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BRIEF REPORT

Joana Silvestre
P. Póvoa
L. Coelho
E. Almeida
P. Moreira
A. Fernandes
R. Mealha
H. Sabino

Is C-reactive protein a good prognostic marker in septic patients?

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J. Silvestre (✉) · P. Póvoa · L. Coelho
Department of Medicine III,
Medical Intensive Care Unit,
São Francisco Xavier Hospital,
Centro Hospitalar de Lisboa Ocidental,
Estrada do Forte do Alto do Duque,
1449-005 Lisboa, Portugal
e-mail: jpssilvestre@clix.pt
Tel.: +351-21-0431104
Fax: +351-21-0431301

E. Almeida · P. Moreira · A. Fernandes ·
R. Mealha · H. Sabino
Intensive Care Unit,
Garcia de Orta Hospital,
Almada, Portugal

Abstract *Rationale:* Several studies have shown that C-reactive protein (CRP) is a marker of infection. The aim of this study was to evaluate CRP as marker of prognosis outcome in septic patients and to assess the correlation of CRP with severity of sepsis. *Methods:* During a 14-month period, we prospectively included all patients with sepsis admitted to an intensive care unit (ICU). Patients were categorized into sepsis, severe sepsis and septic shock. Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA) score, CRP, body temperature and white cell count (WCC) of the day of sepsis diagnosis were collected. *Results:* One hundred and fifty-eight consecutive septic patients (mean age 59 years, 98 men, ICU mortality 34%) were studied. The area under the receiver operating characteristics curves of APACHE II, SAPS II, SOFA, CRP, body temperature and WCC as prognostic markers of sepsis were 0.75 [95% confidence interval (CI) 0.67–0.83], 0.82 (95% CI 0.75–0.89), 0.8 (95% CI 0.72–0.88), 0.55 (95% CI 0.45–0.65), 0.48 (95% CI 0.38–0.58) and 0.46 (95% CI 0.35–0.56), respectively. In the subgroup of patients with documented sepsis we obtained similar results. The ICU mortality rate of septic patients with CRP < 10, 10–20, 20–30, 30–40 and >40 mg/dL was 20, 34, 30.8, 42.3 and 39.1%, respectively ($P = 0.7$). No correlation was found between CRP concentrations and severity of sepsis. *Conclusions:* In septic patients, CRP of the day of sepsis diagnosis is not a good marker of prognosis.

Keywords C-reactive protein · Sepsis · Infection · Organ failure · Prognosis

Introduction

Sepsis is a clinical syndrome that results from the interaction between the infecting microorganism and the host immune, inflammatory and coagulation responses [1]. Measurement of circulating concentrations of biomarkers may prove to be useful in the stratification of sepsis and hypothetically could be used to decide the administration of sepsis specific therapies [2].

Amongst biomarkers, C-reactive protein (CRP) and procalcitonin (PCT), proved to be useful in the infection diagnosis, infection prediction and monitoring response to antibiotics [3, 4]. Besides, the ability of biomarkers to assess sepsis prognosis has also been studied [3–5].

Despite the recent findings, the evaluation of prognosis in septic patients still depends on the assessment of physiological variables and presence of comorbidities [5–8].

The aim of our study was to investigate whether CRP could be used as prognostic marker in septic patients as well as in the subgroup with documented sepsis. Additionally, we evaluated the correlation between CRP concentrations and severity of sepsis.

Patients and methods

A single centre prospective observational cohort study was conducted during a 14-month period (November 2001–December 2002) in the intensive care unit (ICU) of Garcia de Orta Hospital.

Patients were included if they fulfilled criteria for sepsis. Sepsis was considered according to the Centers for Disease Control and Prevention definitions [9]. If the patient presented more than one septic episode only the first was considered.

Severity of illness was assessed by calculating Acute Physiologic and Chronic Health Evaluation (APACHE) II score [10], Simplified Acute Physiology Score (SAPS) II [11] and Sequential Organ Failure Assessment (SOFA) scores [12].

Comparison of CRP levels with clinical severity was performed. Clinical severity was assessed by the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference Criteria [9], and patients were divided in the following groups: sepsis, severe sepsis and septic shock.

C-reactive protein, body temperature and white cells count (WCC) were measured at admission and then daily until discharge or death. The measurements of the day of sepsis diagnosis were used to predict outcome.

Measurement of CRP was performed by an immunoturbidimetric method (Tina-quant CRP; Roche Diagnostics, Mannheim, Germany).

We compared the clinical and laboratory data prospectively collected for survivors and nonsurvivors.

A similar a priori subgroup analysis was performed in patients with documented sepsis. Patients with documented sepsis were those with a defined source of infection who yield positive cultures.

Statistical analyses

The outcome measure was ICU mortality. Continuous variables are presented as mean ± standard deviation (SD). Differences in continuous variables were performed with the nonparametric Mann–Whitney *U*-test, unpaired Student's *t* test, one-way ANOVA or Kruskal–Wallis *H*-test. The Chi-square test was used to carry out comparisons between categorical variables. Numbers of patients were compared by Fisher's exact test. The correlation coefficient (r), coefficient of determination (r^2) or the Spearman rank correlation (r_s) was used to determine the relationship between two variables.

CRP levels were categorized in quintiles and compared with mortality rate. Linear regression analysis was used to compare SOFA with CRP levels.

Discrimination of APACHE II, SAPS II, SOFA, CRP, body temperature and WCC was tested to produce receiver-operating characteristic (ROC) curves. Areas under curves (AUC), with 95% confidence intervals (CI) were calculated in prediction of ICU mortality.

A P value below 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS 13.0 software.

Results

Patients characteristics

During the study period, 158 patients with the diagnosis of sepsis were consecutively included. Mean age was 59 ± 17 years, and 98 were males (Table 1).

Patients were divided according to ACCP/SCCM Consensus Conference criteria into the following groups: 12 patients with sepsis, 60 with severe sepsis and 86 with septic shock. Groups did not differ in sepsis aetiology. Amongst the septic patients, 61 (38.6%) had nosocomial infection; no significant differences were found between survivors and nonsurvivors (32.7 vs. 50%, $P = 0.052$).

Microorganisms were isolated in 76 (48%) septic patients being *Pseudomonas aeruginosa* the predominant microorganism (18, 24%).

The overall ICU mortality was 34.2% ($N = 54$). Nonsurvivors were older ($P = 0.005$) and tended to have higher APACHE II, SAPS II and SOFA scores ($P < 0.001$). Demographic and clinical data are summarized in Table 1.

Evaluation of CRP as prognostic marker of sepsis

C-reactive protein values varied from 2.4 to 85.4 mg/dL (median 24.2 mg/dL) and only 8 (5%) patients had CRP levels below 8.7 mg/dL [13].

We were unable to find any correlation between CRP concentrations and severity of sepsis ($r_s = 0.18$, $r_s^2 = 0.03$), as well as with the degree of organ failure assessed with the SOFA score ($r = 0.2$, $r^2 = 0.04$). We also assessed the influence of CRP levels in ICU mortality. Patients were divided in quintiles according to CRP values, <10, 10–20, 20–30, 30–40 and >40 mg/dL, and the associated mortality rate was 20, 34, 30.8, 42.3 and 39.1%, respectively ($P = 0.7$).

Table 1 Baseline characteristics of the patients with sepsis

	All ($n = 158$)	Survivors ($n = 104$)	Nonsurvivors ($n = 54$)	P values
Age (years)	58.6 ± 16.9	55.9 ± 17.1	63.8 ± 15.3	0.005
Sex (M/F)	98/60	63/41	35/19	0.656
APACHE II	21.2 ± 7.5	18.8 ± 6.3	26.0 ± 7.3	<0.001
SAPS II	47.2 ± 15.1	41.5 ± 11.7	58.2 ± 14.7	<0.001
SOFA	8.1 ± 3.6	6.7 ± 2.7	10.6 ± 3.6	<0.001
CRP (mg/dL)		25.3 ± 13.7	28.2 ± 13.1	0.15
Temperature (°C)		38.0 ± 0.9	37.9 ± 1.1	0.81
WCC (×1,000) mL^{-1}		15.4 ± 10.9	16.2 ± 13.7	0.7
Primary admission diagnosis (N)				0.289
Respiratory	64	46	18	
Cardiovascular	15	11	4	
Neurology	14	10	4	
Surgical	32	15	17	
Trauma	14	10	4	
Obstetrics	6	3	3	
Others	13	9	4	
Comorbidities (N)				
Neoplasm	21	12	9	
Chronic pulmonary disease	19	14	5	
Congestive heart failure	16	11	5	
Diabetes	9	6	3	
Ulcer disease	5	3	2	
Myocardial infarct	3	2	1	
Chronic renal disease	2	1	1	
Dementia	2	1	1	
Mild liver disease	1	0	1	
AIDS	1	0	1	

Values expressed in mean ± standard deviation
AIDS acquired immune deficiency syndrome

There were no differences between survivors and nonsurvivors in CRP levels, temperature and WCC (Table 1).

In a ROC analysis to distinguish between survivors and nonsurvivors, SAPS II had the highest AUC, 0.82 (95% CI 0.75–0.89), being significantly higher than the other studied variables ($P < 0.05$) with the exception of SOFA score (Table 2).

CRP as a prognostic marker in patients with documented sepsis

Seventy-six patients presented documented sepsis. The mean age was 59 years and 49 were males. The primary reason for ICU admission was respiratory failure ($N = 26$).

C-reactive protein values of these patients varied from 5.5 to 43.9 mg/dL (median 19.0 mg/dL). No differences were observed between survivors and nonsurvivors concerning APACHE II score (21.3 ± 6.3), body temperature (38.4 ± 1.1) and WCC (14.4 ± 8.2). However, the SAPS II and SOFA score were significantly higher in nonsurvivors (53.7 ± 13.7 vs. 42.5 ± 11.1, $P < 0.001$ and 9.8 vs. 6.2 ± 2.9, $P < 0.001$, respectively).

The AUC showed a good discriminative power in prediction of ICU mortality only for SAPS II (AUC 0.75, 95% CI 0.63–0.86) and SOFA score (AUC 0.77, 95% CI 0.66–0.88) (Table 2).

Table 2 Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) scores, serum C-reactive protein (CRP), body temperature and white cell count (WCC) of survivors and nonsurvivors of sepsis and documented sepsis

	Sepsis	Documented Sepsis
CRP (mg/dL)	0.55 (0.45–0.65)	0.66 (0.53–0.79)
Temperature (°C)	0.48 (0.38–0.58)	0.44 (0.29–0.59)
WCC (×1,000) mL^{-1}	0.46 (0.35–0.56)	0.6 (0.46–0.73)
APACHE II	0.75 (0.67–0.83)	0.65 (0.51–0.78)
SAPS II	0.82 (0.75–0.89)	0.75 (0.63–0.86)
SOFA	0.80 (0.72–0.88)	0.77 (0.66–0.88)

Discrimination is presented as area under receiver characteristics curve (AUC) with 95% confidence intervals (CI). Values expressed in mean ± standard deviation

Discussion

In our study, the prognosis of sepsis was assessed prospectively with measurements of CRP, body temperature and WCC, in order to identify patient's outcome. In this

context, we evaluated the correlation of CRP levels with sepsis severity, organ failure and ICU mortality and no correlation could be found. However, nonsurvivors tended to have higher APACHE II, SAPS II and SOFA scores, corresponding to a sicker population. In the subgroup of documented sepsis, we found similar results. Based on the present findings, CRP levels poorly predict outcome in terms of survival.

The levels of CRP have been shown to be well correlated with the severity of sepsis and other inflammatory diseases [14]. Chalmers et al. [15] demonstrated that low CRP levels at admission excluded severe community acquired pneumonia (CAP). Oberhoffer et al. [16] observed similar results in septic patients, finding good correlations with mortality with PCT and CRP.

However, some major studies found a poor correlation between CRP and mortality. Muller et al. [17] and Kruger et al. [18], studying CAP patients, found that CRP levels were not a good marker in predicting clinical severity of pneumonia assessed by Pneumonia Severity Score and CRB-65 score, respectively. Similarly, in septic patients, Pettila et al. [8] evaluated the performance of PCT, interleukin-6, CRP, WCC, D-dimer and antithrombin III in prediction of mortality and concluded that these biomarkers are not independently associated with hospital mortality.

The use of biomarkers in the assessment of prognosis of sepsis is a fundamental step for stratification of septic patients. In the present study, we were unable to find any correlation between severity of sepsis and CRP levels.

Besides, in assessing the correlation between CRP levels and organ dysfunction, we found that CRP was equally elevated irrespective of the SOFA score value. These results were similar to those found by Meisner et al. [19]. In opposition, Lobo et al. [20] found that CRP levels were correlated to higher SOFA scores. Our findings do not support the use of CRP, body temperature and WCC in prediction of outcome in critically ill septic patients. Nevertheless, our population had higher APACHE II and SOFA scores, as well as a larger subgroup of patients with septic shock.

Some limitations of the present investigation should be noted. First, this was a cohort single centre study and only ICU mortality was evaluated. Second, a mixed group of medical and surgical septic patients was examined. Finally, because we used clinical and microbiological evidence it might have been difficult to ascertain the precise cause of sepsis in all patients, and this might have introduced some misclassification bias.

Our study design had some distinctions: our main outcome was survival, a larger group of patients was included and we assessed a subgroup of patients with documented sepsis.

Conclusions

Our results demonstrate that despite CRP being a sensitive marker of infection, CRP of the day of sepsis diagnosis predicts poorly the survival outcome. According to our results we do not recommend the use of CRP level of the day of sepsis diagnosis as a marker of prognosis and risk stratification.

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