SIGNA VITAE 2014; 9(2): 47 - 52

ORIGINAL

Predictors of 30-day mortality in medical patients with severe sepsis or septic shock

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ABSTRACT

Objectives. To evaluate independent predictors of 30-day mortality in patients with severe sepsis or septic shock.

Background. Severe sepsis and septic shock are associated with increased mortality. Admission APACHE II score is the gold standard for assessing prognosis in critically ill, but several other predictors of mortality have been evaluated.

Methods. We retrospectively evaluated clinical and laboratory data in adult patients with severe sepsis or septic shock as predictors of 30-day mortality.

Results. Thirty-day mortality was 62.7%. Nonsurvivors in comparison to survivors were significantly more likely to be treated with noradrenalin, renal replacement therapy, mechanically ventilated, to have suffered a fungal infection, had lower admission arterial pH, increased admission Acute Physiology, Age, Chronic Health Evaluation (APACHE) II score and a higher peak lactate level (5.6 ± 6.2 vs 3.1 ± 1.75, p=0.021). Binary logistic regression demonstrated that only peak in-hospital serum lactate level was a significant independent predictor of 30-day mortality (OR 1.367, 95% CI 1.041 to 1.795, p=0.025).

Conclusion. Only peak in-hospital lactate significantly and independently predicts 30-day mortality in severe sepsis or septic shock medical patients.

Key words: severe sepsis, septic shock, 30-day mortality, serum lactate

Introduction

The incidence of severe sepsis is increasing within the last decade, reaching 50-100 cases /100.000 people in the general population and approximately 30% in intensive care units. (1,2) Mortality of patients with sepsis depends on the sepsis stage and co-morbidities. It ranges from 10-20% in patients with uncomplicated sepsis to 20-50% in severe sepsis and up to 80% in patients with septic shock. (1)

Admission Acute Physiology, Age, Chronic Health Evaluation (APACHE) II score is a standard predictor of mortality in critically-ill patients, including septic patients. (3) It is applicable in the majority of critically-ill patients and extensively validated in several countries due to its simplicity as a predictor of mortality. (4,5) The score is obtained from the patient's age and the worst values of 12 physiological parameters within the first 24 hours such as body temperature, mean arterial blood pressure, pulse, arterial pO_2, serum creatinine, potassium, sodium, hematocrit, white blood cell count, Glasgow coma scale, respiratory rate. The higher the APACHE II score, the higher the mortality rate.

A variety of other predictors of mortality in patients with sepsis was evaluated in clinical studies, including inflammatory markers such as C-reactive protein (CRP), lactate clearance, cardiac biomarkers such as troponin and ejection fraction (EF), individual organ system failures, presence of multi-organ failure syndrome (MOFS), etc. (6) These studies were performed in heterogeneous patient populations, ranging from lower risk patients with sepsis to high risk septic shock patients, included from wards to surgical or medical intensive care units (ICU). (4-9)

The primary objective of this study was to investigate which patient characteristics are related to outcome in medical patients with severe sepsis or septic shock.

Participants and methods

We performed a retrospective cohort analysis of all adult patients with severe sepsis or septic shock treated in a medical ICU in 2008, 2009 and 2010. The study was approved by the Ehical institutional review board (No. 156/13) and is in accordance with the declaration of Helsinki.

In all, 102 patients (63 men, 39 women,

Table 1. Admission clinical and laboratory data in all septic patients, survivors and nonsurvivors.

Admission data	All (n = 102)	Survivors (n = 38)	Nonsurvivors (n = 64)	p
Age (mean ± SD, years)	65.1 ± 13.3	63.82 ± 13.9	65.9 ± 12.9	0.452
Men (%)	61.8	60.5	62.5	0.99
APACHE II score (mean ± SD)	29.1 ± 8.3	26.6 ± 8.7	30.5 ± 7.8	0.020
S-glucose (mean ± SD, mmol/L)	12.7 ± 6.4	12.5 ± 25.8	12.9 ± 6.3	0.795
S-Lactate (mean ± SD, mmol/L)	3.8 ± 3.5	2.9 ± 1.9	4.3 ± 4.2	0.062
S-creatinine (mean ± SD, μmol/L)	224.8 ± 155.1	220.2 ± 159.1	227 ± 153.8	0.820
Arterial pH (mean ± SD)	7.28 ± 0.15	7.3 ± 0.1	7.2 ± 0.2	0.005
Pneumonias (%)	50.5	48.6	51.6	0.838
Uroinfection (%)	16.8	21.6	14.1	0.410
Other infections (%)	32.4	26.3	35.9	0.437
G + bacterial infection (%)	28.4	31.6	26.7	0.652
G – bacterial infecrion (%)	36.3	36.8	35.9	1.000
Viral infection (%)	2.9	2.6	3.1	1.000
Fungal infection (%)	14.7	5.3	20.3	0.045
Positive hemocultures (%)	52.9	50	54.7	0.685

APACHE, acute physiology, age, chronic health evaluation; G –, gram-negative; G +, gram-positive; SD, standard deviation.
$p < 0.05$ was statistically significant and was calculated by the two-sided Student's t-test for means ± standard deviations and by the χ^2-test for percentages.

Table 2. In-hospital data of all septic patients, survivors and nonsurvivors.

In-hospital data (means ± SD)	All (n=102)	Survivors (n=38)	Nonsurvivors (n=64)	p
LVEDD (cm)	4.9 ± 0.78	4.8 ± 0.6	5.0 ± 0.9	0.428
Ejection fraction (%)	39.7 ± 15.7	42.6 ± 13.7	38.1 ± 16.8	0.321
Peak serum glucose (mmol/L)	16.6 ± 6.7	16.4 ± 7.8	16.7 ± 6,1	0.822
Peak serum lactate (mmol/L)	4.7 ± 5.2	3.1 ± 1.8	5.6 ± 6.3	0.021
Peak serum creatinine (μmol/L)	304.0 ± 196.5	276.7 ± 190.8	320.2 ± 199.6	0.282
Peak serum CRP (mg/L)	220.2 ± 93.9	212.2 ± 90.8	225.0 ± 96.2	0.508
Peak troponin I (μg/L)	3.1 ± 6.5	3.5 ± 7.6	2.9 ± 5.8	0.721
Nadir serum albumin (g/L)	20.7 ± 12.2	22.7 ± 11.1	19.6 ± 12.8	0.227
Nadir serum glucose (mmol/L)	5.4 ± 1.9	4.9 ± 1.5	5.6 ± 2.1	0.119
ICU stay (days)	11.7 ± 15.1	13.7 ± 12.7	10.6 ± 16.4	0.320

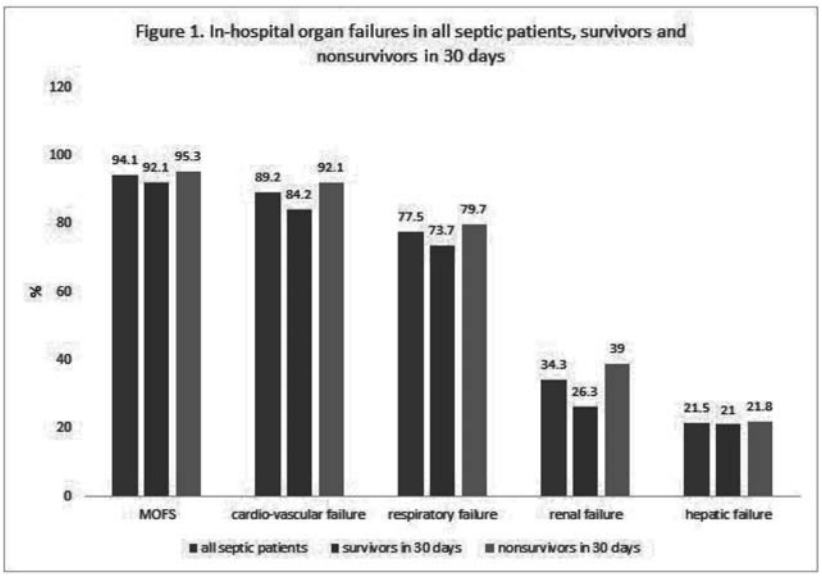
CRP, C-reactive protein; ICU, intensive care unit; LVEDD, left ventricular end-diastolic diameter; SD, standard deviation.
$p < 0.05$ was statistically significant and was calculated by the two-sided Student's t-test for means ± standard deviations and by the χ^2-test for percentages

mean age 65.1 ± 13.3 years) were included.

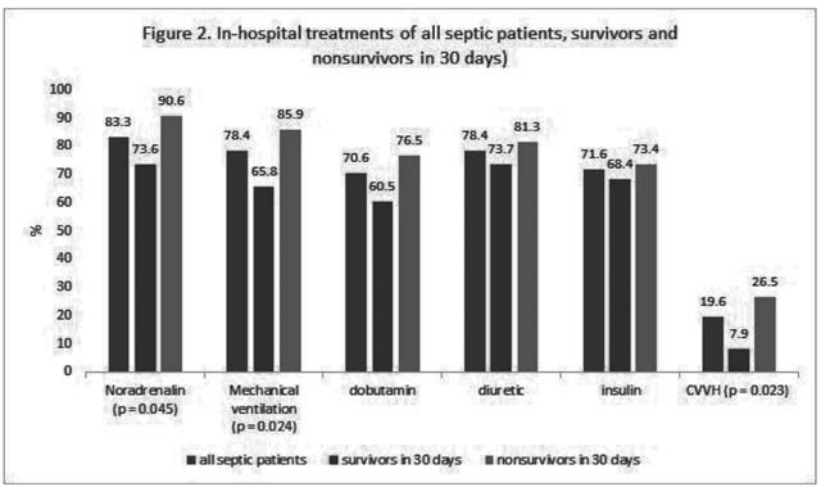
The criteria for severe sepsis were fulfilled if in patients with sepsis there was at least one organ failure or a sign of tissue hypoperfusion. In septic shock patients there were signs of sepsis in addition to acute circulatory failure with decreased systolic blood pressure < 90 mm Hg or mean arterial blood pressure < 65 mm Hg without any other known causes in spite of adequate infusion of fluids. (10)

Patient treatment followed guideline goals. (11) Adequate oxygenation was established by oxygen delivery with or without mechanical ventilation. Adequate perfusion was established by intravenous infusion of fluids, noradrenalin or dobutamine to reach mean arterial pressure > 65 mm Hg, central venous oxygen saturation ($ScvO_2$) > 70% and urine output > 0.5 ml/kg/h within the first 24 hours. EF < 50%, assessed by echocardiography, confirmed systolic cardiac dysfunction. Infection was controlled with intravenous antibiotics, administered within an hour after prior microbiological samples were withdrawn. Low dose hydrocortisone and insulin were administered if necessary. (11)

Vital signs, laboratory test results, ICU treatment characteristics and final out-



MOFS, multi-organ failure syndrome.



CVVH, continuous veno-venous hemofiltration.
$p < 0.05$ was statistically significant and was calculated by the χ^2-test for percentages

come were retrieved from patient medical records.

We registered demographic, admission and in-hospital laboratory and clinical data, treatments and 30-day mortality. Among laboratory data we registered admission and peak arterial pH, CRP, serum creatinine, lactate, troponin I and serum glucose as well as nadir serum glucose and albumin. Among clinical data on admission we registered prior chronic diseases such as chronic cardio-vascular, pulmonary, hepatic, hematological, renal chronic disease, admission mean arterial pressure, pulse, APACHE II score, ratio between arterial oxygen pressure and fraction of inspired oxygen (paO_2/FiO_2).

Among organ failures we registered acute cardiovascular, respiratory, renal and hepatic failure. Acute respiratory failure was defined as arterial hypoxia with $paO_2/FiO_2 < 300$, acute renal failure was defined as oliguria with increased serum creatinine, acute hepatic failure as an increase in serum bilirubin > 35 mmol/L and acute cardio-vascular failure as arterial hypotension (decrease of systolic arterial blood pressure < 90 mmHg or mean arterial blood pressure < 65 mmHg). (10) We also registered positivity of hemocultures, site of infection – pneumonia, urinary tract infection and infection of other sites – in particular of pancreas, gall bladder, meninges, skin or joints. We registered causative microorganisms of infection associated with sepsis as gram-negative and gram-positive bacteria, viruses or fungi, but we also registered microorganisms (gram-negative, gram-positive bacteria, viruses or fungal infection) identified in positive hemocultures.

Among in-hospital data we registered echocardiographic parameters (ejection fraction and left ventricular end-diastolic diameter) and treatments such as the use of noradenaline, inotropic support by dobutamine, mechanical ventilation, iv. diuretics, insulin and renal replacement therapy by continuous veno-venous hemofiltration (CVVH).

Our aim was to evaluate the independent predictive role of demographic, clinical and laboratory data, treatments, individual organ failures and MOFS between survivors and nonsurvivors within 30 days in our patients with severe sepsis and septic shock.

Statistical analysis

Statistical analysis was performed using SPSS statistical package, version 19 (SPSS Inc., Chicago, IL, USA) for Windows. Data were expressed as means ± standard deviations or percentages. Differences between the groups were tested by the two-sided Student's t-test for means ± standard deviations and by the χ^2-test for percentages. A p-value < 0.05 was considered statistically significant. The binary logistic regression model was used to predict relation to 30-day mortality. Goodness of fit of the model was assessed using the Hosmer-Lemeshow test.

Results

During the inclusion period 102 patients were diagnosed with severe sepsis or septic shock. Baseline clinical data are displayed in table 1. In-hospital data are presented in table 2 and in-hospital

Table 3. Binary logistic regression to estimate independent predictors of 30-day mortality in septic patients.

Variables	χ^2	OR	p	95% C.I.
Admission pH	1.568	0.072	0.210	0.001 do 4.429
Noadrenalin therapy	3.272	4.336	0.070	0.885 do 21.249
Mechanical ventilation	1.178	1.954	0.278	0.583 do 6.553
CVVH	2.902	3.720	0.088	0.821 do 16.861
Peak serum lactate	5.057	1.367	0.025	1.041 do 1.795
Admission APACHE II	0.270	1.016	0.603	0.956 do 1.081
Fungal infection	2.361	3.849	0.124	0.690 do 21.470

APACHE, acute physiology and chronic health evaluation; CI, confidence interval; CVVH, continuous veno-venous hemofiltration; OR, odds ratio; χ^2, chi^2.

$p < 0.05$ was statistically significant; Confidence intervals are at 95% probability

organ failures are displayed in figure 1. In-hospital treatments are presented in figure 2.

30-day mortality of our patients with severe sepsis and septic shock was 62.7%.

Regarding admission clinical and laboratory data we observed nonsignificant differences between survivors and nonsurvivors in regard to mean age, gender, admission serum glucose, creatinine and lactate levels, in the incidence of pneumonia, urinary infection and other infections, in positive hemocultures, in the incidence of gram-positive and gram-negative bacterial infection and viral infection, but significant differences in fungal infection (5.3% vs 20.3%, $p = 0.045$), in mean admission arterial pH ($7.3 \pm 0,1$ vs 7.2 ± 0.2, $p = 0.005$) and APACHE II score (26.6 ± 8.7 vs 30.5 ± 7.8, $p = < 0.05$) (table 1).

Between survivors and nonsurvivors within 30 days we observed nonsignificant differences in in-hospital data such as mean levels of left ventricular end-diastolic diameter (LVEDD), EF, peak and nadir serum glucose and albumin levels, peak serum creatinine, troponin I and CRP levels, but significant peak serum lactate levels (3.1 ± 1.8 mmol/l vs 5.6 ± 6.3 mmol/l, $p = 0.021$) (table 2).

Between survivors and nonsurvivors within 30 days we observed nonsignificant differences in the incidence of MOFS, cardio-vascular, respiratory, renal and hepatic failures (figure 1).

In treatments we observed nonsignificant differences between survivors and nonsurvivors within 30 days in dobutamine, diuretics and insulin, but significant differences in treatments by noradrenalin (73.6% vs 90.6%, $p = 0.045$), mechanical ventilation (65.8% vs 85.9%, $p = 0.024$) and CVVH (7.9% vs 26.5%, $p = 0.023$) (figure 2).

In terms of association with outcome, binary logistic regression demonstrated that peak in-hospital lactate level was the most significant independent predictor of 30-day mortality (OR 1.367, 95% CI 1.041 to 1.795, $p = 0.025$) (table 3).

Discussion

We observed that several clinical and laboratory data (admission arterial pH, APACHE II score, peak serum lactate, treatment with noradrenalin, mechanical ventilation and CVVH, fungal infection) were associated significantly with 30-day mortality in our patients with severe sepsis and septic shock.

Thirty-day mortality in our patients with severe sepsis and septic shock was 62.7%, which is similar to other studies. Treatment with noradrenalin, mechanical ventilation and CVVH, significantly associated with mortality, pointed to a predictive role of pronounced cardiovascular, respiratory and renal failure for 30-day mortality in severe sepsis. (1,2)

Mean admission APACHE II score as a gold standard for predicting mortality was 29 in our patients, predicting approximately a 67.2% death rate and was associated significantly with 30-day mortality of our septic patients. (3)

Regarding microorganisms responsible for infection, gram-negative microorganisms were still dominating and identified in 36.3% of patients in contrast to 28.4% of gram-positive bacteria.

According to the data in literature it was not surprising that fungal infections in our severely septic patients were significantly associated with 30-day mortality. (12,13)

However, binary logistic regression confirmed that only peak lactate levels significantly and independently predicted 30-day mortality in our septic patients.

Increased blood lactate levels in critically-ill patients in general are associated with increased morbidity and mortality. (14,15) Patients with preserved blood pressure and elevated lactate levels are at increased risk of dying as well. (16,17) The importance of lactate levels is emphasized in the treatment of sepsis, where some treatment strategies as well as mortality risk depend on lactate levels. (11) A variety of other predictors of mortality have been evaluated in clinical studies, including inflammatory markers such as CRP, lactate clearance, cardiac biomarkers such as troponin and ejection fraction, multiorgan failure syndrome, etc. (4-9)

Lactic acidosis is common in patients with severe sepsis or septic shock. The pathophysiology of lactic acidosis associated with sepsis is not fully understood. Both increased lactate production during anerobic and aerobic metabolism and decreased clearance likely contribute to hyperlactemia. (18,19)

Lactate-to-pyruvate ratio is elevated

in septic shock, suggesting tissue hypoxia as the cause of lactic acidosis. Hyperlactemia in the absence of hypoxia has been documented as well. The additional possible mechanisms for hyperlactemia include activation of glycolysis and inhibition of pyruvate dehydrogenase. Some patients with sepsis have decreased lactate clearance rather than increased lactate production. Hyperlactemia may be secondary to increased lactate production in the gut, liver, lungs, and skeletal muscles, decreased lactate clearance in the liver; or a combination of both. (18-20)

Patients who have an arterial lactate level of more than 5 mmol/L experience poor outcomes, with mortality rate up to 75% and median survival of 28 hours. Roughly 50% of these patients survive 24 hours and about 20% are discharged from the hospital. (17,21,22) Mortality rate is highest for patients with lactic acidosis (56%), compared with anion gap acidosis (39%). Serum lactate, anion gap acidosis, phosphate, and age have been identified as independent predictors of mortality. Overall, patients with metabolic acidosis were nearly twice as likely to die as patients without metabolic acidosis. (21) Patients with elevated lactate levels exhibit hospital mortality rates that increase almost linearly with the concentration of serum lactate. Several studies have shown that vigilant correction of hyperlactemia is associated with decreased morbidity and mortality. The mortality rate of patients with a serum lactate level greater than 2 mmol/L persisting after 24 hours, with associated acidemia, approaches 70%. (22)

Lactate as a marker of disease severity has a number of favourable properties. First, it can be withdrawn from both peripheral venous or arterial blood, making it possible to obtain lactate levels and to risk-stratify patients early, even in the emergency department. No significant differences exist between central venous, peripheral venous or arterial lactate levels. (23) Second, a number of point-of-care machines enable rapid, bedside determination of lactate levels. There seem to be no significant differences between point-of-care and laboratory lactate results. (24) Point-of-care lactate determination makes sense, especially when goal-directed therapy principles are to be observed. (24,25) Third, apart from recognition of critically ill patients, lactate tracking can be used as a tool to evaluate the efficacy of treatment not only in sepsis, but in variety of settings. (11,24) Third, the information that elevated lactate levels provide, is easily integrated into treatment strategies, no additional conversions or calculations are needed.

To conclude, the results of our study confirm the importance of measuring lactate levels on a regular basis in critically ill patients with severe sepsis and septic shock. Increased levels of lactate enable recognition of patients who are at highest risk of dying. The method is simple and can be performed at the bedside. The information that elevated lactate levels provide to the clinician is easily integrated into existing treatment strategies. No additional conversions or calculations are needed in order to appreciate the results. Peak in-hospital lactate level was the only significant independent predictor of 30-day mortality in our patients with severe sepsis and septic shock.

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