD	7.74±2.02	6.99±2.52	10.12±2.11	11.25±2.33	

P is significant if ≤ 0.05

The Brain Natriuretic Peptide (BNP)

BNP in survivors on admission ranged between 80 and 936 with a mean value of 345.01±222.1 pg/ml. This remained stable during day 1, 2 and 3 but decreased on discharge.

In non-survivors BNP ranged between 145 and 1210 pg/ml with a mean of 708.62±305.17 pg/ml on admission and changed significantly during the study period. The mean level decreased on day 1 then increased in day 2 and 3. Survivors had a significantly lower BNP level than the non-survivors on admission and at all three intervals (table 8).

Sequential Organ Failure Assessment score (SOFA)

SOFA score in survivors on admission ranged between 3 and 10 with a mean value of 6.35 ±2.01. This decreased insignificantly during days 1, 2, 3 but significantly on discharge. In non-survivors SOFA ranged between 4 and 12 with a mean of 7.74±2.02 on admission and decreased slightly at day 1 then increased significantly thorough days 2, 3 and till death. Survivors had a significantly lower SOFA score than the non-survivors on admission and at all intervals (table 8).
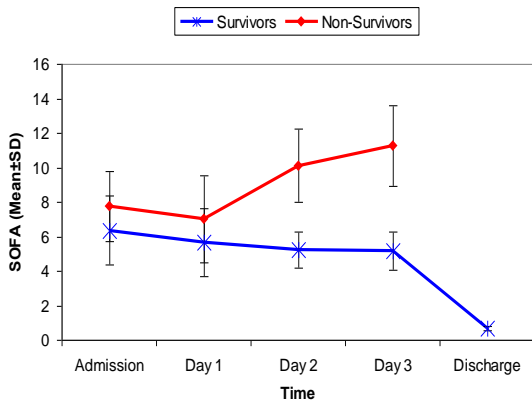
Figure (1): Comparison between survivors and non-survivors regarding BNP at different periods.
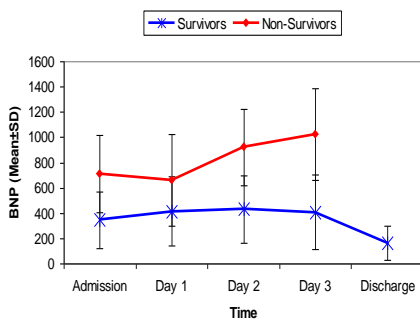

Figure (2): Comparison between survivors and non survivors regarding the SOFA score at different periods.

Sensitivity and specificity of BNP in diagnosing systolic heart failure: The sensitivity of a BNP level more than 100 pg/ml was 94% in detecting systolic heart failure as evidenced by an LVEF<55%. The specificity was 27.5% (table 9).

Table (9): Sensitivity and specificity of BNP in diagnosing systolic heart failure

	LVEF on admission		Total
	< 55%	>55%	
BNP > 100 pg/ml (%)	16 94.1%	21 72.4%	37
BNP < 100 pg/ml (%)	1 5.8%	8 27.5%	9
Total (%)	17 100%	29 100%	46

P is significant if ≤ 0.05

Correlation between the BNP and the left ventricular and atrial measurements and the SOFA score: There were no correlations between the BNP on admission and LVEF, LVESD, LVEDD and LA (table 10). Regarding the SOFA score, the BNP had a significant positive correlation with both the SOFA score and the delta SOFA which represents the change in the SOFA score over the first 48 hours of admission (table 10).

Table (10): Correlation coefficient between BNP and LVEF, LVESD, LVEDD, LA, SOFA and Delta SOFA score.

BNP	Pearson Correlation	P
LVEF	-.141	.349
LVESD	.188	.210
LVEDD	.191	.204
LA	.213	.155
SOFA	.435	.037*
Delta SOFA	.346	.025*

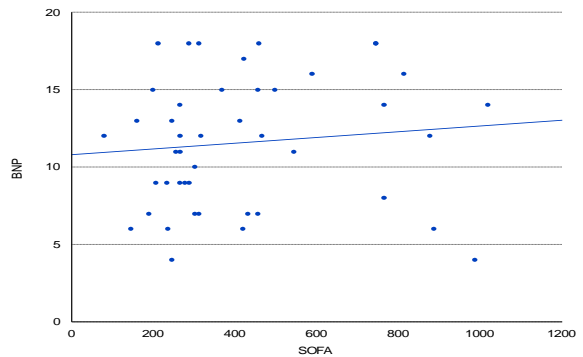Correlation is significant at the 0.05 level.

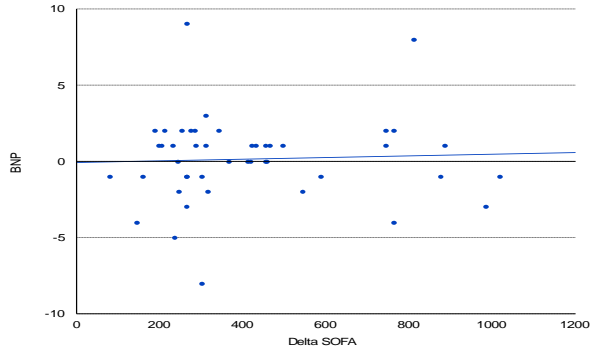**Figure (3): Correlation between BNP and SOFA**

Figure (4): Correlation between BNP and Delta SOFA

The cut off value of the BNP: The Receiver Operating Characteristic curve shown in table (11) demonstrates that a BNP level of 250.5 can signify a sensitivity of 82.8% and a specificity of 64.7% in testing the mortality of patients presenting with severe sepsis and septic shock.

Table (11): ROC Curve
Coordinates of the Curve:

Positive if Greater Than or Equal To(a)	Sensitivity	Specificity
250.50	.828	.647

Test Result Variable(s): BNP 0
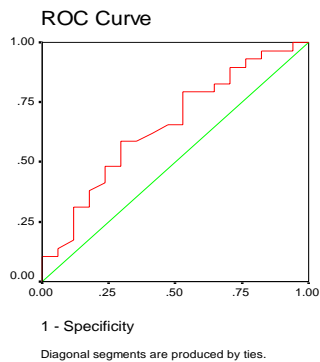
Figure (5): ROC Curve of the sensitivity and specificity of the BNP in detecting mortality

4. Discussions

The aim of the study was to evaluate the role of the brain Natriuretic peptide (BNP) as a diagnostic factor of new onset heart failure in critically ill patients presenting with severe sepsis and septic shock (sepsis induced cardiomyopathy) or as a prognostic factor of survival in the studied patients. We assessed both the left ventricular systolic and diastolic function by Echocardiographic study.

Among the studied patients 30 had severe sepsis and 16 had septic shock during the study. We used the criteria of the 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference to define and classify the patients. There was no significant difference between the two groups concerning the age and the gender. The two compared groups were homogenous.

A comparison between the fate of the patients (survival or not) with the heart rate on admission showed a significant difference between the two groups. This is in agreement with the findings of Parker et al. [4] that on admission, a heart rate less than 106 beats/min was associated with a favorable outcome. It is not known if such tachycardia is a sequence of myocardial dysfunction or is a part of the systemic inflammatory response syndrome. So despite simple the heart rate cannot be used as an argument of heart failure in septic patients.

In our study 47% of survivors and 82% of non-survivors was mechanically ventilation. The main indication of mechanical ventilation in septic patients is acute lung injury and acute respiratory distress syndrome. In addition the management attitude in our hospital is early mechanical ventilation of patients in septic shock which could explain that the majority of the non-survivors were intubated and ventilated. We do not think that such incidence of mechanical ventilation due to ARDS/ALI could alter the utility value of the BNP measurements as shown by recent researches. Berman et al. [40] work demonstrated that there was a significant difference between the cut off value of BNP in heart failure and ARDS (773 pg/mL in heart failure patients significantly higher than in patients with ARDS (123 pg/mL; p<0.001). Another study by Refaie et al [41] designed to explore the correlation of BNP Levels with mortality in patients admitted with septic shock and requiring mechanical ventilation included 576 patients and found a statistically significant association between the BNP and the survival/mortality. The last study was different than our study as it included only mechanically ventilated patients.

The first Echocardiographic examination was done within 12 hours of the patient admission. Concerning the left ventricular ejection fraction (LVEF) there was a significant difference between the survivors and non-survivors over the whole period. We used an ejection fraction of 55% as a threshold of heart failure according to the American Society of Echocardiography committee Recommendations for Chamber Quantification. [37] The left ventricular ejection fraction was less in the survivors than the non-survivors over the four compared measurements. The mean LVEF was 57.03% on admission in survivors group in comparison to 65.19% on admission in non survivors.

We can observe that the mean LVEF was decreasing in the survivor group during their stay then it had normalized at the end.

The relation between the left ventricular ejection fraction and the survival is a matter of debate in the literature. Our results are in agreement with the study carried by Parker et al [4] which found that survivors of septic shock were more likely to have decreased ejection fractions with increased end-diastolic volume index, whereas non survivors were more likely to have preserved cardiac volumes with less significant decreases in ejection fraction. Another study by Omar et al [42] is also in agreement with our study. The researchers in the last study observed on admission mean ejection fraction of 49% in survivors in comparison to 56.4% in the non survivors.

On the other hand our results are not in agreement with the study of Brueckmann et al [43] where 50% of the non-survivors had reduced LVEF against 20% of the survivors. The explanation of the lower left ventricular ejection fraction in the patients who survived was that they had a higher peripheral resistance and a better compliance leading to a better cardiac output and blood pressure despite the lower ejection fraction. Our study results' confirm this point as the survivors had a lower mean ejection fraction through the study with normalization at the end (before discharge), which confirm the reversibility of the myocardial dysfunction in those patients. The study of Parker et al [4] was in accordance with our findings in that the changes in myocardial function and volume were reversible in survivors over a period of 7–10 days. On the other hand, deficient volume resuscitation can explain a lower left ventricular dimensions and a better ejection fraction in the non-survivors as a cause and explanation of the mortality of those patients. Unfortunately studies are lacking correlating a higher ejection fraction with deficient resuscitation and fluid responsiveness. [44]

Twenty nine patients in our study had a normal ejection fraction (63% of the patients in the study) on admission and this is in accordance with the results observed by Brueckmann et al [43] where 63% of his patients had a systolic heart failure on admission. In our study 82% of the survivors and 51.7% of the non survivors had a normal ejection fraction which was similar to 80% and 50% respectively in the last study. The results of our results are nearly comparable to what Brueckmann et al [43] had observed. The incidence of systolic dysfunction as demonstrated as an ejection fraction less than 55% in 17 out of a total of 46 patients included in our study represent a percentage of 36.9% which was less than the 67% in a recent study of Sturgess et al.[45] This recent study published in 2010

had used the tissue Doppler as a new technique in the assessment of the left ventricular function but this alone cannot explain this higher incidence as the ejection fraction less than 55% was also used as the defining criterion of systolic failure despite by another 2-dimensional method (Simpson method). The limited number of patients in the Sturgess et al (n=21) and the higher SOFA score (11.6 ± 3.6 against 6.35 ± 2.01 in survivors and 7.74 ± 2.02 in non-survivors in our study) which denotes a more critically-ill patients could explain this difference in the incidence.

In our study, there was a significant difference between the LVESD with higher mean values in survivors than in non-survivors group all over the study period. The LVEDD was significantly higher in survivor group only at day 3. The difference in the left ventricular end systolic dimensions between the survivors and the non survivors could be explained by the fact that the survivors had a more dilated hearts with lower ejection fraction. There was no such significant difference in the left ventricular end diastolic dimension. There was no significant difference concerning the left atrial dimension.

The previous data confirms a left ventricular dilatation in the survivor group in comparison to the non-survivors which is in agreement with the explanation provided by Parker et al [4] about the left ventricular dilatation as a good prognostic sign in septic cardiomyopathy. Omar et al [42] had confirmed the same findings with a LVEDD and LVESD greater in the survivors than the non-survivor group. The mean values of LVESD in Omar et al [42] study were 4.01 ± 0.4 in survivors against 4.01 ± 0.38 cm in the non survivors. The difference in the LVEDD was insignificant (p=0.179) while it was significant for the LVESD (p=0,008). The insignificant data could be due to the insufficient number of patients (n = 30) included in the study of Omar et al. [42]

Regarding the left atrial diameter in the Parasternal view, there was no significant difference between the different groups regarding this item. To our knowledge only one study by Omar et al [42] explored the left atrial function in sepsis. It found insignificant correlation between the left atrial ejection fraction and the mortality in such patients and concluded that it cannot be used as an outcome predictor. The researchers in the last study used a different parameter than in our study. While we used the left atrial diameter as a simple measurement, they used the left atrial ejection force calculated by an equation. Another study by Sturgess et al [45] measured the left atrial size and found no significant difference between survivors and non-survivors.

The Echocardiographic measurements were used to assess the diastolic functions in our patients.

The parameters measured was the Early wave to Atrial wave ratio (E/A ratio) and the deceleration time (DT) measured in the apical four chamber view by the pulsed wave Doppler at the tips of the mitral valve. There was a significant difference concerning the E/A ratio and the DT.

Diastolic function identified by the mitral E/A ratio and DT could be classified into 4 phases including the normal, impaired LV relaxation, pseudonormal LV filling, and restrictive LV filling. The determination of the pseudonormal LV filling may be difficult by mitral inflow velocities alone. [38] The normal values vary with the age. We used the reference values of the American Society of Echocardiography according to the Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography published in February 2009. [38] In our study we used the tissue Doppler technique to differentiate the pseudonormal pattern of diastolic dysfunction from the normal pattern. A number of variables other than LV diastolic function and filling pressures affect mitral inflow, including heart rate, rhythm, PR interval, cardiac output, mitral annular size, and LA function. Age-related changes in diastolic function parameters may represent a slowing of myocardial relaxation, which predisposes older individuals to the development of diastolic heart failure. [38]

Eighteen patients had diastolic dysfunction in the two groups representing 39.1% of our patients. In the non survivors group thirteen patients out of twenty nine had diastolic dysfunction (44.8% of the group) in comparison to 5 out of 17 patients in the survivor group (29.4% of the group). There was a significant difference between the two groups.

Many studies had over lighted the incidence of diastolic dysfunction in septic patients. The total incidence of 44% in the overall group with a higher incidence in the non-survivors is in agreement with Jafri et al [46] who showed similar results using a transmitral Doppler analysis of 13 patients in septic shock, 10 in sepsis without shock, and 33 controls. Patients with septic shock and sepsis without shock had a significantly altered LV filling pattern in comparison with controls. These findings were confirmed by Poelaert et al [7] who found that 44% of patients with septic shock showed Echocardiographic features of diastolic dysfunction. In this study of systolic and diastolic function using Transoesophageal echocardiography and pulmonary artery catheters in 25 consecutive patients in septic shock, 8 of the 25 patients had no regional wall motion abnormality and a normal LV filling pattern; 11 had evidence of abnormal left auricular filling (pulmonary veins systolic/diastolic waves ratio < 1) but with a preserved systolic function and E/A waves

ratio. According to the investigators, transmitral flow in this group could be considered as 'pseudo-normalized' form of left ventricular diastolic dysfunction. Finally, 6 of the 25 patients exhibited both systolic and diastolic dysfunctions. The authors concluded that the cardiac effects of septic shock can be expressed in various degrees, ranging from a normal pattern, through diastolic dysfunction up to both poor LV systolic and diastolic functions resulting in combined cardiogenic-septic shock.

In another study by Bouhemad et al [47] approximately 20% of patients with septic shock have isolated diastolic dysfunction. Cardiac filling and relaxation were abnormal, whereas systolic function is preserved.

Advanced technology had allowed newer modalities to explore the diastolic dysfunction. Sturgess et al utilized the tissue Doppler as a bedside technique to explore the diastolic dysfunction and demonstrated E/e' as an independent predictor of hospital mortality. [46] In his study the incidence of diastolic dysfunction was 38% in the non-survivors against only 19% in the survivors. These results are in agreement with our results (44% and 29% in non survivors and survivors respectively). The advantage of the last study was the ability to better detect the diastolic dysfunction with a more sensitive technique with better categorization into the four stages of diastolic dysfunction. Diastolic function was graded as normal in nine (43%), impaired relaxation in three (14%), pseudonormal in seven (33%) and restrictive in two patients (10%). Thus, diastolic dysfunction was present in 57% of patients (n = 12). We used the tissue Doppler technique only to differentiate the pseudonormal pattern of diastolic dysfunction from the normal pattern.

The BNP was compared to the echocardiography as a gold standard in the diagnosis of both systolic and diastolic left ventricular function. In order to assess the left ventricular function the left ventricular end systolic and end diastolic diameter in the left Parasternal view was measured in order to calculate the left ventricular ejection fraction (LVEF). The diastolic function was assessed mainly by measuring the pulsed wave Doppler of the mitral inflow in the apical four chamber view.

The role of the BNP as a diagnostic test of heart failure was extensively explored in the recent years. In 2002, Maisel et al [48] demonstrated in his study: The Breathing Not Properly Study (BNP study) - a large multicenter investigation involving 1586 patients who presented to an emergency department (ED) with acute dyspnea – that a serum BNP level is useful to assist in differentiating between heart failure and pulmonary disease as a cause of dyspnea. In this study, a BNP level of 100

pg per mL or higher was 90% sensitive and 73% specific for diagnosing congestive heart failure (CHF).

According to the published researches [10,49] concerning the sepsis induced cardiomyopathy, it has been proposed that myocardial depression contributes to septic shock in at least 50 % of the patients. This study was carried to explore if the BNP could be used to diagnose new onset heart failure in septic patients or it is more likely related to the prognosis and subsequently to the pathophysiology of sepsis in such patients.

It was generally a matter of debate to measure either the BNP or the NT-pro BNP in septic patients. Studies using the NT-proBNP which is a more stable precursor of the BNP in septic patients had delineated its benefit as a prognostic factor. Piechota et al [50] showed in his study this correlation. In his study, the correlation coefficient between NT-proBNP level and SOFA score was R=0.5164. Brueckmann et al [43] studied the Prognostic Value of Plasma Nt pro-BNP in patients with severe sepsis in 57 patients. He found no correlation between the NT-pro BNP and the left ventricular function (r=0.41). NT-proBNP levels of survivors and non-survivors were statistically significant different with higher levels in non-survivors. Septic patients with NT-proBNP levels >1400 pmol/L were 3.9 times more likely to die of sepsis than patients with lower NT-proBNP values (RR, 3.9; 95% CI). With this cutoff, sensitivity (patients who will die with NT-proBNP-test results >1400 pmol/L) was 50.0%, specificity (patients who will survive with NT-proBNP test results <1400 pmol/L) was 90.2%.

In our study we decided to utilize the BNP in our study due to the more reliable measurements of the BNP in renal failure patients − a common finding in critically ill septic patients - as shown by DeFilippi et al [51] who concluded on his review that the NT-proBNP rises disproportionately to BNP at lower eGFRs. Although both BNP and Nt-proBNP could be influenced by the renal function and the age. MCCullough et al [52] had confirmed that NT-proBNP had a stronger correlation with eGFR, and is influenced by the age-related decline in renal function above the lower bounds of normal than the BNP. MCCullough et al [52] concluded that the BNP is influenced by renal filtering function and tubular function but can be used in assisting in the diagnosis and management of combined heart and renal failure.

On admission, days 1, 2, 3 the BNP in non-survivors group was statistically higher than survivors group. The results of our study are in agreement with other studies concerning the role of BNP in septic patients. Cuthbertson et al [53] showed in his study that there was a trend toward higher BNP

levels on ICU admission and at 24 h in survivors. Although this is not in agreement with our study, the trend was not statistically significant in Cuthbertson's study. Sturgess et al [45] found levels of BNP, of 448 ± 607 ng/L and 1289 ± 1155 ng/L in survivors and non survivors respectively but the results were not significant. The difference in the values of the BNP in the different studies could be explained by the different kits of analysis with different sensitivity. The non-significance in the last study could be attributed to the small number of patients included. (n=21)

In our study we calculated the sensitivity and specificity of the BNP (using a cut off value of 100 pg/ml) for the diagnosis of heart failure (ejection fraction less than 55%). The sensitivity of a BNP level was 94% in detecting systolic heart failure. The specificity was 27.5%. This means that the BNP was sensitive but not specific, limiting its role when measured on admission to exclude systolic heart failure.

Regarding the importance of the age as an influencing factor for both the diastolic and the BNP measurements, we cannot consider that there is a significant difference in the mean age of our patients in comparison to patients in other comparable studies. The age ranged from 26 to 79 years with a mean age of 60.1±13.3 years, and this was slightly lower than that observed in the studies concerning the epidemiological data of septic shock patients including that of Annane et al, [54] where the patients had a mean age of 61.4± 16.6 years. Another study by Brueckmann et al (43) studying the role of Nt-pro BNP had a mean age of the enrolled patients at 55.0 ±16.3 years. In comparison to our study which included patients with both severe sepsis and septic shock, the first study included only septic shock patients and the second patients with severe sepsis which can explain the slight difference in the age.

This is important as the relation between age and the levels of natriuretic peptides is well described by Redfield et al [55] and Kato et al [56] in healthy and heart failure subjects. In a large group of healthy adults (n=911), Wang et al. [57] calculated multivariate correlations between BNP and age. After multivariate adjustment, a 10-year increase in age was associated with a 1.4 fold increase in BNP levels. Another large study in healthy subjects (n=216) showed a weak but significant relationship between age and the BNP. [58] Raymond et al. [59] analyzed a healthy sub group (n=130) of a large sample of the general population, and found a strong positive relationship between the NT-proBNP and the age.

The prognostic impact of BNP with respect to mortality was also found by Tung et al [60] in evaluating BNP levels in 49 ICU patients with shock,

mainly of non-cardiac origin. Tung et al [60] found no correlation between BNP and cardiac index and PCWP but a significant higher BNP levels in non-survivors than in survivors, with a correlation between the BNP and the ICU mortality.

The pilot study by Witthaut and coworkers [61] showed an inverse correlation between BNP and cardiac index (r = - 0.56), whereas BNP correlated neither with stroke volume nor left ventricular systolic work index (LVSWI), nor pulmonary capillary wedge pressure (PCWP). Plasma BNP levels in patients with septic shock were higher than those in control subjects, but absolute values were very low, which might have been due to the some technical problems. Despite not using the same hemodynamic parameters as Witthaut et al [61], our study showed also no correlation between BNP and the Echocardiographic findings. In our study there was no correlation between the BNP and the LVEF, LVESD, LVEDD nor the LA dimension.

A small retrospective analysis by Maeder et al [61] revealed that BNP levels in patients with sepsis and preserved systolic left ventricular function can be as high as that in patients admitted to the hospital because of CHF due to severely impaired systolic left ventricular function (sepsis, 6 from 8 patients with a BNP level of > 1,000 pg/mL; CHF, 5 from 8 patients with BNP of > 1,000 pg/mL).

As a conclusion, our study is in agreement with many studies which show the prognostic value of BNP in patients with severe sepsis and septic shock. Despite difficulty to compare the values of the BNP and the NT-proBNP, our study is in agreement with the findings which found a correlation between the NT-proBNP and the survival of patients.

Regarding the prognostic value of the BNP, we used the Sequential Organ Failure Assessment score (SOFA score) as the comparison score. SOFA score in the present study over the whole period from admission to discharge in non survivors group were statistically higher than the survivors group. In the survivor group the SOFA decreased progressively between the admissions till the discharge.

The SOFA Score developed in 1994 by a panel of experts of the European Society of Intensive Care (ESICM), and it quantifies the dysfunction/failure of six organ/systems: respiratory, hematological, hepatic, cardiovascular, neurological and renal, punctuated from 0 (normal function) up to 4 points (severe failure). It presents therefore a maximum score of 24 points. [39] The SOFA has been validated in several contexts, presenting a good behavior in unselected critically ill patients, and in patients with trauma, renal failure, and cardiovascular disorders. The SOFA has been used in several clinical studies. [62]

We selected the SOFA score as a gold standard of comparison to assess the prognosis. As evidenced the non survivors group had a significant higher SOFA score than the non survivors. This is in agreement with other studies. Ferreira et al [63] studied the SOFA score during the first few days of ICU admission and found that it is a good indicator of prognosis. Both the mean and highest SOFA scores are useful predictors of outcome. Apart from the initial score, an increase in SOFA score during the first 48 hours in the ICU predicts a mortality rate of at least 50%.

Studies in the critical care units use the scoring systems to assess the disease severity to secure homogeneity of the comparison groups as well as to correlate the markers to the prognosis. Vosylius et al [64] concluded in his study that the severity of organ dysfunction as represented in the SOFA score proved to be a good factor in discriminating outcome for the patients with severe sepsis. The assessment of organ dysfunction should be used for risk stratification in clinical trials including critically ill patients with severe sepsis.

The admission SOFA score in our study is not different than the study of Piechota et al. [50] In his study, the mean SOFA score were 6.31±3.75 points in the overall group in comparison to 6.35±2.01 and 7.74±2.02 in the groups of survivors and non-survivors respectively in our study. On the other hand, Sturgess et al [45] used the APACHE II and the SOFA scores. The SOFA score in the last study was higher than in our study which was 10.3±2.6 in the survivors group (6.35±2.01 in our study) and 12.3±2.7 in the non survivors (7.74±2.02 in our study). It is obvious that the SOFA score correlates with the selection criteria which could be different in different ICUs in different countries. As previously discussed this had an impact on the results difference between our and Sturgess' study.

In our study, the BNP had a significant correlation with both the SOFA score and the delta SOFA which represents the change in the SOFA score in the first 48 hours of admission. This is in agreement with the study of Piechota et al [50] despite he used the NT-proBNP, as he showed a correlation between the NT-proBNP level and the SOFA score (R=0.5164).

Kandil et al [65] had demonstrated that the SOFA scores, and therefore the severity of sepsis, were higher in patients with sepsis compared with scores of those recovering from sepsis. The analysis in this study demonstrated a significant positive correlation between BNP levels and SOFA scores. This positive correlation was consistent for late septic shock.

There was a significant correlation also with the delta SOFA. The value of the initial trend of the SOFA score was described by Ferreira et al. [63] In this study the trends in SOFA scores during the first 48 hours were analyzed. Regardless of the initial score, the mortality rate was 50% or higher when the score increased, 27% to 35% when it did not change, and less than 27% when it decreased. Differences in the mortality rate were better predicted during the first 48 hours than in the subsequent 48 hours.

Moreno et al [66] recently demonstrated that the initial SOFA score can be used to quantify the degree of organ dysfunction or failure present on admission, that the Delta –SOFA score can demonstrate the degree of dysfunction or failure developing during an ICU stay. They also demonstrated a strong correlation of all these parameters with mortality and outcome.

The significant correlation in our study with the delta SOFA score confirms the prognostic value of the BNP in our patients. We calculated a cut off value for the BNP. A cut off value of 250.5 pg/ml was 82.8% sensitive and 64.7% specific in predicting the mortality in our patients who represents critically ill patients with severe sepsis and septic shock.

Charpentier et al [8] showed that a BNP cut off value of > 190 pg/mL could differentiate survivors from non survivors with a sensitivity of 70% and a specificity of 67% in patients presenting with severe sepsis. This cut off level, sensitivity and specificity is not different from our calculated values.

Ueda et al [67] found that the optimal cut off point for predicting mortality in patients with septic shock was a BNP level of 650 pg/mL on day 2, in which sensitivity and specificity were 92% and 80%, respectively. The difference in the cut off level may be due to the measurements of the BNP on the second day as it increases steadily in non survivors.

In our study the mean duration of stay was 7.62±3.68 ranging from 3 to 18 days. This duration was less that that observed in other studies like the early goal directed therapy in severe sepsis and septic shock by River et al. [68] This could be explained by the higher mortality in our unit for both severe sepsis and septic shock patients. The duration of stay was longer in the non-survivors than the survivors. This is different than what was observed by Zanon et al [69] with a mean of 6 days for the survivors and 5 days for the non-survivors. Because of the different protocols in the different ICUs all over the world, the duration of stay is related more to the local criteria of discharge than the prognosis. In our study, the difference could be explained by the higher rate of late complications and the earlier discharge of the survivor patients from our unit.

The comparison of patients presenting only with severe sepsis (n=30) and those presenting with septic shock (n=16) show that the mortality rate of severe sepsis included in our study was 50% (15 out of 30 patients) and was 87.5% in patients with septic shock (14 out of 16 patients). In the largest epidemiological study concerning sepsis in Europe (SOAP study) [70] the ICU mortality rate of patients with severe sepsis and septic shock was 32.2% and 54.1% respectively. The mortality rate was higher for both severe sepsis and septic shock which could be contributed to the problem of facilities, less implementation of protocols and the difference in the level of training of doctors and the nursing staff.

Limitations:

Our study had not included new modalities in the assessment of the diastolic function as the tissue Doppler except for the differentiation of the pseudonormal pattern of diastolic dysfunction from the normal pattern. This could be explained by the fact that our study protocol was written in 2008 before the new guidelines concerning the diastolic function get published in 2009. Moreover we had not assessed the alteration in the right ventricular function which could be a part of the septic cardiomyopathy.

The ejection fraction despite a good indicator of the left ventricular systolic function is affected by the preload and the afterload, so the left ventricular stroke work index could be a better index but its measurement necessitates an invasive procedure not available in the practical work in our ICU. Also, the Echocardiographic examination had demonstrated an intra-observer and inter-observer bias which could affect the accuracy of the results and depends upon the experience of the investigator.

Last, our study was not a blind study which may affect the results.

There is no conflict of interest in our study.

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References
1. Balk BA. The septic syndrome. Definition and clinical implications. Crit Care Clinics 1998; 5: 1–8.
2. Waisbren BA. Bacteremia due to gram-negative bacilli other than the Salmonella: a clinical and therapeutic study. AMA Arch Intern Med. 1951; 88:467– 88.

3. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29:1303–10.

4. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, Damske BA, Parrillo JE. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med. 1984; 100:483– 90.

5. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP. Septic shock in humans: advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med. 1990; 113: 227–42.

6. Morelli A, De Castro S, Teboul J-L: Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 2005; 31:638–44.

7. Poelaert J, Declerck C, Vogelaers D, Colardyn F, Visser CA. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997; 23: 553–60.

8. Charpentier J, Luyt C-E, Fulla Y: Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med 2004; 32:660–5.

9. Court O, Kumar A, Parrillo JE, Kumar A. Clinical review: Myocardial depression in sepsis and septic shock. Crit Care 2002; 6: 500–8.

10. Charpentier J, Luyt CE, Fulla Y, Vinsonneau C, Cariou A, Grabar S, Dhainaut JF, Mira JP, Chiche JD. Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med 2004; 32: 660–66.

11. Jardin F, Fourme T, Page B, Loubieres Y, Vieillard-Baron A, Beauchet A, Bourdarias JP. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. Chest 1999; 116: 1354–9.

12. Vincent JL, Gris P, Coffernils M, Leon M, Pinsky M, Reuse C, Kahn RJ. Myocardial depression characterizes the fatal course of septic shock. Surgery 1992; 111: 660–7.

13. Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. Circulation. 1986; 73: 637–44.

14. Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W. A circulating myocardial depressant substance in humans with septic shock: septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. J Clin Invest. 1985; 76:1539 –53.

15. Horton JW, Maass D, White J, Sanders B. Nitric oxide modulation of TNF-alpha-induced cardiac contractile dysfunction is concentration dependent. Am J Physiol Heart Circ Physiol. 2000; 278: H1955–H1965.

16. Francis SE, Holden H, Holt CM, Duff GW. Interleukin-1 in myocardium and coronary arteries of patients with dilated cardiomyopathy. J Mol Cell Cardiol. 1998; 30:215–23.

17. Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science. 1992; 257:387–9.

18. Reines HD, Halushka PV, Cook JA, Wise WC, Rambo W. Plasma thromboxane concentrations are raised in patients dying with septic shock. Lancet. 1982; 2:174 –5.

19. Shindo T, Kurihara H, Kurihara Y, Morita H, Yazaki Y. Upregulation of endothelin-1 and adrenomedullin gene expression in the mouse endotoxin shock model. J Cardiovasc Pharmacol. 1998; 31:S541–S544.

20. Khadour FH, Panas D, Ferdinandy P, Schulze C, Csont T, Lalu MM, Wildhirt SM, Schulz R. Enhanced NO and superoxide generation in dysfunctional hearts from endotoxemic rats. Am J Physiol Heart Circ Physiol. 2002; 283:H1108–H1115.

21. Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiol Rev. 2007; 87:315– 424.

22. Raeburn CD, Calkins CM, Zimmerman MA, Song Y, Ao L, Banerjee A, Harken AH, Meng X. ICAM-1 and VCAM-1 mediate endotoxemic myocardial dysfunction independent of neutrophil accumulation. Am J Physiol Regul Integr Comp Physiol. 2002; 283:R477–R486.

23. Azimi G, Vincent J-L: Ultimate survival from septic shock. Resuscitation 1986; 14: 245–53.

24. Hersch M, Gnidec AA, Bersten AD: Histologic and ultrastructural changes in nonpulmonary organs during early hyperdynamic sepsis. Surgery 1990; 107:397–410

25. Cowley RA, Merger WJ, Fisher RS: The subcellular pathology of shock in trauma patients: Studies using immediate autopsy. Am Surg 1979; 45:255–69.

26. Gellerich FN, Trumbeckaite S, Hertel K: Impaired energy metabolism in hearts of septic baboons: Diminished activities of complex I and complex II of the mitochondrial respiratory chain. Shock 1999; 11: 336–41.

27. Suliman HB, Carraway MS, Piantadosi CA: Postlipopolysaccharide oxidative damage of

mitochondrial DNA. Am J Respir Crit Care Med 2003; 167:570–9.

28. Brand MD, Esteves TC: Physiological functions of the mitochondrial uncoupling proteins UCP2 and UCP3. Cell Metab 2005; 2:85–93.

29. Larche J, Lancel S, Hassoun SM: Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality. J Am Coll Cardiol 2006; 48:377–85.

30. Hotchkiss RS, Song SK, Neil JJ: Sepsis does not impair tricarboxylic acid cycle in the heart. Am J Physiol Cell Physiol 1991; 260:50–57+233.

31. Burke, M.A. and Cotts, W.G. Heart Failure Reviews 2007; 12, 23 – 36.

32. Hartemink KJ, Groeneveld J, de Groot MC, Strack van Schijndel RJ, van Kamp G. Thijs LG. a-Atrial natriuretic peptide, cyclic guanosine monophosphate, and endothelin in plasma as markers of myocardial depression in human septic shock. Crit Care Med 2001; 29:80-7.

33. Ellrodt AG, Riedinger MS, Kimchi A, et al. Left ventricular performance in septic shock: reversible segmental and global abnormalities. Am Heart J 1985; 110:402-9.

34. Joseph MX, Disney PJS, Da Costa R, et al. Transthoracic echocardiography to identify or exclude cardiac cause of shock. Chest 2004; 126: 1592-7.

35. Vignon P. Hemodynamic assessment of critically ill patients using echocardiography Doppler. Curr Opin Crit Care 2005; 11: 227-34.

36. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, for the International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530-8.

37. Lang R.M., Bierig M., Devereux R.B., Flachskampf F.A., Foster E., Pellikka P.A. et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18:1440-1463.

38. Nagueh SF., Appleton CP., Gillebert TC, Marino PN, Oh JK, Smiseth OA et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. Journal of the American Society of Echocardiography 2009; 22 (2): 108-28.

39. Berridge JC. Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation. Br J Anaesth. 1992; 69:409-10.

40. Berman B, Spragg R, Maisel A. B-type natriuretic peptide (BNP) levels in differentiating congestive heart failure from acute respiratory distress syndrome (ARDS). Abstracts from the 75th Annual Scientific Meeting of the American Heart Association. Circulation. 2002; 106:S3191.

41. T. Refaie T., Mahmood N., Moammar M.Q., Chaudry F.A., DeBari V. A. and Khan M. A. Correlation of BNP Levels with Mortality in Patients Admitted with Septic Shock and Requiring Mechanical Ventilation. Am J Respir Crit Care Med 179; 2009:A4728.

42. Omar AS., Rahman M., AbuHasna M. Left atrial function as outcome prediction in severe sepsis and septic shock: An echocardiographic study. Indian J Crit Care Med April-June 2009; 13:2: 59-65.

43. Brueckmann M., Huhle G., Lang S., Haase KK., Thomas Bertsch T., Weiß C. et al. Prognostic Value of Plasma N-Terminal Pro-Brain Natriuretic Peptide in Patients With Severe Sepsis. Circulation. 2005; 112:527-34.

44. Coudray A., Romand J.A., Miriam Treggiari M, Bendjelid K. Fluid responsiveness in spontaneously breathing patients: A review of indexes used in intensive care. (Crit Care Med 2005; 33:2757–62.

45. Jafri SM, Lavine S, Field BE, Bahorozian MT, Carlson RW. Left ventricular diastolic function in sepsis. Crit Care Med 1990; 18: 709–14.

46. Sturgess DJ., Marwick TH., Joyce C., Jenkins C., Jones M., Masci P., Stewart D., Venkatesh B. Prediction of hospital outcome in septic shock: a prospective comparison of tissue Doppler and cardiac biomarkers. Critical Care 2010, 14:R44.

47. Bouhemad B, Nicolas-Robin A, Arbelot C, et al. Acute left ventricular dilatation and shock-induced myocardial dysfunction. Crit Care Med 2009; 37:441–7.

48. Maisel AM, Krishnaswamy P, Nowak R, Mccord J, Hollander JE, Duc P, et al. Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure from the Breathing Not Properly (BNP) Multinational study. N Engl J Med 2002; 347:161-7.

49. Rabuel C, Mebazaa A. Septic shock: a heart story since the 1960s. Intensive Care Med 2006; 32: 799–807.

50. Piechota M., Banach MJ, Irzmański R., Piechota-Urbańska M., Kowalski J., Pawlicki L. NT-proBNP levels correlate with organ failure in septic patients: A preliminary report.

51. DeFilippi CR and Christenson RH. B-Type Natriuretic Peptide (BNP)/NT-proBNP and Renal Function: Is the Controversy Over? Clinical Chemistry 2009; 55:7: 1271–3.

52. MCCullough et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the breathing not properly multinational study. Am J Kidney Dis 2003; 41:571-9.

53. Cuthbertson BH, Patel RR, Croal BL, et al. B-type natriuretic peptide and the prediction of outcome in patients admitted to intensive care. Anaesthesia 2005; 60:16–21.

54. Annane D., Aegerter P., Jars-Guincestre MC, and Guidet B. Current Epidemiology of Septic Shock. Am J Respir Crit Care Med 2003; 168: 165–72.

55. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett Jr JC. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002; 40:976– 82.

56. Kato J, Kitamura K, Uemura T, et al. Plasma levels of adrenomedullin and atrial and brain natriuretic peptides in the general population: their relations to age and pulse pressure. Hypertens Res 2002; 25:887– 92.

57. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002; 90: 254–8.

58. Clerico A, Del Ry S, Maffei S, Prontera C, Emdin M, Giannessi D. The circulating levels of cardiac natriuretic hormones in healthy adults: effects of age and sex. Clin Chem Lab Med 2002; 40:371–7.

59. Raymond I, Groenning BA, Hildebrandt PR, et al. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. Heart 2003; 89:745– 51.

60. Tung RH, Garcia C, Morss AM, et al. Utility of B-type natriuretic peptide for the evaluation of intensive care unit shock. Crit Care Med 2004; 32:1643–7.

61. Witthaut R, Busch C, Fraunberger P, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis associated left ventricular dysfunction. Intensive Care Med 2003; 29:1696–702.

62. Vincent JL., Carlet J., Opal SM. The sepsis text. 2002. p 38.

63. Ferreira FL., Bota DP, Bross A., Me´lot C., MD, Vincent JL. Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients JAMA, 2001; 286 (14) 1754-8.

64. Vosylius S., Sipylaite J., Ivaskevicius J. Sequential Organ Failure Assessment Score as the Determinant of Outcome for Patients with Severe Sepsis. Croat Med J 2004; 45:715-20.

65. Kandil E., Burack J., Sawa A., Bibawy H.,Schwartzman A., Zenilman ME.,Bluth MH. B-Type Natriuretic Peptide A Biomarker for the Diagnosis and Risk Stratification of Patients with Septic Shock. Arch Surg. 2008; 143(3):242-6.

66. Moreno R, Vincent JL, Matos A, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care: results of a prospective, multicentre study. Intensive Care Med. 1999; 25:686-96.

67. Ueda S, Nishio K, Akai Y, Fukushima H, Ueyama T, Kawai Y, Masui K, Yoshioka A, Okuchi K. Prognostic value of increased plasma levels of brain natriuretic peptide in patients with septic shock. Shock. 2006 Aug; 26(2):134-9.

68. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345:1368 –77.

69. Zanon F., Caovilla JJ., Michel RS., Cabeda EV., Ceretta DF., Luckemeyer GD., Beltrame C., Posenatto N. Sepsis in the Intensive Care Unit: Etiologies, Prognostic factors and Mortality. Revista Brasileira de Terapia Intensiva 2008; 20 (2): 128-34.

70. Vincent JL., Sakr Y., Sprung CL., Ranieri VM., Reinhart K., Gerlach H. et al. Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 2006; 34:344–53.

1/11/2011