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Can we find accessible and relevant markers for sepsis outcome?

Putem identifica markeri de prognostic accesibili și relevanți pentru sepsis?

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Abstract

Background and Aim: *Sepsis is a life-threatening disease with high mortality, therefore establishing early diagnostic and finding reliable prognostic biomarkers is vital. We aimed to investigate the prognostic role, as a single value, of serum procalcitonin, C-reactive protein, serum lactate, platelets number and serum glucose level in septic patients, all measured in the first 24 hours after hospital admittance.*

Materials and methods: *This retrospective study included 241 adult patients with sepsis, severe sepsis or septic shock. We use data from patients observation sheets. Data that were collected include: demographic parameters, comorbidities, necessity of mechanical ventilation and laboratory variables. We performed the statistical analysis with the chi square test for nonparametric data and to analyse the accuracy of prediction we used the receiver - operator curves with the level of significance set at $p < 0.05$.*

Results: *From 241 patients with a median age of 68 years, 127 (52.69%) were male.113 patients had severe sepsis. 89 patients (36.9%) died and male had an increase mortality rate. Most cases were respiratory sepsis (45.20%). The highest mortality rate was in septic shock (51.2%). Procalcitonin, C-reactive protein and glucose serum level at admittance were not correlated with mortality. The serum levels of creatinine >1.67 mg/dL and serum lactate >1.9 mmol/L at admittance were correlated with mortality ($p < 0.01$).The cutoff value of 121x10³/uL platelets number was also correlated with mortality ($p < 0.01$).*

Conclusions: *Our findings suggest that serum creatinine, serum lactate and the platelets number could be used as prognostic markers in septic patients at admittance.*

Keywords: *sepsis, biomarkers, prognostic, mortality.*

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Rezumat

Premise și scopul studiului: *Sepsisul este o boală amenințătoare de viață cu mortalitate ridicată, de aceea stabilirea precoce a diagnosticului și identificarea biomarkerilor cu rol prognostic este vitală.*

Ne-am propus să identificăm rolul prognostic al concentrației serice a procalcitoninei, a proteinei C reactive, a lactatului si glucozei, precum si a numărului de trombocite, la pacienții cu sepsis, ca valoare unică, toate fiind măsurate în primele 24 de ore după admiterea în spital.

Material și metodă: *Studiul retrospectiv a inclus 241 de pacienți cu sepsis, sepsis sever sau șoc septic. Pentru colectarea datelor am folosit foile de observație ale pacienților. S-au inclus: parametrii demografici, comorbidități, necesitatea ventilației mecanice și variabile de laborator.*

Pentru analiza statistică am utilizat testul chi-pătrat pentru datele nonparametrice și pentru acuratețea predicției curbele receiver – operator ($p < 0.05$).

Rezultate: *Din 241 de pacienți cu vârstă medie de 68 de ani, 127 (52.69%) au fost bărbați. 113 pacienți au avut sepsis sever, 89 (36.9%) au decedat, sexul masculin a avut o rată de mortalitate mai înaltă. Sepsisul respirator (45.20%) a fost majoritar. Șocul septic (51.2%) a avut cea mai înaltă rată de mortalitate. Procalcitonina, proteina C-reactivă și glucoza serică, la admitere, nu s-au corelat cu mortalitatea. Valoarea serică a creatininei >1.67 mg/dL, a lactatului >1.9 mmol/L și valoarea de cut-off de $121x10^3$/uL a numărului de trombocite, la admitere, s-au corelat cu mortalitatea ($p < 0.01$).*

Concluzii: *Creatinina, lactatul seric și numărul trombocitelor, la admitere, pot fi markeri prognostici în sepsis.*

Cuvinte cheie: *sepsis, biomarkeri, prognostic, mortalitate.*

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Introduction

Sepsis is a severe disease with a significant morbidity and mortality worldwide, the highest mortality is associated with septic shock (50%) and epidemiological studies concluded that a fourth of patients with severe sepsis will die during hospitalization, sepsis being a global major public health problem. (1–3)

Identification of patients with increased risk of death is dramatically important, but because of the lack of early diagnosis markers, diagnosis can be delayed and mortality increased. Thus, finding biomarkers for establishing early diagnosis and indicating prognosis of sepsis is very important. (4)

Many proposals were made for sepsis biomarkers like procalcitonin (PCT), which is known for proinflammatory-like effects on leukocytes, various interleukins due to their important role in sepsis pathogenesis and some receptors with important role in host innate immune response. None of the studied biomarkers was specific or sensitive enough to have an impact on mortality. A useful prognostic biomarker in sepsis should be specific, easy to determine and should rise above normal levels early in the course of infection.

The aim of this study is to investigate the prognostic values of procalcitonin (PCT), C-reactive protein (CRP), serum lactate, platelets number, serum glucose and creatinine level in septic patients in the first 24 hours after hospital admittance, trying to identify relevant and accessible combination tests.

Materials and methods

Patients and study design

This retrospective study was performed at the Teaching Hospital of Infectious Diseases, Cluj-Napoca, Romania, between the 1st of January 2013 and the 31st of December 2015 and it included patients with at least two systemic inflammatory response syndrome (SIRS) criteria and suspected bacterial infection at admittance,

all 241 adult patients with sepsis admitted in the ICU department; we used data from patients' observation sheets and all the patients or their relatives signed the informed consent from the observation sheets, which also includes participation to clinical studies. Mortality was recorded for 30 days after admittance.

Sepsis was defined according to ACCP/ SCCM criteria, meaning presence of two or more SIRS criteria (temperature >38˚C or <36˚C, tachypnea >24 breaths/min, tachycardia >90 beats/min, leukocytes > 12000/mm³ or < 4000/mm³) with proven or probable microbial etiology. Severe sepsis is sepsis with one or more organ dysfunctions. Septic shock was defined as sepsis with hypotension (systolic arterial blood pressure <90 mmHg) for at least 1 hour despite adequate fluid resuscitation. Being a retrospective study we did not use consensus definitions for sepsis from 2015 (5).

Subjects under 18 years of age and patients with HIV infection were excluded (7 patients) from this study. The data collected include: demographic parameters (sex, age), comorbidities (diabetes mellitus, cardiac disease, cancer, alcoholism, obesity), the necessity of mechanical ventilation and laboratory variables.

In the first 24 hours after admittance we determined as a single value of serum levels of procalcitonin with VIDAS (BioMerieux), C reactive protein, serum blood urea, creatinine, lactate, glucose with Cobas C311 (Roche Diagnostics) and platelets number were measured using Sysmex XE-2100. All these laboratory variables were determined in all samples immediately after drawing.

The site of infection was based on clinical picture and positive cultures. Patients with double site of infection were included as sepsis of unknown origin. Ethiology was established based on blood culture and other cultures from urine, sputum, pus, stool, CSF, ascites fluid, and pleural effusion. At least two blood cultures were collected after admittance, prior antibiotic administration, from venous puncture or central venous line and blood cultures were processed with BacT/Alert system (BioMerieux). The microorganisms from the blood cultures were identified with Vitek 2 Compact (BioMerieux).

Because this is a retrospective study we did not have the possibility to search for other sepsis biomarkers and we could not use severity sepsis scores because of the lack of data.

Statistical analysis

For statistical analysis, we used the chi square test for nonparametric data, the receiver - operator curves (ROC) with the level of significance set at $P< 0.05$, to analyse the accuracy of prediction by estimating the area under the curve. We performed ROC curves using Excell MedCalc 9.6 version and the multivariate analysis with StatMed. For logistic regression (ENTER method) we used SPSS 15.0 (SPSS Inc, Chicago, USA) and MedCalc v12.5 for calculating DeLong test.

Results

From the 241 enrolled patients, the median age was 68 years old (range18-91), 127 (52.69%) were men. 42 patients had sepsis, 113 patients had severe sepsis and 86 patients were in septic shock at admittance. 89 patients (36.9%) died and the men had an increased mortality rate (55 out of 127 - 43.3%) as compared to women (34 out of 114 - 29.8%) (p=0.03).

Most cases were respiratory sepsis (45.20%) followed by urinary sepsis (17%). 44 patients with respiratory sepsis died (18.25%) (p=0.31) followed by 17 patients with sepsis of unknown etiology (7.05%) (p=0.08).

The most frequent comorbidities of these patients were: diabetes mellitus 47 (19.5%), cardiac disease 32 (13.2%), solid tumors 18

Table 1. Sepsis origin

Sepsis	n	%
Abdominal	29	12.00%
Catheter	3	1.20%
Cerebral	5	2.10%
Cutaneous	15	6.20%
Infective endocarditis	3	1.20%
Genital	1	0.40%
Osseous	1	0.40%
Respiratory	109	45.20%
Urinary	41	17%
Unknown	34	14.10%
Total	**241**	**99.80%**

(7.4%), alcoholism 11 (4.5%) and obesity 9 (3.7%).

The highest outcome mortality rate was observed in septic shock (51.2%) as compared to severe sepsis (35.4%) and sepsis (11.9%) ($p< 0.01$).

The correlation between the number of systemic inflammatory response syndrome (SIRS) criteria and sepsis severity with p value reflecting mortality, was not significant ($p = 0.25$).

Etiology was established for 75 (31.12%) patients. In the bacteremic group 36 (48%) patients had Gram positive bacteremia, 36 (48%) Gram negative bacteremia and 3 (4%) had candidemia with *Candida albicans.*

From 108 patients with mechanical ventilation, 64 (59.3%) patients died. Mechanical ventilation was significantly correlated with mortality ($p <0.01$).

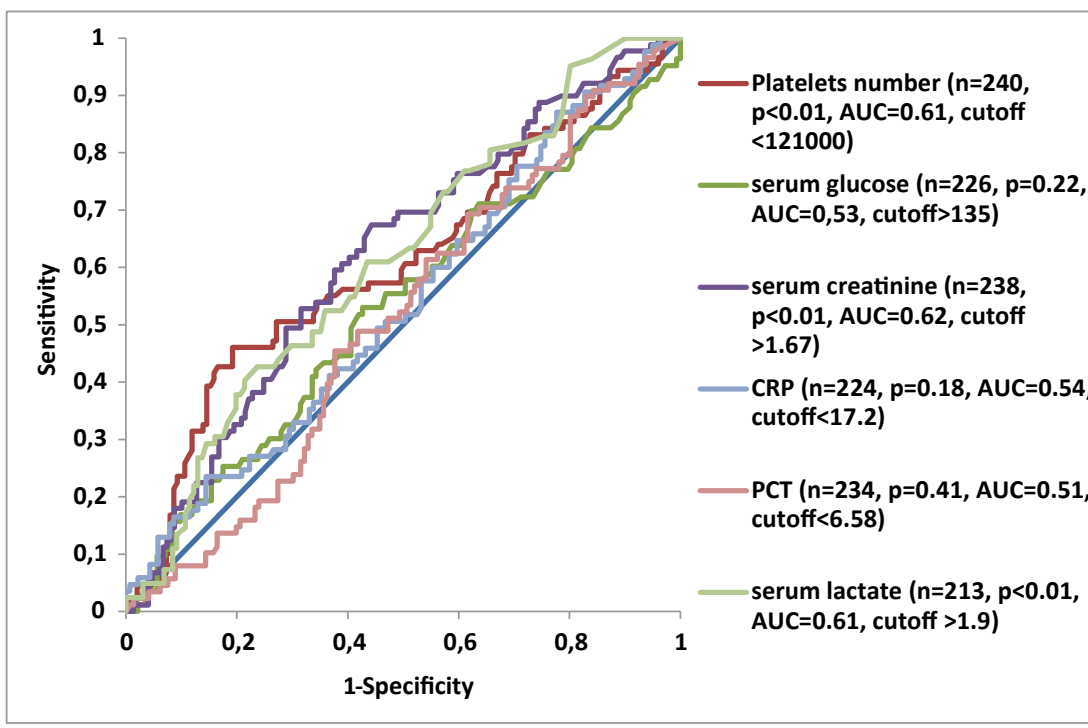

Figure 3. The ROC curve analysis for mortality prediction

First values at admittance of PCT and CRP were not correlated with mortality (p=0.41 and p=0.18) and we did not find any correlation between the glucose serum level and fatal outcome of septic patients (p=0.22).

Serum levels of creatinine higher than 1.67 mg/dL and the serum lactate higher than 1.9 mmol/L, with the cut-off indicating our calculated values, at admittance were significantly correlated with mortality ($p < 0.01$).

In the ROC curve analysis, the cutoff value of $121x10^3$/mL platelets number discriminated between survivors and non-survivors ($p < 0.01$). Figure 1 and table 2 present the ROC curve analysis for mortality prediction.

With DeLong test, only the ROC curve for serum lactate was significantly correlated with mortality (p=0.03, z=2.19). The multivariate analysis of all combined tests had as a significant result only the combination between age (p=0.04, OR=1.02) and mechanical ventilation (p<0.001, OR=5.1) for mortality prediction. Multivariate analysis using logistic regression was correct in 64.2% of cases (Omnibus Tests of Model Coefficients (p=0.02) and Hosmer and Lemeshow Test (p=0.75) were used). In multiple regression, using ENTER method, for death as the dependent variable, only serum lactate, age, mechanical ventilation and platelets number have statistical significance.

Serum glucose, PCT and CRP did not have a significant contribution (p>0.05) and they were excluded. Serum lactate and platelets number were the biomarkers confirmed with the

Table 2. The ROC curve analysis for mortality prediction

Variable	Cut –off	SE	AUC	Sn	Sp	p - value
PCT	6.58 ng/mL	0.043	0.51	0.49	0.58	0.41
CRP	17.2 mg/dL	0.043	0.54	0.49	0.55	0.18
Serum glucose	135 mg/dL	0.044	0.53	0.53	0.57	0.22
Serum creatinine	1.67 mg/dL	0.04	0.62	0.67	0.56	<0.01
Serum lactate	1.9 mmol/L	0.042	0.61	0.61	0.56	<0.01
Platelets number	121000/uL	0.042	0.61	0.51	0.73	<0.01

Sn –sensibility, Sp – specificity, AUC – Area Under the Curve, SE – Standard Error

Table 3. The general multivariable logistic model for predicting mortality

Variables	B	S.E.	p-value	Adjusted OR	95% C.I. for OR	
PCT	0.002	0.003	0.556	1.002	0.99	1.01
CRP	0.017	0.015	0.265	1.02	0.98	1.05
Serum lactate	-0.031	0.02	0.04	0.96	0.93	01.01
Serum glucose	-0.002	0.002	0.452	0.99	0.99	1.003
Age	-0.027	0.012	0.028	0.97	0.95	0.99
Mechanical ventilation	-1.995	0.36	<0.001	0.14	0.07	0.27
Platelets number	-0.001	0.001	0.03	1	1	1
Constant	3.002	1.087	0.006	20.13		

ENTER method; Dependent variable: DEATH; OR: odds ratio; CI: 95% confidence interval; B - estimated unstandardized regression coefficients; SE: standard error; p-value-Wald's test adjusted p value.

Table 4. Serum lactate and platelets number in mortality prediction (the reduced multivariable logistic model)

Variable	B	SE	p-value	Adjusted OR	95% CI for OR	
Serum lactate	-0.03	0.022	0.048	1.2	1.01	1.7
Platelets number	-0.002	0.001	0.02	1.3	1.2	1.9
Constant	0.07	0.28	0.05	1.08		

ENTER method; Dependent variable: DEATH; OR: odds ratio; CI: 95% confidence interval; B - estimated unstandardized regression coefficients; SE: standard error; p-value-Wald's test adjusted p value.

multivariate analysis as having an important role in mortality prediction.

Discussions

Previous studies tried to find the impact of gender and sex hormones in the outcome of sepsis, finding a higher risk for men in developing sepsis; some findings suggest increased mortality for men, but no definite response can be provided from the existing data. Pietropaoli et al. concluded that in severe sepsis and septic shock, mortality was 10% higher in women as compared to men. (6) A recent study performed by Nasir and his colleagues showed an increased mortality rate for male patients with sepsis as compared to females and suggested a possible interdependence with increased serum levels of interleukin-6 in men. (7) Some potential explanations for these differences might be gender difference in the site of infections and in biology, comorbidities, functional status. (6) Our study revealed that men had an increased mortality rate as compared to women.

Data from literature revealed that respiratory infections are the most frequent cause of sepsis, nearly half percent, followed by urinary tract infections. (8) Similarly, we identified that respiratory sepsis was the most frequent (45.20%) followed by urinary sepsis and the highest mortality rate was in respiratory sepsis, followed by sepsis of unknown origin, without being significantly related to mortality.

We found a higher mortality rate compared to sepsis and severe sepsis for patients with septic shock (51.2%), similar to other reports that demonstrated mortality between 40-80%. (2, 3, 8–10)

A recent study showed that SIRS criteria failed to identify 1 of 8 patients with severe sepsis, that 2 SIRS criteria do not represent a cut-off for risk and that the risk of death is increasing linearly with each additional SIRS criteria. (11) We did not find any correlation between the number of SIRS criteria and sepsis severity based on mortality.

A large epidemiological study proved that Gram positive bacteria are the most frequent etiology for sepsis and that the incidence of fungal sepsis is increasing. (8) We found that Gram positive and negative bacteria cause sepsis in the same percentage.

Other studies showed that mechanical ventilation is related to higher mortality in sepsis, due to acute respiratory distress syndrome. Associated complications such as ventilator-associated pneumonia and the increased risk of nosocomial infection due to prolonged ICU stay, might be another explanation (12, 13). Our study reveals that mechanical ventilation is related to mortality.

Many studies searched for the prognostic role of PCT and CRP in sepsis. There is evidence about the diagnostic and prognostic value of PCT in sepsis, being known that PCT value

increases together with sepsis severity and organ dysfunction. Regarding the prognostic role, studies showed that only one measurement of serum PCT at the onset of sepsis is not enough for predicting outcome, repeated measurements of serum values PCT being necessary. (14, 15)

A prospective study performed on 472 critically ill patients demonstrated that an increasing PCT value with >1.0 ng/mL after first reading is an independent predictor of mortality within 90 days and that mortality increased every day that PCT increased. (16) Another study showed that serum PCT values measured in day 2 after hospital admission discriminated between survivors and non-survivor patients with sepsis. (17)

Trying to correlate CRP serum values with sepsis mortality, Devran and his colleagues found out that when on the 3rd day CRP value is > 100 mg/L, this is significantly correlated with mortality in severe sepsis, being a better mortality predictor than first day CRP value. They also showed that 3rd day CRP value > 100 mg/L is comparable with a high SOFA score in predicting mortality. (18) Similarly, a prospective study performed on 313 critically ill patients admitted in ICU demonstrated that a CRP serum value >10mg/dL was significantly correlated with the presence and number of organ dysfunctions and mortality and it also showed that if the high value persists for more than 48 hours after admission, it is an additional risk for mortality. (19)

Similarly to other reports, the current study did not reveal a prognostic value on the first measurement of PCT and CRP in sepsis and this is probably due to the fact that we measured serum levels of PCT and CRP only at hospital admission.

Metabolically, changes like hyperglycemia are frequent in sepsis due to massive cytokines production that activates glycolysis, lipolysis and gluconeogenesis. (20) It was demonstrated that serum glucose level in septic patients can be independently associated with outcome. (21, 22) Trials revealed that both hypoglycemia and hyperglycemia can increase mortality in septic patients. (23–25) In vitro studies showed that acute fluctuations of glucose produce endothelial cell damage and apoptosis. (21) A meta-analysis made by Wiener concluded that tight glucose control in critically ill patients does not reduce mortality. (24) Present studies suggest that targeting a serum glucose level between 140-180mg/dL is more effective on outcome in septic patients. (25) We did not find any correlation between glucose serum level and mortality, probably because of increased incidence of diabetes mellitus in our patients.

Acute kidney injury and its relationship with mortality in septic patients was already established. Acute kidney injury occurs in 20-51% of sepsis cases. Trimarchi et al. showed that acute kidney failure is a high predictor of mortality in sepsis, independent of initial serum creatinine levels. (26) Oppert et al. found out that mortality in septic patients with acute renal failure was significantly higher (67.3%) as compared to septic patients without acute renal failure (42.8%) and concluded that development of acute kidney injury is associated with poor outcome. (27) Increased mortality in septic patients with acute renal failure can be explained by increased oxidant stress and accumulation of oxygen radical species. (28, 29)

In our study increased serum level of creatinine, even as a single value, had a strong and negative impact on mortality of septic patients and should be considered as an independent mortality risk factor. Previous studies reported that elevated serum levels of lactate is an indicator of tissue hypoxia and is correlated with increased mortality in patients with sepsis. (30, 31) In our study we found that a cut-off

value of serum lactate higher than 1.9mmol/L is significantly correlated with mortality. A recent study concluded that a serum lactate value between 1.82-2.7mmol/L is associated with a 30% mortality rate in septic patients. (32) Londono et al. proved that mortality increased in a linear way with serum lactate and Jansen et al. concluded that reduction with 20% per 2 hours of serum lactate value is correlated with significant reduction of mortality. (33–35) We can conclude we found out that serum lactate is an independent parameter correlated with mortality in septic patients as other studies show.

There are studies that associate thrombocytopenia with increased mortality in septic patients and with more disturbed host response during sepsis. (36, 37) In septic patients thrombocytopenia is due to platelet consumption because of exacerbated activation of the coagulation system, also leading to coagulation factor consumption. Boechat et al. proved that a platelet count lower than $150x10^3$/uL was significantly correlated with mortality in patients with sepsis and that normalization of platelet count improved prognosis. (38) Akca et al. have shown that sustained thrombocytopenia without recovery is associated with an additionally increased risk of death in septic patients and late thrombocytopenia is more death-predictive than early thrombocytopenia, suggesting that more than one count is necessary for predicting the outcome. (39) Similarly, we found out that a platelet count lower than $121x10^3$/uL was correlated with mortality. Platelets count can be used as a prognosis factor in sepsis, being an accesible, not expensive and routinely performed test.

In conclusion, our results showed that available parameters like: serum creatinine, serum lactate and platelets number can be reliable, easily and rapidly from a prognostic point of view in septic patients and that CRP and PCT values at admittance are not related to sepsis mortality. Future studies remain to clarify the role of these possible markers, due to conflicting results despite wide investigations, regarding sepsis outcome.

Acknowledgement

The authors declare that they have no conflict of interest.

Abbreviations

PCT	= Procalcitonin
CRP	= C reactive protein
ICU	= Intense critical care unit
ACCP	= American College of Chest Physicians
SCCM	= Society of Critical Care Medicine
HIV	= Human immunodeficiency virus
ROC	= Receiver operating characteristic curve
AUC	= Aria under the ROC curve
SIRS	= Systemic inflammatory response syndrome

References

1. Wang HE, Devereaux RS, Yealy DM, Safford MM, Howard G. National variation in United States sepsis mortality: a descriptive study. Int J Health Geogr. 2010 Feb 15;9:9. DOI: 10.1186/1476-072X-9-9
2. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014 Jan 1;5(1):4–11. DOI: 10.4161/viru.27372
3. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013 May;41(5):1167–74. DOI: 10.1097/CCM.0b013e31827c09f8
4. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med. 2007 May;35(5):1244–50. DOI: 10.1097/01.CCM.0000261890.41311.E9

5. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. Chest. 1992 Jun;101(6):1644–55. DOI: 10.1378/chest.101.6.1644

6. Pietropaoli AP, Glance LG, Oakes D, Fisher SG. Gender differences in mortality in patients with severe sepsis or septic shock. Gend Med. 2010 Oct;7(5):422–37. DOI: 10.1016/j.genm.2010.09.005

7. Nasir N, Jamil B, Siddiqui S, Talat N, Khan FA, Hussain R. Mortality in Sepsis and its relationship with Gender. Pakistan J Med Sci. 2015 Sep-Oct;31(5):1201–6. DOI: 10.12669/pjms.315.6925

8. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther. 2012 Jun;10(6):701–6. DOI: 10.1586/eri.12.50

9. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence. 2014 Jan 1;5(1):36–44. DOI: 10.4161/ viru.25436

10. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Intensive Care Med. 2010 Feb;36(2):222–31. DOI: 10.1007/s00134-009-1738-3

11. Kaukonen K-M, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis. N Engl J Med. 2015 Mar;372(17):1629-38. DOI: 10.1056/ NEJMoa1415236

12. Cohen IL, Lambrinos J. Investigating the impact of age on outcome of mechanical ventilation using a population of 41,848 patients from a statewide database. Chest. 1995 Jun;107(6):1673–80. DOI: 10.1378/ chest.107.6.1673

13. Bochicchio G V, Joshi M, Knorr KM, Scalea TM. Impact of nosocomial infections in trauma: does age make a difference? J Trauma. 2001 Apr;50(4):612–9. DOI: 10.1097/00005373-200104000-00004

14. Giamarellos-Bourboulis EJ, Mega A, Grecka P, Scarpa N, Koratzanis G, Thomopoulos G, et al. Procalcitonin: a marker to clearly differentiate systemic inflammatory response syndrome and sepsis in the critically ill patient? Intensive Care Med. 2002 Sep;28(9):1351–6. DOI: 10.1007/s00134-002-1398-z

15. Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. J Antimicrob Chemother. 2011 Apr; 66 Suppl 2:ii33–40. DOI: 10.1093/jac/dkq523

16. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med. 2006 Oct; 34(10):2596–602. DOI: 10.1097/01.CCM.0000239116.01855.61

17. Pettilä V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Med. 2002 Sep; 28(9):1220–5. DOI: 10.1007/s00134-002-1416-1

18. Devran O, Karakurt Z, Adıgüzel N, Güngör G, Moçin OY, Balcı MK, et al. C-reactive protein as a predictor of mortality in patients affected with severe sepsis in intensive care unit. Multidiscip Respir Med. 2012 Jan; 7(1):47. DOI: 10.1186/2049-6958-7-47

19. Lobo SMA, Lobo FRM, Bota DP, Lopes-Ferreira F, Soliman HM, Mélot C, et al. C- reactive protein levels correlate with mortality and organ failure in critically ill patients. Chest. 2003 Jun; 123(6):2043–9. DOI: 10.1378/chest.123.6.2043

20. Hirasawa H, Oda S, Nakamura M. Blood glucose control in patients with severe sepsis and septic shock. World J Gastroenterol. 2009 Sep 7; 15(33):4132–6. DOI: 10.3748/wjg.15.4132

21. Ali NA, O'Brien JM, Dungan K, Phillips G, Marsh CB, Lemeshow S, et al. Glucose variability and mortality in patients with sepsis. Crit Care Med. 2008 Aug; 36(8):2316–21. DOI: 10.1097/ CCM.0b013e3181810378

22. Waeschle RM, Moerer O, Hilgers R, Herrmann P, Neumann P, Quintel M. The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. Crit Care. 2008 Jan;12(5):R129. DOI: 10.1186/ cc7097

23. Treggiari MM, Karir V, Yanez ND, Weiss NS, Daniel S, Deem SA. Intensive insulin therapy and mortality in critically ill patients. Crit Care. 2008 Jan;12(1):R29. DOI: 10.1186/cc6807

24. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008 Aug 27;300(8):933–44. DOI: 10.1001/jama.300.8.933

25. Merz TM, Finfer S. Pro/con debate: Is intensive insulin therapy targeting tight blood glucose control of benefit in critically ill patients? Crit Care. 2008 Jan;12(2):212. DOI: 10.1186/cc6837

26. Trimarchi H, Nozieres C, Cámpolo Girard V, Lombi F, Smith C, Young P, et al. Acute kidney injury in severe sepsis. Medicina (B Aires). 2009 Jan;69(3):321–6.

27. Oppert M, Engel C, Brunkhorst F-M, Bogatsch H, Reinhart K, Frei U, et al. Acute renal failure in patients with severe sepsis and septic shock--a significant independent risk factor for mortality: results from the German Prevalence Study. Nephrol Dial Transplant. 2008 Mar;23(3):904–9. DOI: 10.1093/ndt/gfm610

28. Metnitz GH, Fischer M, Bartens C, Steltzer H, Lang T, Druml W. Impact of acute renal failure on antioxidant status in multiple organ failure. Acta Anaesthesiol Scand. 2000 Mar;44(3):236–40. DOI: 10.1034/j.1399-6576.2000.440304.x

29. du Cheyron D, Parienti J-J, Fekih-Hassen M, Daubin C, Charbonneau P. Impact of anemia on outcome in critically ill patients with severe acute renal failure. Intensive Care Med. 2005 Nov;31(11):1529–36. DOI: 10.1007/s00134-005-2739-5

30. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009 Jul;32(1):35–9. DOI: 10.1097/SHK.0b013e3181971d47

31. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest. 1991 Apr;99(4):956–62. DOI: 10.1378/chest.99.4.956

32. Schollin-Borg, M; Nordin, P.; Zetterström, H.; Johansson J. Blood Lactate Is a Useful Indicator for the Medical Emergency Team. Crit Care Res Pract. 2016 Mar 3:1–7. DOI: 10.1155/2016/5765202

33. Londoño J, León AL, Rodríguez F, Barrera L, de la Rosa G, Dennis R, et al. Serum lactate in the emergency department as a prognostic factor in patients with sepsis without hypotension. Med clínica. 2013 Sep 21;141(6):246–51.

34. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010 Sep 15;182(6):752–61. DOI: 10.1164/rccm.200912-1918OC

35. Malmir J, Bolvardi E, Afzal Aghaee M. Serum lactate is a useful predictor of death in severe sepsis and septic shock. Rev Clin Med. 2014 Jun 1;1(3):97–104.

36. Claushuis TAM, van Vught LA, Scicluna BP, Wiewel MA, Klein Klouwenberg PMC, Hoogendijk AJ, et al. Thrombocytopenia is associated with a dysregulated host response in critically ill sepsis patients. Blood. 2016 Mar;127(24):3062-72. DOI: 10.1182/blood-2015-11-680744

37. de Stoppelaar SF, van ,t Veer C, van der Poll T. The role of platelets in sepsis. Thromb Haemost. 2014 Jun 26;112(4):666–77. DOI: 10.1160/TH14-02-0126

38. De Oliveira Boechat T, Da Silveira MFBB, Faviere W, De MacEdo GL. Thrombocytopenia in sepsis: An important prognosis factor. Rev Bras Ter Intensiva. 2012 Mar;24(1):35–42.

39. Akca S, Haji-Michael P, de Mendonça A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. Crit Care Med. 2002 Apr;30(4):753–6. DOI: 10.1097/00003246-200204000-00005