Is elevated Extravascular Lung Water Index sign of developing sepsis in burns?

Short title: Signs of developing sepsis in burns

Key words: Extravascular Lung Water Index, Procalcitonin, Sepsis, Burn, Scoring Systems.

Z. Bognar, V. Foldi, B. Rezmann, L. Bogar, C. Csontos

Department of Anaesthesia and Intensive Care, Faculty of Medicine, University of Pecs, Hungary

Correspondence to: Csaba Csontos MD,PhD, Department of Anaesthesia and Intensive Care, Faculty of Medicine, University of Pécs, Akác u. 1, Pécs 7632, Hungary.

E-mail: bognarzsu@gmail.com; Tel.: +36 309375104, Fax: +36 72536800/6960

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Abstract

Sepsis and multiple organ failure remained leading cause of mortality and morbidity in burns. Aim of our study was to analyse the predictive value of extravascular lung water index (EVLWI) regarding development of severe septic complications and mortality.

Records of 38 patients admitted with total burned surface area >20% were analysed (EVLWI, procalcitonin (PCT), intrathoracic blood volume index (ITBVI), positive end-expiratory pressure (PEEP), Baltimore Sepsis Scale (BaSS)). Diagnosis of infection (day 0) was based on consensus conference of the American Burn Association.

EVLWI correlated with PCT ($p<0.001$), BaSS ($p<0.01$), ITBVI ($p<0.001$) and PEEP ($p<0.05$). EVLWI elevated ($p<0.05$) one day before diagnosis of infection (day -1) compared to previous days, whereas PCT was higher ($p<0.05$) on day 0 only. ROC analysis for EVLWI on day -1 and for PCT on day 0 showed the same area under curve (0.760; 0.766, respectively). EVLWI higher than 9 ml kg^{-1} on day -1 predicted sepsis with 89% sensitivity, 72% specificity. After adequate antibiotic treatment EVLWI remained high in non-survivors, decreased in survivors, whereas PCT decreased in both groups.

Our data suggest that EVLWI is an early warning sign of developing infection and its continuous elevation can predict poor prognosis in burnt patients.

Introduction

Burnt patients are susceptible for infections due to a shift towards anti-inflammatory processes caused by trauma. Despite improvements in burn wound care and intensive therapy, sepsis and consequent Multiple Organ Failure (MOF) remained the major causes of death in patients suffering from severe thermal injury [1, 2]. Burnt patients show signs of systemic inflammatory response syndrome (SIRS) without any bacterial infection making early detection of sepsis difficult. Sepsis is usually diagnosed by clinical signs [3]. Early and adequate administration of antibiotics may improve patients' survival [4, 5, 6]. Based on the sepsis surviving campaign, administration of the first dose of antibiotics is necessary within one hour after diagnosis.

Due to existing SIRS the hemodynamic profile of burn injury in septic patients is very similar to non-septic ones. It is characterized by high cardiac index (CI) and low systemic vascular resistance index (SVRI). Using transpulmonary thermodilution monitoring Extravascular Lung Water Index (EVLWI) can be calculated. It has been proven that inhalation injury and fluid resuscitation per se do not influence EVLWI [7, 8, 9], although elevated EVLWI can often be detected during the treatment of burnt patients in the Intensive Care Unit (ICU). According to Tranbaugh and associates elevated EVLWI may be a sign of developing bacterial sepsis in burned patients [7]. Yang and associates showed that EVLWI has prognostic value in critically ill patient suffering from septic shock. EVLWI >14 ml kg^{-1} was associated with a significantly higher in-hospital mortality [10]. Procalcitonin (PCT) is a useful marker of bacterial infection in septic patients [11] and a helpful parameter for detection of developing sepsis in burned patients [2]. According to Nylen and associates it may be an indicator of the severity of inhalation injury [12]. In a study by von Heimburg and associates a cut-off value higher than 3 ng ml^{-1} was found as a reliable indicator for bacterial or fungal infection [13]. Values over 10 ng ml^{-1} were associated with life-threatening

infections. Whereas Housinger and associates and Neely and associates concluded that PCT is less sensitive than platelet count or CRP in the early detection of sepsis in burned children [14, 15]. No reports have found correction between total burned body surface area (TBSA) and PCT values measured on admission however, a significant correlation has been proven between the peak value of PCT and TBSA [13].

The aim of our retrospective study was to analyse EVLWI changes in association with PCT level, Baltimore Sepsis Scale (BaSS) [16] Multiple Organ Dysfunction Score (MODS) [17] and Sequential Organ Failure Assessment (SOFA) [18]. The predictive value of elevated EVLWI regarding the presence of infection, sepsis and mortality has been also studied.

Patients and Methods

Patients

Data files of 38 patients admitted to our tertiary intensive ward between January 2006 and April 2009 with burn injury affecting more than 20% of the body surface area were analysed. Inclusion criteria were development of sepsis during treatment, minimum six days survival and the use of transpulmonary thermodilution haemodynamic monitoring (PiCCO, Pulsion Medical Systems AG, Munich, Germany). Exclusion criterion was the presence of any obvious bacterial infection on admission.

Sepsis criteria

The patients were regularly (twice a day) examined regarding the presence of sepsis and in cases of suspected infection, cultures were taken. The diagnosis of sepsis was based on the criteria of the American Consensus Conference [19]. Signs of developing sepsis were the following: temperature > 39 ºC or < 36.5 ºC, heart rate > 110 bpm, respiratory rate > 25 min^{-1}, in ventilated patients minute ventilation > 12 l min^{-1}, platelet count < 100 G l^{-1}, untreated

plasma glucose level > 11 mmol l^{-1} or intravenous insulin requirement > 7 U h^{-1} or 25% increase in insulin requirement over 24 hours, enteral feeding intolerance or uncontrollable diarrhoea. Presenting two out of the above mentioned signs microbiologic samples were taken from blood and the suspected site(s) of infection. In addition, for sepsis diagnosis the identification of bacterial focus was required: positive cultures identified pathologic tissue source or clinical response to antimicrobials. Based on the clinical outcome, patients were divided into non-survivor and survivor groups. The day when suspicion of severe infective complications appeared and the microbiologic samples (blood culture, tracheal secretion, canule tips) were taken was regarded as day 0 of Bedside Suspicion of Sepsis (BSS 0).

Patient treatment protocol

Patients were treated in a uniform way based on international guidelines for burnt patient care [20]. Fluid resuscitation was guided by intrathoracic blood volume index (ITBVI). Only Ringers Lactate (LR) solution was used for intravenous fluid replacement. The goal of resuscitation was to maintain ITBVI between 800 and 850 ml m^{-2} [20, 21, 22]. The administered fluid volume was higher than predicted by the Parkland formula, similarly to the study by Mitra et al. [22]. The normal range for ITBVI was between 850 and 1000 ml m^{-2}. By targeting the lower limit, we tried to avoid intravenous fluid overload. If inhalation injury was suspected (facial burn, soot in the throat, chest X-ray) bronchoscopy was carried out for verification. Excision and grafting were started within 72 hours and enteral feeding was commenced on the first day following injury when hemodynamic stability was reached. All patients were mechanically ventilated after admission. Tracheotomy was performed before the first grafting in order to avoid complications due to coagulopathy.

EVLWI measurements

EVLWI measurements were performed on admission and 3 times daily thereafter using the transpulmonary single dilution method. Briefly, 20 ml cold (temperature < 8 ºC) isotonic sodium chloride solution was injected via the central venous line. Three readings were taken and the mean value was recorded.

Scoring Systems

Baltimore Sepsis Scale (BaSS) was designed to reflect the severity of septic complications and to predict the outcome in burnt patients. BaSS can be calculated on the basis of 13 selected organ function parameters (heart rate, blood pressure, SVRI, body temperature, positive end-expiratory pressure (PEEP), PaO_2/FiO_2 ratio, base deficit, leukocyte count, platelet count, creatinine, urine output, Glasgow Coma Scale and use of antibiotics) [16].

Multiple organ dysfunction score (MODS) was constructed for the assessment of dysfunction of six organ systems using simple physiologic measures. It correlates strongly with the risk of ICU and hospital mortality. Therefore, it is potentially appropriate to reflect the effects of therapeutic manipulations [17].

Sequential Organ Failure Assessment (SOFA) score was designed to describe the sequence of complications in the critically ill patient. It is not able to predict outcome. It was calculated by record of the worst daily values of six organs [18].

These scores were calculated in each patient daily after admission.

Statistics

Statistical analysis was performed using Statistical Program for Social Sciences 15.0 software for Windows (SPSS®, Chicago, Ill., USA). Correlations between variables were analysed with the Spearman test and variables were compared using the Mann-Whitney U

test, differences over time and differences between groups at different time points were tested with repeated measure ANOVA, distributions between groups were evaluated with Chi-Square test. Receiver Operating Characteristic analysis (ROC) was performed and the respective areas under the curves were calculated for EVLWI and PCT. The sensitivity and specificity were calculated at the best cut-off value. All values are expressed as median and interquartile range (IQR). Statistical significance was ascribed to a p value < 0.05.

Results

This retrospective study included 28 patients (6 females, 22 males). Ten patients were excluded due to insufficient data recordings or death within 6 days (Figure 1). Median age was 52 years (IQR 25-64), median TBSA 37 % (IQR 30-49). Nineteen patients died during their intensive care stay while 9 patients survived the injury.

Demographic and hemodynamic parameters on admission are summarized in Table 1. Albumin level was significantly higher in the survivor-group on admission. Initial MODS, SOFA, and BaSS scores and measured hemodynamic parameters on admission did not show any significant difference between the two groups.

EVLWI significantly correlated with ITBVI, PEEP, PCT, BaSS and SOFA scores (Table 2). It failed to show any correlation with CVP, serum albumin level or and MODS score.

Figure 2 shows the time course of PCT and Figure 3 demonstrates changes of EVLWI levels. PCT levels started increasing significantly in both groups only on day 0 and showed a further increase on day +1 (Figure 2). Significant elevation of EVLWI in both groups could be observed one day before clinical detection of the infection (day -1) (Figure 3). Comparing PCT levels in survivors and non-survivors significant differences could be observed on days

2-3 with higher levels in non-survivors. After administration of adequate antibiotics, PCT level decreased in both groups (earlier in the survivor-group) however, the differences between the two groups remained significant (Figure 2). EVLWI was significantly higher in non-survivors on days 1-3, furthermore, its levels decreased in the survivor group and showed a further increase in the non-survivor group during the study period (Figure 3).

The areas under the receiver operating characteristic curves (AUROC curves) to distinguish presence or absence of sepsis were made for EVLWI on day -1 and for PCT on day 0. AUROC curves for EVLWI was 0.760 and for PCT 0,766 (Figure 4). The optimum cut-off value for EVLWI was 9 ml kg^{-1} with a sensitivity of 89% and specificity of 72%. The optimum cut-off value for PCT was 2 ng ml^{-1} with sensitivity regarding the diagnosis of sepsis of 87% and specificity of 71%.

The rate of the effective antimicrobial therapy was the same in survivors and non-survivors (Table 3). In most of the cases polymicrobal infections were detected (Table 4). Pseudomonas auerginosa caused the majority of opportunist nosocomial infections of the patients.

Discussion

As sepsis remained the major cause of mortality in burnt patients, it needs early diagnosis and specific treatment. Patients suffering from thermal injury are constantly and chronically exposed to microorganism invasion due to extended skin damage. The gastrointestinal tract can be another focus of infection due to impaired circulation in the resuscitation phase of burn injury. Standard criteria for infection and sepsis can not be used in burnt patients due to existing SIRS without bacterial infection. The standard criteria for infection have been modified by the American Burn Association and the diagnosis of the onset of infection was based on these modified sepsis criteria in our study [19]. However, the

diagnosis of infection can not be based only on simple, conventional, clinical signs (alteration in body temperature, heart rate, respiratory rate and decrease of blood pressure and platelets count). More sophisticated markers (e.g. inflammatory markers; PCT, CRP) need be used.

Many papers [8, 9, 23] have shown that burn injury itself with or without inhalation injury and fluid resuscitation per se do not increase EVLWI. It remained within the normal range on admission and during fluid resuscitation. The elevation of EVLWI observed in our patients was associated with the appearance of clinical signs of infection. Inflammatory processes caused by bacterial infection can be an underlying cause of elevated EVLWI. Elevated CD11b/CD18 expression associated with granulocyte accumulation in the lungs is correlated with increased capillary permeability [24]. This result together with our data support the results of Trandaugh and associates who proved that elevated EVLWI could be regarded as a sign of bacterial infection [8].

Neely and associates [2] found PCT to be a useful marker for verification of bacterial infection. Its level increased when clinical diagnosis of sepsis was made and decreased after the administration of adequate antibiotic therapy. Jensen and associates have found that a period of elevated PCT is an independent predictor of mortality in a ninety-day follow up period [25].

Correlations between EVLWI and PCT levels - a verified marker of bacterial infection [2, 11, 12] - support our assumption that EVLWI may be a useful marker in the diagnosis of sepsis in burn injury.

Comparing the diagnostic value of EVLWI to that of PCT the same diagnostic efficiency and the same AUROC curves were found. Moreover, EVLWI showed the developing sepsis one day before the appearance of the clinical signs. 9ml kg^{-1} was found as the best cut-off value for EVLWI with sensitivity of 89% and specificity of 72%.

For the advanced diagnosis of sepsis the ideal parameter should be easy to measure sensitive, specific, and it should predict the outcome. EVLWI is easy to measure in patients requiring intensive therapy using the transpulmonary dilution method. Elevations of EVLWI could be observed in each patient during the septic period. Moreover, it shows the developing sepsis earlier than PCT or clinical signs. In addition, after the administration of antibiotics EVLWI showed a decreasing tendency in survivors, while it remained elevated in the survivor group. In this way the increase or decrease in EVLWI can be a predictor of outcome.

Respiratory therapy was applied in all patients and a strong correlation was found between EVLWI and the applied PEEP value. The relationship between PEEP and EVLWI is currently under debate. Probably sepsis-induced inflammatory processes are the underlying cause of the elevated pulmonary permeability and elevated EVLWI. Our findings support the hypothesis of Szakmany and associates [26]. They report that the alveoli are disposed to collapse due to the elevated EVLWI and PEEP is necessary to keep them open.

Among the scoring systems only BaSS has been developed for the specific recognition of a septic state in burnt patients. MODS and SOFA scores were developed for detection of dysfunction of various organ systems and not for the confirmation of sepsis [17, 18]. Not surprisingly, EVLWI showed significant correlation with BaSS. The correlation between EVLWI and SOFA score can be explained by the effect of sepsis on the different organ functions.

The main limitation of the study is its retrospective design and the relatively small sample size. Our results should be verified by further prospective randomised studies.

In conclusion, early diagnosis of sepsis is essential in severely burnt patients. Our data suggest that EVLWI is an early warning sign of a developing bacterial infection. Its continuous elevation may be a prognostic sign of unfavourable outcome in burnt patients.

Legend for illustrations

Legend for tables

Table 1: Demographic data and initial parameters of the patients

Data are expressed as median and interquartile range. TBSA = total burned surface area, CVP = central venous pressure, MAP = mean arterial pressure, CI = cardiac index, SVRI = systemic vascular resistance index, ITBVI = intrathoracic blood volume index, EVLWI = extravascular lung water index, Temp max = daily maximum body temperature, PEEP = positive end-expiratory pressure, BaSS = Baltimore Sepsis Score, MODS = Multiple Organ Dysfunction Score, SOFA = Sequential Organ Failure Assessment, NS = not significant.

Table 2: Correlations between EVLWI and measured or calculated parameters

CVP = central venous pressure, ITBVI = intra thoracic blood volume index, PEEP = positive end-expiratory pressure, BaSS = Baltimore Sepsis Score, MODS = Multiple Organ Dysfunction Score, SOFA = Sequential Organ Failure Assessment, NS = not significant.

Table 3: Results of the cultures and efficiency of the antimicrobial therapy

Table 4: Results of the microbiologic cultures

Figure 1: Flow chart of the study

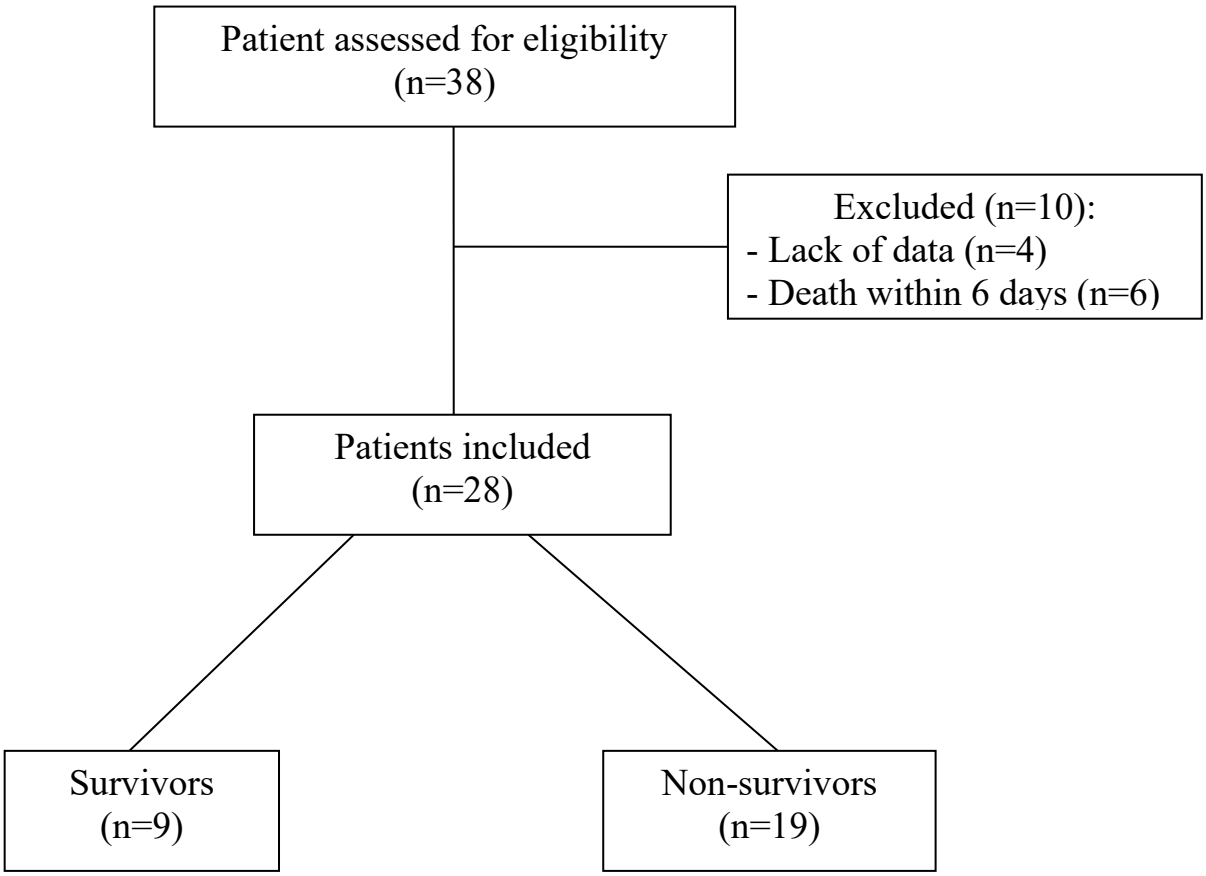


Figure 2: The graph shows the time course of PCT in the survivors and non-survivors

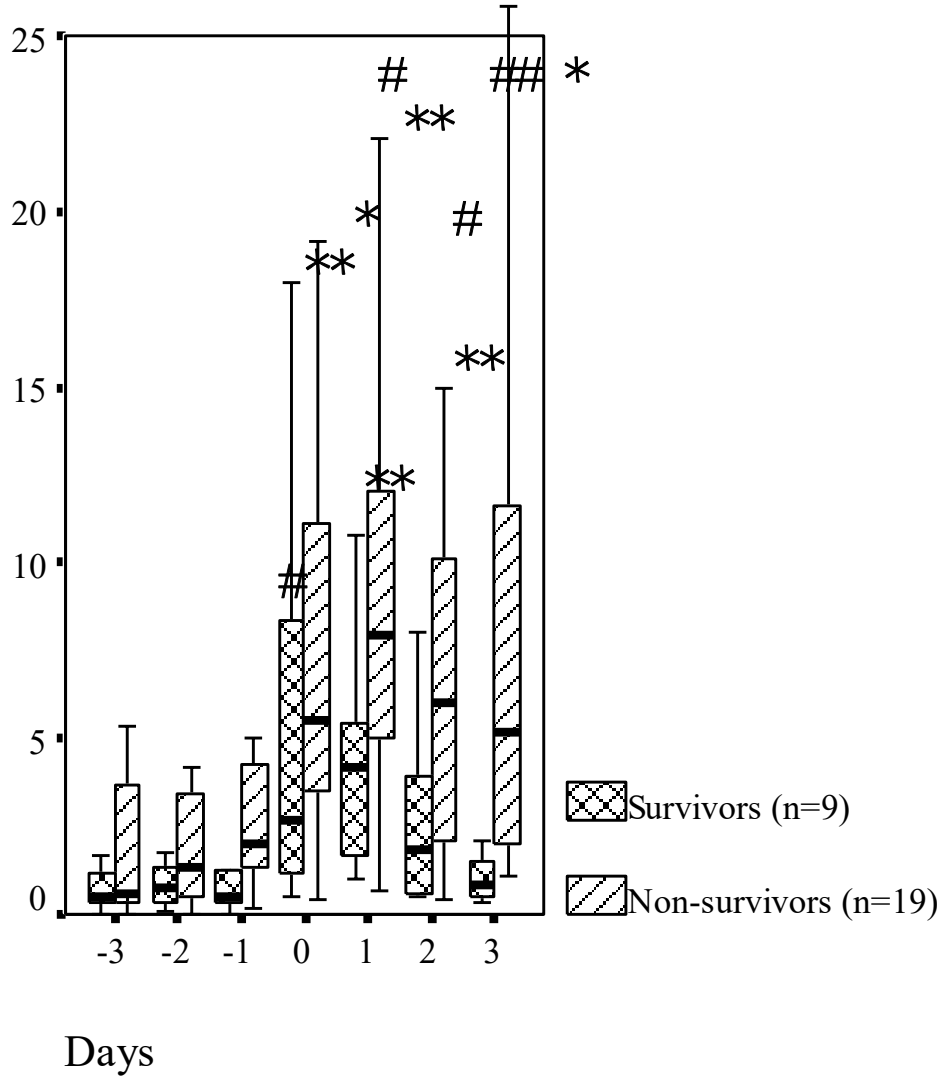


Figure 3: The graph shows the time course of EVLWI in the survivors and non-survivors

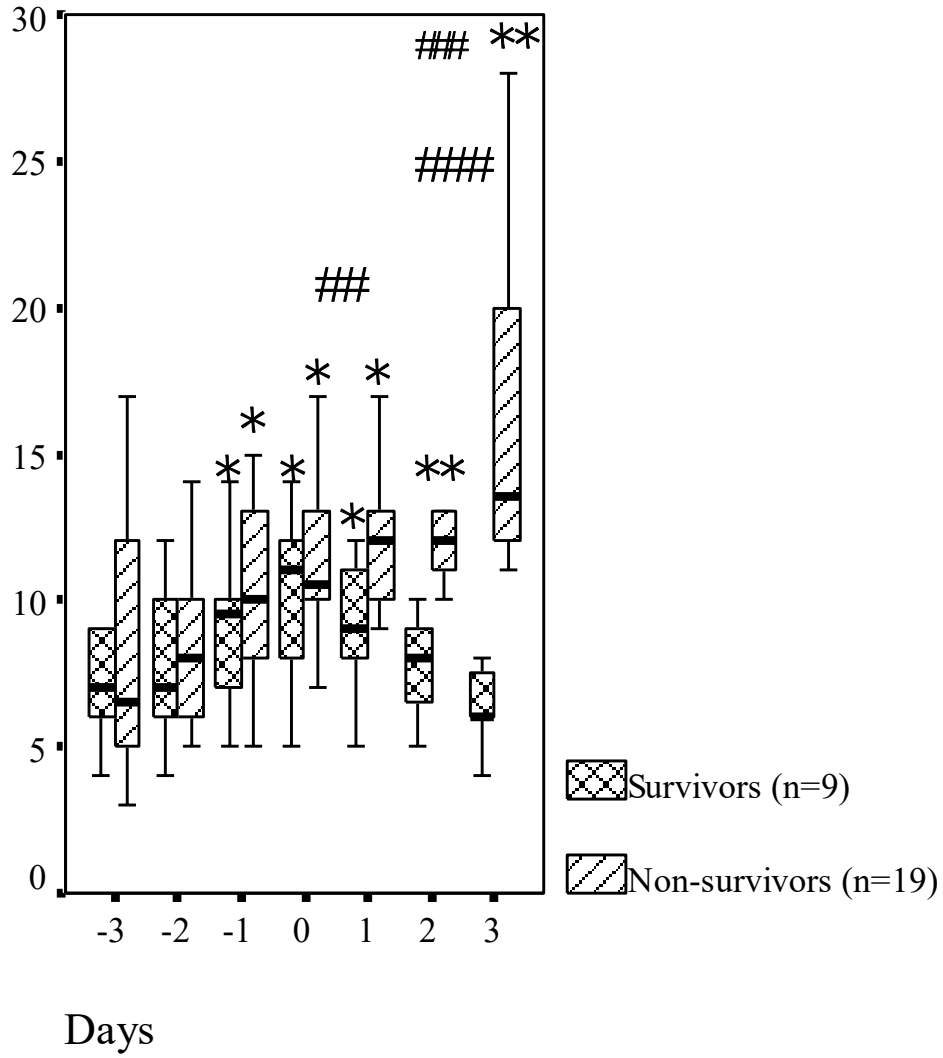


Figure 4: AUROC curves for PCT and EVLWI for diagnosis of sepsis

(AUROC curves of PCT 0,766, AUROC curves of EVLWI 0,760)

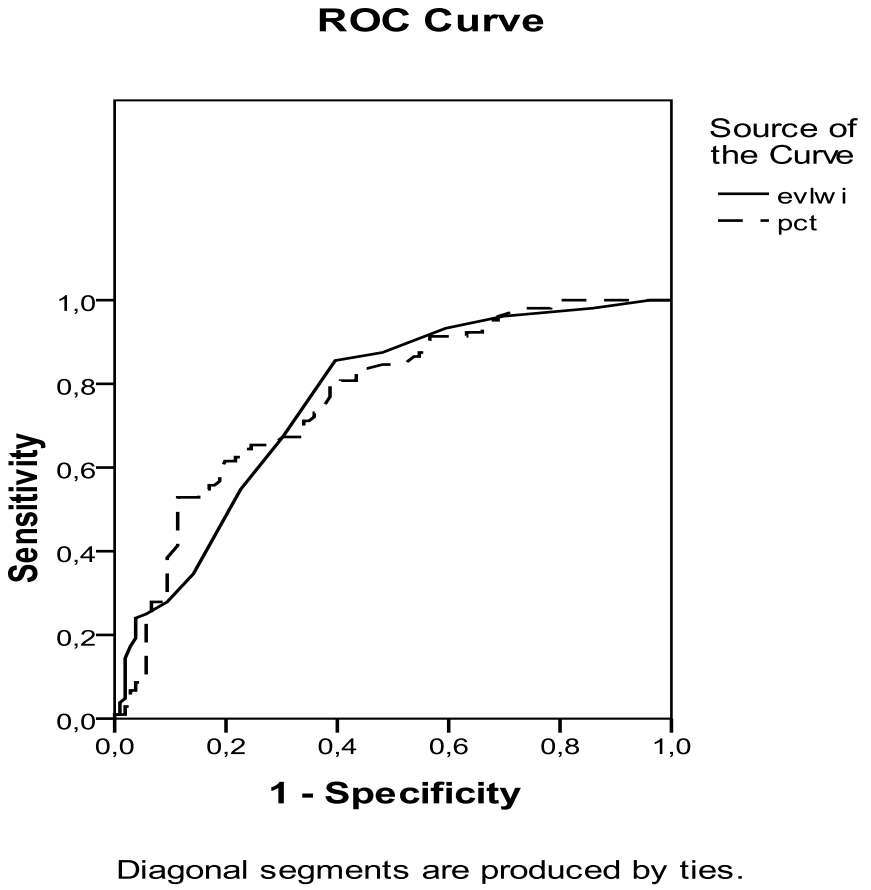


Table 1: Demographic data and initial parameters of the patients

Parameter	Survivors (n=9)	Non-survivors (n=19)	p value
Age (years)	49 (35-63)	53 (38-65)	NS
Male/female	8/1	14/5	NS
TBSA (%)	31 (23-42)	35 (30-50)	NS
Inhalation injury	6/9	13/19	NS
Heart rate (min^{-1})	109 (74-129)	110 (97-120)	NS
MAP (mmHg)	84 (78-106)	80 (74-100)	NS
CVP (mmHg)	7 (3-14)	9 (6-17)	NS
CI ($l\ min^{-1}\ m^{-2}$)	3.9 (2.8-5.9)	3.7 (3.1-5.3)	NS
SVRI ($dyn\ sec\ cm^{-5}$)	1918 (1189-3427)	1968 (1050-2372)	NS
ITBWI ($ml\ m^{-2}$)	733 (658-998)	809 (692-963)	NS
EVLWI ($ml\ kg^{-1}$)	6 (5-9)	8 (6-13)	NS
Temp. max (^oC)	37.1 (35-38.3)	38.1(34.9-38.8)	NS
PaO_2/FiO_2	226 (142-320)	260 (180-301)	NS
PEEP (cmH_2O)	7 (5-11)	5 (4-10)	NS
Lactate ($mmol\ l^{-1}$)	2.4 (1-3.2)	2.5 (1.7-2.8)	NS
Procalcitonin ($ng\ ml^{-1}$)	0.5 (0.2-0.8)	1.2 (0.4-8.2)	NS
Albumin ($g\ l^{-1}$)	32 (24-34)	22 (17-27)	0.004
White blood cells ($G\ l^{-1}$)	13.5 (11.5-19.3)	15.2 (6.9-19.5)	NS
Thrombocytes ($G\ l^{-1}$)	184 (80-240)	210 (150-244)	NS
BaSS	10 (6-18)	11 (7-16)	NS
MODS	5 (4-9)	6 (3-9)	NS
SOFA	8 (6-11)	6 (5-11)	NS

Table 2: Correlations between EVLWI and measured or calculated parameters

Parameter	r value	p value
CVP (mmHg)	r=0.079	NS
ITBWI (ml m^{-2})	r=0.0424	p=0.0003
PEEP (cmH_2O)	r=0.211	p=0.011
Procalcitonin (ng ml^{-1})	r=0.566	p=0.0002
Albumin (g l^{-1})	r=-0.009	NS
BaSS	r=0.275	p=0.001
MODS	r=0.153	NS
SOFA	r=0.208	p=0.012

Table 3: Results of the cultures and efficiency of the antimicrobial therapy

	Survivors (n=9)	Non-survivors (n=19)
Negative samples	5	4
Positive samples	18	30
Wound infection	3	8
Pneumonia	5	12
Blood stream infection	10	10
Adequate antimicrobial therapy	8	17
Inadequate antimicrobial therapy	1	2

Table 4: Results of the microbiologic cultures

Type of microorganism	Survivors (n=18)	Non-survivors (n=30)
Acinetobacter	4	3
Bacillus	0	3
Citrobacter	0	1
Enterobacter	3	1
Enteroccoccus	3	5
Escherichia coli	2	2
Escherichia coli haemolyticus	0	2
Haemophilus parainfluenzae	0	2
Klebsiella pneumoniae	2	3
Klebsiella oxytoca	0	1
Morganella	1	0
Pantoea agglomerans	0	1
Proteus mirabilis	0	1
Pseudomonas aeruginosa	9	13
Staphylococcus aureus	1	4
Staphylococcus coagulase negative	4	9
Streptococcus alfa-haemolysans	0	1
Streptococcus pneumoniae	0	1
Candida albicans	4	3
Candida tropicalis	0	1

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