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Serum C-reactive protein concentrations in early abdominal and pulmonary sepsis

Dosagens séricas de proteína C-reativa na fase inicial da sepse abdominal e pulmonar

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ABSTRACT

Objectives: To evaluate the C-reactive protein serum levels in patients with pulmonary and abdominal sepsis during the first five days of sepsis progression.

Methods: The present investigation was a retrospective cohort study conducted at the university hospital with 345 patients who were admitted to the intensive care unit and diagnosed with sepsis of pulmonary or abdominal origin. Serum C-reactive protein concentrations were measured by the turbidimetric immunoassay. For analysis of C-reactive protein, day 1 was defined as the day on which the patient was clinically diagnosed with sepsis.

Results: Thirty-four patients with sepsis (9.8%), 114 patients with severe sepsis (33.0%), and 197 patients with septic shock (57.2%) were evaluated. The age of the patients was 56.4±19.8 years. The serum C-reactive protein concentrations were higher on the day of sepsis diagnosis in the group with abdominal infection compared with the group with pulmonary sepsis (17.8±10.1 mg/dL versus 14.9±11.1 mg/dL, p=0.025) and remained significantly higher during the first five days of sepsis progression.

Conclusion: The serum C-reactive protein concentrations were significantly higher in the patients with abdominal sepsis compared with the patients with pulmonary sepsis during the first five days of sepsis progression.

Keywords: C-reactive protein; Sepsis/diagnosis; Biological markers

INTRODUCTION

Sepsis is one of the leading causes of death in critically ill patients. Because sepsis has a high prevalence worldwide with high morbidity and mortality rates, standardizing the diagnostic criteria for early recognition of the syndrome is essential. Despite its low sensitivity and specificity for the diagnosis of infection in patients in the intensive care unit (ICU), changes in the body temperature and leukocyte counts are still the only parameters that are considered in the diagnosis of infection in many centers.[1-3] In a recent consensus meeting to reassess the definitions and identify methodologies that increase the accuracy and reliability of the diagnosis of sepsis, new diagnostic criteria were proposed. It was recommended that, together with the conventional parameters (i.e., changes in the leukocyte count, fever or hypothermia, and clinical and hemodynamic parameters), C-reactive protein (CRP) or procalcitonin should be used as a diagnostic aid.[4]

CRP is an acute-phase protein that is synthesized in the liver and rapidly released after the onset of inflammation or tissue injury.[5-7] The serum concentration is determined by the synthesis rate, which depends on the intensity

of the inflammatory stimulus that is mediated, especially by interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-alpha).[5-9] Numerous studies have reported the high sensitivity and specificity of CRP for the diagnosis of sepsis.[5-9] More importantly, the CRP response during the early days of antibiotic therapy may indicate the appropriateness of the treatment response and prognosis of the infection.[10-16] However, differences in serum CRP levels relative to the focus of infection have not been investigated.

Therefore, the objective of this study was to evaluate the serum CRP levels in patients with pulmonary and abdominal sepsis during the first five days starting from the day of the sepsis diagnosis.

METHODS

The present study was a retrospective analysis of a database that was collected prospectively at a tertiary academic hospital. This study was approved by the Research Ethics Committee (Comitê de Ética em Pesquisa - CEP) of the Faculdade de Medicina de São José do Rio Preto, and patient informed consent was waived.

The patients with sepsis, severe sepsis, and septic shock were classified according to the criteria defined by the American College of Chest Physicians (ACCP).[17] Pulmonary and abdominal infections were diagnosed based on the criteria adopted by the Centers for Disease Control and Prevention (CDC).[17] Pneumonia was defined as the presence of a new infiltrate or worsening of a pulmonary infiltrate prior to the chest X-ray and at least one of the following clinical signs: axillary temperature of ≥38ºC or ≤36ºC, leukocytosis >11,000/mm³ or leukopenia <4,000/mm³, and purulent tracheal secretions. In suspected pulmonary infections, samples were collected, and quantitative cultures were performed. The cultures were considered positive for values greater than 10^6 CFU [colony-forming units]/mL for endotracheal aspirates and $\geq 10^4$ CFU/mL for bronchoalveolar lavage. Abdominal sepsis was diagnosed when an infectious focus was discovered upon exploratory laparotomy or confirmed by imaging or microbiological methods. The serum CRP concentrations were measured using a turbidimetric immunoassay. For CRP analysis, day 1 (D1) was defined as the day of the clinical diagnosis of sepsis.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was determined using data obtained within the first 24 hours of ICU admission. The Sequential Organ Failure Assessment (SOFA) was performed using data that were obtained on the day of the sepsis diagnosis.[18,19] The in-hospital mortality rates were evaluated using the hospital records.

The statistical analysis was performed using Student's t-test to compare two groups of continuous variables with independent samples and normal distributions; the Mann-Whitney test was used to analyze the data with non-normal distributions. The categorical variables were expressed as absolute and relative frequencies (%). The cutoff point for the CRP levels was determined based on the receiver operator characteristic (ROC) curve. The significance level was set at 5%, with a 95% confidence interval (CI).

RESULTS

Of the 2,769 patients who were admitted between February 2003 and November 2005 to the clinical-surgical ICU (24 beds), 564 consecutive patients who met the criteria of sepsis, severe sepsis, or septic shock with nosocomial or community origin had their data prospectively recorded in the ICU database. Of the 564 subjects, 345 patients who were diagnosed with sepsis of pulmonary or abdominal origin and who had had at least three measurements of CRP (two of which were performed within the first 72 hours of the sepsis diagnosis) were included in this analysis to evaluate the serum CRP levels during the first five days of sepsis (Figure 1).

Thus, in total, 345 patients (62% male) were evaluated: 34 patients had sepsis (9.8%), 114 patients had severe sepsis (33.0%), and 197 patients had septic shock (57.2%) on the day of the sepsis diagnosis. The average age of the patients was 56.4±19.8 years old, and the APACHE II score at admission was 17.1±8.2. Mechanical ventilation was used in 292 patients (84.6%). The overall mortality rate was 60%.

Infection was of pulmonary origin in 195 patients (56.5%) and of abdominal origin in 150 patients (43.5%) (Table 1).
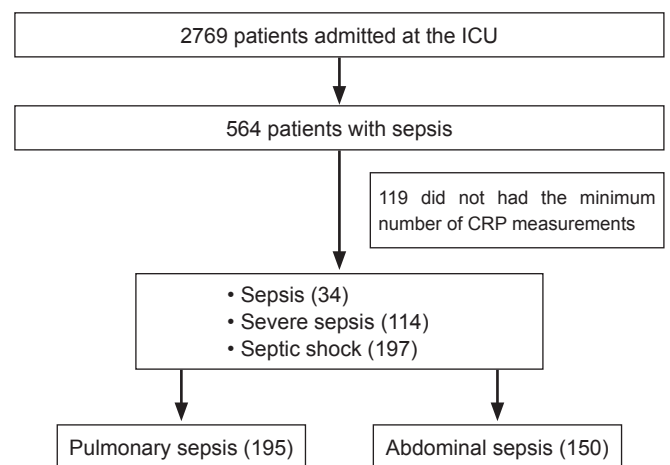

Figure 1 - Flowchart of the patients' inclusion criteria. ICU - intensive care unit; CRP - C-reactive protein.

Table 1 - Patient characteristics

Variables	Pulmonary (N = 195)	Abdominal (N = 150)	p value
Clinical/surgical	71 (36.4)/124 (63.6)	16 (10.7)/134 (89.3)	<0.0001
Community/nosocomial	100 (52)/95 (48)	111 (74)/39 (26)	<0.0001
Age (years)	54.7±20.6	58.6±18.7	0.07
APACHE II at the ICU admission	17.7±8.0	16.4±8.5	0.14
Patients with OD	130 (66.6)	104 (69.3)	0.67
Number of OD	2 [2-3]	3 [1-4]	0.67
Patients with MV	169 (86.6)	123 (82.0)	0.30
MV (days)	11 [6-21]	8 [4-16]	<0.0001
Dialysis patients	41 (21,0)	32 (21.3)	0.95
Dialysis (days)	5 [3-8]	4 [2-10]	0.55

APACHE II - Acute Physiology and Chronic Health Evaluation II; ICU - intensive care unit; OD - organ dysfunctions; and MV - mechanical ventilation. Results expressed as mean ± SD or as indicated.

Table 2 - Serum C-reactive protein concentrations according to the infection site during the first five days of sepsis progression

Day	Pulmonary	Abdominal	p value
1 (mg/dL)	14.9±11.1 (153)	17.8±10.1 (113)	0.026
2 (mg/dL)	16.5±10.3 (169)	21.2±9.9 (136)	<0.0001
3 (mg/dL)	16.5±10.9 (165)	20.5±9.8 (120)	0.002
4 (mg/dL)	13.9±9.8 (153)	17.1±10.8 (118)	0.014
5 (mg/dL)	10.7±7.8 (135)	13.9±8.8 (106)	0.004

Results expressed as the mean±SD (number of measurements).

Table 3 - Values of the area under the ROC curve, sensitivity, specificity, and best cutoff points

ROC curve	AUC (95% CI)	Sensitivity	Specificity	Cutoff (mg/dL)
CRP day 1	0.53 (0.43-0.62)	0.26	0.88	6.12
CRP day 2	0.51 (0.41-0.60)	0.67	0.42	18.6
CRP day 3	0.52 (0.43-0.61)	0.57	0.56	13.6
CRP day 4	0.51 (0.41-0.60)	0.42	0.65	14.2
CRP day 5	0.59 (0.48-0.68)	0.58	0.62	9.10

CRP - C-reactive protein; ROC curve - receiver operator characteristic curve; AUC - area under the ROC curve; and 95% CI - confidence interval of 95%.

Table 4 - Distribution of pathogens among the groups

Agents	Pulmonary sepsis	Abdominal sepsis
Klebsiella sp.	13	20
Escherichia coli	5	17
Pseudomonas aeruginosa	9	11
Staphylococcus aureus	8	7
Acinetobacter baumannii	9	4
Streptococcus pneumoniae	6	7
Proteus mirabilis	0	7
Candida sp.	0	6
Serratia marcenses	1	3
Citrobacter sp.	3	2
Enterococcus sp.	1	2
Enterobacter sp.	2	1
Strenotrophomonas maltophilia	1	0
Others	4	8
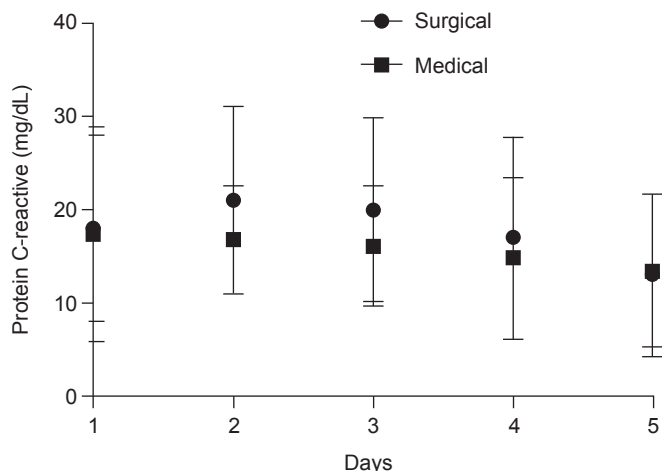
Figure 2 - Values of C-reactive protein (mg/dL) (mean and standard deviation) in the medical (n=16) and surgical (n=134) patients in the abdominal sepsis group.

Of the subjects with abdominal sepsis, 134 (89.3%) were surgical patients, and 16 (10.7%) were medical patients.

The demographic and clinical data are presented in table 1 according to the infection site. More cases of nosocomial infection were observed in the pulmonary sepsis group, and these patients required mechanical ventilation for a significantly longer time than did the group with abdominal sepsis.

The serum CRP concentrations were significantly higher in the group with abdominal sepsis than in the group with pulmonary sepsis during the first five days of sepsis progression (Table 2).

The values of the area under the ROC curve, sensitivity, specificity, and best cutoff points are listed in table 3.

Figure 2 depicts the serum CRP levels in the surgical and nonsurgical patients. There were no statistically significant differences between these groups. Table 4 lists the pathogens that were found in the patients from both groups.

DISCUSSION

CRP is a biological marker for inflammation and has been used extensively to monitor the progression of infectious and inflammatory diseases. The present study evaluated the correlation between the serum CRP levels and the infection sites that were more frequently associated with the occurrence of sepsis in a surgical or mixed ICU. The serum CRP concentrations were significantly higher in the patients with abdominal sepsis than in the patients with pulmonary sepsis during the first five days of sepsis progression. However, the values of the area under the ROC curve were low, suggesting limited accuracy of CRP for distinguishing the infection sites.

Previous studies have demonstrated the utility of serial CRP measurements as a tool for the diagnosis and monitoring of the response to treatment in several conditions, such as community-acquired pneumonia, nosocomial pneumonia, bloodstream infections, and sepsis.[10-16] Different patterns in the CRP kinetics correlate with differences in the adequacy of antibiotic therapy and in outcomes. However, to our knowledge, studies evaluating the serum CRP concentrations in patients with sepsis as a function of the infection site are not available in the literature.

Several conditions may interfere with the CRP kinetics in critically ill patients, including age, comorbidities (e.g., deep-vein thrombosis and cancer), and certain therapeutic interventions (e.g., blood-product transfusions), which increase the CRP levels, in addition to the presence of acute liver failure, which causes decreased serum CRP levels.[20-24] The use of anti-inflammatory drugs may also alter the serum CRP levels.[25,26]

In the present study, the patients with abdominal sepsis had significantly higher serum CRP levels than the patients with pulmonary sepsis. One possible explanation for this phenomenon is surgical trauma in the patients with abdominal sepsis. Surgical trauma causes significant increases in CRP levels compared with the preoperative values, especially on the second day after the trauma, even in non-infected patients; thus, such a mechanism may be responsible for the higher CRP values in abdominal sepsis.[27] However, in this study, the analysis of serum CRP levels in the surgical and non-surgical patients with abdominal sepsis revealed no statistically significant differences, which was most likely due to the small number of non-surgical patients in the sample. However, in children with perforated appendicitis, the time required for CRP normalization did not differ between the surgical and laparoscopic treatments.[28]

Several studies have also evaluated the CRP levels in abdominal sepsis.[27,28] The CRP levels correlate well with the severity of infection in patients with acute appendicitis.[29] Abdominal sepsis is a serious problem in peritoneal dialysis patients, and in these cases, the catheters should always be removed. In peritoneal dialysis patients, the CRP levels were much higher in patients with peritonitis than in the controls.[30] The elevated CRP levels were reported to be the best predictor of spontaneous bacterial peritonitis in asymptomatic patients with decompensated cirrhosis.[30]

Serial CRP measurements are useful during the first week after surgery because they may indicate postoperative septic complications. Despite higher levels after surgical trauma, a persistently elevated pattern from the fourth day or a drop followed by an increase may be indicative of infectious complications.[31] CRP levels of >15 mg/dL or a decrease of <50% on the fifth day have been reported in surgical patients with septic complications.[32]

Of the patients with nosocomial pneumonia, the group with a pattern of poor CRP responses had a worse outcome, with higher overall mortality attributed to pneumonia, when compared with the group with a good CRP response pattern; additionally, there was an association between the poor response and lower adequacy of antibiotic therapy [15] In another study of patients with ventilator-associated pneumonia (VAP), the authors defined the fourth day as the optimal point for the differentiation of patients with worse versus better prognoses.[33] The researchers observed that there were no deaths in the patients with good CRP responses, whereas the mortality rate was nearly 75% in the patients with poor responses.[33] However, the patients in those studies did not had sepsis, which hinders the comparison with the present study because most of the patients progressed to septic shock and did not display improvements around the fourth day.

Despite the presence of significantly higher serum levels in the patients with abdominal sepsis, the accuracy of the CRP values for the differential diagnosis between pulmonary and abdominal sepsis could not be definitively established in this study. The main limitation was the retrospective nature of the analysis, with the loss of a large number of measurements. Furthermore, the CRP levels could not be correlated with surgical trauma because this information had not been evaluated and because the procedures or complications that could have interfered with the CRP kinetics were not identified in the medical records. However, studies conducted in ideal scenarios to assess the real significance of the CRP in discriminating the infection site (with all of the possible variables controlled) would have little applicability at the bedside. Therefore, other markers, such as procalcitonin and IL-6, should be investigated in future studies.

CONCLUSION

The accuracy of CRP for the differential diagnosis of pulmonary and abdominal sepsis is limited, although significantly higher serum levels were observed in patients with abdominal sepsis.

RESUMO

Objetivo: Avaliar os níveis séricos de proteína C-reativa em pacientes com sepse pulmonar e abdominal nos primeiros 5 dias de progressão da sepse.

Métodos: Estudo de coorte retrospectivo em hospital universitário. Foram selecionados 345 pacientes admitidos em unidade de terapia intensiva e diagnosticados com sepse de origem pulmonar ou abdominal. A dosagem sérica de proteína C-reativa foi realizada por imunoensaio turbidimétrico. Para análises da proteína C-reativa, o dia 1 foi definido como o do diagnóstico clínico da sepse.

Resultados: Foram avaliados 34 pacientes com sepse (9,8%), 114 com sepse grave (33,0%) e 197 com choque séptico (57,2%). A idade dos pacientes foram 56,4±19,8 anos. Concentrações séricas de proteína C-reativa foram mais elevadas no dia do diagnóstico de sepse no grupo com infecção de origem abdominal em comparação ao grupo com sepse pulmonar (17,8±10,1 mg/dL *versus* 14,9±11,1 mg/dL; p=0,025) e mantiveram-se significativamente mais elevadas nos primeiros 5 dias de evolução da sepse.

Conclusão: As concentrações séricas de proteína C-reativa foram significativamente mais elevadas nos pacientes com sepse de origem abdominal do que em pacientes com sepse de origem pulmonar nos 5 primeiros dias de evolução da sepse.

Descritores: Proteína c-reativa; Sepse/diagnóstico; Marcadores biológicos

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