Diagnostic utility and Assessment of C-Reactive Protein (CRP) in patients with community acquired pneumonia.

1,2,4Junaid Mahmood Alam, 3Syed Riaz Mahmood, 4Marium Anwer, 4Nerissa Anwer Adam, 1Ishrat Sultana, 1,5Sarah Sughra Asghar  
1Aijaz Ahmed and 6Maqsood Ali Ansari.

ABSTRACT:
It has been researched and agreed upon that pneumonia elicits a powerful inflammatory response with the release of inflammatory mediators or biomarkers, such as acute-phase proteins, interleukin-6 and C-reactive protein (CRP) from activated mononuclear phagocyte cells. It is also known and recommended that the early analysis of serum concentrations of CRP is a significant tool for the diagnosis and monitoring of different acute inflammatory processes. Community-acquired pneumonia (CAP) is documented to be the major cause of death in the western world and effects increasing number of population annually. In present study we have investigated the suggested usefulness of serum CRP levels in patients with CAP at the time of diagnosis and compared it with CRP of healthy controls. One hundred and seventy one (n = 171) 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. 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. A total of 87 patients (50.87%) had an identifiable etiology with bacterial pathogens as the causative agents whereas 32 (18.71%) with viral origin, 12 (7.0%) with other pathogens and 40 patients (23.39%) with negative microbiological findings. CRP values were comparable (non-significant) 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). In conclusion the study noted that in patients with confirmed evidence of pneumonia and bacterial pneumonic pathogens as the causative agents, serum CRP levels are greater, ranged between 95.28 ± 10.75 to 121 ± 18.35 mg/L and thus seems to predict severity of illness, in addition to assist in deciding on the appropriate site of care e.g., hospital or home.

Key Words: C-reactive protein (CRP), Community-acquired pneumonia (CAP), bacterial pathogens. Short Title: Assessment of C-Reactive Protein (CRP) in patients with community acquired pneumonia.

INTRODUCTION:
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%.1,2 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 annually3,4. 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-resistance3,5,6. In addition, as per description, infections of the lower respiratory tract
are common in the community and comprise both acute bronchitis and pneumonia\textsuperscript{7-9}. Differentiating between these two diagnoses by history and physical examination is a challenging issue for clinicians. Henceforth, 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, difficult\textsuperscript{7,10,11}. In this regard, differentiation of pneumonia from acute bronchitis is important because of the therapeutic consequences\textsuperscript{7}. It is well documented that pneumonia elicits a powerful inflammatory response\textsuperscript{3} with the release of inflammatory mediators from activated mononuclear phagocyte cells. Of these mediators, interleukin-6 is a major inducer of acute-phase proteins, in addition to the C-reactive protein (CRP)\textsuperscript{3,6}. The early determination, i.e, 24 to 48 h, of serum concentrations of CRP is a well-established laboratory tool for the diagnosis and monitoring of different acute inflammatory processes. It was strongly established that the determination of the serum concentration of C-reactive protein (CRP) is a rapid, simple and inexpensive procedure and consecutive CRP measurements have become routine clinical practice in the follow-up of patients hospitalized with severe infections and/or CAP\textsuperscript{1,3,7,12}. 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\textsuperscript{1,13}. It is interesting to note that the relationship between serum CRP and interleukin-6 values in patients with CAP, that requires hospitalization has been well reported in earlier studies\textsuperscript{1,14-19}, 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\textsuperscript{1}. Moreover, despite its frequent use, evidence on the 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\textsuperscript{3,20,21}. Interestingly, a more recent study has pointed out that high serum levels of CRP, interleukin (IL)-6 or, procalcitonin (PCT) are associated with a higher risk of treatment failures\textsuperscript{3,22}. 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\textsuperscript{1}, we also investigated the hypothesis that serum CRP levels could facilitate the assessment of etiologic diagnosis and to predict severity of outcome.

**MATERIALS AND METHODS:**

**Patients’ selection and StudyProtocols:**

Protocols of Almirall et al\textsuperscript{1} were followed for all procedural steps to ensure standardization. Patient selection, aged-matched control, clinical information and data collection was done according to prescribed procedures\textsuperscript{1}. The study period was December 2006 to March 2009. Data were also obtained by review of medical records and LAN information system of laboratory. The following information as per instructions\textsuperscript{1} was collected such as age, sex; number of co-morbid conditions, including diabetes mellitus, heart disease (ie, congestive heart failure), chronic bronchitis, diagnosed asthma, lung tuberculosis, neurologic disease, gastric disease and gastric symptoms, chronic liver disease, renal failure, depression/anxiety, and malignant neoplasm; history of smoking and alcohol consumption; radiographic findings; microbiological diagnosis; and decision about inpatient care according to risk factors defined by Fine et al.\textsuperscript{1,23}. Controls were aged-matched adult hospital staff, n = 25 (males = 15, females = 10).

**Diagnostic Criteria and Inclusions:**

All diagnostic and inclusion criteria were observed according to Almirall et al\textsuperscript{1}. One hundred and seventy one (n = 171) 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, Basel). 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: (1) patients with confirmed CAP and related pathogens; (2) patients with viral etiology; (3) patients with pathogens other than pneumonia causing; (4) negative microbiological findings and (5) healthy subjects. In the group of 171 patients with a confirmed diagnosis of CAP, peripheral blood samples for CRP assay were collected at the time of diagnosis. In healthy control subjects, a sample of peripheral blood for CRP assay was collected during initial interviews of each age-matched, sex-matched, and area matched control subjects, and was obtained in 25 persons.

RESULTS:
A total of 87 patients (50.87%) had an identifiable etiology with bacterial pathogens as the causative agents whereas 32 (18.71%) with viral origin, 12 (7.0%) with other pathogens and 40 patients (23.39%) with negative microbiological findings. Streptococcus pneumoniae was the major bacteria causing infections in 21 patients alone, followed by Haemophilus influenzae in 15 and Klebsiella pneumoniae in 10 patients. All three were also found associated with other causative bacteria, such as S.pneumoniae association with K.pneumoniae in 10 cases, association with Staphlococcus aureus, 4 cases and association with different viruses, 2 cases. Similarly H.influenzae was found associated with S.pneumonia in 5 cases, in association with influenza A, 4 cases and with virus, 1 case. There were no 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). 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). Low levels serum CRP values were observed in patients with viral etiologies, as well as in patients with negative microbiological findings. A total of 101 patients (59.06%) with confirmed CAP were admitted to the hospital (mean length of stay, 15.20 ± 2.60 days) of which 15 patients (8.77%) required ICU admission (Table 2). Mean CRP values in hospitalized patients were noted to be 110.15 ± 12.65 mg/L; whereas in ICU patients, 125.50 ± 13.35 mg/L. The patient at home care have comparatively low CRP levels, 89.60 ± 8.50 mg/L; which is moderately significant (P<0.05) when compared with ICU stay of the patients.

DISCUSSION:
CRP was discovered in 1930 and subsequently considered to be an early nonspecific but sensitive marker of inflammation, thus named “acute-phase protein”

An acute phase protein has been defined as the component, which shows an increasing trend in plasma (positive acute-phase proteins) or a decreasing trend (negative acute-phase proteins) by at least 25% during inflammatory disorders

There is a hypothesis speculation that changes in plasma concentrations of CRP could be beneficial when recognizing some foreign pathogens and activating the complement system when bound to one of its ligands. It is suggested many times that CRP has many pathophysiological roles in the inflammatory process

CRP was named as such because during investigations in 1930s and 1940s, it reacted with the pneumococcal C-polysaccharide in the plasma of patients during the acute phase of pneumococcal pneumonia

Thus, there after, CRP clearly was identified as a laboratory test in the context of patients with pneumonia. Then as time passed it began to be 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, myocardial infarction, asthma, leprosy, malignancy, congestive heart failure, blood diseases, allergic diseases, kidney diseases, pneumoconiosis,
and different infectious diseases (tuberculosis, meningitis, poliomyelitis, infectious mononucleosis, syphilis, etc).\textsuperscript{24}

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 (84.10 ± 12.60 to 121.45 ± 18.35 mg/L) than did patients with etiology of viral (75.20 ± 8.45 mg/L) and other pathogenic origin (85.45 ± 13.10 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 10.26 ± 5.21 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 follow-up\textsuperscript{1}.

Earlier studies also have established a correlation between CRP and infection of the lower respiratory tract, either CAP or non-pneumonic respiratory infection\textsuperscript{1}. In a study of lower respiratory tract infection\textsuperscript{27}, 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\textsuperscript{1} 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\textsuperscript{28} 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\textsuperscript{1,24}. Previous publications have recognized that CRP could be useful to predict the pneumococcal etiology\textsuperscript{1,24}. Furthermore it is also helpful to differentiate pneumonia from acute bronchitis and also that higher levels were associated with bacteremia in pneumococcal pneumonia\textsuperscript{24}. Several studies also suggested an indicative role of CRP in the treatment of CAP\textsuperscript{3}. In a recent report Bruns et al.,\textsuperscript{3} agreed that the results of few previous studies concerning the usefulness of consecutive CRP measurements in follow-up of CAP are in line with theirs and several related findings\textsuperscript{3,20-22}. Furthermore, in this regard, Smith et al.\textsuperscript{3,21} 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\textsuperscript{20}. In yet another study Menedez et al.\textsuperscript{22} have demonstrated that continuously high CRP level on days 1 and 3 in follow-up of patients with mild-to-severe pneumonia was independently associated with a higher risk of treatment failure. In the study done by Bruns et al.\textsuperscript{3} patients with an inadequate decline in CRP are highly suggestive of expressing a higher risk of treatment failure. A category of in patients and out patients was also tested for CRP level differentiation and found that the two situations bear two different CRP levels. Henceforth, Castro-Guardiola et al\textsuperscript{1,16} 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 Almirall et al.\textsuperscript{1} reported that 138 mg/L was noted for those CAP patients that required ICU admissions.

As argued by several authors, the most outstanding result that was obtained in a number of very significant studies was the extreme increase in serum CRP values
in patients with CAP in whom the clinical condition was considered to be severe and they were admitted to the hospitals\(^1\). In addition, as stated earlier, serum CRP values showed an increasing trend if the need for ICU admission and/or poor outcome was considered (127 vs 138 mg/L, respectively). These increases, as recommended by Almirall et al.\(^1\), in CRP level according to the site of treatment credited the possibility of using serum CRP level at the time of diagnosis of CAP as a criterion of severity.

As regard the etiological agents, \textit{S. pneumoniae} and \textit{H. influenzae} were found to be the most common causative agents in present study which is also mostly in agreement with previous findings\(^{1,2,29}\). In a number of other studies, when serum CRP values in different etiologic groups were studied, infections caused by \textit{S. pneumoniae} and \textit{L. pneumophila} caused a greater host response to infection, characterized by more important increases of CRP\(^{1,30-33}\). 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 \textit{L. pneumophila} group were significantly higher than those in the group with other diagnoses\(^34\).

In present study the mean serum CRP level in patients with bacterial-pneumonia was 103.28 ± 20.5 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\(^{1,17,18,35}\). Furthermore, it has been strongly suggested that there is a higher increase in CRP in CAP with pneumococcal bacteremia than other etiology\(^1,17\). In 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\(^{1,35}\). Almirall et al.\(^1\) and Macfarlane et al.\(^27\) also reported that in a group of patients with viral etiology and without etiologic diagnosis, a lower CRP level was found compared with that for bacterial pneumonia.

In conclusion, the present study suggest 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 95.28 ± 10.75 to 121 ± 18.35 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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Table 1:  Serum CRP Values in Patients with Community Acquired Pneumonia According to Causative Pathogens

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Cases, No.</th>
<th>Mean ± SD (mg/L)</th>
<th>P Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone or combined with other bacteria or viruses</td>
<td>21</td>
<td>110.10 ± 12.60</td>
<td>a</td>
</tr>
<tr>
<td>Only</td>
<td>16</td>
<td>121.45 ± 18.35</td>
<td>a,c</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone or combined with other bacteria or viruses</td>
<td>15</td>
<td>106.27 ± 13.20</td>
<td>a,b</td>
</tr>
<tr>
<td>Only</td>
<td>10</td>
<td>102.53 ± 10.66</td>
<td>a,b</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone or combined with S pneumoniae or viruses</td>
<td>10</td>
<td>95.28 ± 10.75</td>
<td>b,c</td>
</tr>
<tr>
<td>Only</td>
<td>15</td>
<td>84.10 ± 12.60</td>
<td>b,c</td>
</tr>
<tr>
<td>Viral etiology only</td>
<td>32</td>
<td>75.20 ± 8.45</td>
<td>a,b</td>
</tr>
<tr>
<td>Other pathogens</td>
<td>12</td>
<td>85.45 ± 13.10</td>
<td>b</td>
</tr>
<tr>
<td>Negative microbiological findings</td>
<td>40</td>
<td>40.50 ± 6.25</td>
<td>a,c</td>
</tr>
<tr>
<td>Total patients</td>
<td>171</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy Controls*</td>
<td>25</td>
<td>10.26 ± 5.21</td>
<td></td>
</tr>
</tbody>
</table>

*Aged-matched adult hospital staff. **Comparison of CRP levels for each microorganism, alone or combined with other pathogens, with the remaining patients. aP< 0.001, bP<0.01, cP<0.05 and NS = non-significant

Table 2:  Serum C-Reactive Protein Values in Patients with Community Acquired Pneumonia According to site of clinical care.

<table>
<thead>
<tr>
<th>Site of Care</th>
<th>Cases, No.</th>
<th>Mean ± SD</th>
<th>P Value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I-Home</td>
<td>70</td>
<td>89.60 ± 8.50</td>
<td>a,b</td>
<td></td>
</tr>
<tr>
<td>II-Inpatient care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>15</td>
<td>125.50 ± 13.35</td>
<td>a</td>
<td></td>
</tr>
<tr>
<td>Hospital ward</td>
<td>86</td>
<td>110.15 ± 12.65</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>III-Total</td>
<td>171</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^aP< 0.01, ^bP<0.05