Journal of Acute Disease

Original Article

doi: 10.4103/2221-6189.330743 jadweb.org

Ionized calcium level predicts in–hospital mortality of severe sepsis patients: A retrospective cross–sectional study

Bora Cekmen[1], Ramazan Koylu[1], Nazire Belgin Akilli[1], Yahya Kemal Gunaydin[2], Oznur Koylu[3], Seref Emre Atis[4]✉, Basar Cander[5]

[1]*Department of Emergency Medicine, Konya Education and Research Hospital, Konya, Turkey*

[2]*Department of Emergency Medicine, Ankara Education and Research Hospital, Ankara, Turkey*

[3]*Department of Biochemistry, Konya Education and Research Hospital, Konya, Turkey*

[4]*Department of Emergency Medicine, Mersin City Hospital, Mersin, Turkey*

[5]*Department of Emergency Medicine, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey*

ABSTRACT

Objective: To evaluate the effect of serum ionized calcium levels on the prognosis of severe sepsis patients.

Methods: This retrospective cross-sectional study included sepsis patients who were hospitalized in an intensive care unit between January 2011 and December 2014. The demographic and baseline data of the patients who died and survived were compared. The cutoff value of ionized calcium for in-hospital mortality was determined by the receiver operating characteristics curve (ROC). In-hospital mortalities and the survival rates were compared between patients with different ionized calcium levels. Besides, the risk factor of in-hospital mortality was determined.

Results: This study included 145 patients with 113 patients who died in the hospital. The patients who died had significantly lower ionized calcium levels (U=2.25, P=0.034). A cut-off value of 0.93 mmol/L of ionized calcium was determined by the ROC curve. The patients with ionized calcium>0.93 mmol/L showed a significantly lower morality (χ^2=9.90, P=0.002) and higher survival rate than with ≤0.93 mmol/L (log rank=6.20, P=0.010). Multivariate Cox regression revealed that ionized calcium ≤0.93 mmol/L was a risk factor of in-hospital mortality.

Conclusions: Ionized calcium level≤0.93 mmol/L was an independent predictor of in-hospital mortality of severe sepsis.

KEYWORDS: Ionized calcium; Critically illness; Sepsis; Mortality; In-hospital

1. Introduction

Sepsis has become one of the leading causes of death in intensive care units. Regardless of recent advances in medicine, the incidence of sepsis remains rising[1]. The reasons lie in the increase in resistant infectious agents, high rates of infections in intensive care units, and growth in immune-depressed patients due to radiotherapy, chemotherapy, and transplantation[2]. Mediators and cytokines that play a role in the pathophysiology of sepsis have been identified. Additionally, their mechanisms of action and the metabolic

Significance

Although many working groups and consensus have emerged, sepsis remains a common condition with high mortality. We investigated the effect of calcium on mortality in our study, and found that hypocalcaemia is an independent predictor of mortality.

✉To whom correspondence may be addressed. E-mail: dremreatis@gmail.com

How to cite this article: Cekmen B, Koylu R, Akilli NB, Gunaydin YK, Koylu O, Atis SE, et al. Ionized calcium level predicts in-hospital mortality of severe sepsis patients: A retrospective cross-sectional study. J Acute Dis 2021; 10(6): 247-251.

Article history: Received 25 March 2021; Revision 18 June 2021; Accepted 15 July 2021; Available online 30 November 2021

changes they cause have been determined[3]. Lack or excess of the mediators and cytokines causes deterioration of homeostasis and body resistance, damage to some organs, multiple organ failure, and death[3]. One of these homeostatic balances is calcium metabolism. Low extracellular calcium levels are common in critical diseases, such as acute kidney injury, sepsis, and septic shock.

Studies have reported that hypocalcemia increases mortality of patients in intensive care, and showed a relationship between Acute Physiology and Chronic Health Evaluation (APACHE) Ⅱ scores and ionized calcium levels[4,5]. This study aims to investigate the effect of serum ionized calcium levels measured at the time of initial diagnosis in intensive care patients with sepsis on prognosis.

2. Patients and methods

2.1. Study patients

This retrospective cross-sectional study included sepsis patients who were hospitalized in an intensive care unit from January 2011 to December 2014.

Patients who were hospitalized in the intensive care unit, diagnosed with sepsis, and aged ⩾18 years were included in the study. The presence of a particular focus of infection, an inappropriate response to infection, and life-threatening organ dysfunction (SOFA score ⩾2) were re-evaluated in patients diagnosed with sepsis[6]. Patients who were aged <18 years, pregnant, did not meet any of the existing sepsis criteria and had missing/incomplete disease data were excluded from the study.

2.2. Ethical approval

This study was initiated after the approval of the Clinical Research Ethics Committee of the Necmettin Erbakan University, Faculty of Medicine, in Turkey (Approval no: 2014/77).

2.3. Data collection

Age, sex, comorbid diseases, systolic and diastolic arterial blood pressure measurements at the time of admission, heart rate, respiratory rate, and body temperature of the patients were recorded. White blood cell counts, hemoglobin values, and platelet counts were determined from the blood samples taken at the time of diagnosis. The biochemical analysis included urea, creatinine, sodium, procalcitonin, and C-reactive proteinvalues. HCO_3 values, lactate levels, and ionized calcium levels were recorded as a part of arterial blood gas analysis. APACHE Ⅱ and SOFA scores of the patients were calculated by the researcher who conducted the study. Sepsis foci, presence of growth in the culture samples, type of infectious agent were recorded. The diagnostic value of ionized calcium levels in predicting in-hospital mortality was evaluated.

2.4. Outcomes

The primary outcome of this study was to determine the value of ionized calcium levels, which predict in-hospital mortality of critically ill sepsis patients. The second outcome was to determine the risk factor of in-hospital mortality.

2.5. Statistical analysis

Statistical analyses were performed using SPSS v.15.0 software. Normality of the variables was examined by visual (histogram and probability graphics) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive analyses were presented as mean±standard deviation for normally distributed variables and as median and interquartile ranges (IQR) for non-normally distributed variables. In comparison of the clinical and laboratory characteristics of people who died in hospital and who survived, independent group *t*-test was used for normally distributed variables and a Mann-Whitney *U* test was used for non-normally distributed variables. Categorical data were compared using the *Chi*-square test or Fisher's exact test. Ionized calcium levels, APACHE Ⅱ scores, and SOFA scores were included in this model. The diagnostic value of serum ionized calcium in predicting in-hospital mortality was analyzed by the receiver operating characteristics (ROC) curve. Further, the effect of this cut-off value on the survival of patients with sepsis was investigated using the log-rank test. Kaplan-Meier curve was used for calculating the survival rates. Beside, Cox regression model was used for evaluating the independent relationships between in-hospital mortality and ionized calcium levels. The significance level of this study was set at α=0.05.

3. Results

The study included 177 patients with sepsis hospitalized in the intensive care unit. Of the 177 patients, 32 were excluded from the study due to insufficient data and non-compliance with the sepsis diagnosis criteria. Hence, the study was performed with 145 patients.

The median age of the 145 patients was 74 (IQR: 16) years. Of these, 81 (55.9%) patients were male and 64 (44.1%) were female. The demographic data, vital signs, and laboratory data of the patients are shown in Table 1. The patients were divided into two groups as in-hospital died patients and the survived patients. A total of 113 (77.9%) patients were dead.

Foci infections were found in the respiratory system of 67 (46.2%) patients, urinary system in 53 (36.6%) patients, gastrointestinal system in 13 (9%) patients, central nervous system in 2 (1.4%) patients, and soft tissues in 10 (6.9%) patients. Also, positive culture was observed in 100 (69%) patients. Of these 100 cultures, 46 (46%) were of Gram-positive (+) bacteria, 47 (47%) were of Gram-negative (−) bacteria, and 7 (7%) were of fungi. Anaerobic bacteria, viruses, and parasites were not present in any of the cultures. Furthermore, 42.9% (33) of in-hospital deaths were

Table 1. Baseline characteristics of the patients.

Variables	Non–survived, *n*=113	Survived, *n*=32	$U/\chi^2/t$	*P*
Age, median (IQR)	74.00 (16.00)	75.00 (12.75)	1.77	0.890
Gender, *n* (%)			0.73	0.392
Female	52 (81.3%)	12 (18.8%)	-	-
Male	61 (75.3%)	20 (24.7%)	-	-
Comorbidities, *n* (%)				
Diabetes	18 (72.0%)	7 (28.0%)	0.61	0.293
Coronary arter disease	15 (75.0%)	5 (25.0%)	0.11	0.464
Chronic renal disease	30 (83.3%)	6 (16.7%)	0.81	0.256
Hypertension	23 (76.7%)	7 (23.3%)	0.03	0.513
Cerebrovascular disease	25 (69.4%)	11 (30.6%)	2.00	0.119
Chronic lung disease	23 (85.2%)	4 (14.8%)	1.01	0.231
Congestive heart failure	13 (92.9%)	1 (7.1%)	2.00	0.138
Vital signs				
Pulse rate, median (IQR)	110.00 (28.00)	106.50 (33.50)	1.72	0.470
Systolic blood pressure, mmHg, mean±SD	98.70±22.95	110.34±28.88	−2.09	0.033
Diastolic blood pressure, mmHg, mean±SD	58.55±15.02	62.18±14.01	−1.22	0.540
Laboratory tests				
Urea, mg/dL, median (IQR)	128.00 (105.0)	98.00 (76.50)	1.58	0.283
Creatinine, mg/dL, median (IQR)	2.46 (2.77)	1.84 (1.99)	1.41	0.061
Sodium, mEq/L, mean±SD	139.00±9.72	137.38±6.77	1.22	0.129
Albumine, mg/dL, mean±SD	2.54±0.55	2.78±0.49	−2.27	0.025
C-reactive protein, mg/dL, median (IQR)	173.00 (132.00)	147.50 (101.50)	1.81	0.977
Procalcitonin, ug/L, median (IQR)	6.42 (28.29)	12.59 (52.63)	1.99	0.373
Hco_3, mEq/L, mean±SD	17.33±5.72	20.17±4.65	−2.57	0.036
Initial serum lactate, mmol/L, median (IQR)	2.10 (2.49)	1.51 (1.17)	1.25	0.008
Ionised calcium, mmol/L, median (IQR)	0.85 (0.25)	0.98 (0.27)	2.25	0.034
Hemoglobin, g/dL, mean±SD	10.99±2.50	11.63±2.31	−1.20	0.659
White blood cell count, 10^9/L, median (IQR)	14.38 (11.15)	15.14 (13.24)	1.92	0.570
Platelet count, 10^9/L, median (IQR)	182.00 (161.50)	207.00 (182.00)	1.82	0.404
Culture positive, *n* (%)			1.41	0.244
Gram-negative bacteria	33 (71.7%)	13 (28.3%)	-	-
Gram-positive bacteria	38 (80.9%)	9 (19.1%)	-	-
Fungi	6 (85.7%)	1 (14.3%)	-	-
APACHE Ⅱ score, median (IQR)	23.00 (10.50)	14.50 (5.75)	540	<0.001
SOFA score, median (IQR)	10.00 (5.00)	4.00 (4.00)	297	<0.001

caused by Gram-positive bacteria, 49.4% (38) by Gram-negative bacteria, and 7.8% (6) by fungi.

A statistically significant difference was found between the two groups in terms of ionized calcium levels (*P*=0.034), lactate levels (*P*=0.008), bicarbonate levels(*P*=0.036), systolic blood pressure (*P*=0.033), albumin levels (*P*=0.025), APACHE Ⅱ scores (*P*<0.001), and SOFA scores (*P*<0.001) (Table 1).

Ionized calcium levels in predicting in-hospital mortality were calculated. The cut-off value obtained using the ROC curve for in-hospital mortality was 0.93 mmol/L (sensitivity=67.26; specificity=62.50; AUC=0.63; 95% *CI*: 0.54%-0.70%; *P*=0.03) (Figure 1).

According to the ionized calcium cut-off value, two groups were formed: patients with ionized calcium levels ≤0.93 mmol/L and patients with ionized calcium levels >0.93 mmol/L. A statistically significant difference was found between the two groups concerning in-hospital mortality (*P*=0.002). However, there was no significant difference between the two groups in terms of age, sex, pulse, systolic blood pressure, lactate levels, CRP levels, procalcitonin levels, albumin levels, platelet count, APACHE Ⅱ scores, and SOFA scores (*P*=0.281, 0.957, 0.131, 0.213, 0.130, 0.966, 0.686, 0.073, 0.611, 0.504, 0.071; respectively) (Table 2).

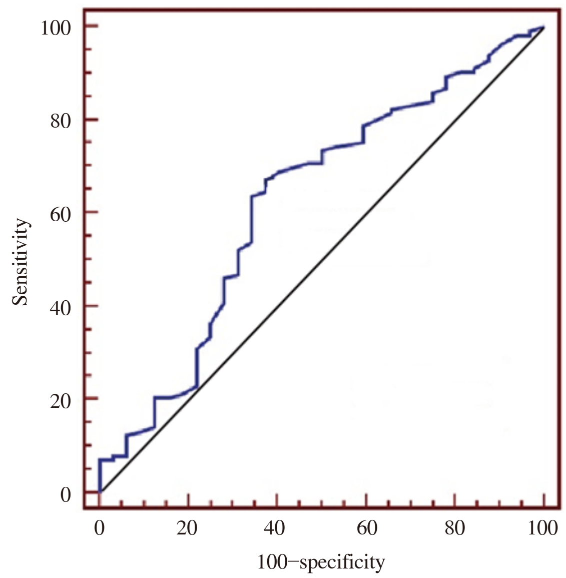

Figure 1. Cut-off value of ionized calcium level using the ROC curve.

Survival rates calculated using the Kaplan-Meier curve in the presence of in-hospital mortality were significantly lower in those with ionized calcium levels ≤0.93 (log rank=6.20; *P*=0.010) (Figure 2).

Table 2. Comparison between patients with different ionized calcium levels.

Variables	≤0.93 mmol/L (*n*=88)	>0.93 mmol/L (*n*=57)	$U/\chi^2/t$	*P*
In-hospital mortality, *n* (%)	76 (67.3)	37 (32.7)	9.90	0.002
Age, median (IQR)	74.5 (14)	71.5 (21)	1.06	0.540
Sex, male, *n* (%)	49 (60.5)	32 (39.5)	1.30	0.520
Pulse, median (IQR)	109.5 (32.7)	108.0 (26.5)	1.06	0.580
Systolic blood pressure, mean±SD	99.6±23.3	104.1±26.9	1.06	0.280
Lactate levels, median (IQR)	2.10 (2.40)	1.76 (1.55)	2.49	0.280
CRP levels, median (IQR)	160.50 (124.3)	155.00 (124.10)	1.06	0.580
Procalcitonin levels, median (IQR)	6.10 (28.40)	8.00 (43.80)	1.24	0.530
Albumin levels, mean±SD	2.58±0.60	2.59±0.47	1.62	0.870
Platelet count, median (IQR)	177.00 (160.20)	188.50 (174.50)	1.68	0.430
APACHE Ⅱ scores, median (IQR)	22.00 (10.00)	20.00 (14.00)	2.50	0.280
SOFA scores, median (IQR)	9.50 (5.75)	8.00 (6.00)	2.42	0.290

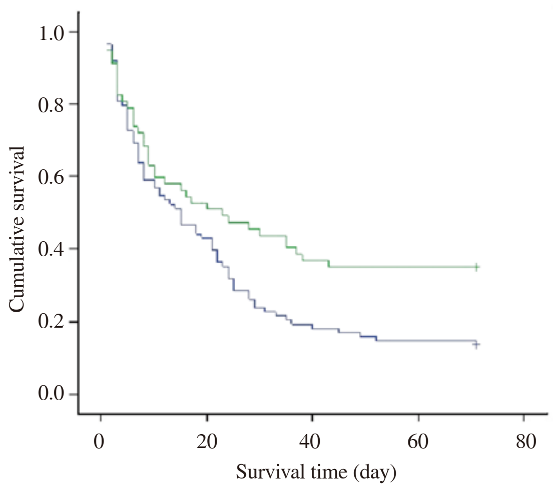

Figure 2. Kaplan-Meier curve in the presence of in-hospital mortality. Green line: Ionized calcium>0.93 mmol/L; Blue line: Ionized calcium≤0.93 mmol/L.

Cox regression model was used for evaluating the independent relationships between in-hospital mortality and ionized calcium levels. Multivariate cox regression model revealed that ionized calcium level ≤0.93 was an independent indicator of in-hospital mortality [HR: 1.05 (95% *CI*: 1.020-1.097, *P*=0.003)] regardless of systolic blood pressure, albumine, HCO_3, lactate levels, Apache Ⅱ scores.

4. Discussion

In this study, ionized calcium levels of ≤0.93 mmol/L have a significantly higher in-hospital mortality compared to that of >0.93 mmol/L. Also, ionized hypocalcemia was found to be an independent indicator for in-hospital mortality in the regression analysis. The significant cut-off value is 0.93. Although abnormal changes in calcium levels are quite common in intensive care patients, hypocalcemia and its correction are more common[7]. In a retrospective study by Wang *et al.*, a high level of ionized calcium was found to have a protective function in children with a diagnosis of sepsis, wherein this value was measured as 0.95[8]. In another study involving 119 patients with sepsis, hypocalcemia and mortality were correlated, wherein the cut-off value was reported as 0.70[9].

In another study, ionized calcium level was reportedly lower in patients with neonatal sepsis compared to those in the control group without sepsis; when these patients with sepsis were further divided into two groups as those with low ionized calcium levels and those without, the rate of progression to mortality and organ failure was higher in the group with low ionized calcium levels[10]. In another study involving 12 599 patients, it was revealed that a decrease in ionized calcium levels raised in-hospital mortality, wherein high ionized calcium levels reduced in-hospital mortality[11]. However, a meta-analysis reported that ionized calcium levels did not affect in-hospital mortality or hospital stay[12].

In a study performed with 262 patients who applied to the emergency department of a tertiary hospital, pneumonia was seen as the most common bacterial infection in patients with sepsis, followed by infections associated with the urinary system, intra-abdominal infections, skin and soft tissue infections, meningitis-related infections, and catheter-related infections, respectively[13]. In a report presenting the epidemiological data of severe sepsis cases admitted to emergency services in Brazil, 57%, 21%, and 11% of the etiology consisted of pneumonia, urinary system infection, and intra-abdominal infection, respectively[14]. Microbiologically documented infection rate ranges from 59% to 68%[15]. In a study by Alberti *et al.*, Gram-negative bacteria, Gram-positive bacteria, and fungi were found to be the cause of sepsis in 49.2%, 37.4%, and 9.7% of the patients, respectively[16]. As in other studies, the etiology rates were found to be similar in our study, and the factor could be detected by the culture at a rate of 69%, and 47% of these were found to be Gram-negative bacteria.

Scoring systems that determine survival and organ failure are mainly used in intensive care patients. The APACHE score developed in 1981 and the SOFA score developed in 1994 are good scoring systems in terms of determining mortality, and with the latest developments, SOFA is now being used in the diagnosis of sepsis[6]. In a study in which 1 176 patients hospitalized in the intensive care unit were examined, sepsis was shown in 554 patients, APACHE Ⅱ and SOFA scores were shown to be significantly higher, and it was reported that approximately 72% of the patients in septic shock died[17]. Studies are showing APACHE Ⅱ and SOFA scores can predict mortality of sepsis[18,19]. In the present study, patients who died had a SOFA score of 10 and an APACHE Ⅱ score of 23.

Many important studies support the measurement of serum lactate levels in the diagnosis and treatment of septic shock[20]. Lactate is known to be a disease-independent mortality marker. In the study by Freund *et al.* with 462 patients, lactate level was the best marker for the diagnosis of severe sepsis[21]. However, other studies reported that its sensitivity was low and specificity was high[22]. In the present study, lactate level was found to be significant in terms of in-hospital mortality, need for vasopressor agents, and need for mechanical ventilators.

This study has certain limitations. First, it was a retrospective study, and although it covered a long period, the number of patients could have been higher. The data collection dates of our study are about 10 years old. However, we think that calcium levels in intensive care patients will be at similar levels regardless of the age of the data. We aim to analyze patients' parameters at the time of admission to the intensive care unit. However, this number may have been low because patients who were hospitalized and died in the general wards were not included in the study. Second, we did not investigate whether there was a change in treatment response concerning ionized calcium levels. Third, as all patients with a diagnosis of sepsis were included to avoid bias in patient selection, the effect of infection status on ionized calcium levels before the diagnosis of sepsis could not be evaluated. Fourth, mortality rates of patients included in this study were high as compared to those of various other studies. The reason could be in-hospital common treatment guidelines have not been developed in our hospital.

In conclusion, ionized calcium level≤0.93 mmol/L is an independent predictor of in-hospital mortality to severe sepsis.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

B.C., N.B.A., O.K.: Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; R.K., S.E.A.: Drafting the work or revising it critically for important intellectual content; B.C., B.C., Y.K.G.: Final approval of the version to be published.

References

[1] Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; **348**(16): 1546-1554.

[2] Bone RC. Sepsis and Septic Shock. *In Infectious Disease* 1993; **3**: 5-25.

[3] Lehr HA, Bittinger F, Kirkpatrick CJ. Microcirculatory dysfunction in sepsis: a pathogenetic basis for therapy? *J Pathol* 2000; **190**(3): 373-386.

[4] Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med* 1992; **20**(2): 251-262.

[5] Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. *Am J Med* 1988; **84**(2): 209-314.

[6] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017; **43**(3): 304-377.

[7] Aberegg SK. Ionized calcium in the ICU. *Chest* 2016; **149**(3): 846-855.

[8] Wang Y, Zhang H, Tang XJ, Li XJ. A retrospective study on risk factors for prognosis of children with sepsis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2020; **32**(6): 707-710.

[9] Fei MM, Li P, Tao XG, Pan A, Wang JQ. Influence of hypocalcemia on the prognosis of septic patients. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2019; **31**(4): 418-421.

[10]Liu Y, Chai Y, Rong Z, Chen Y. Prognostic value of ionized calcium levels in neonatal sepsis. *Ann Nutr Metab* 2020; **76**(3): 193-200.

[11]Thongprayoon C, Hansrivijit P, Petnak T, Mao MA, Bathini T, Vallabhajosyula S, et al. Hospital-acquired serum ionized calcium derangements and their associations with in-hospital mortality. *Medicines* 2020; **7**(11): 70.

[12]Forsythe RM, Wessel CB, Billiar TR, Angus DC, Rosengart MR. Parenteral calcium for intensive care unit patients. *Cochrane Database Syst Rev* 2008; (4): CD006163.

[13]Lai CC, Chen SY, Wang CY, Wang JY, Su CP, Liao ZH, et al. Diagnostic value of procalcitonin for bacterial infection in elderly patients in the emergency department. *J Am Geriatr Soc* 2010; **58**(3): 518-522.

[14]Rezende E, Silva Jr JM, Isola AM, Campos EV, Amendola CP, Almeida SL. Epidemiology of severe sepsis in the emergency department and difficulties in the initial assistance. *Clinics* 2008; **63**(4): 457-464.

[15]Larche J, Azoulay E, Fieux F, Mesnard L, Moreau D, Thiery G, et al. Improved survival of critically ill cancer patients with septic shock. *Intensive Care Med* 2003; **29**(10): 1688-1695.

[16]Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002; **28**(2): 108-121.

[17]Kauss IAM, Grion CMC, Cardoso LTQ, Anami EHT, Nunes LB, Ferreira GL. The epidemiology of sepsis in a Brazilian teaching hospital. *Braz J Infect Dis* 2010; **14**(3): 264-270.

[18]Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; **286**(14): 1754-1758.

[19]Kruse JA, Thill-Baharozian MC, Carlson RW. Comparison of clinical assessment with APACHE II for predicting mortality risk in patients admitted to a medical intensive care unit. *JAMA* 1988; **260**(12): 1739-1742.

[20]Poeze M, Solberg BC, Greve JW, Ramsay G. Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: What is a better predictor of outcome in critically ill septic patients? *Crit Care Med* 2005; **33**(11): 2494-2500.

[21]Freund Y, Delerme S, Goulet H, Bernard M, Riou B, Hausfater P. Serum lactate and procalcitonin measurements in emergency room for the diagnosis and risk-stratification of patients with suspected infection. *Biomarkers* 2012; **17**(7): 590-596.

[22]Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005; **45**(5): 524-528.