Myocardial dysfunction in severe sepsis and septic shock – no correlation with inflammatory cytokines in real-life clinical setting.

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Abstract

Introduction: In-vitro studies suggested that circulating inflammatory cytokines cause septic myocardial dysfunction. However, no in-vivo clinical study has investigated whether serum inflammatory cytokines concentrations correlate with septic myocardial dysfunction.

Methods: Repeated echocardiograms and concurrent serum inflammatory cytokines (IL-1β, IL-6, IL-8, IL-10, IL-18, TNFα and MCP-1) and cardiac biomarkers (high-sensitivity troponin-T and NT-proBNP) were examined in 105 patients with severe sepsis and septic shock. Cytokines and biomarkers were tested for correlations with systolic and diastolic dysfunction, sepsis severity and mortality.

Results: Systolic dysfunction defined as reduced left-ventricular ejection-fraction (LVEF) <50% or <55% and diastolic dysfunction defined as e'-wave <8 cm/sec on tissue-Doppler imaging (TDI) or E/e'-ratio were found in 13 (12%), 24 (23%), 53 (50%) and 26 (25%) patients, respectively. Forty-four (42%) patients died in-hospital. All cytokines, except IL-1, correlated with SOFA and APACHE-II scores and all cytokines predicted mortality. IL-10 and IL-18 independently predicted mortality among cytokines (odds ratio= 3.1 and 28.3, p=0.006 and <0.0001). However, none of the cytokines correlated with LVEF, end-diastolic volume index (EDVI), stroke-volume index (SVI) or s'-wave and e'-wave velocities on TDI (Pearson's linear and Spearman's rank (ρ) nonlinear correlations). Similarly, no differences were found in cytokine concentrations between patients dichotomized to high versus low LVEF, EDVI, SVI, s'-wave or e'-wave

(Mann-Whitney U-tests). In contrast, NT-proBNP strongly correlated with both reduced LVEF and reduced e'-wave velocity and hs-troponin-T correlated mainly with reduced e'-wave.

Conclusions: Unlike cardiac biomarkers, none of the measured inflammatory cytokines correlates with systolic or diastolic myocardial dysfunction in severe sepsis or septic shock.

Key Words: Sepsis, Inflammatory cytokines, Myocardial dysfunction, Mortality, Echocardiography

Abbreviations list:

APACHE-II - Acute Physiology and Chronic Health Evaluation-II score

Hs-troponin-T – high-sensitivity troponin-T

IL – interleukin

LVEF – left ventricular ejection fraction

LVEDVi – left ventricular end-diastolic volume index

LVESVi – left ventricular end-systolic volume index

MCP-1 – monocyte chemoattractant protein -1

NT-proBNP – N-terminyl pro-B-type natriuretic peptide

SOFA - Sequential Organ Failure Assessment score

SIRS – Systemic inflammatory response syndrome

SVi – stroke volume index

TDI – tissue Doppler imaging

TNFα – tumor necrosis factor α,

TTE – trans-thoracic echocardiogram,

BH-FDR – Benjamini and Hochberg, False discovery rate

Introduction

Sepsis is a dysregulated inflammatory over-response of the immune system to the invasion of pathogenic organisms[1]. Mortality from severe sepsis and septic shock is high (30-40%) despite the best available treatments and is mostly the result of septic shock and multi-organ failure. The cardiovascular system plays a key role in the pathophysiology of septic shock, organ failure and death. Since the first clinical demonstrations of septic myocardial depression in the 1980's and the observation that serum obtained from septic shock patients depresses the contractility of isolated rat myocardial cells[2,3], numerous experimental *in-vitro* studies attempted to explore the complex molecular-cellular inflammatory pathways potentially leading to septic myocardial dysfunction[4,5]. *In-vitro* studies showed that circulating inflammatory substances, specifically cytokines, possess cardio-depressant effects[6]. Pro-inflammatory cytokines most intensively studied were tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 [7,8,9,10,11,12,13]. However, despite intensive laboratory efforts, the mechanisms responsible for septic myocardial dysfunction remain elusive and the paucity of clinical evidence for an association of circulating cytokines with septic myocardial dysfunction is notable.

We have recently demonstrated that diastolic dysfunction is more common than systolic dysfunction and strongly predicts mortality in patients with severe sepsis and septic shock[14,15]. In this study we aimed to investigate whether diastolic or systolic dysfunction on echocardiography in severe sepsis and septic shock can be explained by increased circulating inflammatory cytokine concentrations.

Methods

The final 105 patients included in our previously published echocardiography study[14] comprised the patient group for this study. As previously reported[14], after approval by the Institutional Review Board (Hadassah Medical Organization 0034-11-HMO) patients with severe sepsis and septic shock admitted to the General Intensive Care Unit were enrolled. Severe sepsis was defined as the presence of: 1) infection or serious clinical suspicion for infection; 2) at least two signs of SIRS and 3) at least one organ dysfunction[16]. Septic shock was defined as severe sepsis and hypotension (systolic BP< 90 mmHg) lasting > 1 hour, not responding to fluids and requiring vasopressor therapy[17]. Excluded were patients with more than mild mitral and/or aortic valve disease (insufficiency or stenosis), patients with regional myocardial wall motion abnormality on echocardiography suggesting myocardial ischemia or infarction, and patients with poor quality echocardiographic images.

Echocardiography: As previously reported[14], all patients underwent two trans-thoracic echocardiography (TTE) examinations using a Phillips' Sonos 5500 machine and a S4 2-4 MHz probe. The first examination was as early as possible after admission to the ICU with the diagnosis of sepsis and the second was performed on the following day. All echocardiograms were performed by one experienced sonographer and data were analyzed by two experts who were blinded to the treatment and outcome of the patients. Differences in interpretations were resolved by agreement. Measurements included: LVEDV, LVESV, SV and LVEF, peak mitral inflow E and A wave velocities, E wave deceleration time, isovolumic relaxation time and mitral inflow velocity of propagation.

The systolic s' and diastolic e' and a' peak velocities were obtained by tissue Doppler imaging (TDI) at both the septal and lateral mitral origins on 4-chamber apical view, and the LV filling index E/e' ratio were calculated [18,19]. Peak systolic tricuspid insufficiency gradient was measured. Echocardiography results were available for the treating physicians, but patients were not treated to reach any specific echocardiographic goal.

Blood samples were obtained in two different aliquots at the time of echocardiography. Samples were immediately centrifuged and serum stored at -70 ºC. One aliquot was used for measurements of the cardiac biomarkers: high-sensitivity (hs) troponin-T and NT-proBNP, (Roche Diagnostics, Elecsys Assays) and the other for measurements of cytokines: TNF-α, interleukins 1β, 6, 8, 10 and 18, and MCP-1 (normal values: ≤20, ≤5, ≤6, ≤70, ≤10, 250, and 722 pg/ml, respectively). Cytokines were measured by solid phase ELISA kits (R&D Systems, Inc., Minneapolis, MN). These particular cytokines were chosen since they were most frequently cited in the literature in relation to sepsis and to myocardial dysfunction.

Clinical data: All demographic, clinical, hemodynamic, respiratory and lab results, and therapies were prospectively collected. Admission APACHE-II (Acute Physiology and Chronic Health Evaluation) score and daily SOFA (Sequential Organ Failure Assessment) were calculated on the days of echocardiography. In-hospital and up to 2 years mortality data were collected from the hospital's registry continually updated by the Ministry of the Interior. LV systolic dysfunction was defined using two cutoffs levels: LVEF<50% or LVEF<55%. LV diastolic dysfunction was defined as peak septal e'-wave <8cm/sec based on previous observation that these patients have significantly worse survival[14].

Statistics

Student's *t*-test, $\chi 2$ or Mann-Whitney U tests were used to compare the distributions of continuous and dichotomous variables. Normality of distribution of all continuous variables was explored by examining Skewness, Kurtosis and Q-Q plots. Variables with skewed distributions (Skewness or Kurtosis > 2 or < -2) were log-transformed before further analysis. After $\log_{10}$-transformation, all biomarkers (cardiac and cytokines) had close to normal distribution with Skewness or Kurtosis > 2 or < -2. Pearson's linear correlation and Spearman's rank nonparametric correlation were used to assess correlations among all continuous variables. The main echocardiography parameters of systolic and diastolic dysfunction were also dichotomized and the log-transformed cytokine and biomarker concentrations were compared for the dichotomized variables. Benjamini-Hochberg step-up False-discovery-rate (FDR) method was used to adjust p values for multiple comparisons and both adjusted and unadjusted p-values were reported. Univariate and multivariate (backward stepwise selection method with probability for removal of 0.10) logistic regressions and Cox's regression were used to determine the association of variables with in-hospital and overall time-tagged mortality, respectively. Kaplan-Meier log-rank test were used to compare survival curves. Since patients had 2 sets of echocardiograms and biomarkers, each patient's clinical, biochemical, echocardiography and biomarker data were averaged for the purpose of survival analyses (Tables 1 & 2). However, for the purpose of all correlation analyses, the two sets of clinical, echocardiography, cytokine and biomarker data of all patients

were included. Statistical analyses were performed using SPSS 19.0 software (SPSS Inc, Chicago, IL and WinPepi version 11.43).

Results

The study included 105 patients: 30 patients with severe sepsis and 75 with septic shock requiring vasoactive medications: norepinephrine in all 75 patients, epinephrine in 27, vasopressin in 18, and dopamine in 8 patients. Epinephrine dopamine and vasopressin were added to patients if they remained in shock despite escalating doses of norepinephrine. At least one source of infection was identified in 99 (94%) patients and 51 (49%) had positive blood cultures. Hypotension (systolic blood pressure <90 mmHg for >1 hour) occurred in 94 (89%) patients. All patients were tracheally intubated and mechanically ventilated at the time of echocardiography. Fifty-four (51%) patients died during follow up (12.5±11.9 months), 44 (42%) died in-hospital and 30 (29%) died in the ICU. Among septic shock patients 36 (48%) died in-hospital.

All patients had two echocardiography examinations and blood samples, except for 3 who died before their second examination. First examination was within 1.6±1.7 days after admission with the diagnosis of sepsis and the second was on the next working day. Echocardiography revealed LVEF <50% (43%±6), LVEF <55% (48.9±5.8) and e'-wave <8 cm/se (6.5±1.6) or E/e'-ratio in 13 (12%), 24 (23%), 53 (50%) and 26 (25%) patients, respectively in at least one of the 2 examinations. Table 1 summarizes the variables significantly associated with in-hospital mortality. Gender, hypertension, diabetes mellitus, IHD, positive blood cultures, heart rate, CVP, lowest hemoglobin concentration and lowest O2 saturation that did not significantly predict mortality are not included. Figure 1 shows the survival curves of all patients divided into quartiles by

serum cytokine concentrations. Table 2 summarizes the independent predictors of mortality within the following categories: age, severity scores, physiological variables, echocardiography variables, cytokines and cardiac biomarkers. All log-transformed cytokine concentrations, except IL-1 correlated with both SOFA and APACHE-II scores calculated for the specific days of echocardiography and blood sampling (Table 3).

Cytokines, cardiac biomarkers and the heart

None of the log-transformed cytokine concentrations correlated with any of the echocardiography parameters of systolic or diastolic function: LVEF, EDVI, SVI and s'-wave or e'-wave on TDI, not by linear nor by non-linear correlations tests among continuous variables (Table 3). Correlation between cytokine concentrations and echocardiography parameters were even weaker when only patients with septic shock were included in the analyses. No differences in serum cytokine concentrations were found also when patients were dichotomized according to high versus low LVEF (50% or 55%), LVEDVI, SVI, s'-wave or e-'wave velocities, using independent samples Mann-Whitney U-tests (Table 4). In contrast, NT-proBNP strongly correlated with systolic and diastolic dysfunction and hs-troponin-T significantly correlated mainly with diastolic dysfunction (Table s3 & 4). Patients were divided into 3 groups according to their myocardial function: Group N – 39 (37%) –patients with normal systolic and diastolic function: LVEF > 50% (60±6%) and e'-wave > 8 cm/sec (11.2±2.5); Group S – 13 (12%) patients with systolic dysfunction: LVEF ≤ 50% (43%±6); and Group D – 53 (50%) patients with isolated diastolic dysfunction: LVEF > 50% (62±7) and e'-wave ≤ 8 cm/se (6.5±1.6). No significant differences were found among the three groups in any of the cytokine concentrations (Figure 2). In contrast, significant differences were found

among the groups in both NT-proBNP and hs-troponin-T concentrations (ANOVA: F=12.8 and 4.9, p<0.001 and 0.010, respectively).

Discussion

The main finding in the present study is that serum cytokine concentrations do not correlate with echocardiographic evidence of systolic or diastolic myocardial dysfunction nor with LV dimensions, despite the fact that cytokines predict mortality and correlate with organ dysfunction and sepsis severity (APACHE-II and SOFA scores). This is in contrast to concurrent cardiac biomarkers, hs-troponin-T and NT-proBNP which predict mortality and correlate with diastolic and systolic myocardial dysfunction.

In 1985, Parrillo et al showed that sera obtained from septic shock patients depress rat myocardial cells contractility *in vitro*, creating the concept of circulating myocardial depressant substance(s). Kumar et al[9] demonstrated that human TNFα and IL- 1β synergistically depress rodent myocardial cells in-vitro. Pathan et al[13] showed using in-vitro gene-expression profiling that IL-6 is the most probable factor causing myocardial depression in sera of children with meningococcal septic shock[6,13]. Numerous other experimental studies suggested that cytokines cause myocardial dysfunction via mechanisms such as NO overproduction[7] or calcium ion leakage from the sarcoplasmic reticulum[5,7,20,21,22]. However, no clinical study examined the association of circulating cytokine concentrations with myocardial dysfunction in patients. Bouhemad et al[23] found transient diastolic dysfunction and increase in cytokine (TNFα, IL-8 and IL-10) concentrations in septic shock patients with troponin elevations, yet no correlation was shown between the cytokines and echocardiographic indices of myocardial dysfunction.

The present study shows that circulating inflammatory cytokines are probably not the dominant causes of systolic or diastolic myocardial dysfunction in real-life sepsis. Rather, cytokines probably have a weaker clinical role in the pathophysiology of myocardial dysfunction than suggested by the in *in-vitro* experiments or their mechanisms are more complex and indirect than can be detected by correlations between cytokines concentrations and myocardial dysfunction, e.g. serum cytokine concentrations may be different than those adjacent to the myocardial cells and their local biological effects may be independent of the circulating concentrations. However, other explanations are also possible. The pathophysiology of septic myocardial dysfunction is far from being fully understood. Apoptosis in patients and animals who die from sepsis is found almost exclusively in lymphatic and gastrointestinal epithelial cells and very little in other organs, including the heart[24,25]. TNFα and IL-1β, are not consistently high and may even be undetectable in septic patients[26,27,28]. While cytokines are considered the culprits, they are also beneficial in sepsis and attempts to block TNFα and IL-1β led to increased mortality[29,30]. Nitric oxide, an important down-stream mediator of cytokine inflammatory activity held responsible for vasodilatation and hypotension in septic shock also has protective roles in cardiomyocyte survival[31,32]. In addition, cardiac stimulation by inotropes may mask any cardiac dysfunction caused by the cytokines[33]. Alternatively, the physiological stress of critical illness and the accompanying sympatho-adrenal stimulation in patients with even minor preexisting systolic or diastolic dysfunction may have a much stronger effect on observed myocardial dysfunction than the cytokines.

Limitations: 1) All our septic shock patients by-definition were on inotropic medications potentially affecting systolic and diastolic functions[33] and possibly affecting

also serum cytokine concentrations[34,35]. However, if inotropes were the confounding factor masking the effect of cytokines, then this study all the more so shows that serum cytokine concentrations are not the dominant factor determining systolic or diastolic myocardial dysfunctions in real-life severe sepsis and septic shock. 2) We did not have baseline echocardiography examinations prior to the admission with sepsis. Although we excluded all patients with regional myocardial wall motion abnormalities suggesting significant coronary artery disease and all patients with significant valvular disease, we cannot tell whether the systolic or diastolic myocardial dysfunctions occurred *de-novo* as a result of sepsis, or they reflect deterioration of pre-existing cardiac abnormality[36].

Conclusion: While circulating inflammatory cytokine concentrations predict mortality and correlate with sepsis severity, they do not seem to have a dominant effect on systolic or diastolic myocardial dysfunction in real-life sepsis. Rather the main causes for myocardial dysfunction in severe sepsis and septic shock should be searched for in other potential factors such as pre-existing disease and the response to acute physiological-pharmacological stimulations during sepsis.

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Authors contribution:

GL – Conception and design, analysis and interpretation of all data, drafting the Manuscript.

PDL – Conception and design, decision in patients enrollment, collection and interpretation of the data, revising the manuscript.

DG – Conception and design regarding all echocardiography analyses, interpretation of echocardiography data, revising the manuscript.

SG - Collection of patients and clinical data acquisition, critical revision of the manuscript.

MG – Acquisition and analysis of all echocardiography data and involvement in drafting the manuscript

CW – Conception, design and drafting the manuscript.

ASJ – Interpretation of the cardiac biomarker data and involvement in drafting the masnuscript.

CLS - Conception, design and drafting the manuscript.

VB - Conception and design mainly with respect to all cytokine collection, analyses and interpretation. Drafting the manuscript.

In addition to the above, all authors approved the final version of the manuscript and agreed with accuracy and integrity of all parts of the work.

Figure legends:

1) Kaplan-Meier survival curves of all patients divided into quartiles according to their cytokine serum concentrations (except for IL-1β that was divided to only 2 groups since only 9% of the patients had values above pg/ml)
2) Boxplots demonstrating the distribution of cytokines and cardiac biomarkers serum concentrations in all patients divided into 3 groups: N-patients with normal LV systolic function (LVEF≥50%) and no diastolic dysfunction (e'-wave >8cm/sec); S-all patients with LV systolic dysfunction (LVEF<50%); D-all patients with LV diastolic dysfunction (e'-wave <8cm/sec). All cytokines and NT-proBNP concentrations are in $\log_{10}$(pg/ml) while hs-troponin-T is in $\log_{10}$(ng/ml)

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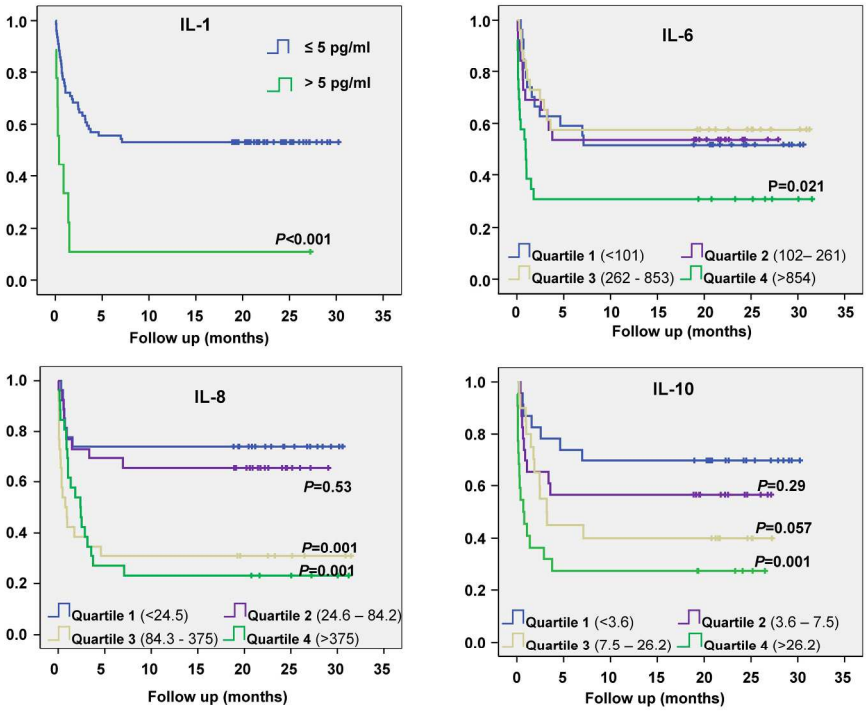

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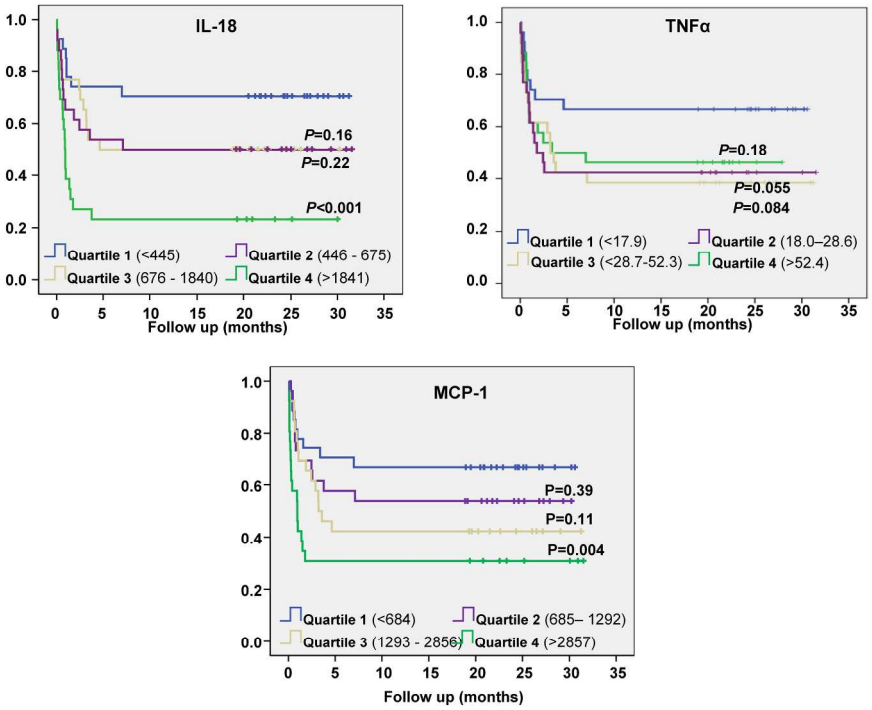

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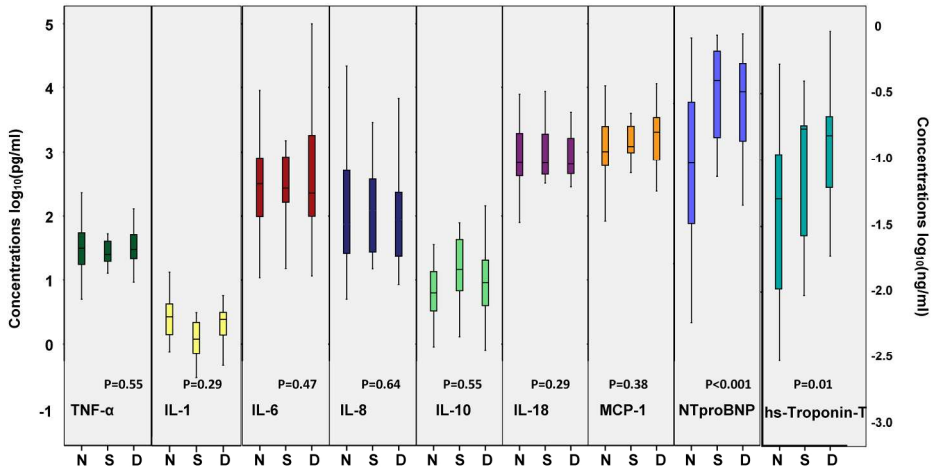
Figure 2.



N – normal systolic and diastolic function, **S** – systolic dysfunction (LVEF <50%), **D** – Diastolic dysfunction (e'-wave < 8cm/sec)

2) Boxplots demonstrating the distribution of cytokines and cardiac biomarkers serum concentrations in all patients divided into 3 groups: N-patients with normal LV systolic function (LVEF≥50%) and no diastolic dysfunction (e'-wave >8cm/sec); S-all patients with LV systolic dysfunction (LVEF<50%); D-all patients with LV diastolic dysfunction (e'-wave <8cm/sec). All cytokines and NT-proBNP concentrations are in log10(pg/ml) while hs-troponin-T is in log10(ng/ml)
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Table 1: Clinical, echocardiographic and biomarker data of patients who died or survived the hospitalization

	Survived N=61 (58%) mean±SD/median [IQR]	**Died N=44 (42%)** mean±SD/median [IQR]	***P* value t test / Mann-Whitney U test**
Age	55±20	67±19	<0.0001
APACHE-II score	19.8±5.5	24.1±7.1	<0.0001
SOFA score	8.8±3.1	10.9±3.7	<0.0001
Physiological variables			
Systolic BP (mmHg) mean/min.	120±22 / 85±11	111±29 / 82±11	0.040/0.23
Diastolic BP (mmHg) mean/min	60±12 / 47±7	56±22 / 44±9	0.014/0.17
Lowest SaO2 (%)	95±3	92±5	0.002
Lowest pH	7.33±0.08	7.23±0.12	<0.001
Creatinine (mmol/lit.) max.	187±161	244±159	0.080
Urine output (ml/24hrs/m^2)	1064±720	713±537	0.006
Fluid balance (ml/24hrs/m^2)	661±980	1088±1107	0.050
Vasoactive medications	39 (63.9)	36 (81.8)	0.045
Echocardiography			
Septal e' (TDI, cm/sec)	9.3±3.4	6.8±2.2	0.004
Stroke volume index (cm^3/m^2)	34.8±8.1	28.5±8.5	0.019
Cardiac index (lit./m^2)	3.2±1.1	2.6±1.2	0.052
TI gradient (mmHg)	21.5±15.8	29.7±17.6	0.015
Cytokines			
TNF-α	23.5 [15.8 – 47.8]	34.0 [24.0 – 60.7]	0.038
IL-1	3.3 [1.2 – 4.1]	3.3 [1.3 – 5.0]	0.001
IL8	38.7 [21.0 – 111.0]	194 [69.6 – 2727.0]	<0.0001
IL6	229 [87.3 – 496]	494 [142 – 4221]	0.011
IL-10	4.7 [2.5 – 11.6]	15.9 [6.3 – 78.8]	<0.0001
IL18	555 [392 – 920]	1665 [578 – 2606]	<0.0001
MCP1	1022 [585 – 2227]	2350 [778 – 4001]	0.003
Cardiac biomarkers			
hs-troponin-T	0.05 [0.008 – 0.12]	0.14 [0.05 – 0.23]	0.0003
NT-proBNP	1993 [326 – 13463]	11672 [3519 - 31903]	0.0001

Table 2: Independent variables associated with in-hospital mortality

	In-hospital mortality Multivariate logistic regression			Overall mortality Multivariate Cox's regression		
	Odds ratio [95% CI]	**Wald stat.**	***p*-value**	**Odds ratio [95%CI]**	**Wald stat.**	***p*-value**
Age	1.03 [1.01–1.06]	8.7	0.003	1.03 [1.01 – 1.05]	13.0	<0.001
APACHE-II score	1.14 [1.06 – 1.22]	12.8	0.0003	1.1 [1.06 – 1.16]	19.6	<0.001
Physiological variables						
Log_{10}(Lowest pH)	0.000 [0.00-0.006]	15.9	<0.0001	0.007 [0.001-0.09]	14.6	<0.001
Urine output				0.999 [0.999-1.00]	4.9	0.026
Echocardiography						
Mitral annular e'-wave	0.77 [0.63 – 0.93]	7.1	0.008	0.85 [0.76 – 0.96]	7.4	0.006
Cardiac biomarkers						
Log_{10}(NT-proBNP)	2.3 [1.2 – 4.3]	6.5	0.011	2.1 [1.5 – 3.1]	16.8	<0.001
Cytokines						
Log_{10}(IL-8)				1.7 [1.2 – 2.3]	11.3	0.001
Log_{10}(IL-10)	3.1 [1.4 – 7.0]	7.4	0.006			
Log_{10}(IL-18)	28.3 [4.9 – 161.3]	14.1	<0.0001	2.1 [1.03 – 4.2]	4.1	0.041

Table 3: Correlations of cytokine and cardiac biomarker concentrations with sepsis severity and echocardiographic parameters (Pearson's linear and Spearman's rank (ρ) nonlinear correlation – the stronger of the two)

	SOFA score	APACHE-II score	Echocardiography						Cardiac biomarkers	
			s'-wave	e'-wave	E/e'-ratio	LVEF	SVI	EDVI	Log_{10}(hs-trop.-T)	Log_{10}(NT-proBNP)
Log_{10}(TNFα)	0.31**	0.23*	-0.10	-0.15	-0.5	-0.14	0.01	0.05	0.33*	0.37**
Log_{10}(IL-1)	0.09	0.11	0.05	-0.13	-0.02	-0.17	0.04	0.13	0.22	0.19
Log_{10}(IL-6)	0.32*	0.24*	0.17	0.06	-0.15	0.16	-0.13	-0.13	0.25*	0.28*
Log_{10}(IL-8)	0.46**	0.35**	-0.19	0.05	-0.14	-0.18	-0.18	-0.10	0.28*	0.36**
Log_{10}(IL-10)	0.37**	0.29*	-0.08	-0.07	-0.09	-0.01	-0.09	0.03	0.35*	0.32*
Log_{10}(IL-18)	0.36**	0.28*	-0.18	-0.07	0.02	-0.11	-0.03	-0.04	0.31*	0.38**
Log_{10}(MCP-1)	0.40**	0.38**	-0.13	-0.11	0.09	-0.08	-0.19	-0.17	0.38**	0.39**
Log_{10}(hs-troponin-T)	0.44**	0.43**	-0.40**	-0.43**	0.19*	-0.27*	-0.35*	-0.26*		0.56**
Log_{10}(NT-proBNP)	0.50**	0.42**	-0.51**	-0.38**	0.20*	-0.37**	-0.18	0.19	0.56**	

* $p<0.05$, ** $p<0.001$

Table 4: Comparisons of inflammatory cytokine and cardiac biomarker concentrations among patients dichotomized according to the main echocardiographic parameters of systolic and diastolic dysfunction

	Log_{10} (TNFα)	Log_{10} (IL-1)	Log_{10} (IL-6)	Log_{10} (IL-8)	Log_{10} (IL-10)	Log_{10} (IL-18)	Log_{10} (MCP-1)	Log_{10} (hs-troponin-T)	Log_{10} (NT-proBNP)
LVEF >50%	1.50±0.39	0.70±0.01	2.60±0.91	2.25±0.86	1.07±0.77	2.96±0.37	3.14±0.41	-1.15±0.61	3.60±0.84
≤50%	1.57±0.39	0.73±0.11	2.89±1.15	2.71±1.16	1.06±0.53	3.15±0.41	3.30±0.41	-1.07±0.51	4.11±0.57
P value	0.33	0.31	0.40	0.11	0.74	0.20	0.26	0.37	0.081
LVEF >55%	1.52±0.34	0.73±0.11	2.64±0.92	2.10±0.89	1.12±0.81	2.96±0.39	3.16±0.39	-1.28±0.63	3.51±0.87
≤55%	1.61±0.49	0.71±0.05	2.61±0.99	2.18±1.01	0.94±0.53	3.03±0.41	3.17±0.49	-1.12±0.52	4.04±0.58
P value	0.30	0.40	0.89	0.76	0.72	0.50	0.95	0.30	**0.018** (0.16)
Septal e' >8cm/sec	1.50±0.36	0.72±0.08	2.67±0.81	2.18±0.87	0.95±0.63	2.86±0.33	3.08±0.45	-1.69±0.65	3.10±0.90
≤8cm/sec	1.57±0.39	0.75±0.18	2.55±0.89	2.08±0.91	1.10±0.74	3.00±0.38	3.18±0.39	-1.1±0.52	3.88±0.72
P value	0.48	0.37	0.23	0.53	0.40	0.18	0.28	**<0.001 (0.009)**	**0.002 (0.008)**
E/e'-ratio < 15	1.56±0.4	0.73±0.16	2.68±0.89	2.17±0.93	1.12±0.71	2.94±0.37	3.16±0.43	-1.53±0.65	3.47±0.90
≥ 15	1.46±0.30	0.72±0.09	2.34±0.63	1.79±0.59	0.90±0.56	2.98±0.36	3.06±0.33	-1.03±0.13	3.76±0.68
p-value	0.37	0.66	0.10	0.08	0.09	0.69	0.36	**0.019 (0.16)**	0.17
Septal s' >10cm/sec	1.60±0.40	0.75±0.20	2.65±0.91	2.12±0.91	1.01±0.69	2.95±0.33	3.20±0.42	-1.23±0.64	3.76±0.72
≤10cm/sec	1.50±0.37	0.71±0.80	2.57±0.83	2.13±0.91	1.05±0.71	2.96±0.41	3.10±0.90	-1.44±0.66	3.24±0.90
P value	0.21	0.40	0.96	0.95	0.91	0.95	0.25	0.19	**0.006** (0.054)
LVEDVI >45 cm3	1.62±0.36	0.75±0.14	2.66±0.98	2.18±0.93	0.97±0.70	2.92±0.35	3.22±0.36	-1.21±0.59	3.65±0.83
<45 cm3	1.46±0.39	0.71±0.15	2.61±0.90	2.07±0.91	1.17±0.77	3.04±0.41	3.10±0.45	-1.26±0.62	3.66±0.85
	0.07	0.11	0.78	0.58	0.28	0.15	0.21	0.69	0.92
LVSVI >22 cm3	1.46±0.35	0.75±0.15	2.57±0.93	2.06±0.87	0.91±0.63	2.93±0.36	3.18±0.36	-1.25±0.59	3.58±0.83
<22 cm3	1.62±0.40	0.71±0.13	2.69±0.94	2.18±0.97	1.21±0.77	3.03±0.46	3.14±0.46	-1.23±0.62	3.74±0.83
	0.060	0.13	0.57	0.54	0.09	0.22	0.65	0.87	0.39

* *p*-values in parentheses are after Benjamini & Hochberg FDR correction for multiple coparisos