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Original

Usefulness of Serum C-reactive Protein in the Management of Adult Community-acquired Pneumonia

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Abstract: C-Reactive protein (CRP) is widely used as a marker of infection, but there is insufficient evidence as to its usefulness in patients with community-acquired pneumonia (CAP). In the present study, we investigated the clinical usefulness of CRP in a retrospective study of 242 patients aged ≥ 14 years who were hospitalized with CAP. Patients were classified into three groups according to the number of days between disease onset and the initial measurement of CRP as follows: Group 1, 0–1 day; Group 2, 2–4 days; Group 3, ≥ 5 days. Patients in Groups 2 and 3, who had more severe pneumonia, had higher CRP levels. Over time, CRP levels decreased in the responders in Groups 2 and 3; specifically, in Group 2, median CRP levels on Days 0, 3, and 7 were 9.85, 5.33, and 0.81 mg/dL, respectively, compared with 9.99, 4.29, and 0.70 mg/dL, respectively, in Group 3. In patients not responding to initial treatment, median CRP levels increased from Day 0 to Day 3 (4.32 vs. 11.70 mg/dL, respectively). In all non-responders, CRP levels on Day 3 were > 50% of levels on Day 0. In conclusion, when measured approximately 48 h after disease onset, CRP is useful for evaluating the severity of pneumonia and predicting the response to treatment. A good clinical outcome is likely when CRP levels on Day 3 are ≤ 50% of those on admission.

Key words: Community-acquired pneumonia, C-reactive protein, pneumonia, prognosis, severity

Introduction

C-Reactive protein (CRP) is a representative acute phase reactant and an important marker of acute inflammation[1)]. In Japan, CRP is a widely used indicator for the diagnosis of infectious diseases, as well as for evaluating patient responses to treatment. However, the clinical value of monitoring CRP in patients with infection has been questioned in the US, and CRP was not included in the Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults published in 2007[2)]. In addition, the 2005 Japanese Respiratory Society (JRS)

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Guidelines for the Management of Community-Acquired Pneumonia in Adults stated that there was no correlation between the severity of pneumonia and CRP levels[3]. However, subsequent studies reported that CRP is useful for evaluating the severity of pneumonia and the response to treatment[4-8], and this was stated in the 2008 JRS Guidelines for the Management of Hospital-Acquired Pneumonia in Adults[9]. Such contradictory reports may originate from a known characteristic of CRP, namely that CRP levels vary considerably at different stages of an illness[10]. In the present study, we divided patients with community-acquired pneumonia (CAP) into three groups according to the interval between disease onset and the initial measurement of CRP and investigated whether CRP levels on admission reflect the severity of pneumonia and whether changes in CRP levels after hospitalization reflect patient response to treatment.

Materials and Methods

Patients

The present study was a retrospective study performed in 299 patients with a diagnosis of CAP who had been admitted to Kawasaki Medical School Hospital or Showa University Hospital (Japan) between January 2004 and March 2009. In the present study, CAP was defined in accordance with the JRS Guidelines for the Management of Community-Acquired Pneumonia in Adults[3] as pneumonia in a patient who had not been hospitalized prior to its onset and who was carrying on normal activities of daily living. CRP levels were determined in all patients at the time of their admission to hospital (Day 0 CRP). Twenty-five patients who received steroid therapy were excluded from the study because steroids influence the kinetics of CRP. Another 32 patients with incomplete data were also excluded from the study, such that data for a total of 242 patients were available for evaluation. Microbiological investigations were based on bacteria isolated from the sputum or from blood cultures obtained upon hospital admission. In the case of *Streptococcus pneumoniae* and *Legionella pneumophila*, positive urinary antigen tests were also accepted.

The study protocol was approved by the ethics committee of our institution.

Methods

The severity of pneumonia in each patient was classified according to the A-DROP score (see Table 1)[3]. This scoring system was devised by modifying the CURB-65 score, which is a prognostic score for patients with CAP that was developed by the British Thoracic Society[11, 12]. An A-DROP score of 0 is defined as mild pneumonia, a score of 1–2 indicates moderate pneumonia, and a score of ≥ 3 indicates severe pneumonia. Because the Day 0 CRP levels would be influenced by the interval from the onset of pneumonia to hospital admission, patients were divided into the following three groups: Group 1, patients who were admitted to hospital on the day of onset or the following day; Group 2, patients admitted 2–4 days after the onset of pneumonia; and Group 3, patients admitted ≥ 5 days

Table 1. The A-DROP scoring system (from the Japanese Respiratory Society guidelines)

A : Age (male ≥ 70 years, female ≥ 75 years)
D : Dehydration or blood urea nitrogen ≥ 21 mg/dL
R : Respiratory failure (SaO_2 < 90%, PaO_2 < 60 mmHg)
O : Orientation disturbed (confusion)
P : Low blood pressure (systolic blood pressure < 90 mmHg)

Mild, none of the five criteria met ; Moderate, 1-2 criteria met ; Severe, 3 criteria met ; Extremely severe, 4-5 criteria met.

after the onset of pneumonia. The day of onset of pneumonia was defined as the day when fever ≥ 38℃, chest pain, purulent sputum, or difficulty breathing was noted by the treating physician in the patient's medical record. The relationship between the severity of pneumonia and Day 0 CRP levels was investigated in each group. In addition, Day 0 CRP levels were compared between the three groups. Changes in CRP levels over time were evaluated in relation to clinical outcome. Patients with defervescence (temperature < 38℃) and improvement of productive cough, chest pain, and dyspnea by Day 3 were defined as responders, whereas all other patients were defined as non-responders. Patients who exhibited minimal changes in their symptoms, making improvements in symptoms difficult to judge, were included in the responder group. CRP levels were determined on Days 0, 3, and 7 for the responders and on Days 0 and 3 for the non-responders, and the CRP profiles of the two groups were compared.

Statistical analyses were performed using JMP® 8.0.2 software (SAS Institute, Cary, NC, USA). The Wilcoxon test, Wilcoxon signed-rank test, and logistic regression analysis were performed as appropriate.

Results

The patients' clinical profiles are given in Table 2. Of the 242 patients in the study, 15 were classified as non-responders ; of these, 13 eventually improved after changes to their treatment and two died. The average age of the responders was 58.6 years, compared with 71.5 years in the non-responder group. Of the 242 patients, 29 were allocated to Group 1, 108 were allocated to Group 2, and 105 were allocated to Group 3. Analysis of the main co-morbidities did not reveal any significant differences between the responders and non-responders. *Streptococcus pneumoniae* was the most frequent isolate, followed by *Haemophilus influenzae* and *Mycoplasma pneumoniae*.

The relationship between the severity of pneumonia and Day 0 CRP levels in each group is indicated in Table 3. In Group 1, median Day 0 CRP levels of patients with mild, moderate, and severe pneumonia were 4.38, 6.88, and 0.67 mg/dL, respectively. There was no association between the severity of pneumonia and Day 0 CRP levels. In Groups 2 and

Table 2. Patient profiles

	All patients	Responders	Non-responders	*P*-value
No. patients	242	227	15 (2 deaths)	
Mean (median, range) age (years)	59.4 (63, 14–94)	58.6 (62, 14–94)	71.5 (78, 30–89)	0.0226
No. men (%)	133 (55)	127 (56)	6 (40)	0.2303
Severity of pneumonia†				0.1895*
Mild	80 (33%)	75 (33%)	5 (33%)	
Moderate	135 (56%)	129 (57%)	6 (40%)	
Severe	27 (11%)	23 (10%)	4 (27%)	
Days from onset until admission				0.0036*
0–1 (Group 1)	29 (12%)	27 (12%)	2 (13%)	
2–4 (Group 2)	108 (45%)	96 (42%)	12 (80%)	
≥ 5 (Group 3)	105 (43%)	104 (46%)	1 (7%)	
Main co-morbidities†				
Chronic lung disease				
COPD	35 (14%)	33	2 (13%)	0.8968
Asthma	20 (8%)	20	0 (0%)	0.1019
Old TB	9 (4%)	9	0 (0%)	0.2785
IIPs	6 (2%)	6	0 (0%)	0.3778
Others	4 (2%)	4	1 (7%)	0.2932
Congestive heart failure	28 (12%)	25	3 (20%)	0.4187
Cerebrovascular disorder	16 (7%)	16	0 (0%)	0.1453
Diabetes	13 (5%)	13	0 (0%)	0.1908
Chronic renal failure	7 (3%)	7	0 (0%)	0.3403
Pathogens isolated†				
Streptococcus pneumoniae	66 (27%)	64	2 (13%)	0.1805
Haemophilus influenzae	25 (10%)	23	2 (13%)	0.7036
Mycoplasma pneumoniae	23 (10%)	23	0 (0%)	0.0784
Moraxella catarrhalis	6 (2%)	6	0 (0%)	0.3778
Staphylococcus aureus	2 (1%)	2	0 (0%)	0.6122
Legionella spp.	1 (0%)	1	0 (0%)	0.7203
Others	6 (2%)	5 (2%)	1 (7%)	0.3640
None	114 (51%)	104 (46%)	10 (66%)	0.1152

In the present study, responders were defined as those patients with defervescence (temperature < 38°C) and exhibiting an improvement in symptoms by Day 3. All other patients were classified as non-responders.
* Comparison among the three groups.
† Data show the number of patients in each group, with percentages given in parentheses.
COPD, chronic obstructive pulmonary disease ; TB, tuberculosis ; IIPs, idiopathic interstitial pneumonia

3, median Day 0 CRP levels of patients with mild, moderate, and severe pneumonia were 4.88, 12.40, and 11.21 mg/dL, respectively, in Group 2 patients and 7.52, 11.58, and 13.53 mg/dL, respectively, in Group 3 patients. In Groups 2 and 3, Day 0 CRP levels were higher in patients with more severe pneumonia, and significant differences were found in Day 0 CRP levels between patients with mild pneumonia and those with moderate or severe pneumonia. The median Day 0 CRP level in patients with moderate or severe pneumonia in Groups 2

Table 3. Day 0 C-reactive protein levels, severity of pneumonia, and interval from the onset of pneumonia to hospital admission in the 242 patients evaluated in the present study

Group (interval from onset until admission)	Severity of CAP (*n*)	Median (range) Day 0 CRP (mg/dL)	*P*-value (Wilcoxon test)
Group 1 (0–1 days ; *n* = 29)	Mild (2)	4.38 (1.95–6.81)	0.4134
	Moderate (24)	6.88 (0.07–39.8)	0.7728
	Severe (3)	0.67 (0.12–16.73)	
Group 2 (2–4 days ; *n* = 108)	Mild (35)	4.88 (1.30–30.95)	0.0002
	Moderate (57)	12.40 (0.54–43.12)	0.0005
	Severe (16)	11.21 (4.23–34.89)	
Group 3 (≥ 5 days ; *n* = 105)	Mild (43)	7.52 (1.42–26.80)	0.0010
	Moderate (54)	11.58 (1.27–45.16)	0.0100
	Severe (8)	13.53 (3.44–19.58)	

CAP, community-acquired pneumonia ; CRP, C-reactive protein.

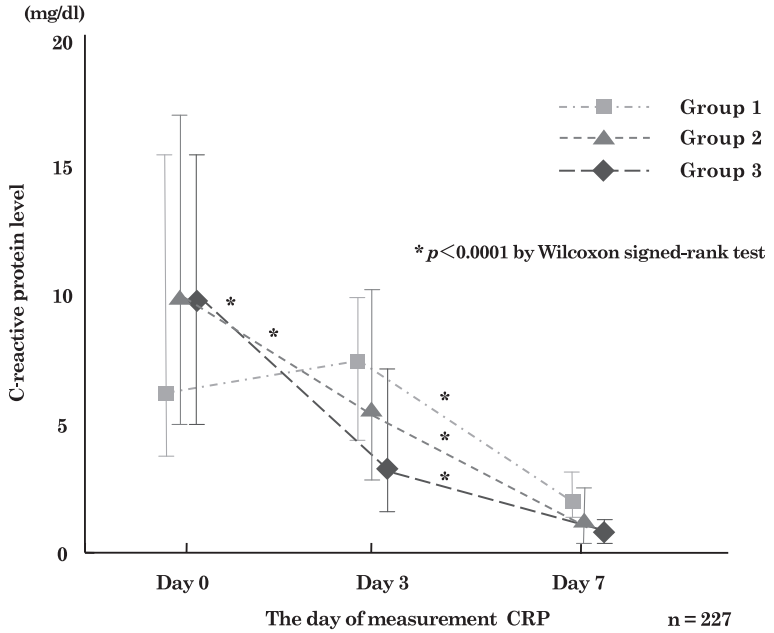

Fig. 1. Changes in C-reactive protein (CRP) levels in responders after the initiation of treatment.

and 3 was ≥ 10 mg/dL.

Figure 1 shows changes in CRP levels in responders with time. In Group 1, median [50% range] CRP levels on Days 0, 3, and 7 were 6.19 [3.63–15.27], 7.03 [4.58–9.58], and 1.44 [0.77–2.88] mg/dL, respectively, with a transient increase observed on Day 3. In Group 2, CRP levels on Days 0, 3, and 7 were 9.85 [5.11–18.44], 5.33 [2.36–9.81], and 0.81 [0.30–1.84] mg/dL, respectively, and in Group 3 the values were 9.99 [5.01–15.42], 4.29 [1.91–6.93], and 0.70 [0.31–1.97] mg/dL, respectively. A decrease in CRP levels over time was observed

Table 4. Changes in C-reactive protein (CRP) levels in relation to clinical outcome and percentage changes in CRP from Day 0 to Day 3 in patients in Groups 2 and 3 ($n = 213$)

Clinical outcome	*n*	Median CRP (mg/dL)			% Change in CRP on Day 3		
		Day 0 CRP	Day 3 CRP	*P*-value	< 50	50–100	> 100
Responders	200	9.97	4.88	< 0.0001	121	55	24
Non-responders	13	4.32	11.70	0.1465	0	5	8

In the present study, responders were defined as those patients with defervescence (temperature < 38°C) and exhibiting an improvement in symptoms by Day 3. All other patients were classified as non-responders.

Table 5. Univariate analysis of factors influencing the clinical course in patients in Groups 2 and 3 (n = 213)

Factor	Odds ratio	95% CI	*P*-value
Age	0.965	0.930–0.996	0.0240
Sex (male)	1.40	0.0449–4.48	0.5593
A-DROP score	0.785	0.498–1.29	0.3237
Day 0 CRP	1.05	0.977–1.16	0.1912
Day 3 CRP	0.823	0.735–0.908	< 0.0001
Day 0/Day 3 CRP ratio	9.91	3.64–36.9	< 0.0001

CI, confidence interval; CRP, C-reactive protein.

in Groups 2 and 3.

Comparisons of the percentage changes in CRP levels from Day 0 to Day 3 between the responders and non-responders are presented in Table 4. These comparisons were only made for patients in Groups 2 and 3 because there was no correlation between the clinical outcome and changes in CRP in Group 1 (Fig. 1). Among the responders, the median Day 0 CRP level was 9.97 mg/dL, which fell to 4.88 mg/dL on Day 3 ($P < 0.0001$). Compared with the CRP levels on Day 0, CRP levels were lower on Day 3 in 175 of 200 responders (87.5%). In contrast, among the non-responders, the median Day 0 CRP level was 4.32 mg/dL and this increased to 11.70 mg/dL on Day 3. None of the non-responders exhibited a decrease in CRP levels on Day 3 to ≤ 50% of values determined in Day 0.

Univariate logistic regression analysis was performed to investigate the factors that influenced clinical outcome, using age, sex, A-DROP score, Day 0 CRP, Day 3 CRP, and the Day 0/Day 3 CRP ratio as variables (Table 5). This analysis revealed that Day 3 CRP and the Day 0/Day 3 CRP ratio were correlated with clinical outcome. Multivariate analysis delivered the same result for Day 3 CRP (odds ratio [OR] = 0.884; $P = 0.0429$) and the Day 0/Day 3 CRP ratio (OR = 8.91; $P < 0.0001$), suggesting that an improvement in CRP levels by Day 3 or the Day 3 CRP itself could be good indicators of clinical outcome.

Discussion

In 1930, CRP was reported to react with bacterial capsular polysaccharide and increased

serum CRP levels were found in patients with pneumococcal infection[13]. CRP is one of the representative acute phase reactants and CRP levels increase markedly in response to tissue damage[1]. Macrophage activation occurs at the site of inflammation, followed by the production of cytokines, such as interleukin (IL)-6, tumor necrosis factor-α, and IL-1, which trigger the release of CRP into the blood from the liver, where it is produced[1,10]. Because this is a cytokine-mediated response, increases in blood CRP levels can be detected from 10 h or more after the onset of inflammation[10]. The half-life of CRP is several hours[14,15], thus levels gradually decline with improvement in inflammation. Therefore, changes in CRP levels occur slightly later than changes in symptoms. In the present study, there was no correlation between Day 0 CRP levels and the severity of pneumonia in Group 1 patients with early disease (Table 3). This was probably because the maximum CRP response had not occurred at the time of measurement, so the CRP levels did not reflect the severity of inflammation. However, in Groups 2 and 3, Day 0 CRP levels reflected the severity of inflammation more closely and a good correlation was found between Day 0 CRP and the severity of pneumonia, most likely because CRP was measured ≥ 48 h after the onset of infection. Despite improvements in symptoms, Day 3 CRP was higher in Group 1 patients, whereas Day 3 CRP decreased with clinical improvement in patients in Groups 2 and 3 (Fig. 1). Therefore, there seems to be a good correlation between Day 0 CRP and the severity of pneumonia in patients who have had pneumonia for at least 48 h, and CRP levels in these patients decrease markedly with clinical improvement. As indicated by the data in Table 4, Day 3 CRP did not decrease to < 50% of the Day 0 value in any of the non-responders. Thus, patients whose Day 3 CRP is < 50% of Day 0 CRP are more likely to be responders. Detailed analysis demonstrated that patients with a Day 3 CRP ≤ 15 mg/dL and < 50% of the Day 0 value were likely to be responders (predictive value = 1.27; 95% confidence interval = 0.872–1.97).

The results presented in Table 5 also suggest that Day 3 CRP and the percentage change in CRP from Day 0 to Day 3 (i.e. the Day 0/Day 3 CRP ratio) are useful for evaluating the efficacy of treatment. Interestingly, there was no correlation between the A-DROP score and the response to treatment, which may have been due to the limited number of patients investigated and their characteristics (see below). Again, the Day 0/Day 3 CRP ratio was related to clinical outcome. This finding is supported by the study of Ruiz-González *et al*, who found that changes in CRP are useful for discrimination between true treatment failure and a slow response to treatment[16]. Accordingly, Day 0 CRP may be an indicator of the severity of pneumonia in patients who have had their infection for at least 2 days, whereas changes in CRP over time can be useful for evaluating the clinical response.

Recently, there have been several reports from outside Japan about the usefulness of CRP in the management of CAP[4-8]. Chalmers *et al* reported that the risk of death or mechanical ventilation within 30 days was low in patients with CAP if CRP levels were ≤ 10 mg/dL at the time of hospital admission, whereas the risk of death within 30 days was

increased if the CRP level on Day 3 was ≥ 50% of that on Day 0[4]. On the basis of our findings, patients with an initial CRP level ≥ 10 mg/dL can be considered as having moderate or severe pneumonia. Bruns *et al*[5] studied patients with severe CAP and concluded that delayed normalization of CRP was associated with a higher likelihood of inappropriate antibiotic treatment. Menéndez[7] reported that the risk of death within 30 days could be predicted more accurately by evaluating CRP in addition to the Pneumonia Severity Index[17] and the CURB-65 score.

Although CRP is widely measured in patients with febrile illness in Japan, there are some problems when using it to monitor the progress of infection. First, CRP levels can increase in patients with any inflammatory disease and CRP is not specific for infections[1, 10]. Conversely, CRP levels will not increase in patients with liver failure or those on anti-IL-6 therapy, even if they have a severe infection[18, 19]. Second, CRP is not useful in determining the causative pathogen. Third, changes in CRP are often slightly delayed compared with changes in symptoms. Although experienced clinicians understand this characteristic of CRP, there is not enough evidence regarding the extent of the delay, and so interpretation of CRP data remains dependent on clinical acumen. The findings of the present study in patients with CAP suggest that measurement of CRP is useful in evaluating the severity of the disease and predicting the outcome if levels are determined at least 48 h after the onset of pneumonia. This is the first report from Japan regarding the usefulness of CRP in the management of CAP. However, the present study was a retrospective study, so the differentiation between responders and non-responders may not be sufficient. In addition, because critically ill patients, such as those with pneumonia and respiratory failure, were not included in the study (we excluded patients on steroid therapy), 89% of patients in the present study had mild or moderate CAP. Therefore, the number of non-responders in the present study was limited to 15 and this sample may not have been large enough. Prospective investigations in a larger patient cohort are needed in the future.

CRP can be determined in addition to other common laboratory tests in a small venous blood sample using a simple, rapid, and inexpensive procedure. CAP is a disease that doctors frequently encounter in clinical practice[20], and it is often difficult to decide whether a patient requires admission to hospital. Thus, in addition to assessment of vital signs (including blood pressure and oxygen saturation) and chest X-ray findings, measurement of CRP may provide useful information to help doctors decide whether hospital admission is needed and to evaluate the response to treatment.

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