ClinicalPractice

Development of sepsis in relation to serum biomarkers concentration like intercellular adhesion molecule-1, macrophage migration inhibitory factor, plasminogen activator inhibitor-1 and soluble Fas ligand

Abstract

Sepsis is a condition with high mortality rates and its diagnosis remains a challenge. Therefore, a new diagnostic biomarker or combinations of biomarkers for diagnosis of sepsis should be developed. In total, 80 patients who were suspected of having sepsis were followed up for 7 days. Quick Sepsis-related Organ Failure Assessment (qSOFA) scores were calculated day 1 and day 7; four biomarkers (intercellular adhesion molecule-1, macrophage migration inhibitory factor, plasminogen activator inhibitor-1 and soluble Fas ligand) results were evaluated the same. In 7 days in sepsis patients, blood serum concentrations of biomarker intercellular adhesion molecule-1 (ICAM-1) increased, p=0.022.

Keywords: sepsis, intercellular adhesion molecule-1, macrophage migration inhibitory factor, plasminogen activator inhibitor-1

Introduction

Sepsis is a complex and life-threatening systemic disease, with various of etiological factors and wide spectrum of severity [1]. A biomarker is a characteristic by which a (patho) physiologic process can be identified. Biomarkers can be of diagnostic value to discriminate infection from noninfectious conditions or to determine the causative pathogen, of prognostic value (assigning risk profiles and predict outcome), and in the future may be aid in selection and monitoring of therapy [2,3].

We assessed epidemiological, clinical data and multiple biomarker profiles with respect to sepsis diagnosis and predictors of outcome. In the last 10 years almost 5000 articles on biomarkers in sepsis have been published [4,5].

Inflammatory mediators, cell adhesion molecules (Intercellular Adhesion Molecule-1/ ICAM-1), redox active substances macrophage Migration Inhibitory Factor/MIF), plasminogen activator inhibitor-1 and soluble Fas ligand must be considered to be central hubs in the inflammatory process. However, their exact pathophysiologic function and prognostic value are still poorly understood. It is well known that endothelial activation is crucial in sepsis. [6,7].

Aim

To determine if serum levels of endothelial adhesion molecule 1 (ICAM-1), macrophage Migration Inhibitory Factor (MIF), Plasminogen Activator Inhibitor-1 (PAI-1) and Soluble Fas Ligand (sFAS) were associated with the development of severe clinical course in adult patients with sepsis.

Material and Methods

■ Study population

Patients were enrolled from October 2017 through April 2019 in the Emergency Department at Pauls Stradiņš Clinical University Hospital in Riga, Latvia.

Explicit criteria for enrollment included 1) age >18 years; 2) suspected or confirmed infection; 3) two or more systemic inflammatory response syndrome criteria.

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Exclusion criteria included 1) age <18 years; 2) need for immediate surgery; and 3) absolute contraindication for a chest central venous catheter.

This study was approved by the Riga Stradins University Research Committee and Pauls Stradins Clinical University Hospital Research Committee and it met criteria for exemption from informed consent.

■ Data collection

The hospitalization course of all patients was followed from admission to discharge. Using a standardized data collection instrument, data were collected on patients. The worst physiological and laboratory measurements within the initial 24 h of admission and second time after 7 days, were noted. The endpoint, all-cause in hospital mortality, was determined by systematically reviewing hospital records resulting from each patient's index hospitalization.

Severity of illness was estimated using the quick Sequential Organ Failure Assessment (qSOFA) score [8,9]. This score was calculated at Emergency Deparment (ED) recognition (day 1) and 7 days after intensive care unit admission. The primary outcome was in-hospital mortality.

■ Measurement of intercellular adhesion molecule-1, macrophage migration inhibitory factor, plasminogen activator inhibitor-1 and soluble Fas ligand

Blood samples from septic patients were collected within 24 h after the time of sepsis diagnosis and second time after 7 days. In all patients we measured two times plasma levels (1st day and 7th day) of sICAM-1, MIF, sFAS ligand and tPAI-1 using reagent kit-Merck Millipore, HCYTOMAG-60K-04.

In Latvia these biomarkers such as ICAM-1, MIF, PAI-1 and sFAS have not been studied previously, the authors chose these biomarkers because, given the pathophysiological mechanisms involved, the concentration of these biomarkers should increase in patients with sepsis.

■ Statistical analysis

The resulting study data were entered into an electronic database (Microsoft Excel 2010) and evaluated using SPSS software (Statistical Package for the Social Sciences, 22.0 version, SPSS).

■ Ethical approval

This study was approved by the institutional review board of Riga Stradins University and Pauls Stadins Clinical University Hospital.

Results

■ Patient characteristics and outcome

During the study period 80 patients fulfilled the inclusion criteria with ages ranging from 18 to 90 years. Patients characteristics and outcomes are shown in **TABLE 1**.

■ Comparison of correlation of biomarkers and qSOFA

All sepsis patients n=80 (100%) within 7 days of hospitalization in intensive care unit, statistically significant increase in score after quick SOFA scale, p=0.002. After qSOFA score 1 point in 1st day were n=48 patients (60%), 2 points were n=27 (33.8%) and 3 points were n=5 patients (6.3%). But after 7 days of hospitalization in intensive care unit, 1 point were n=20 (25%), 2 points were n=43 (53.8%) and 3 points were n=17 (21.3%). The results also showed that mortality was higher in patients with higher qSOFA scores.

We also examined the correlation between 4 biomarkers (intercellular adhesion molecule-1, macrophage migration inhibitory factor, plasminogen activator inhibitor-1 and soluble Fas ligand) levels in 1st day after hospitalization in intensive care unit and second time after 7 days. Sepsis patients showed ICAM-1 concentration on day 1 was Me 12245.347 (Q1 6228.500; Q3 33372.419) pg/ml, but on day 7 Me 11107.250 (Q1 4774.00; Q3 30356.503) pg/ml, p=0.022. The statistician did not change the biomarkers MIF and PAI-1 significantly, on day 1 MIF was Me 93.266 (Q1 47.750; Q3 177.669) pg/ml, but on day 7 Me 99.004 (Q1 45.000; Q3 201.723) pg/ml, p=0.580. PAI-1 concentration on day 1 was Me 5857.250 (Q1 3928.511; Q3 9589.500) pg/ml, on day 7 Me 6222.208 (Q1 4003.950; Q3 8553.728) pg/ml, p=0.337 and no statistically significant association was found between day 1 and day 7 of the sFAS ligand biomarker, respectively, sFAS ligand concentration on day 1 was Me 2321.105 (Q1 1023.006; Q3 6471.201) pg/ml, on day 7 Me 3304.281 (Q1 2466.098; Q3 7698.245) pg/ml, p=0.167.

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TABLE 1. Characteristics of sepsis patients.

| Variables	Total	Survivor	Nonsurvivor	P-value
	(n=80; 100%)	(n=65; 81.3%)	(n=15; 18.8%)	
Sex (Male)	51 (63.8%)	42 (64.6%)	9 (60.0%)	0.727
Sex (Female)	29 (36.3%)	23 (35.4%)	6 (40.0%)	
Age				
18-40 years	8 (10.0%)	7 (10.8%)	1 (6.7%)	0.829
41-60 years	26 (32.5%)	21 (32.3%)	5 (33.3%)	
61-90 years	46 (57.5%)	37 (56.9%)	9 (60.0%)	
Site of primary infection				
Lower respiratory tract infection	37 (46.3%)	30 (46.2%)	7 (46.7%)	0.396
Intra-abdomen infection	16 (20%)	12 (18.5%)	4 (26.7%)	
Skin and musculoskeletal infection	17 (21.3%)	16 (24.6%)	1 (6.7%)	
Urinary tract infection	6 (7.5%)	4 (6.2%)	2 (13.7%)	
Unknown etiology	4 (5.0%)	3 (4.6%)	1 (6.7%)	
Organ dysfunction				
Acute respiratory failure	22 (27.5%)	15 (44.1%)	7 (58.3%)	0.262
Acute renal failure	8 (10.0%)	6 (23.5%)	0 (0.0%)	
Septic shock	11 (13.8%)	7 (20.6%)	4 (33.3%)	
Altered consciousness	5 (6.3%)	4 (11.8%)	1 (8.3%)	
Comorbidities				
Pulmonary disease	17 (21.3%)	11 (21.6%)	6 (42.9%)	0.209
Cardiovascular disease	22 (27.5%)	18 (35.3%)	4 (28.6%)	
Malignancies	6 (7.5%)	5 (9.8%)	1 (7.1%)	
Diabetes mellitus	9 (11.3%)	9 (17.6%)	0 (0.0%)	
Chronic renal disease	4 (5.0%)	2 (3.9%)	2 (14.3%)	
Immune deficiency	3 (3.8%)	2 (3.9%)	1 (7.1%)	
Other	4 (5.0%)	4 (7.8%)	0 (0.0%)	
Severity score (qSOFA*) at day 1				
qSOFA=1	48 (60.0%)	38 (58.5%)	10 (66.7%)	0.002
qSOFA=2	27 (33.8%)	22 (33.8%)	5 (33.3%)	
qSOFA=3	5 (6.3%)	5 (7.7%)	0 (0.0%)	
Severity score (qSOFA*) at day 7				
qSOFA=1	20 (25.0%)	20 (30.8%)	0 (0.0%)	<0.001
qSOFA=2	43 (53.8%)	40 (61.5%)	3 (20.0%)	
qSOFA=3	17 (21.3%)	5 (7.7%)	12 (80.0%)	
*qSOFA=Quick Sepsis-Related Organ Failure Assessment				

FIGURE 1. Intercellular adhesion molecule-1 (ICAM-1) concentration at 1st day after hospitalization in intensive care unit and at 7th day. ICAM-1 concentration level in sepsis patient's blood samples (pg/ml).

1st day in intensive care unit   7th day in intensive care unit
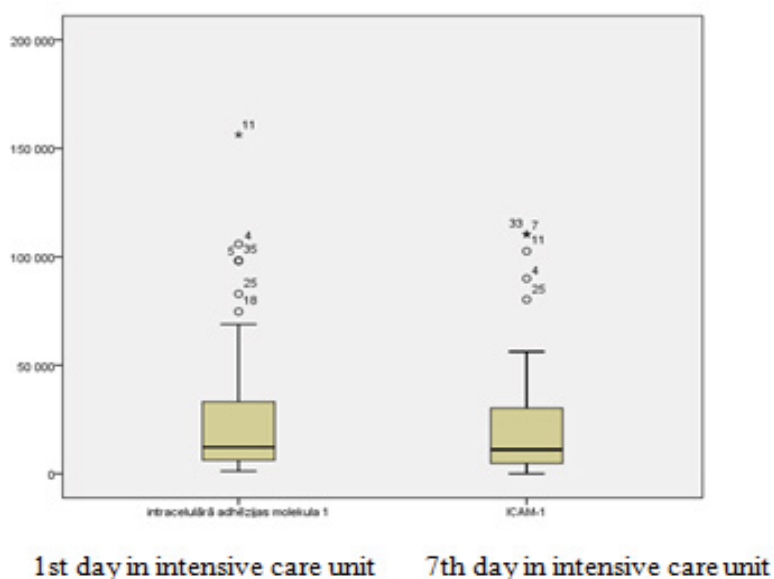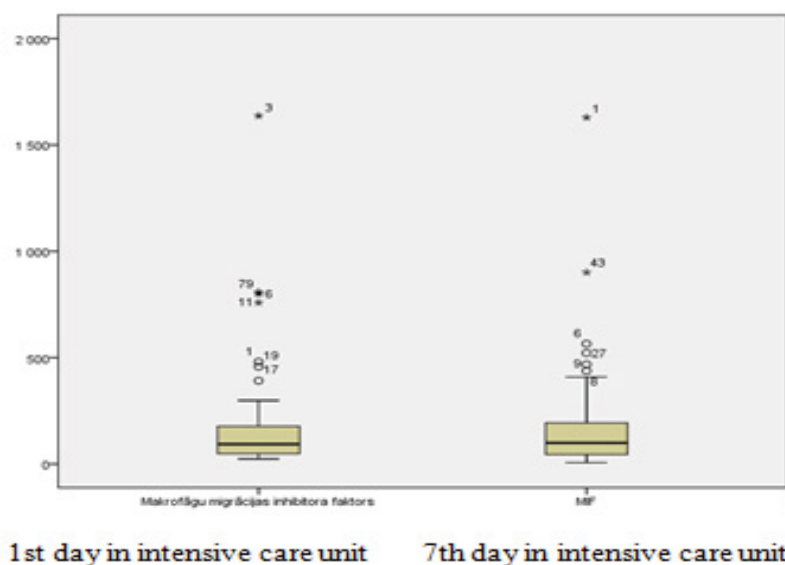
FIGURE 2. Macrophage migration inhibitory factor (MIF) concentration at 1st day after hospitalization in intensive care unit and at 7th day. MIF concentration level in sepsis patient's blood samples (pg/ml).
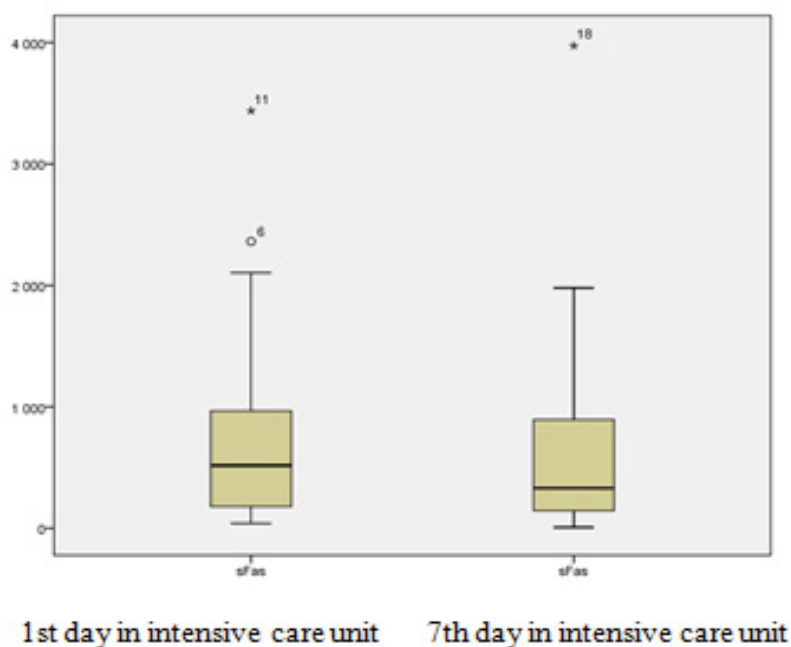
FIGURE 3. Soluble Fas ligand at 1st day after hospitalization in intensive care unit and at 7th day. Solubale FAS ligand concentration level in sepsis patient's blood samples (pg/ml).

On Day 1 and the biomarker t PAI-1, correlation coefficient was r=0.572, p<0.001 as well as day 7 r=0.360, p=0.001. MIF on day 1 r=0.131, p=0.246, on day 7 r=0.122, p=0.281. ICAM-1 on day 1 was r=0.078, p=0.492, but on day 7 r=0.102, p=0.368. And about biomarker sFAS ligand on day 1, correlation coefficient was r=0.126, p=0.265, on day 7 r=0.062, p=0.585.

The box plots of the 4 biomarkers stratified by concentration level in blood samples are showns in **FIGURES 1-4**.

The results also showed that all patients who died had higher levels of biomarkers than those who survived, this was particularly significant for the biomarker tPAI-1 (p=0.017). All results are shown in **TABLE 2**.

Discussion

This study focused on clinical-epidemiological and biomarkers profiles of patients admitted to the public hospital in Pauls Stradiņš Clinical University Hospital in Riga, Latvia for a period of 3 years. Regarding the epidemiological characteristics, predominance of male was in agreement with that reported in previous worldwide studies, [10-12] and the median age was the same than that observed in most centers and private hospitals in Europe.

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FIGURE 4. Plasminogen activator inhibitor-1 (tPAI-1) concentration at 1st day after hospitalization in intensive care unit and at 7th day. tPAI-1 concentration level in sepsis patient's blood samples (pg/ml).

1st day in intensive care unit   7th day in intensive care unit
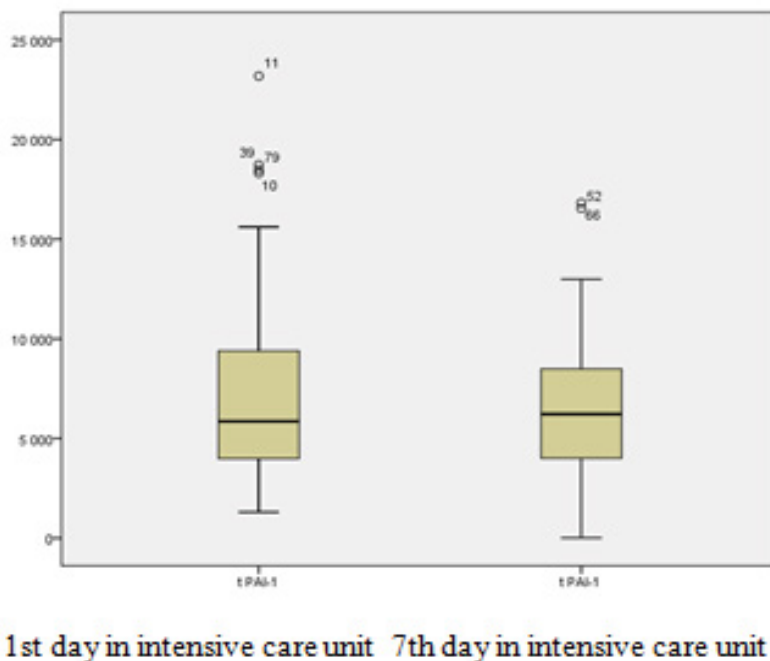
TABLE 2. Concentrations of biomarkers depending on the outcome of sepsis.				
Biomarkers	**Patients outcome**	**N (number; %)**	**Mean Rank (Me) pg/ml**	**P-value**
MIF*	Survivor	65 (81.3%)	39.63	0.486
	Nonsurvivor	15 (18.8%)	44.27	
ICAM-1*	Survivor	65 (81.3%)	40.48	0.985
	Nonsurvivor	15 (18.8%)	40.6	
Sfas*	Survivor	65 (81.3%)	40.15	0.777
	Nonsurvivor	15 (18.8%)	42.03	
tPAI-1*	Survivor	65 (81.3%)	37.52	0.017
	Nonsurvivor	15 (18.8%)	53.4	
*MIF-Macrophage Migration Inhibitory Factor				
*ICAM-1-Intercellular Adhesion Molecule-1				
*sFAS-Soluble Fas Ligand				
*tPAI-1-Plasminogen Activator Inhibitor-1				

The presence or absence of comorbidities influence the outcome, and association was found between sepsis severity and baseline disease. These data are similar when analyzing other epidemiological studies.

Intercellular Adhesion Molecule-1 (ICAM-1), mediating adherence between cells and extracellular matrix, could release in cascade to damage the vascular endothelial cells during sepsis [7]. ICAM-1 has been investigated in sepsis. To date, many studies showed that its level is increased in patients with sepsis [13-15]. Bavunoglu et al. found that ICAM-1 had a high sensitivity (99%) and specificity (99%) for detecting sepsis. Thus, ICAM-1 might be an effective biomarker for diagnosing sepsis [16-19].

Our study also showed that ICAM-1 levels increase with the clinical severity of sepsis. High levels of adhesion molecules have been found in sepsis patients. We found that, in 7 days in sepsis patients, blood serum concentrations of biomarker ICAM-1 increased, p=0.022, what could be a significant biomarker for the evaluation of sepsis severity. Higher mortality was also observed in these patients. It is well known that fibrin removal is severely hindered by inactivation of the endogenous fibrinolytic system, mainly as a result of upregulation of Plasminogen Activator Inhibitor type-1 (PAI-1) [8,9].

In pathogenesis of sepsis, PAI-1 plays a role in several biological processes dependent on the inhibition of plasminogen activators and plasmin

activity. As a consequence, overproduction of PAI-1 may contribute to organ dysfunction in patients suffering from severe infection [20,21]. We demonstrated that serum t PAI-1 also has better correlation with clinical severity (after qSOFA=3 points) than biomarkers MIF and sFAS ligand). For example, those patients with initially high PAI-1 levels may be offered a more proactive management, including early ICU admission, initiation of fluid resuscitation, and inotropic support [21].

About MIF, our results shown that, there was no statistically significant relationship between the MIF and qSOFA scales, i.e., day 1 r=0.131, p=0.246, day 7 r=0.122, p=0.281. However, no sufficient knowledge exists about the prognostic value of these key mediators in severe sepsis [22,23].

Conclusion

In 7 days in sepsis patients, blood serum concentrations of biomarker intercellular adhesion molecule-1 (ICAM-1) increased, p=0.022, what could be a significant biomarker for the evaluation of sepsis severity. The results also showed that all patients who died had higher levels of biomarkers than those who survived, this was particularly significant for the biomarker tPAI-1 (p=0.017). Therefore, the study would be important to continue and increase the number of patients included in the study that could change the statistical results.

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