Original Article

# Incidence and prognostic impact of myocardial dysfunction in Sepsis and Septic shock

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## ABSTRACT

**Introduction:** The high rate of mortality in the ICU has been attributed to severe sepsis and septic shock. Many studies have pursued the impact of sepsis in inducing dysfunctions in the heart with conflicting results. **Objectives:** To evaluate the myocardial dysfunction and tumor necrosis factor-α(TNF- α) as prognosticators of death among these patients. **Patients and method:** A total of 40 patients complaining from severe sepsis or septic shock participated in this prospective observational investigation. All clinical, biochemical and hematological items were collected. Two echocardiographic examinations were done on all patients: the first as soon as they were admitted, and the second 24hrs later. Generally, systolic dysfunction has been known as LVEF ≤ 50%, whereas, diastolic dysfunction has been known as a reduced septal e-wave velocity < 8 cm/s or E/e ratio > 8 on tissue Doppler imaging (TDI). **Results:** Fifty percent of the patients developed myocardial dysfunction (systolic and/or diastolic). Diastolic dysfunction incidence was greatly higher than systolic dysfunction (45% versus 15%). Importantly, diastolic dysfunction was associated with higher ICU mortality, while systolic dysfunction did not show any association with mortality. The patients with myocardial dysfunction were older (66.6±18.7 versus 47±20.5, $p = 0.003$), with elevated values of SOFA and APACHE II score (66.6±18.7 versus 47±20.5, $p = 0.003$). The concentration of lactate in the serum was higher compared to those who maintained normal cardiac function (7.57±3.86 versus 5.5±1.9, $p = 0.008$). Of note, serum TNF-αlevels failed to show a correlation with the indication of the presence of systolic or diastolic myocardial dysfunction by ECO. Moreover, this study also showed that in septic subjects, other predictors of death in ICU were: high serum lactate, elevated SOFA and APACHE II scores, increased vasopressor and mechanical ventilation support as well as low cardiac index, drop in the resistance of vascular system and low index of contractility. **Conclusion:** Myocardial insufficiency precisely occurred in septic shock and severe sepsis. Diastolic dysfunction was accompanying with higher ICU death, while systolic dysfunction had no impact on mortality. Moreover, TNF-α had no correlation with systolic or diastolic dysfunction confirmed by ECO, and had no effects on the outcomes.

**Keywords:** sepsis, Septic shock, Myocardial dysfunction, TNF, Mortality.

## Introduction

Systemic and harmful body reaction to infection or injury has been known as sepsis, which leads to severe sepsis and consequently septic shock, which in ICU are responsible for elevating the percentage of morbidity and death [1]. Moreover, the sepsis pathogenicity mainly depends on the cardiovascular system, which is responsible for spreading infection in the whole body. Most of the studies which have been carried out along 50 years have recorded that in septic individuals, the myocardial dysfunction is predominate and more than half of the subjects with sepsis have complained from the symptoms of myocardial dysfunction. However, the precise clinical importance of sepsis that is capable for inducing dysfunction in the myocardium (SIMD) has remained indefinable. The heart and blood vessels are the components of cardiovascular system (CVS), where the heart represents only one main part of this system, regularly affected to any changes in the peripheral hemodynamics, so, it is not easy to discriminate between cardiac replies to changes in preload, afterload or/and neurohumoral action in sepsis and the direct effect of clinical location of sepsis on the heart [2]. Advanced research studies revealed that in most of the clinical investigations, the

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myocardial dysfunction was linked with the elevated mortality rate among the septic affected subjects [3, 4]. It has also been investigated that the prediction of mortality in patients has been affected with severe sepsis and septic shock which have been mainly depended on diastolic disability than the systolic ones [5]. Therefore, in the current work, it was tried to clarify the incidence of dysfunction in both systolic and diastolic subjects, and to evaluate their prognostic impacts on the patients' outcomes.

Moreover, the pathophysiology of dysfunction in cardiac muscles in the septic condition is a complicated multifactorial process. Numerous inflammatory substances have been incriminated as myocardial depressant factors including IL-6. TNF-α, tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1 and attributed to disturbance of the intimate links amid endothelial cells, leading to enhanced absorptivity to plasma fluid and blood proteins with comprehensive tissue swelling and subsequent organ dysfunction [6]. Hence, it was tried to clarify the relationship among the concentration of TNF-αin the serum and degree of myocardial dysfunction. Further, the impact of high TNF-α level as an interpreter of deaths in individuals with severe sepsis and septic shock has been evaluated.

## Methods

This investigation was a prospective observational work that included 40 adult patients (25 females and 15 males, with the age range of 56.8±21.8), who were initially diagnosed at the time of admission with severe sepsis and/or septic shock. The study was conducted in the Critical care department of Cairo University during the time period from January 2016 to November 2016. The research was permitted by the local ethical committee. The subjects were classified into 2 groups: 20 subjects were suffering from the dysfunction in the cardiac muscles (systolic and/or diastolic), and 20 patients with the normal cardiac function.

### Inclusion criteria:

All severe septic or septic shock subjects admitted to the ICU, were joined in the study. Septic shock was known as sepsis-induced hypotension (SBP < 90 mmHg) lasting for more than 1 hour, not responding to aggressive fluid therapy, and requiring vasopressor therapy to keep MAP more than 65 mmHg. The patients were managed according to the ICU management protocol guided by Surviving Sepsis Campaign guidelines.

### Exclusion criteria:

The presence of echocardiographic evidence of local wall motion irregularity suggested regional ischemia or previous infarction.

Patients with known history of heart failure, presence of significant pericardial effusion, major cardiac arrhythmias, presence of more than mild aortic or mitral valve disease, known diagnosis of systemic or pulmonary arterial hypertension were excluded from the study.

Detailed case history was taken from all subjects joined in the study and thorough clinical examination. Haemodynamic parameters including central venous pressure (CVP), mean arterial pressure (MAP), central venous o2 saturation (ScvO2), SaO2 and heart rate (HR), were all recorded, and the mean values were calculated. Routine labs including arterial blood gases, complete blood count (CBC), C-reactive protein (CRP), serum albumin, and serum creatinine levels, were also recorded and the mean values were calculated. Serum lactate level was assayed on the onset of admission and after 6 hours. The need for vasopressor therapy, renal replacement therapy and mechanical ventilation was also recorded. The source of sepsis and the results of pan cultures including microbial blood cultures were positive, and the type of organism (if present) was also documented. APACHE II score value at the onset of admission as well as the maximal daily calculated SOFA score were recorded. The period of remaining in the ICU, and also, the ICU mortality were registered for all patients.

### Tumor necrosis factor-alpha (TNF)

TNF-α values in the serum at different intervals of 12 hours and 48 hours after the admission (Detection range is 15.6-1000 pg/ml) were assayed. They were measured by enzyme-linked immunosorbent assay kits (ELISA). This particular cytokine was chosen because it has been one of the most frequently cited cytokines in scientific papers and its correlation with sepsis and dysfunction of cardiac muscle has been declared.

### Transthoracic echocardiography (TTE)

Echocardiography was performed to all patients using Siemens Acuson X 300 PE Ultrasound machine. All patients underwent 2 transthoracic echocardiographic examinations, at or shortly after the admission, or diagnosis of septic and/or septic shock patients. The second one was performed 24hrs after the admission to confirm the stability of the results. There was a non- significant variation among the two sequential studies in any of the parameters measured, hence the results of all the measurements from both studies were averaged, and only the averaged results were documented and used for the further analysis. The assays described below were performed by means of the customary parasternal and apical views.

### Left ventricular systolic function:

LV end-diastolic, end-systolic volumes (EDV and ESV),LV ejection fraction (LVEF), EDD, ESD as well as LA diameter were considered. Systolic dysfunction was defined as reduced to LVEF < 55%.

### Left ventricular diastolic function:

### Mitral inflow signals:

Peak mitral inflow E (peak early filling) and A (late diastolic filling) velocity waves on pulsed-wave Doppler, E/A ratio, E-wave deceleration time (DT), and isovolumic relaxation time (IVRT) were considered. The latter was measured via putting the pointer of continuous wave (CW) Doppler in the LV outflow zone to show the onset of mitral inflow, and the termination of aortic ejection.

### Tissue Doppler imaging (TDI):

Pulsed wave (PW) TDI was performed in the apical 5-chamber view to measure the mitral annular velocities. The systolic (s´),

early diastolic (e′) and late diastolic (a′) velocities were measured. In this study, it was focused on the peak septal mitral annular e′-wave velocity. The E/e ratio was then derived by dividing the E-wave mitral inflow velocity by the e′-wave mitral annular velocity. LV diastolic dysfunction was defined as E/e ratio > 8 or peak septal e′-wave velocity < 8 cm/s, based on a previous observation that these patients had a significantly worse survival [7].

## Impedance cardiography (ICG):

Thoracic electrical bioimpedance (TEB) which has been recently called impedance cardiography (ICG), has been a new tool which transforms the changes in impedance to variations in the volume along the time. The volumetric alterations arising throughout the cardiac cycle can be detected by ICG. Four surface electrodes were fixed on the skin; 2 electrodes on the left side of the neck and 2 electrodes on the lower thorax in the midaxillary line. The discontinuous current was conveyed via the chest. The current search was done on the path of low resistance (the blood-filled aorta). Standard impedance to current was recorded. Each heartbeat, blood velocity and volume in aorta were changed. The resultant alterations in the impedance were then applied with ECG to give hemodynamic measures. The following hemodynamic parameters were measured:

Cardiac Output (CO/CI): volume of blood ejected per minute.
Stroke Volume (SV/SI): volume of blood ejected per heartbeat.
Thoracic Fluid Content (TFC): total fluid volume in the thorax.
Systemic Vascular Resistance (SVR): afterload indicator.
Index of Contractility (ICON): indicator of LV contractility.

ICG determinations were gotten at the same time of echocardiographic study. Similarly, the outcomes were in the form of means, and only the averaged data were used for further analysis.

## Statistical analysis:

The data were statistically analyzed in terms of mean Mean±SD, range and median, or percentages and frequencies when appropriate. The comparison of different variables within the tested groups was performed by applying Student t test for independent samples for comparing normally distributed data, and Mann Whitney *U* test for the independent samples for comparing not-normal data. For comparing the categorical data, Chi-square test was performed. Exact test was used instead when the expected frequency was less than 5. The correlation between various variables was done using Spearman rank correlation equation. Univariate and multivariate analysis models were used to test for the independent predictors of ICU mortality. *P* values less than 0.05 were considered statistically significant. All analytical statistical methods were made by computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) 22 for Microsoft Windows.

# Results

## Demographic and baseline clinical data:

A total number of 40 subjects participated in the current study. The study included 15 males (37.5%) and 25 females (62.5%) with the age range of 56.8±21.8. Among the patients, 20 patients (50%) developed sepsis-induced myocardial dysfunction (systolic, diastolic or both). Among these 20 patients, 2 patients (5%) had systolic dysfunction only, 14 patients (35%) had diastolic dysfunction only, and 4 patients (10%) were suffering from both systolic and diastolic dysfunction.

The foremost origins of sepsis were: chest (50%), abdomen (25%) and urine (20%). Positive blood cultures were isolated in 14 patients (35%). In half of the patients, hypotension persisted despite the aggressive fluid resuscitation, and vasoactive medications were initiated to maintain blood pressure. Also, 50% of the subjects' requisite mechanical aeration was due to the respiratory compromise, and only 5% of the patients started renal replacement therapy.

## Age and gender:

In the comparison between both groups, the subjects who had advanced dysfunction of myocardium were older than those who maintained normal cardiac function (66.6±18.7 versus 47±20.5, P value 0.003). A non-significant prevalence was observed in gender between both groups (Table 1).

## Comorbid risk factors:

The results recorded a non-significant variation within the two groups as regards to the occurrence of associated comorbid conditions (Table 1).

**Table 1: Clinical, biochemical and demographic data in myocardial dysfunction vs normal function**

| | Myocardial dysfunction (n=20) | Normal cardiac function (n=20) | P value |
|---|---|---|---|
| Age (years) | 66.6±18.7 | 47±20.5 | 0.003 |
| Gender(female) | 13 (65%) | 12 (60%) | 1.0 |
| Diabetes | 35% | 50% | 0.52 |
| COPD | 25% | 5% | 0.181 |
| Malignancy | 25% | 25% | 1.0 |
| CKD | 20% | 20% | 1.0 |
| Liver disease | 10% | 10% | 1.0 |
| TNF-α (pg/ml) | 32±11.1 | 31.5±8.6 | 0.892 |
| Lactate (mmol/L) | 7.57±3.86 | 5.5±1.9 | 0.038 |
| CRP (mg/dl) | 84.4±58 | 102.7±68 | 0.367 |
| TLC (103/mm3) | 33.3±8.2 | 18.05±7 | 0.345 |
| PH | 7.34±0.09 | 7.36±0.07 | 0.455 |
| HCO3 (mEq/L) | 21.5±4.7 | 20.4±5.4 | 0.494 |
| HB (g/dl) | 9.8±2 | 9.4±1.8 | 0.449 |
| Platelets (103/mm3) | 162±83 | 241±173 | 0.072 |
| Creatinine (mg/dl) | 1.65±1.15 | 2.34±2.4 | 0.261 |
| Albumin (g/dl) | 2.7±0.7 | 2.6±0.6 | 0.443 |
| APACHE II score | 16.9±6.9 | 13.1±4.5 | 0.05 |
| SOFA score | 8.9±4.6 | 6±3.4 | 0.029 |
| Renal replacement therapy (%) | 1 (5%) | 1 (5%) | 1.0 |

| | | | |
|---|---|---|---|
| Mechanical ventilation (%) | 12 (60%) | 8 (40%) | 0.34 |
| Length of ICU stay (days) | 10.7±5.2 | 9.8±4.9 | 0.603 |
| ICU mortality | 13 (60%) | 5 (30%) | 0.024 |

## The sepsis markers and routine laboratory data:

The current study pointed to a non-significant variation among the two groups regarding the serum level of tumor necrosis factor-α (32±11.1 versus 31.5±8.6, P value 0.439). However, the individuals who had advanced myocardial dysfunction demonstrated a rise in the concentration of lactate in the serum (7.57±3.86 versus 5.5±1.9, P value 0.008) matched to the subjects with normal cardiac function. Although the average CRP value was lower in subjects with dysfunction in the cardiac muscle, there was a trend towards the continuous increase in CRP levels compared to the patients who maintained normal LV function.

Other laboratory results did not significantly vary between both groups (Table 1; Figures 1 & 2).

## Severity of illness:

APACHE II score was higher (P value 0.05) in subjects who developed myocardial dysfunction at the time of admission and maximal daily calculated SOFA score (P value 0.029) matched to the normal cardiac function subjects. The results revealed a non-significant variation among both groups regarding the necessity of renal replacement treatment and mechanical ventilation. The period of ICU staying was almost similar between the both groups. Also, the results revealed a non-significant variation between both groups with respect to the usage and doses of vasoactive medications (Table 1 & Figure 3).

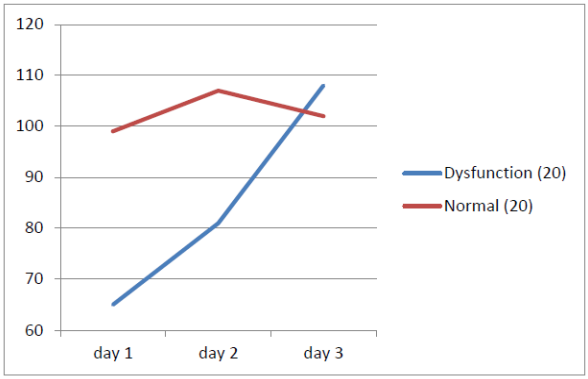


**Figure 1:** CRP levels in patients with myocardial dysfunction versus normal function

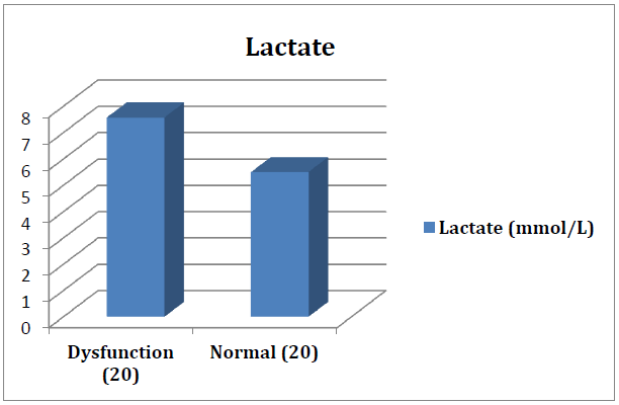


**Figure 2:** Lactate in myocardial dysfunction versus normal function

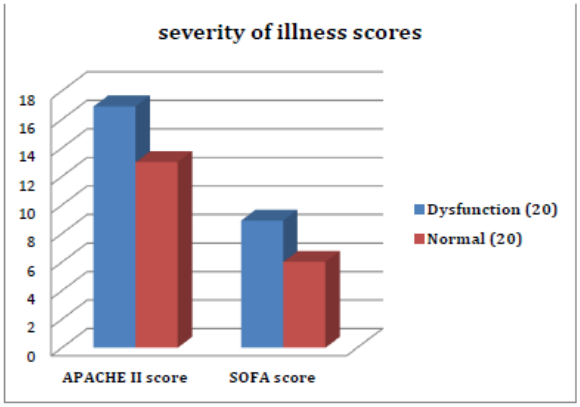


**Figure 3:** Sternness of illness scores in myocardial dysfunction versus normal function

## ICU mortality:

ICU mortality was significantly higher (P = 0.024) in individuals who developed myocardial disability in comparison to the persons with normal cardiac activity. Surprisingly, when comparing isolated diastolic dysfunction only versus normal LV utility, only tendencies to higher deaths (P = 0.163) were observed. However, both systolic and diastolic dysfunctions were associated with higher ICU mortality compared to the normal LV function (P = 0.020).

## Comparison between survivors and non-survivors

## Clinical and biochemical data:

Among all patients, ICU mortality rate was 45% (18 patients). Of note, the mortality in ICU was significantly higher (P value 0.016) in subjects with increased serum lactate levels (5.45±1.9 versus 7.85±3.93,). TNF-α value in the serum was almost similar between both groups, and there was not any statistically significant difference (P value 0.767). Also, none of the other parameters or comorbid conditions showed significant statistical difference between both groups (Table 2).

**Table 2: Clinical, biochemical, echocardiographic, and hemodynamic, data in survival vs mortality**

| | Survivors (n=22) | Non-survivors (n=18) | P value |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Age (years) | 55.6±20.3 | 58.2±24 | 0.709 |
| MAP (mmHg) | 82.7±9.1 | 76.6±10.5 | 0.056 |
| SaO2 (%) | 94.9±6.8 | 90.9±15.7 | 0.282 |
| Lactate (mmol/L) | 5.45±1.9 | 7.85±3.93 | 0.016 |
| TNF-α (pg/ml) | 31.36±8.6 | 32.3±11.49 | 0.767 |
| HCO3 (mEq/L) | 20.5±5.1 | 21.5±5 | 0.228 |
| PH | 7.36±0.07 | 7.33±0.09 | 0.573 |
| HB (g/dl) | 9.6±1.7 | 9.7±2.1 | 0.922 |
| Platelets (103 /mm3) | 221±136 | 178±145 | 0.348 |
| CRP (mg/dl) | 87.9±65 | 100.5±61 | 0.540 |
| Albumin (g/dl) | 2.7±0.5 | 2.6±0.8 | 0.539 |
| LVEF (%) | 61.8±7.9 | 62±11 | 0.964 |
| Septal é-wave (TDI, cm/s) | 11.44±2.33 | 8.9±2.86 | 0.004 |
| E/é ratio | 8.3±1.4 | 10.7±2.5 | 0.001 |
| Cardiac index (L/m2) | 4.12±0.6 | 3.54±0.76 | 0.012 |
| Stoke index (cm3/m2) | 36.3±8.2 | 39.5±8.4 | 0.238 |
| Thoracic fluid content (1/kOhm) | 34.6±3.4 | 25.2±3.77 | 0.001 |
| Systemic vascular resistance (dyne/sec/cm-5) | 1056±316 | 986±231 | 0.439 |
| Index of contractility | 51.4±7.07 | 34.6±3.95 | 0.001 |
| APACHE II score | 11.86±3.38 | 18.56±6.6 | 0.001 |
| SOFA score | 4.05±2.25 | 10.56±3 | 0.001 |
| Renal replacement therapy (%) | 4.5% | 5.6% | 1.0 |
| Mechanical ventilation (%) | 18.2% | 88.9% | 0.001 |
| Positive blood cultures (%) | 27.3% | 44.4% | 0.327 |

## Echocardiographic and hemodynamic parameters:

The mortality in the ICU was elevated significantly in subjects suffering from LV diastolic dysfunction, with reduced mitral annular septal-e velocity (P < 0.004) and increased E/e ratio (P <0.001). However, no statistically significant variation was found among both groups regarding the reduced LV ejection fraction (Table 3 & figure 4, 5, &6 ). Moreover, ICU mortality was risen in subjects with small cardiac index (P< 0.012,), low thoracic fluid content (P< 0.001) and low index of contractility (P<0.001) (Figs. 5 & 6, Table 2).

## Severity of illness and patient outcome:

The mortality in ICU was significantly higher in individuals with the higher score of APACHE II and maximal daily calculated SOFA score (P value 0.001 and 0.001, respectively). ICU mortality was also significantly elevated in subjects who required assisted mechanical ventilation (88.9% versus 18.2%, P value 0.001). Also, the patients who did not survive required more vasopressor and inotropic support, with higher doses of noradrenaline and adrenaline (P value 0.001 and 0.03, respectively) compared to the survived patients. Furthermore, the source of sepsis and presence of positive blood cultures was non-significantly varied between both groups (Table 2 & Figure 7).

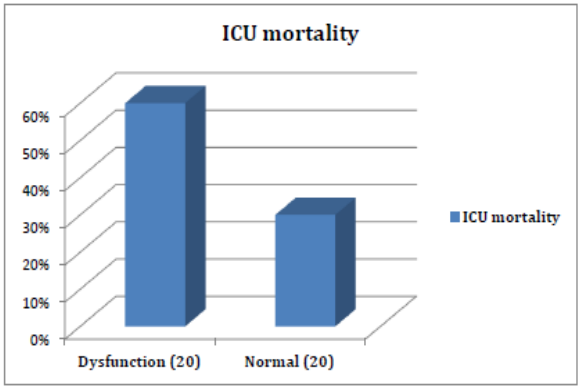


**Figure 4:** The percentage of mortality in ICU in subjects with myocardial dysfunction versus normal function

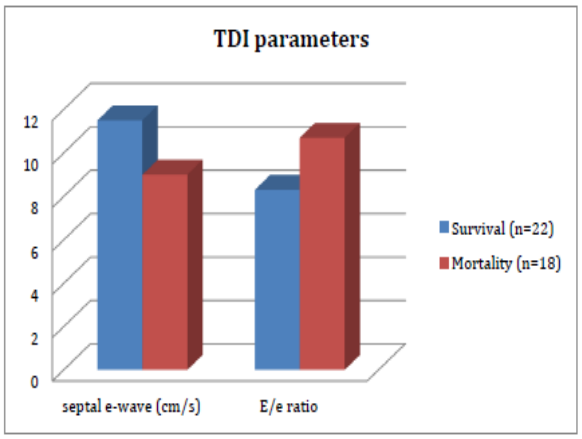


**Figure 5:** Echocadiographic parameters of DD in survival versus mortality

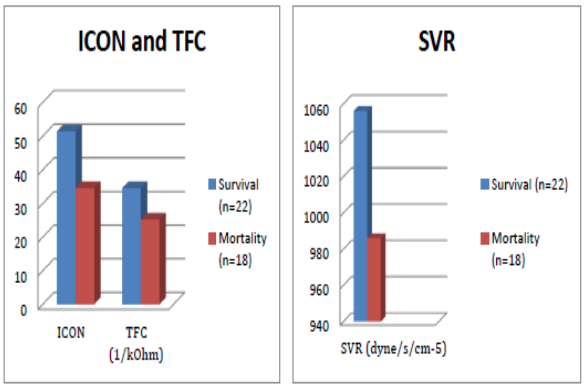


**Figure 6:** Cardiometry parameters in survival versus mortality

## Correlation between TNF-α, echocardiographic data, and severity of illness scores

The serum tumor necrosis factor-αconcentrations did not associate with echocardiographic indication of systolic or diastolic myocardial dysfunction (LVEF, septal e-wave velocity and E/e ratio). There was only a correlation at the admission with APACHE II score (P = 0.04). Moreover, serum TNF-α levels were similar among the survivors and non-survivors (P = 0.767) (Table 3).

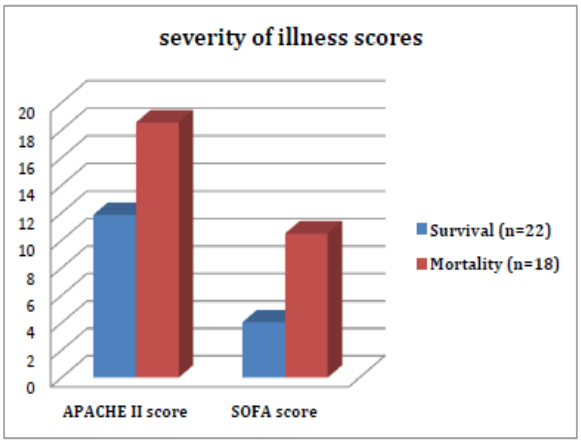


**Figure 7:** Severity of illness scores between survival and mortality

**Table 3: Correlation of TNF-α with sepsis severity and echocardiographic parameters (Spearman rank correlation)**

| | SOFA score | APACHE II score | Septal e-wave | E/e ratio | LVEF |
|---|---|---|---|---|---|
| Serum TNF-α concentrations | 0.01 (P=0.92) | 0.32 (P=0.04) | -0.02 (P=0.85) | 0.08 (P=0.62) | -0.09 (P=0.55) |

## Discussion

The obtained data in the current work, revealed that 50% of the patients developed myocardial dysfunction (systolic and/or diastolic). Diastolic dysfunction was considerably higher than systolic dysfunction (45% versus 15%). Importantly, diastolic dysfunction was associated with higher ICU mortality, while systolic dysfunction did not show any association to mortality. The subjects with dysfunction in cardiac muscle were older, with higher sternness of illness scores (SOFA and APACHE II scores). They also had elevated lactate value in the serum compared to those who maintained the normal cardiac function. Of note, serum TNF-αconcentrations failed to show a correlation with echocardiographic sign of diastolic or systolic myocardial dysfunction.

Moreover, this study showed that other predictors in septic patients of mortality in ICU were: high serum lactate, elevated SOFA and APACHE II scores, increased vasopressor and mechanical ventilation support as well as low cardiac index, little systemic vascular resistance, and low index of contractility.

## Incidence and risk factors:

The current results revealed that the dysfunction in myocardium in cases of sepsis and septic shock was very common (half of the patients), and specifically, LV diastolic dysfunction (45%) was more common than LV systolic dysfunction (15%). Ten percent of patients suffered from both systolic and diastolic dysfunction.

Many studies have addressed the myocardial dysfunction in sepsis, and found variable incidence of 20% to 60%. In 2016, a prospective observational investigation conducted at Mayo clinic on 58 subjects with severe sepsis and septic shock showed that 40% of patients developed myocardial dysfunction. Unlike the current study, systolic dysfunction was more common than diastolic dysfunction (29.3% versus 19%), and 8.6% of them exhibited both abnormalities [8]. Pulido et al., also showed that the average percentage of myocardial dysfunction incidence reached to 64% (n=68). Whereas, 37% of cases had ELV diastolic dysfunction, and about 27% of cases had LV systolic dysfunction [9]. The difference in incidence between different studies might be related to the difference in the sample size, and to the variations in the criteria for defining the diastolic dysfunction in sepsis (E/e ratio >15 versus E/e ratio >8 in the current study).

In line with this study, a study was conducted on 262 subjects suffering from severe sepsis and septic shock which showed that diastolic dysfunction was much higher than systolic dysfunction (50% versus 23.3%) [7]. Also, a study of 106 individuals complaining from septic shock and severe sepsis revealed that 50% of patients were suffering from LV diastolic dysfunction, whereas, only 12% of the patients had LV systolic dysfunction [10].

In the current study, the individuals complaining from myocardial dysfunction were older than the subjects with normal LV function (66.6±18.7 versus 47±20.5, p = 0.003). They had higher score of APACHE II and maximal daily calculated SOFA score (66.6±18.7 versus 47±20.5, p = 0.003).

Conversely, a non-significant significant difference was found regarding associated comorbid conditions, the clinical or biochemical data except for the concentration of lactate in the serum which was elevated significantly in subjects who developed myocardial dysfunction (7.57±3.86 versus 5.5±1.9, p = 0.008). Although the CRP value was lower in subjects with myocardial dysfunction, there was a trend towards the continuous increase in CRP levels compared to the patients who maintained normal LV function.

These findings indicated that LV myocardial dysfunction might be a marker of severity of illness in septic patients. It may be resulted from the cumulative impacts of several factors including autonomic dys-regulation, high plasma levels of catecholamines, impaired myocardial responsiveness, metabolic acidosis, and increased release of inflammatory mediators, which all will cause myocardial depression in this group of patients.

A potential work on 106 of subjects complaining from severe sepsis and septic shock revealed that subjects with LV diastolic dysfunction were older, with more hypertension and coronary artery diseases. Most physiologic characteristics were similar when matched to the normal LV function. Regarding LV systolic function, a non-significant variation in clinical characteristics except for higher lactate levels was parallel to the normal LV function [9]. Similarly, another prospective study revealed that subjects with dysfunction in the myocardium were older, with elevated value of lactate in the serum and more noradrenaline use when paralleled to the subjects without systolic or diastolic function. But, they didn't differ significantly in other baseline, laboratory or clinical data [8].

## Correlation between TNF-α and myocardial dysfunction:

The obtained data in the present work indicated that serum tumor necrosis factor-α level didn't relate with echocardiographic confirmation of diastolic or systolic myocardial dysfunction (LVEF, septal e-wave velocity and E/e ratio). There was only correlation with APACHE II scores (P = 0.04). Also, serum TNF-α levels were similar among survivors and non-survivors (P = 0.767).

This finding could be explained by the fact that the pathophysiology of septic shock is a multifactorial process that involves a constellation of mechanisms other than inflammatory mediators and cytokines, including mitochondrial dysfunction, reactive oxygen species, cardiomyocyte apoptosis, neuroimmunomodulation, and other mechanisms. Hence, serum TNF-αconcentrations might not be a best marker of the ongoing physiological and structural changes that eventually lead to myocardial depression in sepsis.

Similarly, a prospective observational study was carried out on 105 persons suffering from severe sepsis and septic shock. Recurrent ECG and coexisting serum cytokines e.g. IL-8, il-1, IL-10, IL-6, and TNF-α were examined. None of the cytokines were connected with echocardiographic measures of diastolic or systolic dysfunction of myocardium. However, unlike the current study, all cytokines predicted mortality, and all cytokines, except IL-1, were linked with the scores of SOFA and APACHE II [10]. In another study that evaluated the profile of cytokine levels and relationship with organ dysfunction, a negative significant relationship was recorded amongst the cardiac index (CI) and the concentrations of IL-6, IL-8 and TNF-α [11].

## Myocardial dysfunction and mortality:

The current study found that individuals suffering from developed myocardial dysfunction had significantly higher ICU mortality matched to the normal LV function (P = 0.024). Specifically, the mortality of patients inside ICU was significantly elevated in subjects complaining from LV diastolic dysfunction, with reduced mitral annular septal-e velocity < 8 cm/s and increased E/e ratio > 8 (P value 0.004 and 0.001, respectively). However, LV systolic dysfunction was not associated with ICU mortality. Surprisingly, when comparing isolated diastolic dysfunction only versus normal LV activity, it was merely recorded inclinations to a high mortality rate (P = 0.163). However, dysfunction in both systolic and diastolic orders was associated with higher ICU mortality compared to the normal LV function (P = 0.020).

In fact, it might be logical that systolic function is not a best marker of mortality as it can be affected by several factors. Many theories have protected this finding. A transient decrease in LVEF might be attributed to a physiological acclimatization in those individuals and consequently was reflected on a range of the whole dilated vascular tone compared with an intrinsic contractility. Besides, the customary indicators of LV systolic function like, cardiacindex, stroke volume and LVEF have been affected by preload and resuscitation fluids. Inadequate resuscitation would lead to lower volumes which could be translated into poor outcome [12]. Also, in mechanically ventilated patients, it was found that positive pressure ventilation might counterbalance the harmful impacts resulted from LVEF reduction by momentarily tamponing the deteriorating ventricle [13]. Therefore, recent parameters used for measuring LV function comprising maximum rate of pressure change, speckle tracking echocardiography and strain echocardiography might afford more delicate estimations of the systolic activity [14, 15].

In contrast, LV diastolic dysfunction was estimated by septal e-wave velocity, the tissue Doppler imaging (TDI) and E/e ratio which were less load-dependent than the conventional measurements. This was particularly important in septic patients where left atrial and ventricular diameters were susceptible to variations due to the insult and subsequent resuscitation. Additionally, since fluid restoration has been the essential support of hemodynamic control in septic patients, the occurrence of diastolic inactivity should make the caregiver aware to adopt more conventional methodology throughout the restoration. For this reason, E/e ratio should be used as a routine screening test in subjects suffering from septic shock, and can be used to predict fluid responsiveness during resuscitation.

Several clinical trials have been performed in order to pursue the impact of myocardial dysfunction on the outcome in septic patients, with conflicting results. In line with this study, the results of a study conducted on a group of 262 subjects complaining from septic shock or severe sepsis revealed that diastolic dysfunction is a major predictor of mortality; in addition, the higher significant judgment of deaths was reduced (P < 0.0001) mitral annular e-wave [7]. Also, a systematic review and meta-analysis of 636 septic patients have demonstrated a significant association between diastolic dysfunction and mortality (P = 0.02). Regarding the subgroups, there was a tendency to higher mortality versus isolated diastolic or both systolic and diastolic versus normal LV activity (P = 0.10 and p = 0.05, respectively). Systolic inability was not associated with mortality [4].

In contrast to the current study, Pulido et al., revealed that myocardial dysfunction (systolic or diastolic) was not accompanied with elevated mortality rate after one month or 1-year [9]. Another prospective observational study conducted on 106 peoples who were complaining from severe sepsis and septic shock failed to demonstrate any association between LV systolic or diastolic dysfunction and mortality [8]. Moreover, a systematic review and meta-analysis of 585 individuals complaining from septic shock or severe sepsis concluded that the finding of new LV systolic dysfunction was neither a sensitive nor a specific forecaster of death [16].

## Study limitations

This was a single work in one center which included a decrease in the number of cases (sample size), and therefore it has been probable that the local management protocols, resuscitation

strategies and use of vasoactive medications could have affected the measurements and, hence, the outcomes. Moreover, the rapid and variable hemodynamic responses during sepsis make the echocardiographic measurements like a ´snapshot` of hemodynamics during the course of sepsis, and may not reflect the actual hemodynamic profile. That's why it was frustrating to overwhelm these limitations by obtaining two echocardiographic measurements on two subsequent days. Furthermore, prior ventricular function was not known. Accordingly, it was not probable to distinguish whether myocardial dysfunction was a result of sepsis or due to a pre-existing disease. Nonetheless, in this study, the patients with the history of hypertension, coronary artery illness and valvular heart disease were excluded in an attempt to overcome this limitation. Overall, this study has provided a good scale of myocardial dysfunction in septic shock and severe sepsis, and further large randomized controlled studies are warranted.

## Conclusion

Myocardial dysfunction is a precise disorder in septic shock and severe sepsis. Diastolic dysfunction has been much more common than systolic dysfunction in these patients. Diastolic dysfunction has been associated with high ICU mortality, while systolic dysfunction had no impact on the outcomes of severe sepsis and septic shock. TNF-α had no correlation with sepsis-induced myocardial dysfunction or mortality, and can not be used as a prognostic marker in severe sepsis and septic shock.

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