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The progression of biochemical parameters and disease severity scores in patients with septic shock: a study of sequential measurements

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ABSTRACT

Aims: Sepsis and septic shock are critical conditions that contribute significantly to morbidity and mortality in intensive care units worldwide. Early diagnosis and treatment are crucial for improving survival, yet traditional diagnostic methods lack sensitivity. Biomarkers like C-reactive protein and procalcitonin, along with disease severity scores such as APACHE II, SOFA, and MODS, are increasingly used to assess patient status and predict outcomes. This study aims to explore the relationship between inflammatory biomarkers and disease severity scores in critically ill patients with septic shock.

Methods: This prospective study included 20 patients with septic shock admitted to the intensive care unit between July and September 2009. C-reactive protein, procalcitonin, cortisol, brain natriuretic peptide, lactate, and other physiological parameters were monitored over a three-day period. Disease severity was assessed using APACHE II, SOFA, and MODS scores, with mortality outcomes recorded. Data was analyzed using Spearman's correlation analysis.

Results: The study found no significant correlation between APACHE II scores at admission and 28-day mortality. However, both SOFA and MODS scores showed significant correlations with 28-day mortality when measured on the second and third days of intensive care unit admission. C-reactive protein and procalcitonin levels were elevated in all patients, yet no direct correlation with 28-day mortality was identified. Sequential monitoring of SOFA and MODS scores was more predictive of patient outcomes than single-day measurements.

Conclusion: Sequential assessments of disease severity scores provide valuable insights into the progression of septic shock. While C-reactive protein and procalcitonin are useful in monitoring infection, they alone may not be sufficient to predict mortality. In contrast, dynamic measurements of SOFA and MODS scores are better indicators of patient prognosis, particularly when combined with biomarker data. Continuous monitoring of disease severity scores, particularly SOFA and MODS, alongside biomarkers such as C-reactive protein and procalcitonin, enhances the prediction of mortality in septic shock patients. These tools, when used together, offer a comprehensive approach to managing critically ill patients in the intensive care unit, allowing for timely and effective interventions.

Keywords: Apache, biomarkers, organ dysfunction scores, sepsis, septic shock

INTRODUCTION

Sepsis defined as a systemic response to an infection is a major cause of morbidity and mortality, especially in the elderly, immunosuppressed, and critically ill patients.[1,2] Sepsis and septic shock represent significant healthcare challenges, impacting millions of individuals globally each year.[3] Early diagnosis and treatment of sepsis are the most important determinant factors of survival and outcome.[4] Microbiological results typically require a minimum of 2–3 days to be finalized

and are often not highly sensitive, particularly when cultures are obtained while patients are on antimicrobial treatment. As a result, around 40–50% of sepsis cases are classified as culture-negative.[5,6] Biomarkers have been investigated for their role in predicting sepsis, diagnosing the condition, evaluating the response to sepsis treatment, and guiding antibiotic therapy based on biomarker levels.[7] Currently, traditional clinical findings and laboratory tests such as white blood cell count, sedimentation rate, and C-reactive protein often lack sufficient sensitivity and specificity and may be inadequate for diagnosis. The greatest challenge remains the heterogeneity of the disease, complicating diagnosis and classification. Although numerous biomarkers have been investigated as potential indicators for sepsis, none have yet achieved the precision necessary to be universally accepted as definitive 'markers.'

Acute phase reactants such as C-reactive protein (CRP) are more useful in diagnosis and have prognostic significance in sequential measures.[7,8] Although procalcitonin (PCT) is elevated in nonseptic conditions such as cardiopulmonary bypass or pancreatitis, it is useful in diagnosis and follow-up.[9,10] There is no universally accepted cutoff value for procalcitonin in the diagnosis of sepsis; studies in the literature have either not specified a cutoff point or have used values ranging from 0.5 to 2 µg/L.[11]

Scoring systems are used for several purposes in intensive care units (ICUs); to facilitate the identification of patient groups requiring intensive care treatment, to facilitate the identification of patient groups to be included in clinical trials, to compare ICUs in terms of performance, to assess the performance of the same ICU in different time periods, and to arrange and follow the treatment of any patient.[12] Two main scoring systems are described for ICUs; the first scoring systems are based on physiological changes; these in groups are focused on single point and used in predicting mortality. Acute Physiology and Chronic Health Evaluation (APACHE) score is also a scoring system helping to predict mortality based on physiological changes.[13] The second group is a scoring system based on organ dysfunctions; these in groups are also referred to as follow-up scores and define morbidity. This group includes Multiple Organ Dysfunction Score (MODS) and Sequential Organ Failure Assessment (SOFA)[14,15] (Table 1).

Table 1. Comparison of mortality and morbidity estimation scoring systems

	Mortality (APACHE II)	Morbidity (MODS, SOFA)
Purpose	Predict mortality	Defines morbidity (organ failure)
Ease of use	Often complex calculations	Usually, simple
Timing	On acceptance or within the first 24 hours	Can be measured again and again (daily)
Disease process	Does not provide information for any organ function	Provides information about a desired organ function

APACHE: Acute Physiology and Chronic Health Evaluation, MODS: The Multiple Organ Dysfunction Score, SOFA: Sequential Organ Failure Assessment score

In our study, we aimed to investigate the association between inflammatory parameters and disease severity scores in patients with septic shock. Through this analysis, we aim to contribute to better risk stratification and potentially guide more effective treatment strategies in critically ill patients.

METHODS

This study was designed as a prospective observational study. Between July and September 2009, twenty patients with septic shock who were admitted to the ICU were included in this study. The study protocol was approved by the institutional ethics committee (Date:29.06.2009 Decision No:154-4922), and informed consent was obtained from all patients or, in the case of unconscious or sedated patients, from their legal representatives. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients who declined to participate or were under 18 years of age were excluded.

Upon admission, demographic characteristics and medical data, including age, gender, body weight, reasons for ICU admission, major diagnoses, and previous health status, were recorded. Radiological and microbiological examinations were performed under the supervision of the ICU coordinator, when necessary, to identify the potential infection site both at admission and during the ICU stay.

Blood samples were collected from each patient for three consecutive days, and disease severity scores were calculated. The diagnoses of systemic inflammatory response syndrome, local infection, sepsis, and septic shock were based on the society of critical care medicine consensus conference criteria.[16] Venous blood samples were obtained for biochemical analyses, including serum CRP, procalcitonin levels, and complete blood count, within approximately two hours of septic shock diagnosis.

Leukocyte counts, hemodynamic parameters, thrombocyte counts, cortisol levels, brain natriuretic peptide levels, lactate levels, high-density lipoprotein (HDL) levels, albumin levels, CRP levels, procalcitonin levels, central venous pressure (CVP) measurements, mixed venous oxygen saturation (SvO_2) measurements, and PaO_2/FiO_2 ratios were monitored over a three-day period. The APACHE II score was used to predict the severity and mortality of critical illness, while SOFA and MODS scores were calculated to document the severity of sepsis and organ dysfunction both at admission and on a daily basis.

All patients included in the study were monitored throughout their hospitalization to gather clinical outcome data, even after discharge from the ICU. Data recorded included the length of stay in both the hospital and ICU, hospital and ICU mortality, and 28-day mortality rates.

Statistical Analysis

The data obtained from the study were presented as median, minimum-maximum values, and mean±standard deviation (mean±SD). Statistical significance was set at $p<0.05$. Descriptive statistics and comparisons between groups for nonparametric data were performed using the Kruskal-Wallis and Mann-Whitney U tests. Spearman's Rho correlation analysis was employed for correlation assessments. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software (SPSS 16.0 for Windows, 2007, SPSS Inc., USA).

RESULTS

The demographic and medical data including the age, gender, their clinics before ICU admission, the presence of trauma, APACHE II, SOFA and MODS scores of the patients at the admission, are shown in Table 2.

Of the patients, 15 had a history of surgery, 13 had undergone emergency surgery, while two had undergone elective surgery. Five patients were admitted to ICU because of medical reasons.

Eight patients who suffered from trauma were followed up in ICU.

Table 2. Demographic and medical characteristics of patients

Age (years), SD		51.40±18.44
Sex, n (%)	Female	7 (35)
	Male	13 (65)
Accepted from, n (%)	Transferred from ward	2 (10)
	ICU	12 (60)
	Operating room	6 (30)
History of trauma, n (%)	Yes	8 (40)
	No	12 (60)
APACHE II score (mean), SD		20.95±7.22
MODS score (mean), SD		5.80±3.22
SOFA score (mean), SD		6.0±3.1

APACHE II: Acute Physiology and Chronic Health Evaluation, MODS: The Multiple Organ Dysfunction Score, SOFA: Sequential Organ Failure Assessment score, ICU: intensive care unit. Plus–minus values are means ±SD, n: number of patients.

The parameters including ICU and hospital stays, ICU - hospital and 28-day mortality are shown in Table 3. Of the total 20 patients, eight were dead in the ICU, the treatment of nine patients were continued in another service or another ICU, and three were discharged to their home.

Table 3. Clinical outcome of patients

Length of stay in ICU (days)	29.85±25.02
Length of stay in hospital (days)	47.70±26.78
ICU mortality (%)	40
Hospital mortality (%)	50
28 days mortality (%)	35

ICU: intensive care unit, plus–minus values are means ±SD

The relationships between scoring systems, some biomarkers values used to describe disease severity on the first day and follow up 24 and 48 hours and 28-day mortality were investigated. Analyses were used by Spearman's correlation analysis.

The progression of the patients' follow-up parameters, including leukocyte counts, hemodynamic parameters, thrombocyte counts, cortisol levels, brain natriuretic peptide levels, lactate levels, HDL levels, albumin levels, CRP levels, procalcitonin levels, CVP measurements, SvO_2 measurements, and PaO_2/FiO_2 ratios over a three-day period, are shown in Table 4.

Table 4. The progression of the patients' follow-up parameters

	On the day of septic shock diagnosis	24th hour	48th hour	p
Leukocyte, /mm³	13750	12950	10700	0.064
Thrombocyte, / mm³	176000	133500	137000	0.101
Cortisol, mcg/dL	28.5	31	20.5	0.421
BNP, pg/mL	1230	1033	932	0.672
Lactate, mmol/L	1.75	1.65	1.60	0.335
HDL, mg/dL	5	6	6	0.494
Albumin, g/dL	2.1	2.3	2.35	0.250
CRP, mg/dL	135	138	121	0.449
Procalcitonin, mcg/L	5.35	8.35	8.20	0.513
CVP, cmH_2O	8.5	10	7.5	0.082
SvO_2 sat, %	67.5	72.5	74.5	0.005
Horowitz Index	228	213	225	0.350

Values are the mean results BNP: brain natriuretic peptide, CRP: C-reactive protein CVP: central venous pressure, SvO_2 sat central venous oxygen saturation

No significant correlation was found between the MODS and SOFA values and 28-day mortality on the first day of septic shock diagnosis (p=0,084 p=0,059) but there was a significant positive correlation (moderate-high) between the MODS and SOFA scores and the 28-day mortality on the second and third days of septic shock (p2=0.030 p2=0.019 p3=0.007 p3=0.004). Comparisons of patients' disease severity scores according to the 28-day mortality status are shown in Figure 1 and Figure 2.

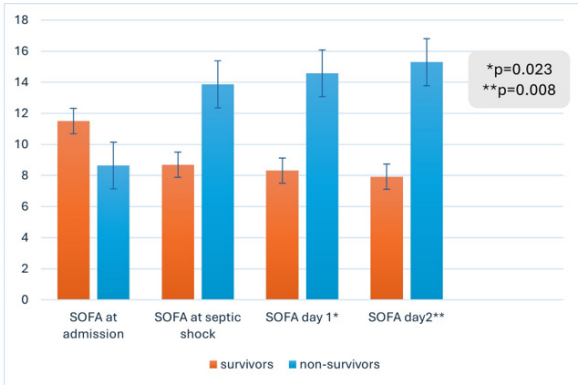

Figure 1. Comparison of SOFA to 28-day mortality
SOFA: sequential organ failure assessment

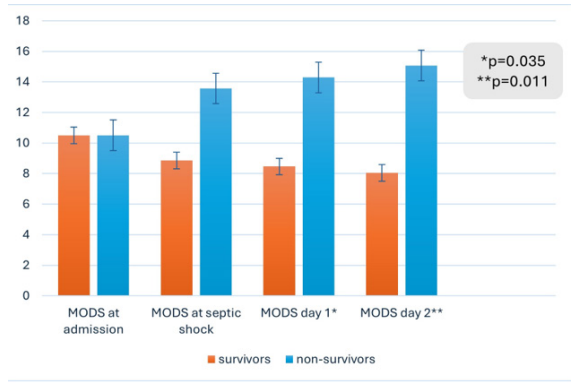

Figure 2. Comparison of MODS to 28-day mortality
MODS: multiple organ dysfunction score

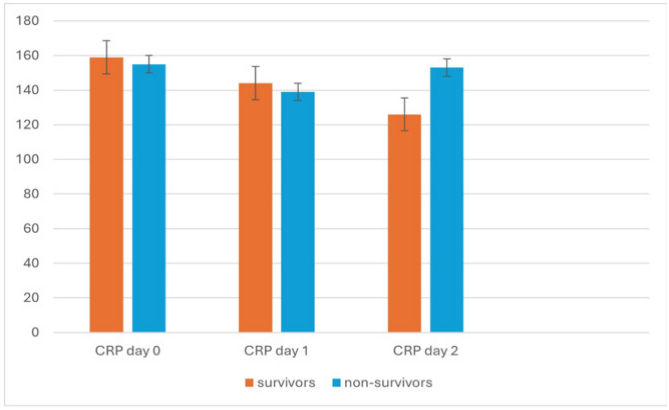

Figure 3. CRP and mortality
CRP: C-reactive protein, day 0; septic shock diagnosed, p values are > 0.05

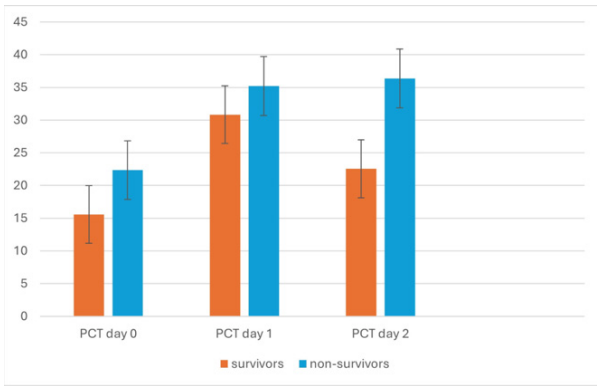

Figure 4. Procalcitonin and mortality
PCT: procalcitonin, day 0; septic shock diagnosed, p values are > 0.05

No correlation was observed between CRP and procalcitonin levels measured over three days and 28-day mortality. CRP and procalcitonin used in the diagnosis and follow-up of the infection were not associated with the 28-day mortality. In addition, there was no significant difference between

ICU-hospital mortality and serum lactate, HDL, CRP, and procalcitonin levels when compared to the survivors and deaths.

DISCUSSION

In this study, we evaluated the relationship between biochemical parameters and disease severity scores in patients diagnosed with septic shock. Our findings revealed that sequential measurements of inflammatory biomarkers were associated with worsening clinical status, as reflected by the APACHE II, SOFA, and MODS scores. This data emphasizes the utility of continuous biomarker monitoring for assessing disease progression and guiding therapeutic interventions in septic shock.

The primary objective of our study was to evaluate the prognosis of sepsis by analyzing 28-day mortality, intensive care mortality, and hospital mortality among patients with septic shock. The secondary objective was to investigate the relationship between inflammatory biomarkers, such as CRP and procalcitonin, and disease severity scores (APACHE II, SOFA, and MODS). We believe that understanding these parameters is crucial for improving patient outcomes. Sequential measurements of SOFA and MODS are particularly useful for predicting mortality, reflecting the dynamic nature of organ dysfunction in critically ill patients. By integrating these sequential scores with other biomarkers, we aim to enhance the accuracy of mortality predictions and guide more tailored treatment approaches.

In comparison to other models, it has been demonstrated that the SAPS III and LODS models offer superior discrimination for 28-day mortality compared to SIRS, SOFA, and SAPS II models.[17] In particular, the SAPS III model exhibited the best discrimination capacity for predicting 28-day mortality. While our study focused on the APACHE II and SOFA scores, future research could benefit from exploring the SAPS III model's capacity for improving mortality predictions in septic shock patients.

Previous research has demonstrated that CRP levels correlate well with the severity of sepsis and other inflammatory diseases.[18] A single measured CRP value has been shown in meta-analysis lack sufficient sensitivity for the diagnosis of sepsis.[19,20] A study conducted in Belgium highlighted a relationship between elevated CRP levels (>10 mg/dL) and increased incidence of organ failure and mortality in ICU patients.[21] However, other studies have suggested that CRP alone is insufficient to predict sepsis outcomes, and the relationship between sepsis severity and elevated CRP levels remains unclear.[22] While several studies have shown a correlation between serum PCT levels and the severity of sepsis and organ dysfunction, not all have supported this finding.[23,24] Recent evidence suggests that presepsin, as a biomarker, not only serves as a diagnostic tool for systemic bacterial infections but also offers significant prognostic value, making it useful in guiding clinical decisions in sepsis management.[25]

There is no gold standard for diagnosing sepsis in critically ill patients. Microbiological cultures, which are often insensitive and nonspecific, take time to produce results. Therefore, biomarkers like procalcitonin, which are stable, easy to measure, and provide rapid results, may be more useful. Although procalcitonin performance is not ideal for critically ill patients, it is considered superior to CRP.[26]

The varying results in published literature suggest that while CRP monitoring can be helpful for infection prediction and assessing antibiotic response in ICUs, it may not be sufficient for sepsis diagnosis or prognosis.[24] In our study, the median CRP level was 135 mg/L (±82.7), and the median procalcitonin level was 5.35 ng/mL (±26.3) in patients with septic shock. These values were significantly higher than the upper limits (CRP: 0-3 mg/L, procalcitonin: 0-2.0 ng/mL).

Scoring systems have become crucial in predicting mortality risk and intensive care outcomes. Several scoring systems have been developed for use in intensive care. The MODS and SOFA scoring systems can be rapidly calculated at the bedside using routinely gathered patient data, offering clinicians crucial insights into patient morbidity, disease progression, and response to treatments. They also provide an overview of organ function. Although both systems have been validated for daily use, the timing of data collection and the methods used to calculate scores differ.

The APACHE II score, widely used in ICUs to stratify acutely ill patients based on their severity of disease, provides a measure of mortality risk through a combination of physiologic data, age, and pre-existing health status. However, the APACHE II score has limitations in mortality prediction, as it may overestimate mortality risk due to dynamic physiological variables influenced by ongoing treatments, and the difficulty in selecting a single principal diagnostic category for patients with multiple comorbidities.[27]

The scoring systems employed in our study include APACHE II, MODS, and SOFA. Severity scores were calculated on the day of ICU admission and on two consecutive days after diagnosis. The median APACHE II score was 19.50 (±7.22) at admission. No statistically significant difference was observed between APACHE II scores at admission and ICU-hospital mortality or 28-day mortality.

No significant relationship was found between SOFA and MODS scores (organ failure scores) at the time of admission and mortality. However, the scores measured on the first and second days after septic shock significantly differed between survivors and non-survivors at 28 days.

Although our knowledge about the pathophysiology of sepsis has increased in recent years, sepsis is still an important cause of mortality and morbidity in critically ill patients in ICUs and is a major burden on the healthcare system.[28] Sepsis-related mortality is closely related to early diagnosis and early treatment of sepsis. Nowadays, the ideal markers to be used in early and accurate diagnosis are not yet available, so the search for the ideal markers has been continuing.

In this study, some markers used in sepsis, the diagnosis of septic shock, and follow up period were investigated. In addition, disease scores used to measure disease severity were calculated. It was seen that the levels of CRP and procalcitonin were significantly higher than the upper limit determined by the laboratory. These elevations continued during the follow-up period. Disease scores were also found to be higher, which was similar to the biochemical markers. When compared the survivals to the deaths in the following days, SOFA and MODS were found to be significantly associated with 28-day mortality.

Limitations

This study has several limitations. Firstly, the small sample size reduces the statistical power and limits the generalizability

of the results to a wider population. Additionally, the study was conducted in a single ICU at Ankara University, which may limit the applicability of the findings to other centers with different patient populations or treatment protocols. The follow-up period was relatively short, focusing on the monitoring of parameters over just three days. This may not fully capture the long-term trends or changes in biomarkers that could influence the progression of sepsis and septic shock. Furthermore, the absence of a control group, consisting of either non-septic patients or those with milder infections, makes it challenging to determine if the observed findings are specific to septic shock or applicable to other conditions. There is also the issue of measurement variability, as parameters such as hemodynamic data and biomarkers like CRP and procalcitonin can be influenced by ongoing treatments such as fluid resuscitation and antimicrobial therapy, introducing potential bias. Lastly, the retrospective nature of some data collection may result in incomplete or inconsistent information compared to a prospective study design.

Recent studies have shown that dynamic nomograms, incorporating variables such as SBP, cerebrovascular disease, and oxygenation index, may offer improved accuracy and discrimination in predicting 28-day mortality in septic shock patients compared to traditional scoring systems like SOFA and APACHE II.[29]

This study offers several notable strengths. First, it provides a comprehensive analysis of various biomarkers, including CRP, procalcitonin, cortisol, brain natriuretic peptide, and lactate, alongside physiological and hemodynamic parameters. This holistic approach enhances the understanding of the inflammatory response and organ function in patients with septic shock. Another significant strength is the sequential monitoring of these biomarkers and clinical parameters over a three-day period, which offers valuable insights into disease progression in critically ill patients.

Moreover, the study utilizes well-validated scoring systems such as APACHE II, SOFA, and MODS to assess disease severity and mortality risk. The use of these established scoring systems strengthens the methodology and allows for comparison with other research in critical care. The focus on prognostic indicators is also a highlight, as it underscores the role of disease severity scores and biomarkers in predicting ICU, hospital, and 28-day mortality, providing clinically relevant insights for prognosis in septic shock patients.

Additionally, the study demonstrates the potential utility of sequential SOFA and MODS scores in mortality prediction, making these tools practical for daily use in clinical practice to monitor septic patients and guide treatment decisions. Finally, the real-world ICU environment in which the study was conducted reflects actual clinical conditions and challenges, ensuring the findings are highly applicable to everyday critical care settings.

CONCLUSION

Consecutive measurements of disease severity scores, such as APACHE II, SOFA, and MODS, may provide valuable insights not only into the progression and severity of the disease but also in guiding treatment decisions and predicting patient outcomes in critically ill patients in ICUs. Regular monitoring of these scores, alongside key biomarkers like CRP and procalcitonin, can aid clinicians in evaluating treatment efficacy, adjusting interventions accordingly, and potentially improving patient survival rates. These tools, when used together, offer a more comprehensive approach to managing septic shock and other critical conditions, ensuring timely and effective care.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ankara University ethic committee (Decision No: 154-4922, Date: 29.06.2009).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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