Original Article

PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN AND APACHE II SCORING SYSTEM

Dr. Chaitanya B Karande[1], Dr. Durga Krishnan[2], Dr. Ponmalar Manivannan[3]

[1]Final year Postgraduate, Department of General Medicine, CHRI, Kelambakkam, Tamil Nadu.
[2]Professor, Department of General Medicine, CHRI, Kelambakkam, Tamil Nadu.
[3]Assistant Professor, Department of Community Medicine, SBMCH, Chennai.

DOI: 10.47750/pnr.2023.14.02.236

Abstract

Background: One of the most frequent reasons for death in an intensive care unit is sepsis. To evaluate the severity and prognosis of sepsis, a number of clinical grading systems and biochemical indicators have been employed. Objective: To study the outcome of patients with sepsis by using both scoring system (APACHE II) and acute phase reactant (CRP).

Methods: 50 patients participated in this prospective trial. At the time of admission, serum CRP and the factors used to determine the APACHE II score were taken. In relation to the severity and course of the disease, the values of CRP concentrations and APACHE II score were compared.

Results: Mean CRP value in patients who recovered from the illness was 140.6 mg/dl and mean CRP value in patients who died was 191.1 mg/dl. We observed CRP level of > 137 mg/dl, has sensitivity of 60% and specificity of 60% in predicting mortality in patients with sepsis and was not statistically significant. The mean admission APACHE II score in our patients was 21.4. Mean APACHE II score in patients who died was 24.2, compared to the patients who recovered from the illness was 18.5. The derived predicted mortality estimate was 48% and the actual mortality observed in our study was 26%. The admission APACHE II predicted mortality and the mortality observed in our study group was almost similar. We observed that CRP when compared with APACHE II score <24hrs and from 48-72hrs were both statistically significant with a p value of 0.01 each respectively. When we take both CRP level of > 137 mg/dl and APACHE II score of > 21 to predict the mortality in patients with sepsis, we observed sensitivity 92.85 % and specificity 36.36% in predicting the mortality, which was statistically significant (p 0.01).

Conclusion: Combining CRP and APACHE II is preferable than using either one alone for predicting death in sepsis patients.

Keywords: APACHE II, C-reactive Protein (CRP), Mortality, Sepsis.

INTRODUCTION

The word "sepsis" derives from an ancient Greek word that means "putrefaction." This word is now used to refer to the host systemic response to viral stimuli, which is characterized by inflammatory, clinical, hemodynamics, and biochemical responses[1]. One of the main reasons why individuals who are very unwell die is still sepsis[2].

Clinicians frequently wrestle with the questions of whether a patient is infected or not, and if the antibiotic therapy they are administering is working. It might be challenging to distinguish between an infection and sepsis. If the process remains localised, infection without sepsis may happen. Additionally, diseases including trauma and pancreatitis[3] frequently present with a sepsis-like state without infection.

The clinician's focus must be on making an early diagnosis of infection4. Negative cultures do not rule out the presence of infection, although bacteriological evidence may be challenging to obtain. Additionally, sepsis symptoms including fever, leukocytosis, and tachycardia are neither sensitive nor specific indicators of infection or indicators of how well a treatment is working [5].

A better understanding of the many inflammatory cascade mechanisms has led to new discoveries and the development of a number of markers that, when used in conjunction with other sepsis symptoms, can serve as indicators of infection. One such marker is C-reactive protein (CRP).

"A measure that identifies a normal biologic state or that forecasts the existence or severity of a pathologic process or Disease" has been characterised as a marker of sepsis. [7]

To evaluate the severity and prognosis of sepsis, a variety of clinical grading systems and biochemical indicators are employed. If only one prognostic approach is employed, it must be straightforward, easily accessible, and have a high level of sensitivity and specificity.

Infection, inflammation, trauma, and neoplasms all result in high levels of acute phase reactants, which are non-specific. CRP levels are frequently used as a broadly applicable indicator of inflammation. Numerous studies have shown elevated CRP levels in sepsis patients; rising or continuously high levels indicate a poor prognosis, and vice versa.

Acute Physiology and Chronic Health Evaluation (APACHE) II is general measure of disease severity based on current physiological measurements, age and previous health condition. Physiological measurement includes rectal temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, HCO_3, K^+, Na^+, serum creatinine, hematocrit, total leucocyte count, GCS. APACHE II score ranges from minimum 0 to maximum 71; increasing score is associated with an increasing risk of hospital death.

In the current investigation, serum CRP concentrations were measured and compared for predictive significance in the assessment of severity and mortality in all patients admitted to the emergency with clinical sepsis.

In the present study, serum CRP concentrations in all patients admitted to the emergency ward with clinical sepsis were measured and compared their prognostic value in the assessment of severity and mortality.

MATERIALS & METHODS

This was a prospective study conducted in Chettinad Medical College hospital, after approval from the institute's ethical committee. The study was conducted over the period of 6 months (July 2022 – December 2022Using simple random sampling, about fifty patients who had recently developed cough with expectoration, vomiting, burning micturition, dyspnea, disorientation, or jaundice and had visited an outpatient or emergency room were chosen. Either the patient or his or her caretaker provided a thorough history, which covered previous instances of jaundice, diabetes mellitus, hypertension, coronary artery disease, seizures, CVA, COPD, h/o prior surgery, malignancy, blood transfusion, and retroviral status.

A thorough physical examination was performed, along with daily or more frequent monitoring of the patient's vital signs (temperature, pulse rate, respiration rate, and blood pressure). Renal functions, liver functions, complete blood count, HBs Ag, HIV, Widal test, MSAT, QBC for MP, blood-culture and sensitivity, serum CRP, prothrombin time, and arterial blood gas analysis were among the several blood tests performed. Urine analysis, urine-C/S, ECG, chest X-ray, USG abdomen, and, if necessary, CT-Chest and CT-Abdomen were among the other investigations that were performed.

On the third day (48–72 hours), the CBC, RFT, and LFT were performed once again, and on the first and third days, the APACHE–II and SOFA scores were computed. Clinical chemistry analyzers were used to perform an immunoturbidimetric assay to assess the C-reactive protein in serum.

Inclusion Criteria

Patients older than 18yrs of age admitted in medical ward with criteria for sepsis, i.e,

Two or more of the following conditions:

1. fever (oral temperature >38°C) or hypothermia (<36°C);
2. tachypnea (>24 breaths/min);
3. tachycardia (heart rate >90 beats/min);
4. leukocytosis (>12,000/ L),
5. Leukopenia (<4,000/L), or >10% bands; plus, proven orsuspected microbial etiology.

Exclusion Criteria

1. Patients less than 18 years of age
2. Patients with rheumatic heart disease and collagen vascular disease
3. Patients with malignancy
4. Pregnant women
5. Patients on hormone replacement therapy
6. Patients who received antibiotics in prior 7 days

Following the collection of data, it was recorded in excel sheet and analysis were done using SPSS software version 21.

OBSERVATION AND RESULTS

A total of 50 patients, 27 (54%) males and 23(46%) females, in the age group of 20-80 years, with the predominant age group of 40-60 years were included in the study. 26% mortality was noted in our study. Normal C - reactive protein (CRP) value of our lab is < 10 mg/dl (range: 15.9 - 502 mg/dl). C-reactive protein was significantly elevated in elderly and in patients with ≥ 3 organ system involvement. Mean CRP value in patients who recovered from the illness was 140.6 mg/dl and mean CRP value in patients who died was 191.1 mg/dl. We observed CRP level of > 137 mg/dl, has sensitivity of 60% and specificity of 60% in predicting mortality in patients with sepsis and was not statistically significant. The mean admission APACHE II score in our patients was 21.4. Mean APACHE II score in patients who died was 24.2, compared to the patients who recovered from the illness was 18.5. The derived predicted mortality estimate was 48% and the actual mortality observed in our study was 26%. The admission APACHE II predicted mortality and the mortality observed in our study group was almost similar. We observed that CRP when compared with APACHE II score <24hrs and from 48-72hrs were both statistically significant with a p value of 0.01 each respectively.

When we take both CRP level of > 137 mg/dl and APACHE II score of > 21 to predict the mortality in patients with sepsis, we observed sensitivity 92.85 % and specificity 36.36% in predicting the mortality, which was statistically significant (p 0.01).

Figure 1: Distribution based on the sex and mortality

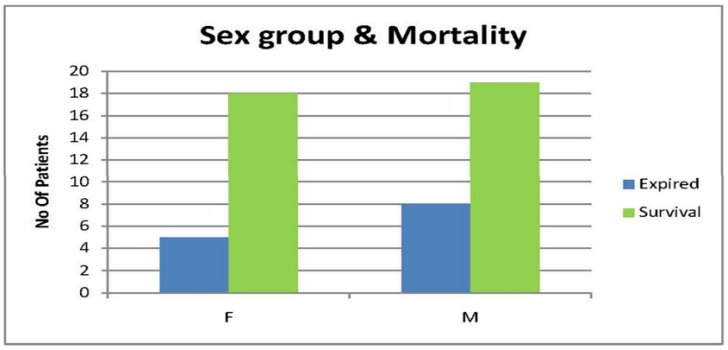

Figure 2: Distribution based on age and mortality

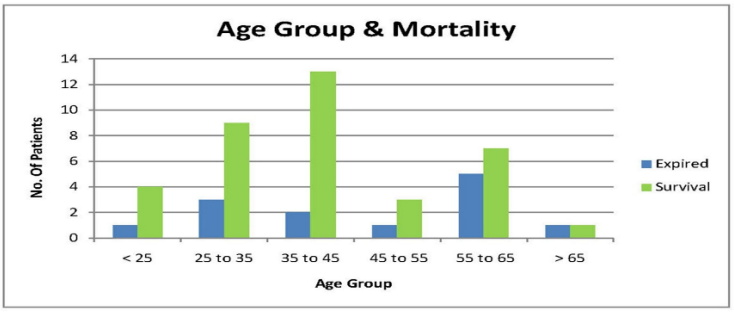

Table 1: Association of CRP vs Apache II < 24 hrs

Apache II<24 hrs			
CRP (mg/dl)	**<=10**	**> 10**	**Grand Total**
<= 10	8	2	10
> 10	14	26	40
Grand Total	22	28	50

P = 0.01 SIGNIFICANT

Figure 3: Correlation of CRP Vs Apache II, Correlation coefficient = 0.63

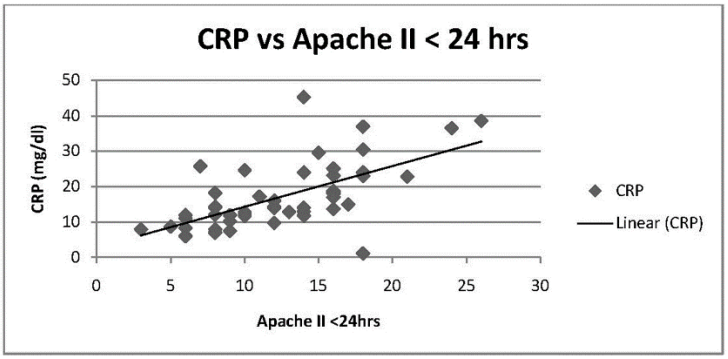

Table 2: Association of CRP Apache II 48 - 72 hrs

Apache II 48-72hrs			
CRP (mg/dl)	**<=10**	**> 10**	**Grand Total**
<= 10	9	1	10
> 10	20	20	40
Grand Total	29	21	50

P = 0.01 SIGNIFICANT

Figure 4: Correlation of CRP Vs Apache II 48-72hrs

Correlation coefficient = 0.61

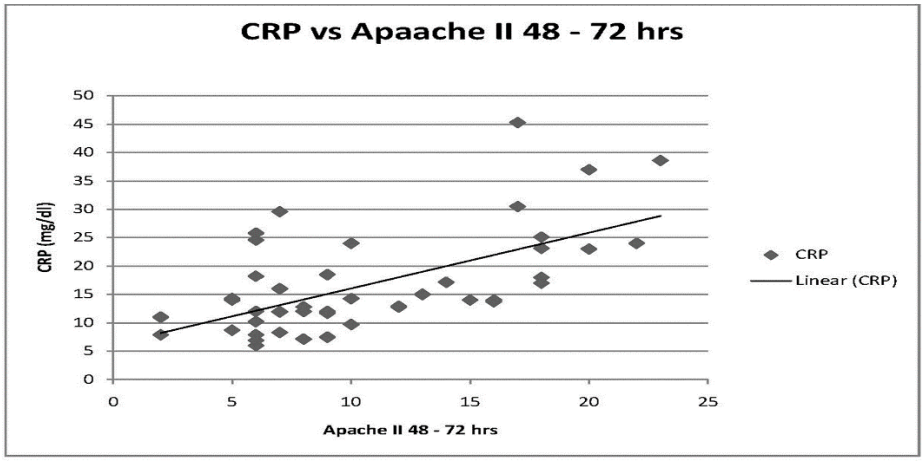

Table 3: P Value and CC

	APACHE II <24HRS	**APACHE II48-72 HRS**	**SOFA <24HRS**	**SOFA 48-72 HRS**
ESR	P =0.07	P =0.99	P =0.48	P =0.42
(mm/hr)	CC =0.39	CC =0.29	CC =0.45	CC =0.33
CRP	P =0.01	P =0.01	P =0.07	P =0.07
(mg/dl)	CC =0.63	CC =0.61	CC =0.45	CC =0.59

DISCUSSION

Early infection diagnosis must be the focus of the clinician's attention4. Negative cultures do not rule out the presence of infection, although bacteriological evidence may be challenging to obtain. Additionally, sepsis symptoms including fever, leukocytosis, and tachycardia are neither sensitive nor specific indicators of infection or indicators of how well a treatment is working [5].A better understanding of the many inflammatory cascade mechanisms has led to new discoveries and the development of a number of markers that, when used in conjunction with other sepsis symptoms, can serve as indicators of infection. **C-reactive protein (CRP)**

is one such marker.

The progression of infections and inflammatory illnesses has been tracked using the inflammation marker CRP. In recent years, CRP has been recognised as both an active regulator of the inflammatory response and as a biochemical marker of inflammation. In this context, we assessed the relationship between CRP levels and early-after-admission mortality in a diverse patient population. Increased CRP levels were discovered to be linked to organ failure, extended critical care, and high infection and death rates. CRP levels greater than 10 mg/dL at admission were linked to an especially high mortality.

The family of proteins known as pentraxins, from which C-reactive protein is descended, forms a cyclic pentamer out of five identical, non-glycosylated subunits. In the presence of calcium, C-reactive protein binds to various polysaccharides and peptido-polysaccharides found in bacteria, fungi, and parasites. These complexes function as opsonins and stimulate phagocytosis by activating the traditional complement pathway10.

The only acute phase protein directly implicated in the clearance of microorganisms, together with complement components, is CRP. In 99% of normal samples, the serum concentration of CRP is below 10 mg/l in the normal human population, with a median of 0.8 mg/l (interquartile range, 0.3-1.7 mg/l)11,12. A disease process may be present if these readings are abnormally high.

The liver produces the majority of CRP, primarily in reaction to interleukin 6. (IL-6). There is a strong association between CRP and IL-6 concentrations13. Aside from TNF and IL-1, other regulatory mediators of CRP production include them. Within 4-6 hours of the stimulus, CRP secretion starts; it doubles every 8 hours; it peaks between 36 and 50 hours.

Even in patients with compromised immune systems, systemic fungal infections, acute Gram-positive and Gram-negative bacterial infections, and both generate substantial increases in CRP. In contrast, CRP levels are typically lower in the majority of acute viral infections. The exception to this rule is that simple adenovirus, measles, mumps, and influenza infections can occasionally be accompanied by elevated CRP levels.

As has been demonstrated for organ dysfunction score systems, evaluating changes in variables over time may be highly helpful to determine the effects of therapies. According to Lopes Ferreira et al.28, a rise in SOFA score over the course of the first 48 hours in the ICU indicates a mortality rate of at least 50%, whereas a decline in SOFA score indicates a mortality rate reduction from 50% to 27%. Presterl et al. 29 showed a link between the APACHE III and mortality probability model II scores and plasma levels of CRP, IL-6, and tumour necrosis factor-sR in sepsis patients. The non-survivors' scores on both scoring systems and CRP levels were considerably greater than those of the survivors. From day 3 onward, non survivors had significantly higher CRP levels. According to our research on the correlation between CRP concentrations, APACHE II, and SOFA scores, each of these metrics are helpful predictors of severity and prognosis.

According to Bonig et al., CRP levels greater than 10 mg/dL were indicative of a poor outcome following paediatric hematopoietic stem cell transplantation. The aetiology of cardiovascular illnesses is influenced by chronic inflammation, and in otherwise healthy individuals, increasing serum CRP levels are linked to an increased risk of myocardial infarction and sudden cardiac death.

High CRP levels in hemodialysis patients were found to be closely correlated with high levels of vascular atherogenic risk factors and cardiovascular mortality, according to Zim, mermann et al. In the pre-dialytic stage of renal failure, it has been demonstrated that serum levels of CRP and IL-6 are negatively correlated with renal function. The current study found that having extracorporeal assistance for a longer period of time was related to higher CRP levels at admission.

The overall mortality rate in our study was 26%. Male mortality was 29.5% and female mortality was 21.7%. The death rate increased with age, reaching 50% in individuals over 65 and 41.6% in those between the ages of 55 and 65. Patients with serum CRP levels beyond 10 mg/dl had a 30% death rate while those with levels under 10 mg/dl had a 10% mortality rate. Additionally, the patients with blood CRP levels above 10 mg/dl had extended hospital stays and various organ dysfunctions. In our investigation, there were 40 patients with blood CRP levels above 10 mg/dl and 10 patients with serum CRP levels below that level.

The mean Apache II score was 8.3 on admission and 6.55 after 48 hours in the group with srCRP 10 mg/dl. The mean SOFA score was 4.3 at admission and dropped to 3 after 48 hours. SrCRP greater than 10 mg/dlgroup, the average Apache II score was 13.3 upon admission and 11.64 at 48 hours. The mean SOFA score was 6.4 at admission and 5.57 at 48 hours. This is consistent with other research, like Lopez et al. (2011).

LIMITATIONS OF STUDY

We discovered that various sample size restrictions in our study precluded us from acquiring statistical significance for a number of variables related to the severity of sepsis. Due to financial limitations, serum CRP was measured in our study just once, at the time of presentation, making it impossible to track changes over the course of the hospital stay. Since CRP levels are solely based on the rate of synthesis, changes are extremely helpful in both diagnosing a condition and tracking a patient's reaction to treatment.

CONCLUSION

CRP measurement is a simple, reliable, and affordable diagnostic that is accessible in practically all hospitals. With rising SEPSIS severity, serum CRP has been reported to be significantly higher, which could enhance the risk of morbidity and mortality.

1. The ESR is a poor prognostic indicator for sepsis

2. As a patient becomes older, sepsis mortality rises.

3. Serum CRP levels exhibited low correlation with SOFA score but were well connected with Apache II score at admission and 48 hours later.

4. Both at admission and 48 hours later, serum ESR levels did not correspond with the Apache II score or the SOFA score.

REFERENCES

1. Póvoa, P. C-reactive protein: a valuable marker of sepsis. Intensive care medicine, 2002; 28: 235-243.

2. Rangel-Frausto, M.S., Pittet, D., Costigan, M., Hwang, T., Davis, C.S., Wenzel, R.P. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. Jama, 1995; 273(2): 117-123.

3. Bone, R.C., Grodzin, C.J., Balk, R.A. Sepsis: a new hypothesis for pathogenesis of the disease process. Chest, 1997; 112(1): 235-243.

4. Wheeler, A.P., Bernard, G.R. Treating patients with severe sepsis. New England Journal of Medicine, 1999; 340(3): 207-214.

5. Gabay, C., Kushner, I. Acute-phase proteins and other systemic responses to inflammation. New England journal of medicine, 1999; 340(6): 448-454.

6. Marshall, J.C., Vincent, J.L., Fink, M.P., Cook, D.J., Rubenfeld, G., Foster, D., Reinhart, K. Measures, markers, and mediators: toward a staging system for clinical sepsis. A report of the Fifth Toronto Sepsis Roundtable, Toronto, Ontario, Canada, October 25–26, 2000. Critical care medicine, 2003; 31(5): 1560-1567.

7. United States Patent – Repine et al. Patent number: 5,369,269 and Date of Patent: June 17,1997.

8. 18th edition of Harrison's Principles of Internal Medicine – Chapter 271: Severe sepsis and septic shock.

9. Tillett, W.S., Francis Jr, T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. The Journal of experimental medicine, 1930; 52(4): 561.

10. Mold, C., Gewurz, H., Du Clos, T.W. Regulation of complement activation by C-reactive protein. Immunopharmacology, 1999; 42(1-3): 23-30.

11. Pepys, M.B., Baltz, M.L. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum

amyloid A protein. Advances in immunology, 1983; 34: 141-212.

12. Vigushin, D.M., Pepys, M.B., Hawkins, P.N. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. The Journal of clinical investigation, 1993; 91(4): 1351-1357.

13. Oberhoffer, M., Karzai, W., Meier-Hellmann, A., Bögel, D., Fabinder, J., Reinhart, K. Sensitivity and specificity of various markers of inflammation for the prediction of tumor necrosis factor-α and interleukin-6 in patients with sepsis. Critical care medicine, 1999; 27(9): 1814-1818.

14. Jaye, D.L., Waites, K.B. Clinical applications of C-reactive protein in pediatrics. The Pediatric infectious disease journal, 1997; 16(8): 735-747.

15. Young, B., Gleeson, M., Cripps, A.W. C-reactive protein: a critical review. Pathology, 1991; 23(2): 118-124.

16. Povoa, P., Almeida, E., Moreira, P., Fernandes, A., Mealha, R., Aragao, A., Sabino, H. C-reactive protein as an indicator of sepsis. Intensive care medicine, 1998; 24: 1052-1056.

17. Ugarte, H., Silva, E., Mercan, D., De Mendonca, A., Vincent, J.L. Procalcitonin used as a marker of infection in the intensive care unit. Critical care medicine, 1999; 27(3): 498-504.

18. Suprin, E., Camus, C., Gacouin, A., Le Tulzo, Y., Lavoue, S., Feuillu, A., Thomas, R. Procalcitonin: a valuable indicator of infection in a medical ICU? Intensive care medicine, 2000; 26: 1232-1238.

19. Cox, M.L., Rudd, A.G., Gallimore, R., Hodkinson, H.M., Pepys, M.B. Real-time measurement of serum C-reactive protein in the management of infection in the elderly. Age and ageing, 1986; 15(5): 257-266.

20. Smith, R.P., Lipworth, B.J., Cree, I.A., Spiers, E.M., Winter, J.H. C-reactive protein: a clinical marker in community-acquired pneumonia. Chest, 1995; 108(5): 1288-1291.

21. Eriksson, S., Olander, B., Pira, U., Granström, L. White blood cell count, leucocyte elastase activity, and serum concentrations of interleukin-6 and C-reactive protein after open appendicectomy. The European journal of surgery= Acta chirurgica, 1997; 163(2): 123-127.

22. Cunha, J., Glória, C., Vilela, H., Lopes, V. C-reactive protein: a good parameter for sepsis diagnosis (abstract). Intensive Care Med, 1997; 23: S61.

23. Adnet, F., Borron, S.W., Vicaut, E., Giraudeaux, V., Lapostolle, F., Bekka, R., Baud, F.J. Value of C-reactive protein in the detection of bacterial contamination at the time of presentation in drug-induced aspiration pneumonia. Chest, 1997; 112(2): 466-471.

24. Dale, D.C., Fauci, A.S., Wolff, S.M. Comparison of agents producing a neutrophilic leukocytosis in man. Hydrocortisone, prednisone, endotoxin, and etiocholanolone. The Journal of clinical investigation, 1975; 56(4): 808-813.

25. Aouifi, A., Piriou, V., Bastien, O., Blanc, P., Bouvier, H., Evans, R., Lehot, J.J. Usefulness of procalcitonin for diagnosis of infection in cardiac surgical patients. Critical care medicine, 2000; 28(9): 3171-3176.

26. Cheval, C., Timsit, J.F., Garrouste-Orgeas, M., Assicot, M., De Jonghe, B., Misset, B., Carlet, J. Procalcitonin (PCT) is useful in predicting the bacterial origin of an acute circulatory failure in critically ill patients. Intensive care medicine, 2000; 26: S153-S158.

27. Zein, J.G., Lee, G.L., Tawk, M., Dabaja, M., Kinasewitz, G.T. Prognostic significance of elevated serum lactate dehydrogenase (LDH) in patients with severe sepsis. Chest, 2004; 126(4): 873.

28. Ferreira, F.L., Bota, D.P., Bross, A., Mélot, C., Vincent, J.L. Serial evaluation of the SOFA score to predict outcome in critically ill patients. Jama, 2001; 286(14): 1754-1758.

29. Presterl, E., Staudinger, T., Pettermann, M., Lassnigg, A., Burgmann, H., Winkler, S., Graninger, W. Cytokine profile and correlation to the APACHE III and MPM II scores in patients with sepsis. American Journal of Respiratory and Critical Care Medicine, 1997; 156(3): 825-832.

30. Bönig, H., Schneider, D.T., Sprock, I., Lemburg, P., Göbel, U., Nürnberger, W. 'Sepsis' and multi-organ failure: predictors of poor outcome after hematopoietic stem cell transplantation in children. Bone marrow transplantation, 2000; 25(2): S32-S34.