Consecutive Measures of CRP Correlate with Length of Hospital Stay in Patients with Community-Acquired Pneumonia

Raymond Farah[1,4], Rola Khamisy-Farah[2] and Nicola Makhoul[3,4]

[1]Department of Internal Medicine B, Ziv Medical Center, Safed, Israel
[2]Clalit Health Services, Akko, Israel
[3]Respiratory Intensive Care Unit, Galilee Medical Center, Nahariya, Israel
[4]Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

ABSTRACT: **Background:** Accurate diagnosis of community acquired pneumonia (CAP) is crucial to its proper management and to combating antibiotic resistance. Levels of C-reactive protein (CRP) have been shown to distinguish pneumonia from other pathological conditions and can be used to control the severity of infection during admission.

Objective: To investigate an association between consecutive measurements of CRP and the severity of CAP in hospitalized patients.

Methods: A total of 500 patients with CAP were admitted to the hospital. Traditional markers of inflammation including CRP, leukocyte count, body temperature, were measured on the first, second, and fifth days of hospitalization. Correlations between these measures and the length of the hospital stay were calculated.

Results: Mean levels of CRP, body temperature, and leukocyte count were significantly lower on the second day after hospital admission and even lower on the fifth day. A positive correlation of medium strength was found between the level of CRP on the second day of hospitalization and the length of hospital stay ($P < 0.001$, $r_s = 0.447$), and a negative correlation was noted between the decrease in CRP level from the first to second day and the length of hospital stay.

Conclusions: CRP levels correlated with body temperature and leukocyte count, traditional markers of inflammation. A greater decrease in CRP level between the first and second day of hospitalization was associated with shorter hospital stay and rapid improvement. These findings support the use of CRP as a marker for the severity and complication of CAP.

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KEY WORDS: antibiotic therapy, community acquired pneumonia (CAP), C-reactive protein (CRP), diagnosis, hospitalization

Lower respiratory infections, which result in pneumonia, are the third leading cause of death worldwide [1]. Lung infection is the only infectious factor of the top 10 causes of death in high-income countries [1]. Accurate diagnosis and appropriate management of community-acquired pneumonia (CAP) are crucial for reducing medical costs, length of hospital stay, mortality rates, and antibiotic resistance. The latter has become a public health problem on a global scale [2]. However, over- and underestimation of the severity of CAP is not uncommon, especially when based on clinical judgment alone [3]. In the absence of generally accepted criteria for determining the severity of CAP and the ensuing management of the infection, the search has intensified for reliable biomarkers for diagnosis, risk prediction, and disease management [4].

C-reactive protein (CRP) is an acute phase protein synthesized by the liver, primarily in response to interleukin-6. Its measurement is inexpensive and widely accessible. CRP levels have been shown to discriminate between pneumonia and healthy status [5,6], as well as between pneumonia and exacerbations of chronic obstructive pulmonary disease [7], heart failure [8], and asthma [9]. CRP levels have also been shown to distinguish between causative pathogens [5,10], including bacterial and non-bacterial causes [6,11]. A recent investigation of patients with CAP reported higher CRP levels at hospital admission among patients directly admitted to an intensive care unit (ICU), transferred subsequently to an ICU, or who died in the hospital [12].

The purposes of the current study were to investigate an association between consecutive measurements of CRP and the severity, complications, and prognosis of CAP, and to compare this biomarker with the traditional markers of inflammation: body temperature and leukocyte count.

PATIENTS AND METHODS

We conducted a prospective observational cohort study of patients hospitalized in the internal medicine department and the general and respiratory ICUs of one medical center between June 2012 and December 2014. Inclusion criteria were age over 18 years and the absence of any other infection. All patients had been diagnosed with CAP according to accepted clinical criteria: rise in body temperature, cough,

difficulty breathing, elevated white blood cell count, the presence of an infiltrate on chest X-ray, and symptoms onset before hospital admission. Exclusion criteria were the presence of a severe infection other than pneumonia; an active autoimmune disease such as rheumatoid arthritis; and any heart, kidney, and liver diseases. In addition, we excluded patients diagnosed with interstitial lung disease, cystic fibrosis, severe neutropenia (< 0.5 × 109 neutrophils/L), or human immunodeficiency virus infection or those known to be intravenous drug users. Patients with a pneumonia severity index (PSI) less than class IV and a CURB-65 score (confusion, urea, respiratory rate, blood pressure and age > 65 years) less than 3 points were excluded.

For each patient, CRP was measured by particle enhanced immunoturbimetric assay (Tina-quant CRP- latex; Roche Diagnostic Corporation, Indianapolis, IN, USA). The reference range for this assay is less than 5 mg/L. For each patient, CRP was measured at hospital admission, on the second day, and on the fifth day of hospitalization. For patients who stayed more than 5 days, CRP was measured at the time of discharge. In addition, albumin was measured on the first and last days of hospitalization, and leukocytes on the first, second, and fifth days, and at discharge. Body temperature was measured three times daily throughout hospitalization. The following demographic and clinical data were accessed: age; gender; history of smoking; the side of the body on which pneumonia was detected; and diagnoses of diabetes, chronic obstructive pulmonary disease, and cardiovascular disease. The outcomes investigated were length of hospital stay (LOS) and the need for mechanical ventilation. Medical treatment was administered according to hospital protocols, which included antibiotic treatment such as ceftriaxone and azithromycin, without regard to inclusion in the study.

All patients signed an informed consent and the ethics committee approved the study.

STATISTICAL ANALYSIS

Descriptive analysis included calculations of mean, standard deviation, median, minimum, and maximum. Correlations between variables were assessed using chi-square and Fisher's exact test.

Quantitative variables were described by means and standard deviations, medians and ranges. Qualitative variables such as gender and background diseases were described by frequency and percentage. At admissions, days two and five, and discharge, correlations were calculated for the examined measures: body temperature, white blood cell count, and CRP. The Pearson and Spearman correlation coefficient tests were used as appropriate. Applying the same statistical tests, correlations between changes in quantitative variables were calculated. We used four different thresholds of fractional decrease in CRP on the second day of admission (CRP2) of 25%, 30%, and 60%. Fractional decrease was calculated according to the following formula: (CRP1D-CRP2)/CRP1 × 100%.

RESULTS

Five hundred patients met the study criteria. Their demographic and clinical characteristics are presented in Table 1. Their distribution between the internal medical and ICUs is presented in Table 2, together with statistics on LOS. At hospital admissions, CRP was elevated in 499 (99.8%) patients. Only for one patient was the level within normal range (a patient admitted for other reasons, who developed pneumonia on the first day of hospitalization).

Table 1. Demographic and clinical data

Characteristic	Value
Male gender, n (%)	245 (49)
Age, years, mean ± SD (median)	63.4 ± 20.1 (68)
Smoking, n (%)	190 (38)
CURB-65	2.52
Diabetes, n (%)	140 (28)
Chronic obstructive pulmonary disease, n (%)	75 (15)
Cardiovascular disease, n (%)	225 (45)
Double sided pneumonia, n (%)	60 (12)
Left-sided pneumonia, n (%)	120 (24)
Right-sided pneumonia, n (%)	230 (46)
Positive blood culture, n (%) *Streptococcus pneumoniae* *Klebsiella pneumoniae* *Haemophilus influenza* *Mycoplasma pneumoniae*	105 (21) 10% 5% 4% 2%

CURB-65 = confusion, urea, respiratory rate, blood pressure and age › 65, SD = standard deviation

Table 2. Characteristics and symptoms of hospitalization

Department at admission	
Internal medicine, n (%)	455 (91)
Intensive care unit, n (%)	45 (9)
Length of hospital stay, days, mean ± standard deviation	7.5 ± 7.3
Up to 4 days, n (%)	155 (31)
More than 4 days, n (%)	255 (51)
Complications as empyema formation, n (%)	2 (0.004)
Required mechanical ventilation, n (%)	45 (9)
Non-survivors, n (%)	20 (4)
CRP in day 1 in non-survivors, n (%)	262 ± 91
CRP in day 5 in non-survivors, n (%)	233 ± 100
Frequent symptoms Productive cough, n (%) Fever, n (%) Dyspnea, n (%)	 400 (80) 460 (92) 150 (30)

CRP = C-reactive protein

Of the 500 patients, 300 were still in the hospital on the fifth day, and 200 of these were discharged after more than five days due to prolong fever or changing antibiotic treatment after excluding empyema. Mean levels of CRP, body temperature, and leukocyte count were significantly lower on the second day than at hospital admission, and on the fifth than on the second day [Table 3]. For those hospitalized more than five days, mean body temperature at hospital discharge was significantly lower than on the fifth day [Table 3].

Correlation was found between the level of CRP on the second day of hospitalization and the LOS ($P < 0.001$, $r_s = 0.447$). The higher the level of CRP, the longer the hospital stay. The decrease in CRP from the first to the second day of hospitalization correlated negatively – the smaller the decrease, the longer the hospital stay. Mean CRP levels were higher at hospital admission and on the second day of hospitalization for patients who were hospitalized for 5 or more days than for those hospitalized for fewer than 5 days.

Increased body temperature from the first to second day of hospitalization correlated positively with LOS ($P = 0.005$, 1-sided, $r_s = 0.364$). The strength of relationship was weak to medium. The greater the rise in temperature, the longer the hospital stay. A negative correlation was found between the level of albumin at hospital admission and LOS ($P < 0.001$, $r_s = -0.279$), the lower the level of albumin, the longer the hospital stay. No relation was found between the level of CRP at hospital admission and the need for mechanical ventilation during hospitalization. The two patients with empyema had a high level of CRP (> 300) with increment during the admission. CRP in non-survivors was more than 240 at admission and still high during the entire hospitalization.

To examine the associations of the different variables in CRP at the second day of hospitalization (CRP2) with the 30 day all-cause mortality, we performed multiple regression analysis [Table 4], which revealed that the following were associated with 30 day all-cause mortality in patients with complicated severe CAP according to CURB-65:

- Age: odds ratio (OR) of 0.43, 95% confidence interval (95%CI) 0.27–1.23, $P = 0.62$
- Male gender: OR of 2.10, 95%CI 1.78–2.80, $P = 0.029$
- Fractional decrease in CRP2 less than 25%: OR of 3.06, 95%CI 2.83–5.01, $P = 0.002$
- CURB-65 of 3 points or higher: OR of 5.68, 95%CI 5.30–6.34, $P < 0.001$

Table 3. Inflammatory measures during hospitalization

Laboratory Test	At admissions n=500	Day 2 n=500	Day 5 n=300	At discharge (for those hospitalized more than 5 days) n=200
CRP				
Mean ± SD	168 ± 83	114.6 ± 75.8*§	82.4 ± 74.5*§	48.6 ± 34.1§
Median (range)	151 (8–415)	95.5 (12–396)	59 (4–390)	39 (5–129)
Body Temperature, °Celsius				
Mean ± SD	38.3 ± 0.9	37.4 ± 0.6*§	36.7 ± 0.5*§	36.6 ± 0.3*§
Median (range)	38.4 (35–39)	37.5 (35–39)	37 (36–38)	36.7 (36–37)
Leukocytes (× 10^3/ml)				
Mean ± SD	13568 ± 6601	11503 ± 5277*§	10322 ± 3558.5*§	8506 ± 2541§
Median (range)	11750 (1900–40000)	10200 (740–24700)	9800 (2700–20400)	8100 (2300–14000)
Albumin, mg/dl				
Mean ± SD	3.6 ± 0.5	3.5 ± 0.5	3.4 ± 0.5	3.4 ± 0.5§
Median (range)	3.6 (2.7–4.8)	3.5 (2.5–4.8)	3.5 (2.5–4.6)	3.4 (2.5–4.4)

*P ‹ 0.05 in relation to the measurement at the previous time point, at least 1 day after admission (before the second day) or any value before the fifth day or before the discharge day

§P ‹ 0.05 in relation to the measurement at admissions, compared to the first value at admission

CRP = C-reactive protein, SD = standard deviation

Table 4. Multiple logistic regression analysis between the different variables and the 30-day all-cause mortality

Variables	OR (95%CI)	*P*
Age	0.43 (0.27–1.23)	0.62
Male gender	2.10 (1.78–2.80)	0.029
FD ‹ 25% in CRP2	3.06 (2.83–5.01)	0.002
CURB-65 › = 3 points	5.68 (5.30–6.37)	‹ 0.001

FD = fractional decrease, CRP2 = C-reactive protein on the second day of admission, OR = odds ratio, 95%CI = 95% confidence interval, CURB-65 = confusion, urea, respiratory rate, blood pressure and age › 65

DISCUSSION

In this study of patients hospitalized with pneumonia, CRP levels correlated with the traditional markers of inflammation (body temperature and leukocyte count), which supports the use of CRP as a marker for the severity of pneumonia. Others have found CRP to be a better marker of infection than temperature and leukocyte count [11,13].

In the current study, we performed consecutive testing of CRP rather than relying on laboratory tests at hospital admissions alone. We showed that the decrease in CRP levels from the first day until the second day correlated with a shorter hospital stay. Most investigations of associations between CRP levels and pneumonia were based on single measurements of CRP. Measurement of CRP has demonstrated effectiveness in distinguishing between CAP, which requires antibiotics, and other pathological conditions that do not require antibiotics [5,8,9]. However, in a study of elderly hospitalized patients with CAP, CRP at admission was not associated with the need for transfer to an ICU or with mortality [14].

The current study supports other investigations that have shown the effectiveness of consecutive measurements of CRP in distinguishing the severity of CAP. In a prospective study of 294 hospitalized patients, Menéndez et al. [15] found that CRP levels measured 72 hours after treatment initiation, together with clinical criteria, predicted the absence of severe complications of CAP. Furthermore, consecutive CRP measurements during

the first week of hospitalization have demonstrated usefulness for assessing the appropriateness of antibiotic treatment for CAP. Bruns et al. [10] found delayed normalization of CRP levels, specifically, a decrease by more than 60% in 3 days and by more than 90% in 7 days, to be associated with a higher risk of receiving inappropriate antibiotic treatment for severe CAP. Ruiz-González and co-authors [16] found that CRP levels at day 4 were useful in distinguishing between failure to respond to antibiotic treatment for CAP and slow response to treatment. Chalmers et al. [17] reported that a decrease in CRP levels of less than 50% within the first 4 days of hospitalization was associated with an increased risk for 30 day mortality and a need for mechanical ventilation or inotropic support. In contrast, we did not find any relationship between the changes in CRP and the need of mechanical ventilation.

The duration of hospital stay in our population, 5 or more days among 62% of the patients, is comparable to the average of 5 or more days reported in a review of studies conducted in the United States and Canada [18]. Furthermore, the 11% rate of admission to an ICU in the current study is within the 10–20% range reported in the same review [18].

The absence of data on the use of steroids is a limitation of this study. However, the effect of steroids on CRP levels is inconclusive, with some investigations showing them to influence CRP levels [10] and others not showing influence [19,20]. Furthermore, we did not consider causative pathogens in our interpretation of CRP levels, despite findings of their differential effects [10,21].

While singular measurements at hospital admissions have demonstrated the usefulness of CRP in the diagnosis of pneumonia, consecutive measurements support a role for this biomarker in the therapeutic management of this illness. We demonstrated the usefulness of CRP as a marker of disease progression already by the second day of hospitalization, as evidenced by the correlation with length of hospital stay. In addition to the clinical implications, appropriate initiation of antibiotic therapy has public health implications due to the importance of minimizing excessive antibiotic use.

CONCLUSIONS

CRP levels correlated with the traditional markers of inflammation (body temperature and leukocyte count). A greater decrease in CRP level between the first and second day of hospitalization was correlated with a shorter hospital stay. In borderline situations, such as in a case of sub-febrile temperature, a low CRP value made it easier to make a decision whether to discharge. These findings support the use of CRP as a marker for the severity and complications of pneumonia. Further investigation is needed, primarily to test the existence of correlation between CRP and other new inflammatory markers such as procalcitonin and clinical parameters, such as CURB-65 or PSI, to strengthen its effectiveness.

Correspondence
Dr. R. Farah
Dept. of Internal Medicine B, Ziv Medical Center, Safed 13100, Israel
Phone: (972-4) 682-8966
Fax: (972-4) 682-8116
email: raymond.f@ziv.health.gov.il

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