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The Relations Between Levels of Acute Phase Reactants and Severity of Community-Acquired Pneumonia

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Abstract

Objectives: We investigated the relationship between the severity of pneumonia and the levels of acute phase proteins, such as C-reactive protein (CRP), fibrinogen and erythrocyte sedimentation rate (ESR), at both the initial presentation and at the end of therapy. **Methods:** One hundred and sixty patients were included in the study and these patients were classified into four groups according to the severity of pneumonia as recommended by the 2001 American Thoracic Society (ATS) and 2002 Turkish Thoracic Society (TTS) guidelines. The serum acute phase reactants (APR) and white blood cell (WBC) counts were measured upon admission as well as at the end of therapy. Patients underwent a posteroanterior and lateral chest radiograph on their day of admission and every three days thereafter. Complication was defined as the presence of pleural effusion, empyema and cavity. **Results:** One hundred and sixty patients were included in the study. The mean age was 48.6+20.6 years; 97 patients (60.6%) were male and 63 patients (39.4%) female. Fifty-three patients had chronic disease, the most frequent being chronic obstructive pulmonary disease (14%) and diabetes mellitus (11%). Ten patients died during their hospital stay. On admission, all patients had elevated CRP levels. The severity of disease was associated with admission levels of CRP and WBCs, but not with ESR and fibrinogen. CRP levels were statistically higher in those patients who died than in those who survived. **Conclusions:** CRP seems to be better suited for use in the monitoring of response to treatment and for estimating the risk of mortality and complications than the alternative APR.

Keywords: pneumonia, severity of pneumonia, acute-phase reactants

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INTRODUCTION

Community-acquired pneumonia (CAP) continues to be a major clinical problem in terms of morbidity and mortality, despite the availability of potent new antibiotics. It continues to be a major cause of death due to infectious disease, and is the sixth leading cause of death in the United States. It is the sixth leading cause of hospital death in our country [1,2]. The incidence and morbidity of pneumonia have not declined over the past 30 years. A delay in diagnosis and determination of an appropriate antibiotic treatment has been ascertained to increase the mortality rate [3].

Patients presenting with CAP were divided into four groups according to guidelines set by the American Thoracic Society (ATS) and the Turkish Thoracic Society (TTS), which are based on the presence of coexisting disease, age, need for hospitalization and the severity of the illness [1,4,5].

Acute phase reactants (APR) are released in response to physiological changes that lead to tissue damage, such as infection, malignancy and physical trauma. APR can neutralize inflammatory agents, help to reduce the extent of local tissue damage, and participate in tissue repair and regeneration [6-8]. Major components of APR are C-reactive protein (CRP), fibrinogen, haptoglobin, erythrocyte sedimentation rate (ESR) and complement [9].

The determination of high levels of ESR may be useful in monitoring how the disease activates. Nonetheless, its diagnostic value is limited. CRP level is a sensitive marker of pneumonia unlike other clinical and laboratory markers. In particular, pneumonia is a potent stimulus, with marked elevation in serum CRP levels within a few hours, which fall rapidly with appropriate antibiotic therapy. CRP is used to monitor the severity of inflammation and the efficacy of disease management. Plasma CRP levels were higher in septicemic patients but did not correlate with the threat of death during the follow-up period [7-10].

Studies exist regarding the relationship between the severity of the disease and APRs in patients with pneumonia, and in bacteremic and septic patients especially [11-13]. However, to our knowledge, no study exists that investigates the relationship between severity, as in the categorization suggested by ATS, and APRs.

In this study, we investigate the relationship between the severity of CAP and the levels of APRs, such as CRP, fibrinogen and ESR, on admission and at the end of therapy.

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Table 1. Demographic characteristics of the patients

	n	%	Age (year)	Female	Male	Coexisting illness		Complication		APACHE II	Mortality	
						n	%	n	%		n	%
Group 1	45	28.1	34.2±14.8	20	25	0	0	0	0	3.18±2.4	0	0
Group 2	38	23.7	71.1±12.6	16	22	15	39.4	0	0	9.7±2.3	0	0
Group 3	41	25.6	51.5±19.1	18	23	16	39.1	7	17.07	12.4±3.9	1	2.4
Group 4	36	22.6	51.3±21.8	9	27	22	61.1	16	44.4	17.9±5.7	9	25.0

MATERIALS AND METHODS

Study design

One hundred and sixty patients with a diagnosis of CAP admitted to Osmangazi University Medical Faculty Hospital and Eskisehir Tuberculosis Control Dispensary between May 1997 and May 2002 were enrolled in this study. The patients were classified into four groups according to the severity of pneumonia as recommended in the 2001 ATS and 2002 TTS guidelines [1,4]. Group 1 consisted of patients younger than 60 years with no coexisting disease/condition (malnutrition, splenectomy, alcohol consumption) and who were treated in an outpatient setting; group 2 were outpatients with pneumonia together with a coexisting disease/condition and/or 60 years of age or older; group 3 included patients with mild-moderate infection which required hospitalization; and group 4 were severe hospitalized patients who required intensive care unit (ICU) therapy.

CAP severity was also assessed using the acute physiology and chronic health evaluation (APACHE II) score system, within 24 hours of admission [14,15]. Patients with hospital- acquired pneumonia, immunosuppression and malignancy were excluded.

Pneumonia was defined as the presence of new infiltrates on a chest X-ray and at least one of the major or two of the minor criteria as follows [16]:

Major criteria: cough, sputum production or fever (temperature of ≥38°C).

Minor criteria: dyspnea, pleuritic chest pain, pulmonary consolidation on physical examination or WBC count >12,000/ml.

The study protocol was approved by the University of Osmangazi Ethical Committee, and written informed consent was obtained for each patient before entrance into the study.

Methods

Clinical data was collected for each patient. Blood samples were taken from all patients for APR and WBC. The serum APR and WBC counts were measured upon admission and at the end of therapy. The serum CRP concentration was measured using the immuno-nephelometric method with a commercially available kit (Behring; Marburg, Germany). WBC, fibrinogen and ESR were measured by "Coulter STKS", "STA compact" and manual, respectively.

Patients underwent a posteroanterior and lateral chest radiograph on the day of admission and every three days thereafter. Resolution is accompanied by diminution of the density of opacity as air returns to the lobe, and it is usually complete, with the lung architecture being restored to normal [17,18]. Complications were defined as the presence of pleural effusion, empyema and cavity [19].

Analysis

All analyses were performed with the SPSS 10.0 statistical computer program. Results are expressed as mean±SD. According to the statistical distributions, Student's unpaired t-test or distribution free Mann-Whitney test was used for comparison of qualitative variables and x^2 test for comparison of qualitative variables. For all tests, the significance level was fixed at ≤ 0.05.

RESULTS

A total of 160 patients were included in the study. The mean age of the patients was 48.6±20.6 years with 63 (39.4%) patients being female and 97 (60.6%) male. Fifty-seven percent of the patients were smokers. Fifty-three patients (33.1%) had an underlying chronic disease, the most common of which were chronic obstructive pulmonary disease (14%), diabetes mellitus (11%) and cardiopathies (8%). The presence of coexisting illnesses was assessed as 61.1% of group 4 CAP patients. The mean APACHE II score was 12.6±6.9.

Patients with group 4 CAP had higher mean APACHE II scores than patients in the hospitalized and outpatient groups. Complications developed in 16 patients (44.4%) with group 4 CAP and in 7 patients (17.1%) with group 3 CAP. Complications were not seen in groups 1 and 2 CAP patients. Of the group 3 inpatients, only 1 (2.4%) died, while in the group 4 severe case hospitalized patients, a total of 9 (25.0%) died during their ICU stay. The demographic characteristics of the patients are given in Table 1.

Table 2. Serum levels of WBC, APR and APACHE II score of the patients according to mortality, coexisting disease and complications

	Coexisting illness			Mortality			Prior antibiotic use			Complication			Smoking		
	(+)	(-)	p	(+)	(-)	p	(+)	(-)	p	(+)	(-)	p	(+)	(-)	p
WBC 1 (10^3)	18.6+9.1	15.1+6.8	<0.05	16.1+12.2	16.5+7.5	>0.05	14.1+6.7	17.4+8.4	<0.05	18.6+8.1	15.9+6.5	>0.05	18.1+8.5	15.1+7.1	>0.05
WBC 2 (10^3)	9.7+6.3	7.4+2.8	>0.05	14.1+12.2	7.7+2.6	<0.01	7.3+3.5	8.1+5.0	>0.05	8.8+3.1	7.9+4.1	>0.05	8.4+5.7	7.8+2.3	>0.05
CRP 1	213.1+75.2	150.1+55.7	=0.001	314.4+99.4	161.9+55.3	<0.001	148.3+59.2	180.4+71.3	>0.05	174.2+60.3	163.7+60.2	>0.05	176.6+75.1	165.4+58.8	>0.05
CRP2	23.3+24.4	25.1+30.3	>0.05	67.8+28.8	22.6+25.7	<0.05	30.3+31.2	21.3+21.4	>0.05	41.7+15.3	20.1+14.2	<0.01	28.9+29.8	18.3+14.3	>0.05
Fibrinogen 1 (10^2)	8.4+3.8	7.8+4.3	>0.05	8.31+0.3	8.1+4.1	>0.05	6.93+2.54	8.71+4.68	>0.05	8.69+4.23	7.92+3.75	>0.05	8.12+0.41	7.83+3.94	>0.05
Fibrinogen 2 (10^2)	4.7+1.5	4.8+2.4	>0.05	3.41+0.2	5.1+1.9	>0.05	4.25+1.50	5.28+2.08	>0.05	5.18+2.12	4.86+1.68	>0.05	5.12+2.08	4.60+1.74	>0.05
ESR 1	76.2+35.3	81.2+36.3	>0.05	54.2+14.9	80.9+36.1	<0.01	81.2+38.5	75.8+34.2	>0.05	83.5+35.4	78.1+31.3	>0.05	76.1+36.1	83.5+35.6	>0.05
ESR2	59.6+37.8	58.8+43.1	>0.05	40.3+44.1	62.4+40.9	>0.05	55.1+41.9	61.9+40.9	>0.05	68.6+39.4	58.8+40.4	>0.05	62.1+40.4	56.7+42.2	>0.05
APACHE II	19.7+8.1	9.9+5.8	<0.001	21.1+4.7	11.7+6.5	<0.001	11.1+6.5	12.5+7.1	>0.05	14.3+6.4	12.1+5.8	>0.05	13.1+7.1	12.5+6.7	>0.05

1: On admission. 2: End of therapy. WBC: /mm^3. CRP: mg/L. Fibrinogen: mg/dl. ESR: mm/s.

The median serum concentrations of WBC, APR and the APACHE II score of the patients according to coexisting illness, mortality, previous use of antimicrobial drugs and complications are shown in Table 2.

On admission, the median serum concentrations of CRP, WBC and fibrinogen were higher in patients with coexisting illness compared with those without, but only CRP and WBC differences were statistically significant. The mean serum levels of CRP, WBC and fibrinogen were lower in those patients who had received antibiotics prior to their admission. However, only WBC difference was statistically significant ($p<0.05$). The APRs of those patients who experienced complications were high but not to a level of significance. The median CRP levels were significantly higher in patients who died when compared with the survivors ($p<0.001$). WBC, CRP and fibrinogen were found to be higher in patients who smoked but this was not significant statistically ($p>0.05$).

The APACHE II score was higher in those patients who had a coexisting disease and died than in the others ($p<0.001$). The APACHE II score was correlated with the serum levels of the CRP ($r=0.433$, $p=0.000$), WBC ($r=0.452$, $p=0.000$) and fibrinogen ($r=0.260$, $p=0.020$).

At the end of the therapy, the mean serum CRP levels of the patients who had complications were higher than in those without any complications ($p<0.01$). The mean serum CRP, WBC and fibrinogen levels of the smokers were higher than of the non-smokers ($p>0.05$). The serum WBC and APR concentrations of the patients upon admission and at the end of therapy are given in Table 3.

On admission, the serum levels of WBC and CRP were seen to increase in parallel to the severity of CAP, yet these increases were not observed in ESR and fibrinogen. Lower serum fibrinogen levels were seen in group 2 CAP and higher levels in group 4 CAP (Figure 1A, B, C and D).

Upon comparison of the groups according to WBC, CRP, fibrinogen and ESR, statistically significant differences were seen, as presented in Table 4. Comparison between groups revealed a significant difference in CRP among the follow-up values. No significant differences were determined between WBC, ESR and fibrinogen values. As to the values observed at admittance, the determination of high levels of CRP, in group 4 in particular, was of statistical significance.

The WBC, CRP, fibrinogen ($p<0.01$) and ESR ($p<0.05$) values of inpatients were determined to be significantly higher than those of outpatients at the commencement of the treatment.

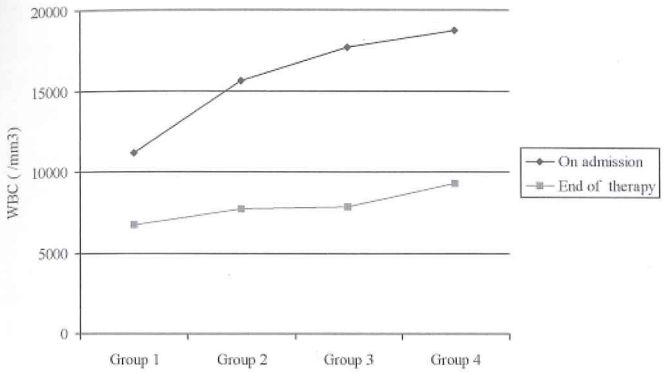

Figure 1A. Serum WBC levels of the patients on admission and at the end of therapy.

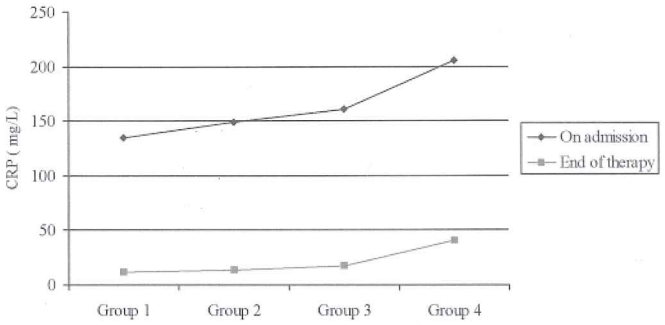

Figure 1B. Serum CRP levels of the patients on admission and at the end of therapy.

DISCUSSION

Pneumonia creates a powerful inflammatory response, both locally and systemically. CRP is an APR synthesized by the liver in response to tissue injury and inflammation. It is a good indicator of bacterial infections [6,20]. The plasma CRP level is a sensitive marker of pneumonia, unlike other more commonly used clinical markers such as body temperature and WBC [12]. Studies into the relationship between the severity of the disease and APRs were carried out on bacteremic and septic patients. These studies determined the bacteremic and septic patient's hypoxemia and disease severity to be higher. The CRP levels were also found to be higher, but after appraisal this was found to be insignificant. Along the same lines, CRP has been reported to be a more sensitive marker as regards its response to WBC and fever in the determination of sepsis [11,12].

In our study, all patients admitted to hospital and the dispensary with CAP had an elevated CRP level at the time of admission. Serum levels of CRP and WBC were lowest in group 1 CAP and highest in group 4 CAP patients on admission, parallel to the severity of the pneumonia. Serum levels of WBC and CRP increased in line with the severity of CAP. This increase was not seen in fibrinogen and ESR. The serum fibrinogen levels were lowest in group 2 CAP and highest in group 4 CAP. ESR values were lowest in group 2 CAP and highest in group 3 CAP. At the end of therapy, the levels of WBC and CRP were also lowest in group 1 CAP and highest in group 4 CAP, but this did not correlate to the severity of CAP.

The high CRP levels were significantly correlated with the hospitalization of low risk patients. Almirall et al. [13] showed that the median CRP levels in hospitalized patients were significantly higher than those of outpatients [21]. In our study, the CRP values in groups 3 and 4 were higher than in groups 1 and 2. As can be assumed from the comparison made between the study groups, CRP seems to be a more significant factor in the determination of patients, particularly those in group 4.

The APACHE II score had been shown to predict the prognosis of patients requiring intensive care treatment, including those patients with severe pneumonia. APACHE II was determined to be the lowest in group 1 and the highest in group 4. As the severity of the disease increased, correlated increases in APACHE II scores were observed. Hedlund and Hansson [11] showed that the APACHE II score was not associated with admission serum levels of CRP. In the present study, the APACHE II score was also strongly associated with admission serum levels of CRP,

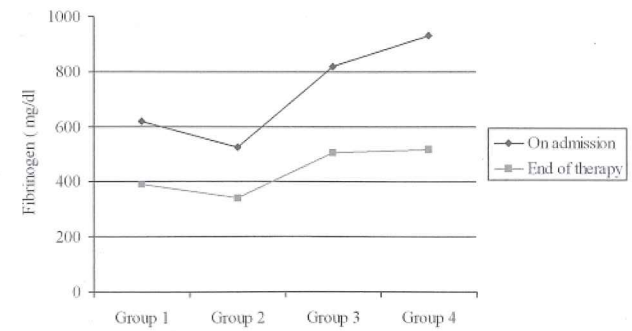

Figure 1C. Serum fibrinogen levels of the patients on admission and at the end of therapy.

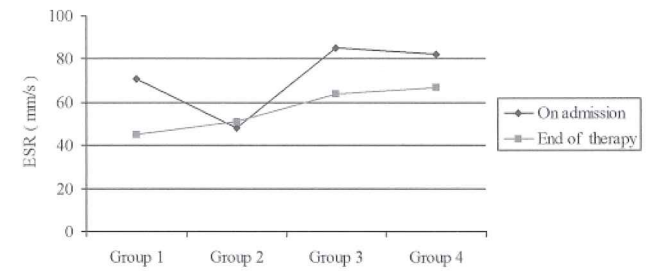

Figure 1D. Serum ER levels of the patients on admission and at the end of therapy.

Table 3. Serum levels of WBC and APR in patients according to severity of CAP

	Group 1	Group 2	Group 3	Group 4
WBC 1	11.2±4.4	15.6±5.5	17.7±6.8	18.7±9.2
WBC 2	6.7±1.2	7.7±1.8	7.8±3.1	9.3±6.6
CRP 1	135.7±49.9	149.6±49.1	161.4±62.2	205.8±73.7
CRP 2	12.5±12.2	14.9±10.6	17.7±20.9	41.5±35.3
Fibrinogen 1	6.32±2.15	5.30±2.29	8.19±3.49	9.31±4.92
Fibrinogen 2	3.89±1.50	3.42±1.97	5.05±2.38	5.18±1.62
ESR 1	71.3±29.4	48.3±49.9	85.3±37.3	81.9±33.3
ESR 2	45.3±39.7	51.0±38.2	64.5±40.6	66.9±43.1

1: On admission. 2: End of therapy. WBC: /mm^3. CRP: mg/L. Fibrinogen: mg/dl. ESR: mm/s.

Table 4. Comparison of the groups according to WBC and APR

	Group 1-2	Group 2-3	Group 3-4	Group 1-3	Group 1-4
WBC 1	**< 0.05**	NS	NS	**< 0.001**	**< 0.001**
WBC 2	NS	NS	NS	NS	NS
CRP 1	NS	NS	**< 0.05**	NS	**< 0.001**
CRP 2	NS	NS	**< 0.01**	NS	**< 0.001**
Fibrinogen 1	NS	**< 0.05**	NS	**< 0.05**	**< 0.001**
Fibrinogen 2	NS	NS	NS	NS	NS
ESR 1	NS	**< 0.05**	NS	NS	NS
ESR 2	NS	NS	NS	NS	NS
APACHE II score	**< 0.001**	**< 0.05**	**< 0.001**	**< 0.001**	**< 0.001**

1: On admission. 2: End of therapy.

WBC and fibrinogen. However, such association between the APACHE II score and admission ESR levels was not observed, and the APACHE II score was correlated with severity of CAP.

In our study, significant decreases were determined in the levels ESR, CRP, WBC and fibrinogen with treatment. In comparison with the initial levels, improvement levels in CRP were as much as five times more in groups 1, 2 and 3 and decreases by as much as five times in group 4. There was a two-fold decrease in WBC levels in all groups. Fibrinogen decreased by two-thirds and ESR by one-fifth. While WBC levels returned to normal with treatment, only CRP levels in group 4 CAP were slightly higher than normal. ESR and fibrinogen levels retained their levels above normal. Despite a significant improvement in fibrinogen and ESR levels following treatment, it was a marked improvement when it responded well. Improvement was much slower when compared with CRP.

In recent studies, there was no correlation between the recognized mortality risk factors and plasma CRP levels; however, CRP levels were higher in those patients who died [7,10,11,22]. In our study, plasma CRP levels were higher in the patients who died and mortality was connected to higher CRP levels on admission.

CRP levels are important for monitoring patient outcome. Monitoring the treatment response is the most useful role for CRP assay in the management of pneumonia. CRP falls rapidly and significantly with appropriate antibiotic therapy [8,10,23]. However, MacFarlane et al. [25] found that high CRP levels were not related to outcome, which suggests that knowing the results is unlikely to influence management and outcome. Indeed, it may paradoxically increase unnecessary antibiotic prescription.

The advantage of CRP over the alternative APR is its rapid increase, in less than 24 hours, which drops exponentially within 24 hours of appropriate antibiotic therapy. This decrease also occurs prior to a decrease in ESR, fever, respiration rate and fibrinogen, this being the earliest symptom responding to the treatment [8,10,23]. A persistently high or increasing CRP level suggests either treatment failure or development of complications, or that the patient has developed antibiotic colitis [8,22]. In determination of bacterial complication, CRP has been reported to be a more sensitive marker in comparison with WBC and fever [25]. Studies in the literature have reported that no significant decrease in CRP levels has been determined in patients with parapneumonic pleural effusions [7,10,11]. In our study, CRP, ESR, WBC and fibrinogen levels were higher in those patients who had experienced complications than in those who had not. However, this increase was significant in CRP levels recorded only after the treatment. Our study results seem to indicate that CRP is the best marker for the development and treatment of complications secondary to treatment.

Almirall et al. [13] showed that serum CRP levels were higher in patients with coexisting illness than in patients with no underlying illness. In our study, WBC, CRP and fibrinogen levels were higher in the patients who had a coexisting illness. While this increase was significant in WBC and CRP, differences in serum fibrinogen levels were not found to be statistically significant. The serum levels of WBC, CRP and fibrinogen were higher in patients who had not received antibiotics prior to hospital admission than in those who had. However, WBC levels were statistically significant. As for those patients on antibiotics, due to the possibility of a decrease in their APR levels, CRP, WBC and fibrinogen levels may mislead determination of the severity of the pneumonia.

In this study, serum CRP level was higher in patients who died, experienced complications or had coexisting disease. The serum level of CRP is lower in patients who received antibiotics prior to hospital admission. Our results suggest that CRP seems to be best suited for the monitoring of response to treatment and estimating the risk of mortality and complication than the other APRs.

The most important feature of this study is that no other study in the literature has looked into the determination of mortality and CRP levels, as well as the relationship between the severity of disease (in accordance with the suggestion by ATS) and acute phase reactants. Restrictions in our study were due to an insufficient number of patients available for research as well as the relatively small number of severe cases leading to death. There is a need for further studies into the relationship between acute phase reactants and the severity of disease and mortality, involving a broader patient database.

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