Research Article

Diagnostic accuracy of c-reactive protein in immunocompromised patients with sepsis in intensive care units

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Abstract

Background: It is very crucial to recognize infection in immunocompromised patients. Since CRP levels rise significantly 24 to 48 hours after the onset of inflammation it can be employed as a useful indicator of sepsis. **Aims and Objective:** To find out the diagnostic utility of CRP in immunocompromised patients with sepsis. **Materials and Methods:** This was a cross-sectional study, which included immunocompromised patients with suspected sepsis. Patients were classified into two diagnostic groups: those with nonbacterial sepsis and those with bacterial sepsis, and the values of CRP were estimated. **Results:** Of 94 patients (63 men and 31 women) with a median age of 56 years (95% CI 53.9–59.3), 74 (78.5%) had immunosuppression with nonbacterial sepsis and 20 (21.4%) had immunosuppression with bacterial sepsis. CRP concentrations were higher in the group with bacterial sepsis [30.94 ng/ml (95% CI 25.13–36.74)] than those with nonbacterial sepsis [7.46 ng/ml (95% CI 7.05–7.87), $P < 0.0001$]. CRP concentrations that were >6 mg/L had 93.33% sensitivity but only 63.20% specificity for diagnosing sepsis. The accuracy of diagnosis was 87.23%. The area under the receiver-operating characteristic curve was 0.82 (0.72–0.92). **Conclusion:** Despite limited specificity in critically ill immunocompromised patients, CRP concentrations may help to rule out bacterial infection.

KEY WORDS: C-reactive protein; Immune deficiency; Bacterial sepsis; Non-bacterial sepsis

Introduction

Infectious complications in immunocompromised patients on long-lasting immunosuppressive treatments pose serious problems. Sepsis is a systemic inflammatory reaction that is triggered by an infective agent (such as bacteria, viruses, fungi, or parasites). Bacterial or fungal infections can be a serious consequence of immunosuppression, which can lead to morbidity or mortality.[1] Diagnosis of bacterial infections is sometimes challenging as clinical presentation of infections by different causative agents can be similar; for example, it may be difficult to differentiate viral from bacterial infections in certain instances.[2] Similarly, fungal infections represent cases in which delayed or inappropriately targeted treatments can have fatal consequences. The morbidity and mortality associated with infection acquired because of immunosuppression remain the greatest clinical problems of these patients. Early diagnosis of infection is required as there is initially a paucity of clinical information and that obtaining results for microbiological tests may take considerable amount of time. Under these circumstances, necessity calls for the availability of such a laboratory test that would assist the physician in decision making. Two such laboratory parameters that fit this purpose are C-reactive protein (CRP) and interleukin-6

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(IL-6).[3] CRP is an acute-phase protein used mostly as a biochemical inflammatory marker in cancer. Levels of CRP will significantly increase 24–48 h after the onset of inflammation. Serum concentrations of CRP are proportional to the degree of tissue damage and the activity of the basal malignant disease. IL-6 concentration presents with low specificity and furthermore, its estimation is costly.[4–6] Hence, the aim of our study was to check the diagnostic accuracy of CRP as a marker of inflammation or sepsis in immunocompromised patients.

Materials and Methods

This was a retrospective, cross-sectional study conducted in a tertiary-care hospital. A study protocol was designed before undertaking this study, and it was approved by institutional ethics review committee. CRP data of the patients was collected after applying inclusion and exclusion criteria. Because no extra samples were collected and patients' information were not disclosed, the consent form was waivered off. The study included 94 patients admitted within the first 24 h of developing signs of sepsis. Patients were classified into two diagnostic groups: (1) immunosuppression with nonbacterial sepsis and (2) immunosuppression with bacterial sepsis. Clinical and laboratory data collected included age, gender, and diagnosis on admission based on clinical symptoms. Samples were collected for cultures of blood and other body fluids, depending on the symptoms. Patients in whom the pathogen was not explicitly identified or in whom a suspicion of mixed pathogenic agent was held were excluded. Furthermore, patients with rheumatic disease, tissue injury, burns, and autoimmune disorders were also excluded from the study because CRP increases in these conditions as well. CRP levels were measured by latex slide agglutination method.

Statistical Analysis: Unpaired *t*-test was used to show significance of CRP levels between different groups. Receiver-operating characteristic curve (ROC) analysis of CRP was conducted, and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio were calculated. The entire data was analyzed using the software MedCalc, version 12.5. A *P*-value of <0.05 was considered to be significant.

Results

This study comprised 94 individuals (63 men and 31 women) between the age of 30 and 80 years with a median age of 56 years (95% CI 53.9–59.3) of which 74 patients (78.5%) had immunosuppression with nonbacterial sepsis. Causes of immunosuppression were hematological disorders (34 patients, 36.1%), solid cancers (21 patients, 22.3%), HIV infection (14 patients, 14.9%), and fungal infection (5 patients, 5.2%). Bacterial sepsis was diagnosed in 20 patients (21.4%) (Table 1).

The CRP values for the bacterial sepsis group and nonbacterial sepsis group are given in Table 2. In the case of bacterial sepsis group, the upper 95th percentile was 36.74 mg/L as compared to 7.87 in the case of nonbacterial sepsis group. To find out whether there was any correlation of serum CRP levels in between bacterial sepsis group and nonbacterial sepsis group, unpaired *t*-test was performed and *P*-value was derived. A *P*-value of <0.001 suggested significant difference in values of CRP between these two groups. It was obvious that values of CRP were significantly higher in case of bacterial sepsis group as compared to nonbacterial sepsis group (Figure 1).

The ROC curves were constructed to test the performance of CRP to diagnose sepsis. By taking cutoff as >6 mg/L, the area under ROC curve was 0.82 (95% CI 0.72–0.92) (Figure 2). Sensitivity, specificity, NPV, PPV, positive likelihood ratio, and negative likelihood ratio calculated from the ROC curve were 93.3%, 63.2%, 92.7%, 68.6%, 2.22, and 0.12 respectively (Table 3). Finally, diagnostic accuracy was calculated, which was found to be 87.23%.

Discussion

Severe sepsis may result in systemic inflammation, multiorgan failure, and septic shock. It is one of the major health concerns worldwide and also the predominant reason for intensive care unit (ICU) admission and a leading cause of mortality in critically ill patients despite the use of modern management strategies.[7] Early diagnosis of sepsis may be challenging as clinical presentations are often nonspecific, bacterial cultures are time-consuming and laboratory tests lack sensitivity and

Table 1: Proportions of immunosuppressive patients who had classified into two subgroups.

Classification	Diagnoses	Patients, N (%)	Males	Females
Immunosuppresion with non-bacterial sepsis (N= 74)	Hematological disorders	34 (36.1)	27	07
	Solid tumors	21 (22.3)	14	07
	HIV infection	14 (14.9)	07	07
	Candida Albicans	2 (2.1)	01	01
	Pneumocystis Jirovecii	2 (2.1)	01	01
	Aspergillus Fumigatus	1 (1)	01	00
Immunosuppresion with bacterial sepsis (N= 20)	Enterobacteria	8 (8.5)	05	03
	Pseudomonas Aeruginosa	5 (5.4)	03	02
	Streptococcus	4 (4.3)	02	02
	Coagulase negative Staphylococcus	3 (3.2)	02	01

Table 2: comparison of serum CRP levels between bacterial sepsis and non-bacterial sepsis study group.

Variables	Bacterial sepsis	Non-bacterial sepsis
Sample size	20	74
Mean value (mg/L)	30.94	7.46
95% Confidence interval	25.13 to 36.74	7.05 to 7.87
t value	-5.598	
Degree of Freedom	131.0	
P value	P = <0.001	

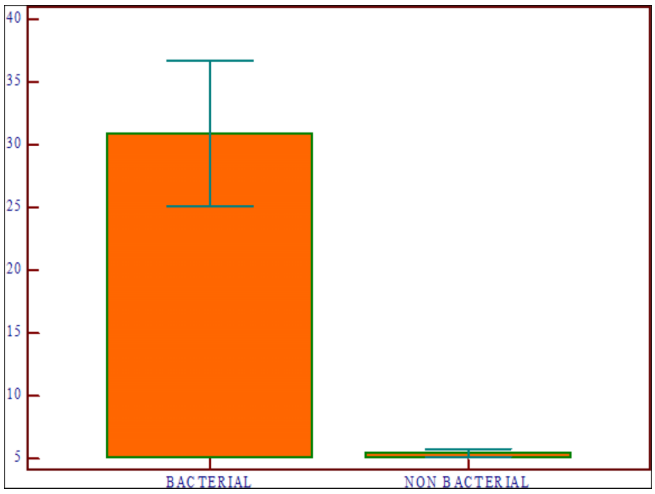

Figure 1: comparision of serumCRP levels between bacterial sepsis and non-bacterial sepsis study group.

specificity. The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, humoral and cellular reactions, and circulatory abnormalities.[8,9] To reduce the morbidity and mortality associated with sepsis, there is an urgent requirement for effective markers for the diagnosis and monitoring of sepsis.

The diagnosis of sepsis and evaluation of its severity are complicated by the highly variable and nonspecific nature of the signs and symptoms of sepsis, which may lead to delay in the diagnosis and subsequent treatments have been shown to increase mortality. However, the early diagnosis and stratification of the severity of sepsis is very important, increasing the possibility of starting timely and specific treatment.[10] In this study, it was observed that the serum CRP concentrations were significantly higher in the bacterial sepsis group than in the nonbacterial sepsis group with good accuracy of diagnosis. A CRP value above 6 mg/L was highly predictive of infection

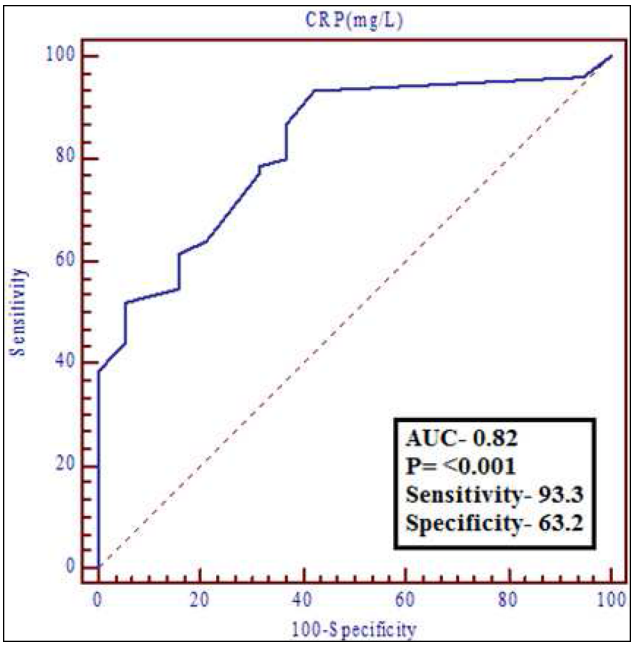

Figure 2: ROC curve for CRP for the diagnosis of sepsis:

with high sensitivity but poor specificity when performed within the first 24 h of developing signs of sepsis.

Chan et al.[11] conducted a study in 150 patients with bacterial infections and levels of CRP were estimated. The sensitivity, specificity, NPV, and PPV were 67.1%, 94.8%, 67.9% and 94.6% respectively, whereas the area under ROC curve was 0.88. In case of our study, the corresponding values were 93.3%, 63.2%, 92.7%, and 68.6% respectively, whereas the area under ROC curve was 0.82. In the study of Chan et al.[11] specificity and PPV were higher as compared to our study but sensitivity and NPV were lower. For effective management in emergency department, NPV is most essential as negative CRP value helps to rule out sepsis.

In a study conducted by Ugarte et al.[12], in patients with sepsis, the sensitivity and specificity of CRP were 71.8% and 66.6%, respectively, whereas in the similar study conducted by Suprin et al.[13] sensitivity and specificity of CRP were both 74%. Muller et al.[14] conducted a study in which sensitivity and specificity of CRP were 71% and 78%, respectively. In this study, sensitivity of CRP is higher as compared to earlier-mentioned studies although having lower specificity.

Some studies have proposed CRP as a biological marker of infection and a diagnostic criterion for sepsis, but others have drawn attention to its limitations such as its poor diagnostic

Table 3: Sensitivity, Specificity, Diagnostic Accuracy, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (PLR), Negative Likelihood Ratio (NLR) and Area Under the Curve (AUC) of CRP for the diagnosis of sepsis.

Parameter	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)	PPV	NPV	PLR	NLR	AUC
CRP (mg/L)	93.3	63.2	87.23	68.6	92.7	2.22	0.12	0.824

specificity and slow kinetics. CRP values cannot be used in isolation to obtain a specific diagnosis, although their value in infectious diseases is beyond doubt. CRP induction requires IL-6 and either IL-1 or tumor necrosis factor-alpha. Therefore, CRP synthesis and secretion usually reflect proinflammatory cytokine production and may be considered its surrogate marker. It perhaps is not surprising, therefore, that the search for a highly accurate biomarker of sepsis has become one of the holy grails of medicine.

Conclusion

CRP may help to rule out bacterial infection in immunocompromised patients admitted to the ICU as the chances of false-negative results are less. Although the performance of CRP concentrations as a diagnostic tool in this setting was limited because of the chances of false-positive results and small study group, we believe that it should be investigated further in a larger study, and that an interventional study of antibiotic prescriptions guided by repeated CRP measurements in non-immunocompromised patients is required.

References

1. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546–54.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–10.
3. Hansson LO, Lindquist L. C-reactive protein: its role in the diagnosis and follow-up of infectious diseases. Curr Opin Infect Dis. 1997;10:196–201.
4. Lehrnbecher T, Venzon D, de Haas M, Chanock SJ, Kuehl J. Assessment of measuring circulating levels of interleukin-6, interleukin-8, C-reactive protein, soluble Fc gamma receptor type III, and mannose-binding protein in febrile children with cancer and neutropenia. Clin Infect Dis. 1999;29:414–9.
5. Katz JA, Mustafa MM, Bash RO, Cash JV, Buchanan GR. Value of C-reactive protein determination in the initial diagnostic evaluation of the febrile, neutropenic child with cancer. Pediatr Infect Dis J. 1992;11:708–12.
6. Engel A, Mack E, Kern P, Kern WV. An analysis of interleukin-8, interleukin-6 and C-reactive protein serum concentrations to predict fever, gram-negative bacteraemia and complicated infection in neutropenic cancer patients. Infection. 1998;26:213–21.
7. Farag NA, Taema KM, Abdel-Latiff E, Hamed G. Differentiating sepsis from non-infective systemic inflammatory response syndrome: comparison between C-reactive protein and Leptin. Egypt J Crit Care Med. 2013;1(3):111–118.
8. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003;348(2):138–50.
9. Gullo A, Bianco N, Berlot G. Management of severe sepsis and septic shock: challenges and recommendations. Crit Care Clin. 2006; 22(3):489–501.
10. Zambon M, Ceola M, Almeida-de-Castro R, Gullo A, Vincent JL. Implementation of the Surviving Sepsis Campaign guidelines for severe sepsis and septic shock: we could go faster. J Crit Care. 2008;23(4):455–60.
11. Chan Y, Liao H, Tsay P, Chang S, Chen J, Liaw S. C-reactive protein as an indicator of bacterial infection of adult patients in the emergency department. Chang Gung Med J. 2002;25(7):437–44.
12. Ugarte H, Silva E, Mercan D, De Mendonca A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. Crit Care Med. 1999;27:498–504.
13. Suprin E, Camus C, Gacouin A, Le Tulzo Y, Lavoue S, Feuillu A, et al. Procalcitonin: a valuable indicator of infection in a medical ICU? Intensive Care Med. 2000;26:1232–8.
14. Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med. 2000; 28:977–83.

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