IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 5 Ver. 11 (May. 2018), PP 23-28
www.iosrjournals.org

Prognostic Utility of Procalcitonin, NT-ProBNP and Sofa Score in ICU Patients

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Abstract
Introduction: *The availability of appropriate diagnostic tests and treatment is more important in the first few hours of admission in Intensive Care Unit (ICU), where the patients are more likely to be unstable and require utmost care. Thus, it is necessary to identify those patients who are at risk, either through readily available laboratory biomarkers or clinical criteria or both.* ***Aims and objectives****: To evaluate the prognostic utility of Procalcitonin (PCT), NT-proBNP and Sequential Organ Failure assessment (SOFA) score in patients admitted to ICU.* ***Materials and Methods****: 56 consecutive patients admitted to the ICU were enrolled for the study . The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from the patient or patient's first degree relatives. They were classified into sepsis or non-sepsis group according to SEPSIS-3 criteria. Demographic and clinical data including age, gender, preexisting co- morbidities, presence of ventilatory and vasopressor support, duration of ICU stay, SOFA score and outcome were recorded. NT-proBNP and PCT were estimated by electrochemiluminescent immunoassay. Data were analyzed using MedCalc software. Logistic regression analysis was done to determine the independent predictors of outcomes. A Kaplan-Meier curve was used to illustrate the cumulative proportions of survival. A two-tailed $P < 0.05$ was considered statistically significant.* ***Results:*** *Median of Age, PCT and SOFA score were higher in sepsis group in comparison to non sepsis group and is statistically significant (P=0.04, 0.0001, 0.0002 respectively) where as only PCT and SOFA score are higher in the non survivor group (P=0.0007 for both) compared to survivor group.* ***Conclusion:*** *Markedly elevated levels of PCT were observed in Sepsis and Non survivor groups. NT-proBNP is found to be an independent predictor of morbidity indicating the requirement of vasopressor and ventilator support. SOFA score is an independent predictor of mortality.*
Key words: *Sepsis, Procalcitonin(PCT), NT-proBNP, SOFA score.*

Date of Submission: 07-05-2018 Date of acceptance: 22-05-2018

I. Introduction:

Intensive care units (ICUs) and multi-disciplinary team management have evolved improving the survival of critically ill patients. Timely decision making is very essential to improve the outcome of critically ill patients at the extremes of physiologic deterioration, as they often have multi organ failure and various comorbidities ,that require special care. Common causes of ICU admission include sepsis, trauma and organ failure (heart, lung, liver, kidney and circulatory) without infection.

Sepsis is a major cause of morbidity and mortality and the second leading cause of death in intensive care units (ICU) worldwide.[1] Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[2-4] Organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Epidemiological data on sepsis come mostly from western literature, data from India are sparse . Pathophysiology of sepsis is complex ,toxins released as a result of bacteremia activates various pro inflammatory cytokines like interferon gamma (IFN-γ), TNF-α and interleukins 6, 8, 10, 12, 1β when released cause the production of acute-phase proteins, increase vascular permeability, leakage and the recruitment of neutrophils to the inflammation site. Early identification and timely action is needed otherwise sepsis may lead to inflammation induced organ injury. The purpose of this study is to identify the prognostic factors associated with the outcome of severe sepsis patients , admitted in ICU in our hospital.

Procalcitonin (PCT) has been used as a marker of bacterial sepsis in critically ill patients. PCT is a precursor of calcitonin a 116 amino acids protein.[5,6] PCT has a much longer half-life as 25-30 hr . In healthy persons, PCT levels are barely detectable.[7] Bacterial lipopolysaccharide (LPS) has been shown to be a potent inducer of PCT release into the systemic circulation.[8]Procalcitonin concentration starts to rise from 3-4 hr after

an endotoxin challenge, peak about 6 hr, and remain increased for over 24 hr. PCT can be used for early detection of sepsis and prediction of outcome after major trauma.

NT-proBNP: In humans, BNP and NT-proBNP are mainly synthesized and secreted from ventricles . An *in vitro* study demonstrated that the expression of the BNP gene can be stimulated by many factors, such as stress, ischemia, mechanical tension, and cytokines (including tumor necrosis factor, interleukin, and endothelin). The half-life of NT-proBNP is 120 min in blood, but NT-proBNP remains in the circulation for 12 hrs. some studies showed endotoxin injection or sepsis may elevate NT-proBNP even without hemodynamic changes or cardiac dysfunction,[9,10] hence elevated NT proBNP levels have been used to predict the outcome of critical illness after surgery or sepsis.[11,12,13]

The Sequential Organ Failure Assessment (SOFA) is a simple tool developed to estimate morbidity and mortality in patients admitted in emergency department. The SOFA score made up of six variables, each representing an organ system. Each organ system is assigned a point value from 0 (normal) -4(high degree of dysfunction).the SOFA score ranges from 0-24.Increasing SOFA score was associated with a higher mortality rate .

II. Materials And Methods:

This is a Prospective observational study carried out from June to August 2017 approved by the institutional ethics committee. Patients over 18 years meeting the criteria for severe sepsis admitted in ICU or with ICU stay ≥ 24hrs were included in the study. This study included 56 subjects. Informed consent was taken from them. Severe sepsis was defined as sepsis and sepsis induced organ dysfunction or tissue hypoperfusion.[14]

Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation.[15]Data related to demography, co-existing illness and other relevant clinical data regarding the source of infection and supportive measures given were collected. Length of stay in ICU were noted. Blood samples were collected at the time of admission and analyzed for laboratory parameters of Sequential Organ Failure Assessment(SOFA) score. NT proBNP and Procalcitonin were estimated by ECLIA.

STATISTICAL ANALYSIS:

Statistical analysis was done using MedCalc version 17.9.2. Results were expressed as median and quartiles. Mann-whitney U test used to for comparison of non-normally distributed variables and logistic regression analysis for predicting outcome . Receiver Operating Characteristic (ROC) curves were constructed. A Kaplan-Meier curve was used to illustrate the cumulative proportions of survival. A two-tailed $P < 0.05$ was considered statistically significant.

III. Results

A total of 56 patients were included in the study. Most common comorbidities associated was DM - 45%, HTN - 40%, Respiratory diseases - 10%, others - 5%. Based on SEPSIS-3 criteria, they were divided into Sepsis and Non sepsis groups. Based on outcome, Survivors & Non survivors .

Table-1 shows Demographic, Clinical and laboratory characteristics of sepsis and non sepsis patients. Medians of Age, PCT and SOFA score are high in the sepsis group and the difference between the two groups is statistically significant (p=0.04, 0.0001, 0.0002 respectively).

Table-2 shows Demographic, Clinical and laboratory characteristics of Survivor and non survivor patients. Medians of PCT and SOFA score are high in the Non survivors compared to survivors and the difference is statistically significant. (p=0.0007 for both).

TABLE.1: Demographic, Clinical and laboratory characteristics of sepsis and non sepsis patients.

	Sepsis(n=35)		Nonsepsis(n=21)		
Parameter	Median	IQR	Median	IQR	P value
Age(yrs)	50	38-57	40	28-47	0.04*
Hospital stay(Days)	10	9-11	8	6-10	0.05
Ventilator requirement(Days)	1	0.2-1	0	0-1	0.2
Vasopressor requirement(Days)	1	0-1	1	1-1	0.2
SOFA score	12	8-15	4	2.5-7.3	0.0001**
PCT(ng/ml)	8.6	1.8-14	0.8	0.3-1.2	0.0002**
NT-proBNP(pg/ml)	4532	2641-27201	4118	1879-13539	0.5

*significant **highly significant

TABLE-2 Demographic, Clinical and laboratory characteristics of Survivor and non survivor patients.

Parameter	Survivors(n=44)		Nonsurvivors(n=12)		
	Median	IQR	Median	IQR	P value
Age(yrs)	47	35-55	35	26-69	0.1
Hospital stay(Days)	9	6.5-11.5	9	6.5-10.5	0.5
Ventilator requirement(Days)	0	0-4.5	1	1-1	0.3
Vasopressor requirement(Days)	4	0-7.5	1	1-1	0.8
SOFA score	6	4-13	15	11-17	0.0007**
PCT(ng/ml)	1	0.4-10	26	3-79	0.0007**
NT-proBNP(pg/ml)	3853	1225-27678	11941	3889-35000	0.07

**Highly significant

Independent predictors of outcome:-

Table-3 shows Independent predictors of mortality. Of these variables SOFA score is found to be an independent predictor of mortality which is statistically significant (P=0.01), higher the SOFA score, higher is the mortality.

TABLE-3- Independent predictors of mortality

Variable	Coefficient	Std. Error	Wald	P
AGE	-0.0090836	0.029164	0.09701	0.7554
NT-proBNP	0.000016940	0.000029420	0.3316	0.5647
Procalcitonin	0.029344	0.016005	3.3614	0.0667
SOFA score	0.23890	0.10217	5.4676	0.0194*
HD	-0.29671	0.19309	2.3611	0.1244
Constant	-1.71489	1.73439	0.9776	0.3228

HD-Hospital stay duration.* significant

Table-4&5 shows independent predictor of morbidity(requirement of vasopressor & ventilator respectively). Of these variables, NT-proBNP is found to be an independent predictor of requirement of both vasopressor and ventilator, i.e, higher the NT-proBNP, higher is the chance of vasopressor and ventilator requirement(P=0.04&0.007 respectively)**.**

TABLE-4- Independent predictor of vasopressor requirement

Variable	Coefficient	Std. Error	Wald	P
AGE	0.0073861	0.021304	0.1202	0.7288
Procalcitonin	0.013735	0.017863	0.5912	0.4420
NT-proBNP	0.000062852	0.000030797	4.1650	0.0413*
SOFA score	0.051687	0.071300	0.5255	0.4685
HD	-0.0030455	0.068910	0.001953	0.9647
Constant	-0.70688	1.18903	0.3534	0.5522

HD-Hospital stay duration. *significant.

TABLE-5- Independent predictor of ventilator requirement

Variable	Coefficient	Std. Error	Wald	P
AGE	0.0016435	0.022646	0.005267	0.9421
Procalcitonin	0.0072738	0.017299	0.1768	0.6741
NT-proBNP	0.000084132	0.000031377	7.1895	0.0073*
SOFA score	0.15115	0.079245	3.6380	0.0565
HD	0.0045327	0.074956	0.003657	0.9518
Constant	-2.00381	1.29293	2.4020	0.1212

HD-Hospital stay duration. *significant

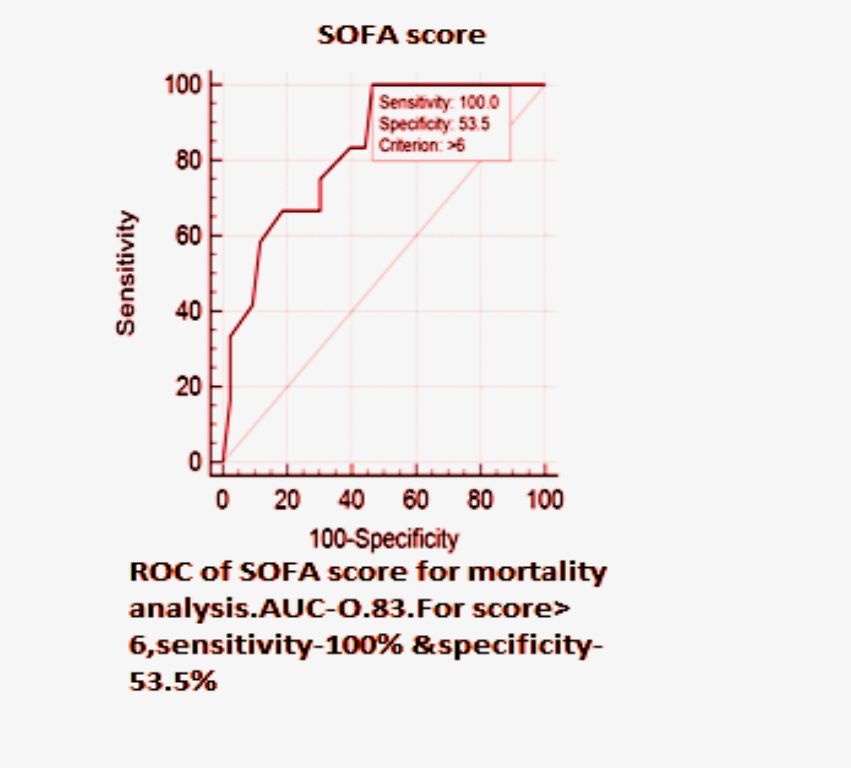

FIGURE-1-Mortality analysis- Receiver operating characteristic curve analysis for SOFA score.

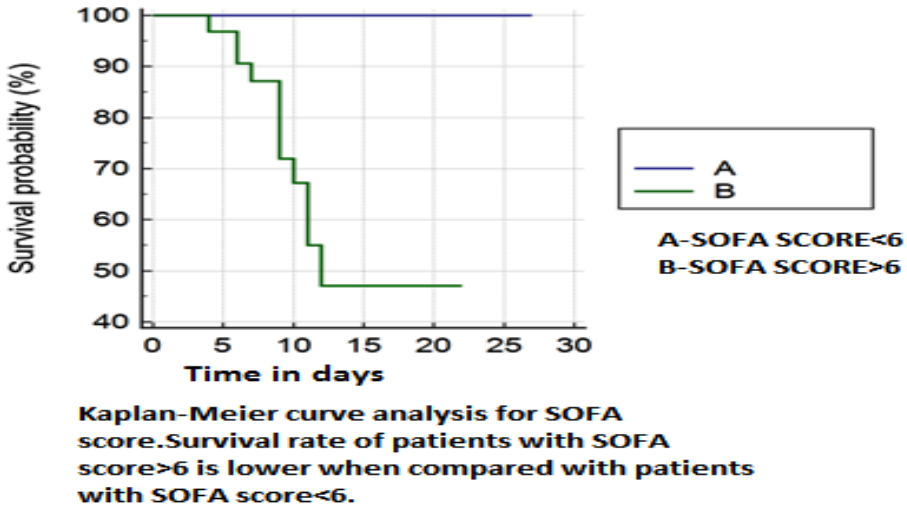

FIGURE-2 showing Kaplan-Meir curves for SOFA score<6(A) and SOFA score >6(B)

IV. Discussion

This study was conducted to see whether SOFA score ,PCT and NT-pro BNP are helpful in predicting the outcome i.e, mortality in patients admitted in intensive care units. A total of 56 subjects were included in the study. In the study group 45% were diabetics, 40% were hypertensives, 10% had respiratory disease and others were 5%. The median age in sepsis group 50yrs which indicates most of the subjects were elderly and type 2DM. Patients with type 2DM have an increased risk of developing infections and sepsis. In type 2DM both innate and adaptive immune system is suppressed. The production and release of essential effector molecules, such as ROS and cytokines, is significantly impaired leading to bacterial persistence and the development of sepsis.[16]

Identification of subjects who are at risk of poor prognosis is done by SOFA score. Among the various scoring system SOFA score is considered to be simple method, which helps in identifying organ dysfunction in

critically ill patients. In our study we observed that PCT and SOFA score were high in sepsis and non-survival group when compared to non-sepsis and survival group and we found that SOFA score to be an independent predictor of mortality. This result is in concordance with study conducted by Acharya et al and Charan et al.[17,18]

NT-proBNP levels at admission were significantly higher in nonsurvivors (median, 11941 pg/mL) compared with survivors group(median, 3853 pg/mL; p = 0.07).Most of the studies showed correlation between mortality and NT-proBNP levels in ICU patients[19,20,21] and considered NT-proBNP as independent predictor of mortality and morbidity.[21]But in our study we observed that NT-proBNP has shown to predict ventilator and vasopressor requirement (morbidity), but not mortality. Increased level of Pro-brain natriuretic peptide (ProBNP) is a consequence of cytokine production independent of myocardial dysfunction. Tumor necrosis factor-α and interleukin-β1 are important cytokines released during sepsis, which are associated with myocardial depression. These proinflammatory cytokines upregulate the BNP gene expression and secretion.[22,23,24,25] endotoxins secreted mediate myocardial depression in septic shock by a mechanism that involves nitric oxide release. They also modulate BNP expression and secretion.[26,27] endopeptidase required for degradation of pro-BNP decreases its activity in septic shock rather than in sepsis. Finally, ProBNP clearance decreases because of renal dysfunction accompanying severe septic shock.[28,29]

The serum concentration of PCT correlates with the severity of inflammatory activation. In the present study though there is significant difference of PCT levels between sepsis and non sepsis patients also between survivors and non survivors, it could not predict either mortality or morbidity. Reasons for this might be due to small sample size and measurement at a single point of time. Procalcitonin clearance (PCTc) has been an important tool for monitoring the PCT levels during sepsis[30,31]. PCT clearance measures the relative changes in PCT to the baseline PCT and is postulated to be a better predictor of outcome.

The results of the present study suggest that SOFA score to be an independent predictor of mortality in the ICU and high score at the time of admission, significantly correlated with mortality[32,33]. NT-proBNP and PCT could predict ventilator and vasopressor requirement (morbidity), but not mortality.

V. Conclusion:

The mortality of ICU patients remains high despite various advancements in supportive care. Hence utilization of SOFA score and biochemical markers like PCT and NT-proBNP levels may be useful in early identification of high risk patients in ICU and thus help in enhancing their outcome.

LIMITATIONS OF THE STUDY: Small sample size, single time measurement of biochemical parameters and use of only single scoring system.

References:

[1]. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: Sampling, selection, and society. Crit Care 2004;8:222-6.
[2]. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10. 10.1001/jama.2016.0287
[3]. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87. 10.1001/jama.2016.
[4]. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762-74. 10.1001/jama.2016.0288
[5]. Weinschenk NP, Farina A, Bianchi DW. Premature infants respond to early-onset and late onset sepsis with leukocyte activation. J Pediatr. 2000;137:345–350.
[6]. Chiesa C, Panero A, Rossi N. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. Clin Infect Dis. 1998;26:664–672.
[7]. Athhan F, Akagunduz B, Genel F, Bak M, Can D. Procalcitonin: A marker of neonatal sepsis. J Trop Pediatr . 2002;48:10–14.
[8]. Carrol ED, Thomson AP, Hart CA. Procalcitonin as a marker of sepsis. Int J Antimicrobe Agents. 2002;20:1–
[9]. R. Shor, Y. Rozenman, A. Bolshinsky, D. Harpaz, Y. Tilis, Z. Matas, A. Fux, M. Boaz, A. HalabeBNP in septic patients without myocardial dysfunctionEur. J. Intern. Med., 17 (2006), pp. 536-540
[10]. G. Vila, M. Resl, D. Stelzeneder, J. Struck, C. Maier, M. Riedl, M. Hülsmann, R. Pacher, A. Luger, M. ClodiPlasma NT-proBNP increases in response to LPS administration in healthy menJ. Appl. Physiol., 105 (2008), pp. 1741-1745
[11]. J. Charpentier, C.-E. Luyt, Y. Fulla, C. Vinsonneau, A. Cariou, S. Grabar, J.-F. Dhainaut, J.-P.Mira, J.-D. ChicheBrain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis PROBNP
[12]. R.H. Tung, C. Garcia, A.M. Morss, R.M. Pino, M.A. Fifer, B.T. Thompson, K. Lewandrowski, E.Lee-Lewandrowski, J.L. JanuzziUtility of B-type natriuretic peptide for the evaluation of intensive care unit shock Crit. Care Med., 32 (2004), pp. 1643-1647
[13]. A.S. McLean, S.J. Huang, S. Hyams, G. Poh, M. Nalos, M. Balik, B. Tang, I. Seppelt Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock Crit. Care Med., 35 (2007), pp. 1019-1026
[14]. Levy MM, Fink MP, Marshall JC, et al. SCCM/ESICM/ ACCP/ATS/SIS. International Sepsis Definition Conference. Intensive Care Med 2003; 29: 530-8.
[15]. Dellinger R, Levy MM, Carlet JM, et al. International Surviving Sepsis Campaign Guidelines Committee: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296-327.
[16]. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest (2003) 112:1821–30.10.1172/JCI19451

[17]. Acharya SP, Pradhan B and Marhatta MN (2007): Application of "the sequential outcome in ICU patients with SIRS. Kathmandu University Medical journal, 4:475-483.

[18]. Charan B, Arjun LK, Varsha SD and Zubin DS (2013): Sequential organ failure assessment score as prognostic marker in critically ill patients in a tertiary care intensive care unit.I J of Medicine and Public Health,3:155-

[19]. Januzzi JL, Camargo CA, Anwaruddin S, et al. The N-terminal pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol. 2005;95:948–54

[20]. Varpula M, Pulkki K, Karlsson S, Ruokonen E, Pettila V. Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. Crit Care Med. 2007;35:1277–83

[21]. Cuthbertson BH, Patel RR, Croal BL, et al. B-type natriuretic peptide and the prediction of outcome in patients admitted to intensive care. Anaesthesia. 2005;60:16–21.

[22]. Almog Y, Novack V, Megralishvilli R, et al. Plasma level of N terminal pro-brain natriuretic peptide as a prognostic marker in critically ill patients. Anesth Analg 2006; 102:1809-15.4

[23]. Castillo JR, Zagler A, Carrillo-Jimenez R, Hennekens CH. Review brain natriuretic peptide: a potential marker for mortality in septic shock. Int J Infect Dis 2004; 8:271–274

[24]. Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. J Exp Med 1996; 183:949–958

[25]. Witthaut R, Busch C, Fraunberger P, Walli A, Seidel D, Pilz G, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsisassociated left ventricular dysfunction. Intensive Care Med 2003; 29:1696–1702.

[26]. Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by proinflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. J Mol Cell Cardiol 2004; 36:505–513.

[27]. GM, Foster SJ, Hinds CJ, Thiemermann C. A cell wall component from pathogenic and non-pathogenic Gram-positive bacteria (peptidoglycan) synergises with endotoxin to cause the release of tumour necrosis factor-alpha, nitric oxide production, shock, and multiple organ injury/dysfunction Wray in the rat. Shock 2001; 15:135–142.

[28]. Van der Zander K, Houben AJ, Kroon AA, De Mey JG, Smits PA, de Leeuw PW. Nitric oxide and potassium channels are involved in brain natriuretic peptide induced vasodilatation in man. J Hypertens 2002; 20:493–499.

[29]. Pirracchio R, Deye N, Lukaszewicz AC, Mebazaa A, Cholley B, Matéo J, et al. Impaired plasma B-type natriuretic peptide clearance in human septic shock. Crit Care Med 2008; 36:2542–2546.

[30]. J. Guan, Z. Lin, and H. Lue, "Dynamic change of procalcitonin, rather than concentration itself, is predictive of survival in septic shock patients when beyond 10 ng/mL," Shock, vol. 36, no. 6, pp. 570–574, 2011.

[31]. J. C. Ruiz-Rodr´ıguez, J. Caballero, A. Ruiz-Sanmartin et al., "Usefulness of procalcitonin clearance as a prognostic biomarker in septic shock. A prospective pilot study," Medicina Intensiva, vol. 36, no. 7, pp. 475–480, 2012

[32]. Moreno R, Vincent JL, Matos R, Mendonca A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive Care Med 1999;25(7):686–96.

[33]. Bale, et al.: Sequential organ failure assessment score as predictor of mortality in intensive care unit.

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