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Prognostic evaluation of severe sepsis and septic shock: Procalcitonin clearance vs Δ Sequential Organ Failure Assessment☆

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ABSTRACT

Purpose: The purpose of the study is to compare the clearance of procalcitonin (PCT-c) in the first 24 and 48 hours of treatment of severe sepsis and septic shock with another early prognostic marker represented by the 48-hour Δ Sequential Organ Failure Assessment (SOFA).
Materials and methods: Prospective, observational cohort study conducted in a general intensive care unit including patients with severe sepsis and septic shock. The PCT-c was determined at the diagnosis of sepsis and after 24 and 48 hours. The SOFA score was determined at the time of intensive care unit admission and after 48 hours.
Results: One hundred thirty adult patients with severe sepsis and septic shock were studied over an 18-month period. The 24- and 48-hour PTC-c scores were significantly higher in survivors ($P < .0001$). In nonsurvivors, the initial SOFA was significantly higher, and the 48-hour Δ SOFA was significantly smaller ($P = .01$). The area under the receiver operating characteristic curve was 0.68 for Δ SOFA and 0.76 for 24- and 48-hour PCT-c.
Conclusions: The 48-hour Δ SOFA score and the clearance of 24- and 48-hour PCT are useful markers of prognosis in patients with severe sepsis and septic shock. A decrease in PCT-c in the first 24 hours of treatment should prompt the reassessment of the appropriateness and adequacy of treatment.

1. Introduction

Sepsis, defined as the systemic inflammatory response to infection, represents one of the major challenges of medicine today. Sepsis is the leading cause of death among critically ill patients [1]. The incidence of sepsis has increased substantially in the last 3 decades, attributed to the increase of the aging population, the increasing use of immunosuppressive drugs, and the growth of multiresistant bacterial infections [2].

The diagnosis of sepsis is not simple; the manifestations of systemic inflammatory response syndrome (SIRS) do not differ from those of noninfectious conditions [3,4]. In most cases, the treatment of sepsis is established based on clinical data that point to a source of infection.

In addition to the early institution of therapeutic interventions, it is important that possible outcomes be assessed after 24 to 48 hours of treatment. The early identification of patients who are unresponsive to therapy and, therefore, exhibit unfavorable outcomes could permit reviews of the treatment plan.

Organ dysfunction is associated with high mortality and an increase in hospitalization costs. The Sequential Organ Failure Assessment (SOFA) score developed by Vincent et al [5] sequentially evaluates the presence and severity of organ dysfunction. Moreno et al [6] previously evaluated sequential measurements of SOFA and correlated these measures with outcomes. Studies on the Δ SOFA (difference between the SOFA score on second or third day of evolution and SOFA on arrival) have reported correlations with mortality [7,8].

Procalcitonin (PCT) is the prohormone of calcitonin, the hormone involved in calcium homeostasis. Normally, all PCT is cleaved, and serum levels are undetectable in healthy individuals. During severe systemic manifestations of infections, serum PCT may rise above 100 ng/mL. Under these conditions, PCT is likely produced by extrathyroid tissues. Recently, PCT kinetics have been used as a biological marker of prognosis [9,10]. In severe sepsis and septic shock, isolated determinations of serum PCT have shown variable results. Most studies indicate that the predictive value of individual determinations of PCT on mortality is poor [11,12]. Encouraging results were obtained in studies involving patients with severe sepsis and septic shock, revealing that serial determinations of PCT correlate with outcome [13-15]. Recently, Ruiz-Rodriguez et al [16] and Suberviola et al [17] introduced the concept of clearance of PCT (PCT-c). Both studies reported impressive improvement in PCT-c in survivors and reduction in nonsurvivors after 24 to 72 hours.

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The identification of a prognostic marker that could predict patient outcomes after 24 to 48 hours of treatment of severe sepsis and septic shock would be useful to reassess the patient and identify sources of perpetuators of severity, allowing interventions and changes in management. The addition of this marker for the routine evaluation of patients treated according to the strategies of the Surviving Sepsis Campaign [18] could help reduce morbidity and mortality.

The aim of this study was to compare the PCT-c in the first 24 and 48 hours of treatment of severe sepsis and septic shock with another early prognostic marker represented by the 48-hour Δ SOFA.

2. Materials and methods

This is a prospective observational cohort study, approved by the Research Ethics Committee of the São Domingos Hospital, São Luis, MA, Brazil, under number 009/2012. The need for informed consent was waived. ClinicalTrials.gov identifier: NCT01841190.

The study included 130 patients admitted to a 37-bed general intensive care unit (ICU) of a tertiary hospital in São Luis, MA, Brazil, over an 18-month period (from May 2012 to October 2013).

Inclusion criteria were as follows: older than 18 years, nonpregnant, and fulfilled the International Sepsis Consensus Conference for severe sepsis or septic shock [19], that is, sepsis associated with at least 1 organ dysfunction and/or tissue hypoperfusion signs without response to volume expansion and the need for vasopressive drug.

All patients were treated according to the institutional protocol for management of severe sepsis and septic shock, based on the recommendations of the Surviving Sepsis Campaign, modified to meet recent evidence from the literature [20,21].

2.1. Data collection

Data collection included demographics data, medical or surgical patient information, Acute Physiology and Chronic Health Evaluation IV score, SOFA score on arrival and after 48 hours, number of SIRS criteria at diagnosis, site of infection, results of blood cultures taken in the first hour, checklist package of the first 6 hours, use of corticosteroids for septic shock, use of protective ventilation, blood glucose control, mean blood glucose levels over the first 24 hours, the PCT clearance after 24 and 48 hours, and outcome (ICU mortality).

2.2. Collection of blood samples and analysis

Serum PCT was measured at the diagnosis of sepsis and repeated at the end of the first 24 and 48 hours of treatment. The measurements were made by electrochemiluminescence immunoassay using the COBAS e 411 equipment (Hoffmann-La Roche, Inc, Basel, Switzerland). The reagent used in these assays was developed in collaboration with Brahms Diagnostica, Berlin, Germany.

Clearance of PCT-c was calculated using the following formula: initial PCT minus PCT at 24 or 48 hours, divided by the initial PCT and then multiplied by 100. The 48-hour Δ SOFA represented by the difference between the initial and 48-hour SOFA score.

2.3. Statistical analysis

The results are presented as mean ± SD, median with interquartile range (IQR) or proportions. Comparisons between continuous variables were made using the Student *t* test or Mann-Whitney *U* test. The prognostic accuracy of the PTC-c and Δ SOFA was expressed as the area under the receiver operating characteristic (ROC) curves (AUCs). An AUC of 0.5 implies that the tested variable is no more accurate than a coin toss, whereas an AUC of 1.0 indicates a perfect predictive power. Values of 0.7 or greater suggest that the variable may have clinical utility. To compare the prognostic classification obtained from the cutoff point of the variable 24-hour PCT-c with the cutoff of the 48-hour PCT-c, 48-hour Δ SOFA, and the outcome variable, we used the nonparametric test of McNemar. To check the calibration of the model, the Hosmer-Lemeshow test was applied. All testing was 2 tailed, and $P < .05$ was considered statistically significant.

To calculate the sample size, we used the results of a study that compared the plasma concentration of PCT between the first and third day after the admission of survivors and nonsurvivors with severe sepsis [20] and a study that analyzed the variation of the SOFA score between the first and third day after the admission of survivors and nonsurvivors with severe sepsis and septic shock [7]. The calculated sample size was 128 (including 10% possible losses).

3. Results

3.1. Study population

A total of 135 patients were eligible for the study; 130 were finally enrolled. The reasons for the exclusion of the 5 patients included death before 48 hours (3 patients) and missing data (2 patients). Table 1 presents the characteristics of studied population. Ninety-nine (76%) were medical patients. The source of sepsis was pulmonary in 55 cases (44%), urinary infection in 27 (21.6%), abdominal in 24 patients (19.2%), soft tissue in 10 cases (8.0%), and others in 9 (7.2%). In 5 patients (3.8%), the source of sepsis was not identified. Eighty-three patients exhibited severe sepsis, and 47 patients exhibited septic shock. The overall mortality was 33 patients (25.4%), 11 (13.2%) with severe sepsis and 22 (46.8%) with septic shock.

3.2. Twenty-four-hour PCT-c, 48-hour PCT-c, and 48-hour Δ SOFA

One hundred thirty PCT measurements were performed at the diagnosis of sepsis and after 24 hours, and 125 measurements were taken after 48 hours. All patients had 48-hour Δ SOFA measurements. The initial SOFA, 48-hour Δ SOFA, initial PCT concentration, and 24- and 48-hour PCT-c values in survivors and nonsurvivors are presented in Table 2. The initial PCT concentration did not differ significantly different between survivors and nonsurvivors, but the 24- and 48-hour PCT-c values were significantly higher in survivors ($P < .0001$). The initial SOFA was significantly higher, and the 48-hour Δ SOFA 48 was significantly smaller in nonsurvivors ($P = .01$).

The area under the ROC curve was 0.68 (95% confidence interval [CI], 0.56-0.79; $P = .004$) for 48-hour Δ SOFA, 0.76 (95% CI, 0.66-0.86; $P < .0001$) for 24-hour PCT-c, and 0.76 (95% CI, 0.66-0.86; $P < .0001$) for 48-hour PCT-c (Figure). The Hosmer-Lemeshow test showed good

Table 1
Characteristics of the study population (n = 130)

Age, y, mean (SD)	66.7 (20.4)
Women, n (%)	65 (50)
Clinical/surgical, n	99/31
APACHE IV, mean (SD)	69.0 (29.4)
Initial SOFA score, mean (SD)	5.2 (3.4)
No. of organ dysfunctions, mean (SD)	2.5 (0.9)
Mechanical ventilation, n (%)	50 (38.4)
Vasopressor therapy, n (%)	47 (36.1)
RRT, n (%)	18 (13.8)
Site of sepsis, n (%)	
Lung	55 (44)
Urine	27 (21.6)
Abdomen	24 (19.2)
Soft tissue	10 (8.0)
Others	9 (7.2)
Unknown	5 (3.8)
Severe sepsis/septic shock, n	83/47
ICU mortality, n (%)	33 (25.4)
Severe sepsis	11 (13,2)
Septic shock	22 (46.8)

APACHE indicates Acute Physiology and Chronic Health Evaluation; RRT, renal replacement therapy.

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Table 2
Results of determinations of Δ SOFA and PCT-c in survivors and nonsurvivors

	Survivors, n = 97	Nonsurvivors, n = 33	*P*
Initial SOFA score, mean(SD)	4.77 (3.31)	6.55 (3.49)	.01
Δ SOFA 48 h, mean (SD)	0.58 (2.77)	−0.75 (2.38)	.01
Initial PCT (ng/mL), median (IQR)	6.16 (1.26-16.45)	3.30 (0.73-11.30)	.25
PCT-c 24 h (%), median (IQR)	10.0 (−75.0 to 40.0)	−100.0 (−870.0 to −10.0)	<.0001
PCT-c 48 h (%), median (IQR)	35.5 (−40.0 to 70.0)	−170.0 (−887.5 to 7.5)	<.0001

Δ SOFA = initial − 48 hours.

calibration (48-hour Δ SOFA, 0.50; 24-hour PCT-c, 0.85; and 48-hour PCT-c, 0.67). A cutoff value of 0.5 for 48-hour Δ SOFA was associated with a sensitivity of 61.3%, specificity of 71.4%, positive predictive value of 36.5%, negative predictive value of 85.9%, and efficiency of 61.4% for identifying survivors. A cutoff value of −73% for 24-hour PCT-c exhibited 76.3% sensitivity, 67.9% specificity, 47.7% predictive positive value, 85.4% negative predictive value, and 72.2% efficiency, and a cutoff value of −25% for 48-hour PCT-c exhibited a 73.8% sensitivity, 64.3% specificity, 45% positive predictive value, 86.1% negative predictive value, and 71.4% efficiency.

4. Discussion

Sepsis and its complications represent the main cause of death in ICUs. Although the Surviving Sepsis Campaign [18] has brought substantial improvement to patient survival, the Campaign failed to incorporate markers that can identify patients with unfavorable prognosis. This identification would allow the reassessment of patients with respect to the diagnosis of complications and the need for changes in treatment in time to improve their unfavorable course.

In this prospective observational study, we found that the initial SOFA score, the 48-hour Δ SOFA score, and the 24- and 48-hour PCT-c proved to be accurate predictors of prognosis in patients with severe sepsis and septic shock. On the other hand, the initial serum concentration of PCT exhibited no correlation with prognosis.

Organ dysfunctions are associated with high rates of ICU morbidity and mortality and account for a high proportion of the ICU budget. The SOFA score [5] sequentially evaluates the presence and severity of organ dysfunction. Moreno et al [6] demonstrated that sequential measurements of SOFA correlated with outcome. Both the initial and the Δ SOFA scores (difference between the SOFA score on the second or third day of evolution and the SOFA score on arrival) exhibited a correlation with mortality. Jones et al [7] analyzed 248 patients with severe sepsis and septic shock and demonstrated that the initial and the Δ SOFA (initial − 72 hours) scores correlated strongly with mortality. The study revealed that any increase in Δ SOFA was associated with a 35% inhospital mortality rate, whereas any decrease in Δ SOFA was associated with 10% mortality. Ferreira et al [8] studied 352 patients admitted to a surgical ICU and demonstrated that the mean SOFA and Δ SOFA correlated strongly with mortality. The authors suggested that the Δ SOFA could be used to assess response to treatment, allowing reassessments of therapeutic plans in patients who develop worsening of organ dysfunction after 48 to 72 hours of treatment.

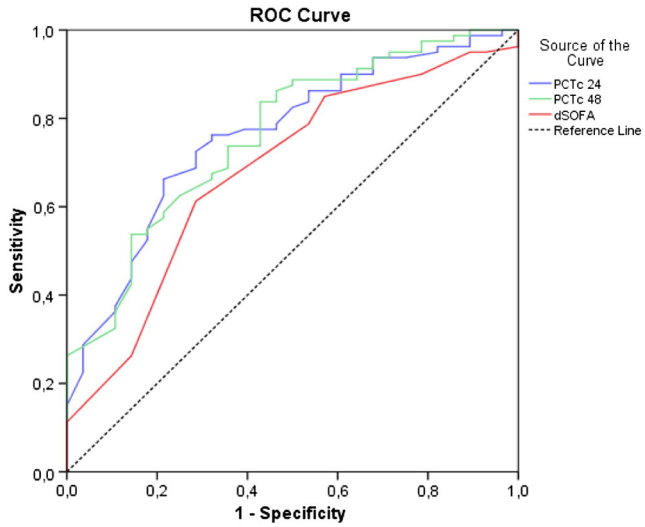

Fig. 1. Receiver operating characteristic curves of 48-hour Δ SOFA, 24-hour PCT-c, and 48-hour PCT-c.

With regard to our findings, both the initial SOFA score and the 48-hour Δ SOFA score correlated significantly with the prognosis. Although the initial SOFA score has been shown to be relevant as a prognostic indicator, the purpose of this study was to identify patients with unfavorable evolution after the first 24 to 48 hours of treatment, with the objective of providing reassessment of the patient and changes in the therapeutic plan. In the analysis of ROC curves, the 48-hour Δ SOFA (AUC, 0.68) was less significant than the 24- and 48-hour PCT-c (AUC, 0.76).

Our study demonstrated that 24-hour PCT-c is able to identify patients who will not survive sepsis. The 24-hour PCT-c of survivors was 10.0% (IQR, −75 to 40), which was substantially higher than nonsurvivors (−100.0%; IQR, −870 to −10) ($P < .0001$). The AUC of 24-hour PCT-c was 0.76. The best cutoff value was −73%. The 48-hour PCT-c 48 was also effective in predicting outcome, with an AUC of 0.76 and a best cutoff of −25%. The ability to identify patients with unfavorable outcome after 24 hours of treatment and to reassess the treatment plan will no doubt provide greater chances to modify patient outcome.

In severe sepsis and septic shock, isolated determinations of serum PCT have produced variable results [11,12]. Most studies have reported that it is not possible, based on high levels of PCT, to predict the outcome of critically ill patients. On the other hand, the evaluation of the evolution of PCT levels is more useful in assessing prognosis [9,10]. In patients with pulmonary sepsis reductions in PCT concentrations greater than 30% between the second and third day of evolution were identified as determinants of survival with odds ratio of 2.9 [22,23]. In patients with community-acquired pneumonia decreased PCT from days 1 to 3 was related to survival, with 89% specificity, 82% negative predictive value, and 71% positive predictive value [24]. Karlsson et al [9] recently reported that mortality in patients with severe sepsis is smaller in those patients in whom the PCT concentration decreased more than 50% compared with baseline values. Claeys et al [13] analyzed patients with septic shock and demonstrated that 48 hours after admission, PCT levels decreased substantially only in survivors. Guan et al [14] prospectively analyzed 37 patients with septic shock and reported that all survivors exhibited lower levels of PCT during treatment and all nonsurvivors exhibited progressive elevation of PCT levels. Recently, Ruiz-Rodriguez et al [16] and Suberviola et al [17] introduced the concept of PCT-c to assess the evolutive behavior of PCT and its relationship with mortality. In both studies, the clearance of PCT was determined by the following formula: initial value − final value/initial value × 100. Suberviola et al [17] studied 88 patients with septic shock admitted to a general ICU. The study revealed that the mortality in patients with increased PCT-c in the first 72 hours of treatment was significantly lower than in patients who had a reduction of clearance over the same period (15.4% vs 58.8%; $P < .01$). Ruiz-Rodriguez et al [16] determined the PCT-c 24, 48, and 72 hours after treatment in 27 patients with septic shock and demonstrated a significant increase in the clearance of PCT in survivors and a reduction in nonsurvivors.

Some patients in our population were in various stages of acute kidney injury. Meisner et al [25], analyzing a population of patients admitted to a general ICU, demonstrated that the presence of varying

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degrees of renal injury did not influence the rate of clearance of plasma PCT. Suberviola et al [17], analyzing the behavior of PCT-c in patients with septic shock with and without renal dysfunction, reported that although the plasma levels of PCT levels were higher in patients with renal injury, no differences were observed between the 2 groups with respect to PCT-c.

This study confirms the findings of previous articles reporting that the initial concentration of PCT does not have prognostic value and demonstrates that the determination of PCT-c as early as 24 hours correlates with the prognosis of patients with severe sepsis and septic shock.

Our study has limitations. First, this is a single-center study. Large and multicenter studies are necessary to confirm our results. Second, these results cannot be applied to patients who have sepsis without organ dysfunctions or septic shock. Third, we did not collect information regarding the appropriateness of antibiotic for the pathogen-causing infection.

5. Conclusions

The 48-hour Δ SOFA score and the clearance of 24- and 48-hour PCT are useful markers of prognosis in patients with severe sepsis and septic shock. A decrease in PCT-c in the first 24 hours of treatment should prompt the reassessment of the appropriateness and adequacy of treatment.

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