DIAGNOSTIC SIGNIFICANCE AND DETERMINATION OF C-REACTIVE PROTEIN (CRP) IN ADULT PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA

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ABSTRACT

OBJECTIVE: to study the diagnostic significance and determination of serum C-reactive protein (CRP) levels in patients with community acquired pneumonia (CAP) at the time of diagnosis and compared it with CRP of healthy controls.

METHODOLOGY: This study was conducted from December 2005 to Dec 2009 on 162 adult patients and 30 (males=15, females=15) healthy controls. All microbiological assays were performed according to standardized procedures; whereas CRP was measured in serum samples by an automated turbidimetric method with normal reference of ≤ 5.0 mg/L.

RESULTS: A total of 85 patients (52.46%) had an identifiable etiology with bacterial pathogens as the causative agents, 31 (19.31%) had viral origin, 10 (6.17%) had other bacterial pathogens and 36 patients (22.22%) with negative microbiological findings. Mean serum CRP levels were 101±15.60 mg/L, 84.50±12.60 mg/L,76.50±11.60 mg/L and 90.35±11.50 mg/L, 85.10±10.15 mg/L & 79.10±15.20 mg/L for Klebsiella pneumonia, Streptococcus pneumonia, Haemophilus influenzae alone and in combination with other pathogens respectively. Mean serum CRP was 60.45±9.10 mg/L in viral etiology only and 4.10 ± 2.25 mg/L in controls. CRP values were comparable in different etiologic groups of bacterial origin, except Streptococcus pneumoniae and Klebsiella pneumoniae groups (P<0.05), whereas highly significant when compared viral etiology, other pathogens (P<0.01) and negative microbiological findings (P<0.001).

CONCLUSION: In adult patients with CAP and bacterial pneumonic pathogens as the causative agents, serum CRP levels are greater, ranging between 76.50±11.60 to 101±15.60 mg/L and thus seems to predict severity of illness and assisting in deciding the appropriate site of care, whether hospital or home.

KEY WORDS: C-reactive protein (CRP), Community-acquired pneumonia (CAP), bacterial pathogens.

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INTRODUCTION

Infections of the lower respiratory tract are common in the communities and comprise both acute bronchitis and pneumonia[1-3]. In this regard it is reported that the annual incidence rate of community-acquired pneumonia (CAP) in adults varies between 1.6 and 13.4 per 1,000 population, with hospitalization rates ranging between 22% and 51%[4,5]. Community-acquired pneumonia (CAP) is documented to be the major cause of death in the western world and accounts for an increasing number of ≥20 admissions per 1,000 population annually[6,7]. Consequently, it was noteworthy that management of severe CAP accounts for high utilization of healthcare resources and antibiotic usage, leading to a risk of elevating drug-resistance[6,8,9].

It was discussed thoroughly that differentiating between bronchitis and pneumonia by patient's history and physical examination is sometimes challenging issue for clinicians. Hereafter, several studies show that making a diagnosis of pneumonia, defined as a new infiltrate on a chest radiograph, on the basis of clinical findings is sometimes, complicated[1,10,11]. Henceforth, differentiation of pneumonia from acute bronchitis is extremely significant because of the remedial outcomes.[1] It is well documented that pneumonia elicits a powerful inflammatory response[6] with the release of inflammatory mediators from activated

mononuclear phagocyte cells. Of these mediators, inteleukin-6 is a major inducer of acute-phase proteins, in addition to the C-reactive protein (CRP)[6,9]. An early analysis of serum concentrations of CRP of patients between 24 to 48 h, of is a well-established laboratory tool for the diagnosis and monitoring of different acute inflammatory processes. It has been strongly established that the determination of the serum concentration of C-reactive protein (CRP) is a rapid, simple and inexpensive procedure to assess progression of treatments.[1,4,6] Additionally consecutive CRP measurements have become routine clinical practice in the follow-up of patients hospitalized with severe infections and/or CAP.[1,4,6,12] It has been emphasized that the prognosis of CAP is dependent on early diagnosis and treatment, but, despite advances in diagnostic testing, most investigators cannot identify a specific etiology for CAP in up to half, or more, of all patients.[4,13] It is interesting to note that the relationship between serum CRP and patients with CAP, that requires hospitalization has been well reported in earlier studies,[4,14-19] still the potential of acute-phase protein levels as early indicators of etiology and outcome of CAP in population-based studies has not been thoroughly assessed[4]. Moreover, despite its frequent use, evidence on the thorough usefulness of CRP analysis or consecutive measurements for severe CAP is lacking. In this regard, few studies have addressed CRP kinetics in the follow-up of CAP previously, and these are on a relatively small scale and have not taken etiology on broader perspective into consideration.[6,18,20] Interestingly, a more recent study has pointed out that elevated serum levels of CRP, interleukin (IL)-6 or, procalcitonin (PCT) are associated with poor prognosis and thus a higher risk of treatment collapse.[6,21] Therefore the aim of the present study is to investigate the usefulness of serum CRP levels in patients with CAP at the time of diagnosis and to compare it with CRP of healthy control subjects. In addition, as per pointed out in an earlier study,[4] we also investigated the hypothesis that serum CRP levels could facilitate the assessment of etiologic diagnosis and to predict severity of outcome.

METHODOLOGY

Selection of Patients' and Protocols:

Protocols of Almirall et al[4] were followed for all procedural steps to ensure standardization. Adult patient selection, age-matched control, clinical information and data collection was done according to prescribed procedures[4]. This study was conducted from December 2005 to Dec 2009, at department of biochemistry laboratory services, Liaquat national hospital and medical college, Karachi Pakistan. Data were also obtained by review of medical records and LAN information system of laboratory. The information as per instructions[4] was collected from individuals such as age, gender; number of co-morbid conditions, including diabetes mellitus, heart disease (e.g, suspicion of congestive heart failure), chronic bronchitis, diagnosed asthma, lung tuberculosis, any neurologic, gastric, hepatic disease or symptoms, history of smoking and alcohol consumption; radiographic findings; microbiological diagnosis; and decision about inpatient care according to risk factors defined by Fine et al.[4,22] Controls were aged-matched adult hospital staff, n = 30 (males = 15, females = 15).

Diagnostic Criteria and inclusions:

All diagnostic and inclusion criteria were observed according to Almirall et al[4]. One hundred and sixty two (n = 162) patients were included in the study and classified according to presence of pathogens/etiology in individual capacity as well as in combination with other organisms.

CRP and microbiological Assay:

All microbiological assays were performed according to earlier described procedures, whereas CRP was measured in serum samples by an automated turbidimetric method on Hitachi 912 chemistry analyzer (Roche Diagnostics, Basil). The cut off value of the assay was ≤ 5.0 mg/L. To assess the usefulness of serum CRP levels, study subjects were divided into five groups as per described protocols[4,22]: (1) patients with confirmed CAP and related pathogens; (2) patients with viral etiology; (3) patients with pathogens other than those causative of pneumonia; (4) negative microbiological findings and (5) healthy subjects. In the group of 162 patients with a confirmed diagnosis of CAP, blood samples for CRP assay were collected at the time of diagnosis. In healthy control subjects, a sample of blood for CRP assay was collected during initial interviews of each age-matched, sex-matched, and area matched control subjects, and was obtained in 30 persons.

RESULTS

A total of 85 patients (52.46%) had an identifiable etiology with bacterial pathogens as the causative agents whereas 31 (19.15%) with viral origin, 10 (6.17%) with other pathogens and 36 patients (22.22%) with negative microbiological findings. Streptococcus pneumoniae was the major bacteria causing infections in 35 patients, alone or combined with other bacteria, followed by Klebsiella pneumonia in 28 and Haemophilus influenzae in 25 patients. All three were also found associated with other causative bacteria. There were no major significant differences in serum CRP values when the different etiologic groups of bacterial origin were compared with each other except S.pneumoniae and K.pneumoniae groups ($P<0.05$), whereas highly significant when compared viral etiology, other pathogens ($P<0.01$) and negative microbiological findings ($P<0.001$). Mean serum CRP levels for Klebsiella pneumonia, Streptococcus pneumonia and Haemophilus influenzae (alone) were 101±15.60 mg/L, 84.50±12.60 mg/L and 76.50±11.60 mg/L respectively. While the mean serum CRP levels for Klebsiella pneumonia, Streptococcus pneumonia, Haemophilus influenza, in combination with other pathogens were 90.35±11.50 mg/L, 85.10±10.15 mg/L and 79.10±15.20 mg/L respectively. Slightly higher CRP levels were observed

in patients with pneumonia caused by S pneumoniae and H. influenzae than those in the remaining etiologies of bacterial origin (Table 1). Comparatively low levels of serum CRP values were observed in patients with viral etiologies, as well as in patients with negative microbiological findings. A total of 102 patients (62.96%) with confirmed CAP were admitted to the hospital (mean length of stay, 14.10 ± 4.52 days) of which 11 patients (6.79%) required ICU admission. Serum CRP values in hospitalized patients are given in Table 2. The patient at home care have comparatively low CRP levels (P<0.05) when compared with ICU stay of the patients.

DISCUSSION

Discovery of CRP in 1930 was a significant event as subsequently it was considered to be an initial nonspecific but sensitive marker of inflammation, thus named as "acute-phase protein".[23-25] There was a hypothetical suggestion that changes in plasma concentrations of CRP could be beneficial in recognizing some foreign pathogens. It is suggested many times that CRP has many patho-physiological roles in the inflammatory process[23]. During early research it was shown that it reacted with the pneumococcal C-polysaccharide in the plasma of patients during the acute phase of pneumococcal pneumonia and thus, it was identified as a laboratory test in the context of patients with suspicion or confirmed diagnosis of pneumonia. By the passage of time CRP has been routinely used as a diagnostic tool for determining the degree of activity, and as a therapeutic guide of a number of conditions that commonly lead to substantial changes in the plasma concentrations of acute-phase proteins, including rheumatic fever, allergic diseases, pneumoconiosis, and different infectious diseases such as tuberculosis, meningitis, poliomyelitis and infectious mononucleosis.[23]

In the present study we have reported serum CRP levels in patients with pneumonia acquired through community-means according to clinical data obtained from a population and laboratory studies. The present results provide strong evidence for the usefulness of CRP assay, somewhat in the diagnosis of CAP as well as assessment of the severity of CAP. Patients with confirmed CAP and diagnosed bacterial etiology showed higher CRP levels (76.50 ± 11.60 to 101.25 ± 15.65 mg/L) than patients with etiology of viral (60.45±9.10 mg/L) and other pathogenic origin (65.15 ± 12.25 mg/L). Moreover, on the other hand, CRP levels in CAP patients that were hospitalized, either in wards or ICU, showed higher CRP levels than those who were treated as outpatients or stayed at home. CRP levels in healthy people, who were selected from same population but devoid of any apparent and microbiological signs of CAP, was noted to be 4.10 ± 2.25 mg/L. As suggested earlier, the data indicate that a CRP value below this cut off point practically excludes the diagnosis of CAP. It is well argued that in the presence of a clinical picture compatible with pneumonia, serum CRP levels have been shown to be useful in confirming the diagnosis, since they were significantly higher in patients with true CAP than in those in whom the diagnosis was not confirmed at followup.[4]

Earlier studies also have established a correlation between CRP and infection of the lower respiratory tract, either CAP or non-pneumonic respiratory infection[4].

TABLE 1: SERUM CRP VALUES IN PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA ACCORDING TO CAUSATIVE PATHOGEN [N = 162]

Pathogens		Frequency (n=162)	Mean ± SD (mg/L)	P Value**
Streptococcus pneumonia	Combined with other bacteria	20	90.35 ± 11.50	< 0.001
	Alone	15	101.25 ± 15.60	<0.05
Haemophilus influenzae	Combined with other bacteria	16	85.10 ± 10.15	0.01
	Alone	09	84.50 ± 12.60	< 0.001
Klebsiella pneumoniae	Combined with Streptococcus pneumonia	14	79.10 ± 15.20	<0.01
	Alone	14	76.50 ± 11.60	<0.01
Viral etiology only		31	60.45 ± 9.10	< 0.001
Other pathogens		10	65.15 ± 12.25	<0.01
Negative microbiological findings		36	25.50 ± 4.70	< 0.001
Healthy Controls*		30	4.10 ± 2.25	

*Aged-matched adult hospital staff. **Comparison of CRP levels for each microorganism, alone or combined with other pathogens, with the remaining patients.

TABLE II: SERUM C-REACTIVE PROTEIN VALUES IN PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA ACCORDING TO SITE OF CLINICAL CARE

Site of Care		Frequency (n=162)	Mean ± SD	P value
Home		60	56.30 ± 8.10	< 0.01
Inpatient care	ICU	11	89.10 ± 8.65	< 0.01
	Hospital ward	91	84.55 ± 10.70	<0.05

In a previous study of lower respiratory tract infection[2], it was reported that 65% of patients with radiographically confirmed disease showed high serum CRP levels (ie, ≥ 50 mg/L). This report and the one reported earlier[4] are in agreement with our findings and suggestive of the fact that there is a certain relationship between the degree of infection and serum CRP concentrations. Moreover, another study[26] demonstrated a serum CRP level of ≥ 50 mg/L with specificity of 95% for the diagnosis of CAP in patients with respiratory infections. One of the important points which came out of several studies was the role of CRP in the detection of the etiology of CAP.[4,23] Previous publications have recognized that CRP could be useful to predict the pneumococcal etiology.[4,23] Furthermore, it is also helpful to differentiate pneumonia from acute bronchitis and also that higher levels were associated with bacteremia in pneumococcal pneumonia.[23] Furthermore, in this regard, Smith et al.[6,18] studied the usefulness of CRP as marker in a number of patients and concluded that CRP could be of aid to clinicians. Another study in a larger group of patients with severe CAP, admitted to the ICU, also showed that identification of CRP patterns may be of value in follow-up of treatment.[20] Comparative study in admitted patients and out patients was also tested for CRP level and noted that in these two conditions, two different CRP levels emerges. Henceforth, Castro-Guardiola et al[4,16] reported that for CAP diagnosed at the hospital emergency department, mean serum CRP levels of 181 mg/L were observed in cases of confirmed CAP, and Almirll et al.[4] reported that 138 mg/L was noted for those CAP patients that required ICU admissions.

In present study as regard the etiological agents, S pneumoniae and H.influenzae were found to be the most common causative agents, which is also mostly in agreement with previous findings.[4,5,27] In a number of other studies, when serum CRP values in different etiologic groups were studied, infections caused by S pneumoniae and L pneumophila caused a greater inflammatory response to infection, characterized by more noted increases in CRP levels.[4,28-31] Similarly in a recent study in which CRP levels were analyzed in 258 patients with CAP with a single etiologic diagnosis, the mean CRP values in the L pneumophila group were significantly higher than those in the group with other diagnoses.[32]

In present study the mean serum CRP level in patients with bacterial-pneumonia was 85.83±17.65 mg/L and noted to be moderately significant higher than found in the remaining patients of the rest of etiologies. Our findings have been supported by earlier studies as well.[4,17,18,33] Furthermore, it has been strongly suggested that there is a higher increase in CRP in CAP with pneumococcal bacteremia than other etiology[4,17]. In an another report, very low levels of CRP were found in patients with negative microbiologic findings, as well as comparatively lowest in those with infection caused by other pathogens, as well as in patients with viral infection.[4,33]

In conclusion, the present study suggests that in adult patients with symptoms of CAP, a high serum CRP level is a useful marker for assistance in admission and treatment. Moreover, in patients with radiographic evidence of pneumonia, serum CRP levels are greater when pneumonia pathogens were the causative agents. In these cases, serum CRP levels of 76.50±11.60 to 101.25±15.60 mg/L seem to predict severity of illness, in addition to assist in deciding on the appropriate site of care e.g., hospital or home. Present results are although in agreement with several previous findings, however, still needs larger cohort to sturdily advocate CRP as highly useful tool in the primary care setting for patients with suggestive clinical features of CAP.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

JAB: Conception and design, acquisition and analysis of data, drafting the manuscript, final approval of the version to be published

JMA: acquisition and analysis of data, final approval of the version to be published

ZIM: analysis of data, drafting the manuscript, final approval of the version to be published

AH: acquisition data, final approval of the version to be published

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