

Contribution of C-Reactive Protein to the Diagnosis and Assessment of Severity of Community-Acquired Pneumonia*

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Study objective: To assess the usefulness of serum C-reactive protein (CRP) in the diagnosis and treatment approach of patients with community-acquired pneumonia (CAP).

Design: Population-based case-control study.

Setting: A mixed residential-industrial urban area of 74,368 adult inhabitants in the Maresme region (Barcelona, Spain).

Patients: From December 1993 to November 1995, all subjects who were > 14 years of age, were living in the area, and had received a diagnosis of CAP, which had been confirmed by chest radiographs and compatible clinical outcome, were registered. Patients from residential care facilities were excluded. Serum samples were assayed for CRP in the acute phase of the disease. Data from 201 patients with CAP were compared with 84 healthy control subjects matched by age, sex, and municipality, as well as with 25 patients with initially suspected pneumonia that was not confirmed at follow-up. Median CRP levels were 110.7, 1.9, and 31.9 mg/L, respectively. The thresholds of the test for discriminating among these three groups of subjects were 11.0 and 33.15 mg/L.

Results: Eighty-nine patients (44.8%) had an identifiable etiology. The most common pathogens were *Streptococcus pneumoniae*, viruses, and *Chlamydia pneumoniae*, followed by *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Coxiella burnetii*. There were statistically significant differences in the median CRP levels in pneumococcal (166.0 mg/L) and *L pneumophila* (178.0 mg/L) etiologies compared to other causative pathogens. Lower levels of CRP were found in pneumonia caused by viruses and *C burnetii* as well as in negative microbiological findings. The median CRP levels in hospitalized patients were significantly higher than in outpatients (132.0 vs 76.9 mg/L, respectively; $p < 0.001$). Considering a cut point of 106 mg/L in men and 110 mg/L in women for deciding about the appropriateness of inpatient care, CRP levels showed a sensitivity of 80.51% and a specificity of 80.72%.

Conclusions: Serum CRP level is a useful marker for establishing the diagnosis of CAP in adult patients with lower respiratory tract infections. High CRP values are especially high in patients with pneumonias caused by *S pneumoniae* or *L pneumophila*. Moreover, high CRP values are suggestive of severity, which may be of value in deciding about the appropriateness of inpatient care. (CHEST 2004; 125:1335-1342)

Key words: acute-phase reactants; community-acquired pneumonia; C-reactive protein; differential diagnosis

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; ROC = receiver operating characteristic

Community-acquired pneumonia remains a major reason for hospital admission and a common cause of death in developed countries.¹ The annual incidence rate of community-acquired pneumonia (CAP) in adults varies between 1.6 and 13.4 per 1,000 inhabitants, with hospitalization rates ranging between 22% and 51%.² Pneumonia elicits a power-

ful inflammatory response. The release of inflammatory mediators from activated mononuclear phagocyte cells constitutes an important part of the host response to infection. Of these mediators, interleukin-6 is a major inducer of acute-phase proteins, including the C-reactive protein (CRP).³ The early determination (*ie*, 24 to 48 h) of serum concentra-

tions of CRP is a well-established laboratory test for the diagnosis and monitoring of different acute inflammatory processes.

The prognosis of CAP is dependent on early diagnosis and treatment, but, despite advances in diagnostic testing, most investigators cannot identify

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a specific etiology for CAP in up to half, or more, of all patients.⁴ On the other hand, the clinical features of CAP cannot be reliably used to establish the etiologic diagnosis with adequate sensitivity and specificity,^{5,6} and, in most cases, the initial approach involves empiric antibiotic therapy based on the presence of relevant factors that influence likely etiologic pathogens. Early markers for guiding the clinician in the initial selection of antimicrobial drugs and site of care are therefore needed.⁷

Although a relationship between serum CRP and interleukin-6 values in patients with CAP requiring hospitalization has been reported,^{8–13} the potential of acute-phase protein levels as early indicators of etiology and outcome of CAP in population-based studies has not been previously assessed. The aim of the present study was to investigate the usefulness of serum CRP levels in patients with CAP who were selected from a population-based study.² Serum CRP concentrations were assayed in peripheral blood at the time of diagnosis and were compared with data obtained from healthy control subjects, as well as in a group of patients with initially suspected CAP not confirmed at follow-up. We also investigated whether serum CRP levels could help to identify etiologic diagnosis and to predict severity of outcome.

PATIENTS AND METHODS

Study Population

Patients included in the study were selected from a case-control study² of risk factors for CAP, the details of which have been previously published. From December 1993 to November 1995, all subjects > 14 years of age with clinical suspicion of CAP from a mixed residential-urban industrial population in the Maresme region (annual population size of 74,368 inhabitants) on the Mediterranean coast in Barcelona, Spain, were registered. All physicians working in public primary health-care centers, private clinics, and emergency departments of reference hospitals participated in the reporting of cases. For each case, three control subjects were recruited. Control subjects were randomly selected from the municipal census and were matched by municipality, sex, and age (± 5 years). The study was approved by the ethics committees of the participating hospitals.

Information was obtained by personal interviews that were carried out by trained health-care personnel for case patients and control subjects at home, except for some inpatients who were interviewed at the end of the hospital stay. Data also were obtained by the same research team by the review of medical records of the corresponding centers at which patients were attended. The following information was collected: age; sex; number of comorbid 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; decision about inpatient care according to risk factors defined by Fine et al¹⁴ in 1990; and severity of outcome according to the need of admission to the ICU and mortality. ICU admission was required in the presence of one or more of the following conditions: respiratory rate of > 30 breaths/min; $\text{PaO}_2/\text{fraction of inspired oxygen index}$ of < 250; need for mechanical ventilation; chest radiograph showing bilateral involvement or rapidly expansive infiltrates; shock; requirement for vasopressors; and oliguria or acute renal failure.

Diagnostic Criteria

Predefined criteria for case registration were based on symptoms of acute lower respiratory tract infection in association with the appearance of previously unrecorded focal signs on physical examination of the chest.¹⁵ Patients with aspiration pneumonia or active pulmonary tuberculosis and patients coming from nursing homes or having been discharged from the hospital < 7 days before the onset of symptoms were excluded. *Nursing home* in our country refers to long-stay centers in which patients with chronic diseases requiring nursing care are also living, so that pneumonia in these residents is considered nosocomial. Patients with HIV or active malignancy also were excluded from the study. New radiologic findings suggestive of pneumonic infiltrates, which were reevaluated on the fifth day of illness and at monthly intervals until complete recovery, also were required for entry into the study. Of the total of 292 cases of suspected CAP, 51 (17.5%) were discarded after finding another disorder, including bronchiectasis in 12 cases, respiratory infection other than CAP in 7 cases, pleural synechiae in 5 cases, lung neoplasm in 7 cases, atelectasis in 5 cases, pulmonary tuberculosis in 3 cases, aspiration pneumonia in 2 cases, lung abscess in 1 case, chronic organizing pneumonia in 1 case, acute pulmonary edema in 1 case, and chronic vasculitis in 1 case.

In patients with fever (*ie*, temperature of $\geq 38^\circ\text{C}$), two blood cultures were drawn. When pleural effusion was observed,

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This work was supported by a grant (No. 97/0718) from Fondo de Investigaciones Sanitarias, Madrid, Spain.

Manuscript received January 17, 2003; revision accepted October 30, 2003.

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thoracentesis and pleural fluid culture were performed. When lower respiratory tract secretions (obtained via BAL with plugged double catheter) were obtained, they were cultured. Paired serology at the moment of diagnosis and within the fourth week were assessed for seroconversion of antibody titers for *Chlamydia pneumoniae*, influenza virus A and B, parainfluenza virus 1 to 3, adenovirus, respiratory syncytial virus, *Chlamydia psittaci*, *Coxiella burnetii*, *Mycoplasma pneumoniae*, *Legionella pneumophila* (serogroups 1 to 6), and hantavirus (Puumala and Hantaan strains).

When varicella pneumonia was suspected, testing for antibodies was performed by the standard complement-fixation technique. Urine samples also were collected during the acute phase of the disease and were tested for pneumococcal polysaccharide capsular antigen and *Haemophilus influenzae* type B capsular antigen. An etiologic diagnosis was based on the growth of a potential respiratory tract pathogen in a set of blood cultures, in bronchial aspirates, or in pleural fluid, on the detection of urinary antigen, or at least on a fourfold rise in IgG titers between paired serum samples.

CRP Assay

CRP was measured in serum samples by an automated latex-enhanced turbidimetric assay (CRP, Cat 3000–2092; Biokit SA; Barcelona, Spain) with an analyzer (Hitachi 717; Boehringer Mannheim; Mannheim, Germany). The coefficients of variation for within-run and between-run imprecision were < 5% and < 7%, respectively. The assay was linear from 3 to 200 mg/L.

To assess the usefulness of serum CRP levels, study subjects were divided into three groups: (1) patients with confirmed CAP; (2) patients with clinical suspicion of CAP not confirmed at follow-up; and (3) healthy subjects. In the group of 241 patients with a confirmed diagnosis of CAP, peripheral blood samples for CRP assay were collected at the time of diagnosis. However, 40 patients were excluded for the following reasons: HIV infection in 17 patients because it has been shown that the CRP level cannot be used to discriminate between *Pneumocystis carinii* pneumonia and bacterial pneumonia in HIV-infected patients¹⁶; active malignancy in 6 patients; and blood samples not available at the time of diagnosis for logistic reasons in 17 patients.

In the group of 51 patients with unconfirmed CAP, blood

samples for CRP assay at the time of suspected clinical diagnosis were available in 25 (49%). In healthy control subjects, a sample of peripheral blood for CRP assay was requested during interviews at home in one each of age-matched, sex-matched, and municipality-matched control subjects, and was obtained in 84 persons.

Statistical Analysis

The results of serum CRP values are presented as the median, the 5th percentile, and the 95th percentile due to the skewed distribution of data. The Mann-Whitney *U* test was used for the comparison of two groups of continuous data, and the Kruskal-Wallis test was used for the comparison of three or more groups.

The diagnostic usefulness of serum CRP values was assessed by means of the receiver operating characteristic (ROC) curves, according to sensitivity and specificity for different cut points, for discriminating patients with confirmed CAP from the remaining study subjects. Statistical analysis was focused on the ability of serum CRP values to predict the diagnosis of confirmed CAP. For this purpose, logistic regression models adjusted by risk factors for CAP and including serum CRP levels were constructed.¹⁷ The relative risk for having a confirmed CAP was estimated by the odds ratio (OR) and 95% confidence interval (CI).

The usefulness of serum CRP values for the management and prognosis of CAP was limited to the group of patients with confirmed disease using the same statistical tests. The analysis was focused on the ability of serum CRP to differentiate pneumonia caused by some specific pathogen, or to predict the severity of outcome and the decision for inpatient care.

RESULTS

CRP in Patients With and Without CAP

The distribution of subjects by age groups and sex, as well as serum CRP levels is shown in Table 1. Fifty-eight percent of patients with CAP were men, with a mean age of 57 years (SD, 20 years). The remaining 42.3% were women with a mean age of 52

Table 1—Serum CRP Values in Subjects According to Age and Sex*

Sex	Age, yr	Confirmed CAP†				Unconfirmed CAP‡				Healthy Control Subjects§			
		%	Median	5th	95th	%	Median	5th	95th	%	Median	5th	95th
Men	15–44	29.3	88.1	4.2	169.5	25.0	69.1	6.8	131.3	34.7	1.6	0.1	5.4
	45–75	50.0	116.9	3.0	182.9	50.0	43.1	31.8	160.1	46.9	1.7	0.7	16.7
	> 75	20.7	151.9	23.9	182.1	12.5	149.5	149.5	149.5	18.4	7.6	2.2	13.1
	Total	100.0	116.9	4.9	182.1	50.0	43.1	6.1	160.1	58.3	1.9	0.1	13.1
Women	15–44	45.9	109.6	4.0	183.1	25.0	31.0	30.0	31.9	40.0	1.6	0.3	7.4
	45–75	31.8	78.5	11.4	179.7	37.5	12.9	1.5	109.0	31.4	1.6	0.1	10.3
	> 75	22.4	123.9	2.9	188.6	0.0	0.0	0.0	0.0	28.6	4.9	1.1	21.7
	Total	100.0	106.6	9.4	183.1	50.0	30.4	1.5	109.0	41.7	2.0	0.3	10.3
Total	15–44	36.3	102.3	4.0	178.1	25.0	31.0	6.8	131.3	36.9	1.6	0.1	5.4
	45–75	42.3	97.2	10.9	181.4	43.8	33.0	1.5	160.1	40.5	1.7	0.1	16.7
	> 75	21.4	141.4	13.6	184.8	6.3	149.5	149.5	149.5	22.6	5.0	1.1	21.7
	Total	100.0	110.7	8.0	182.1	100.0	31.9	1.5	160.1	100.0	1.9	0.3	11.0

*5th = 5th percentile; 95th = 95th percentile.

†Men, 116 patients; women, 85 patients.

‡Men, 8 patients; women, 8 patients. Total CRP values in patients with unconfirmed CAP was based on 25 cases.

§Men, 49 subjects; women, 35 subjects.

years (SD, 21 years). Median CRP levels were significantly higher ($p < 0.05$) in patients with confirmed CAP (median, 110.7 mg/L; 5th to 95th percentiles, 8.0–182.1 mg/L) compared to those with unconfirmed pneumonia at follow-up (median, 31.9 mg/L; 5th to 95th percentiles, 1.5 to 160.1 mg/L) and control subjects (median, 1.9 mg/L; 5th to 95th percentiles, 0.3 to 11.0 mg/L). These differences also were found when study subjects were stratified by age groups and sex. CRP levels were markedly increased in patients > 75 years of age and, in general, were higher in men than in women. The best cut points for discriminating patients with CAP from healthy control subjects and patients with unconfirmed pneumonia were 11.0 mg/L (sensitivity, 94%; specificity, 95%; area under the ROC curve, 0.97) and 33.15 mg/L (sensitivity, 83%; specificity, 44%; area under the ROC curve, 0.69), respectively.

In the group of patients with confirmed CAP, there were differences in serum CRP values according to the number of comorbid conditions present (patients with no underlying illness: median, 99.5 mg/L; 5th to 95th percentiles, 4.2 to 178.1 mg/L; patients with one concurrent illness: median, 105.9 mg/L; 5th to 95th percentiles, 8.0 to 182.9 mg/L; and patients with two concurrent disorders: median, 144.1 mg/L; 5th to 95th percentiles, 12.1 to 188.6 mg/L; $p = 0.03$). On the other hand, higher CRP levels also were detected in patients with diabetes (median, 150.3 mg/L; 5th to 95th percentiles, 10.9 to 188.8 mg/L; $p = 0.02$), immunosuppressive disorders (median, 143.9 mg/L; 5th to 95th percentiles, 10.9 to 187.6 mg/L; $p = 0.004$), debilitating disorders (median, 125.4 mg/L; 5th to 95th percentiles, 14.2 to 184.8 mg/L; $p = 0.03$), and consumption of > 50 g ethanol per day (median, 144.1 mg/L; 5th to 95th percentiles, 0.6 to 186.6 mg/L; $p = 0.02$). Serum CRP levels in ex-smokers were higher (median, 135.7 mg/L; 5th to 95th percentiles, 2.1 to 183.1 mg/L) than in never-smokers (median, 100.7 mg/L; 5th to 95th percentiles, 4.9 to 187.6 mg/L), and current smokers (median, 97.2 mg/L; 5th to 95th percentiles, 3.0 to 178.0 mg/L; $p = 0.03$). In the logistic regression analysis, for each underlying illness, the risk of confirmed CAP in relation to unconfirmed pneumonia decreased with an OR of 0.15 (95% CI, 0.04 to 0.59; $p = 0.006$). In the final model, serum CRP level also was associated with confirmed CAP with an OR of 1.01 (95% CI, 1.00 to 1.03; $p = 0.06$). According to these independent variables, the best cut point for discriminating between confirmed and unconfirmed CAP was 33.2 mg/L (sensitivity, 83%; specificity, 62.5%; area under the ROC curve, 0.73) [Fig 1].

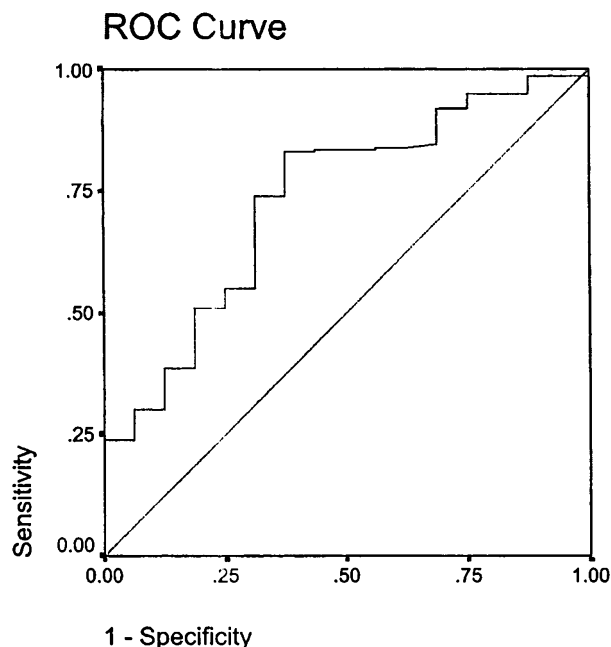


FIGURE 1. A ROC curve is shown with the best cut point of serum CRP with clinical features, which is suggestive of CAP in discriminating between confirmed pneumonia and unconfirmed pneumonia at follow-up.

CRP in Confirmed CAP

A total of 89 patients (44.3%) had an identifiable etiology (single pathogen, 80 patients; two pathogens, 9 patients). *Streptococcus pneumoniae* was identified in 25 cases (in association with *C pneumoniae*, 1 case; in association with *M pneumoniae*, 1 case; and in association with different viruses, 5 cases). *C pneumoniae* was identified in 21 cases (in association with *S pneumoniae*, 1 case; and in association with adenovirus, 1 case). There were no differences in serum CRP values when the different etiologic groups were compared. However, median CRP levels in patients with pneumonia caused by *S pneumoniae* and *L pneumophila* were significantly higher than those in the remaining etiologies (Table 2). The lowest serum CRP values were observed in patients with pneumonia caused by *C burnetii* and viral etiologies, as well as in patients with negative microbiological findings.

A total of 118 patients (58.7%) with confirmed CAP were admitted to the hospital (mean length of stay, 11.7 days), and 18 patients (9%) required ICU admission. Median CRP values in hospitalized patients (132 mg/L; 5th to 95th percentiles, 4.9 to 184.8 mg/L) were significantly higher than those in patients treated in the outpatient setting (76.9 mg/L; 5th to 95th percentiles, 8.0 to 165.9 mg/L; $p < 0.001$) [Table 3]. In the multivariate analysis,

Table 2—Serum CRP Values in 89 Patients With CAP According to Causative Pathogen*

Pathogen	Cases, No.	Median (5th–95th percentile)	p Value†
<i>S pneumoniae</i>			
Alone or combined with other bacteria or viruses	25	166.0 (35.4–188.6)	0.0002
Only	18	142.9 (24.0–188.6)	
<i>C pneumoniae</i>			
Alone or combined with other bacteria or viruses	21	137.7 (4.2–173.5)	NS
Only	19	125.8 (2.9–175.8)	
<i>M pneumoniae</i>			
Alone or combined with <i>S pneumoniae</i>	8	115.6 (0.3–181.9)	NS
Only	7	106.4 (0.3–155.4)	
<i>C burnetii</i>			
Alone or combined with influenza A virus	5	47.4 (1.2–121.8)	0.056
Only	4	57.4 (32.5–121.8)	
Viral etiology only‡	25	98.3 (8.0–172.4)	NS
<i>L pneumophila</i>	5	178.0 (94.7–182.1)	0.033
Other pathogens§	2	124.1 (72.0–154.7)	NS
Negative microbiological findings	112	95.5 (10.9–182.9)	0.039

*NS = not significant.

†Comparison of CRP levels for each microorganism, alone or combined with other pathogens, with the remaining patients.

‡Includes respiratory syncytial virus, influenza A, influenza B, parainfluenza virus, varicella-zoster virus, and adenovirus.

§Includes *H influenzae* and *Serratia marcescens*.

site of care (adjusted by age, sex, number of comorbid conditions, history of diabetes, immunosuppressive disorder, debilitating illness, alcohol abuse, and cigarette smoking), age (OR, 1.08; 95% CI, 1.05 to 1.10), male sex (OR, 7.34; 95% CI, 1.63 to 33.08), and serum CRP level (OR, 1.02; 95% CI, 1.01 to 1.03) were independent factors associated with inpatient care. The best cut points for differentiating inpatient care from outpatient care in men and women were 106 and 110 mg/L, respectively. The area under the ROC curve was 0.86, with a sensitivity of 80.51% and a specificity of 80.72%.

DISCUSSION

We have reported here serum CRP responses in patients with CAP according to data obtained from a population-based study that includes all spectra of the disease together with strict criteria for unequivocal diagnosis.² The present results provide evidence for the usefulness of the CRP assay in the diagnosis and assessment of the severity of CAP. Patients with confirmed CAP showed higher CRP levels than did

patients with other conditions resembling CAP that later were ruled out. Moreover, differences remained when study subjects were stratified by age groups and sex. On the other hand, CRP levels in patients requiring inpatient care were also higher than those found in patients with CAP who were treated as outpatients.

With regard to the comparison of serum CRP levels obtained in patients with CAP and those acquired in healthy people, a cut point of 11 mg/L showed a sensitivity and specificity of 94% and 95%, respectively. These data indicate that a CRP value below this cut point practically excludes the diagnosis of CAP. At the same time, in the presence of a clinical picture compatible with pneumonia, serum CRP levels have also 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. A cut point of 33 mg/L would discriminate between these two groups, with a sensitivity of 83% and a specificity of 44%.

Other authors also have established a relationship

Table 3—Serum CRP Values in Patients With CAP According to Site of Care

Site of Care	Cases, No.	Median	5th Percentile	95th Percentile	p Value
Home	83	76.9	8.0	165.9	< 0.0001
Inpatient care	118	132.0	4.9	184.8	
ICU or death	18	138.6	18.8	183.1	0.87
Hospital ward	100	127.0	4.5	187.2	
Total	201	110.7	8.0	182.1	

between CRP and infection of the lower respiratory tract, either CAP or nonpneumonic respiratory infection. Macfarlane et al,¹⁸ in a study of lower respiratory tract infection in patients attended to in the outpatient setting, reported that 65% of patients with radiographically confirmed disease showed high serum CRP levels (*ie*, > 50 mg/L) compared with 40% in patients with radiographic findings that were consistent with infection, and 11% in patients who had no changes consistent with infection. These data, which are in agreement with our findings, suggest that there is a certain relationship between the degree of infection and serum CRP concentrations. On the one hand, Melbye et al¹⁹ showed that serum CRP level of > 50 mg/L (measured with a semiquantitative technique) in patients with symptoms of respiratory infection for > 1 week who had been treated as outpatients had a sensitivity of 54% and specificity of 95% for the diagnosis of CAP. When the duration of symptoms was < 1 week, a sensitivity of 43% and specificity of 86% was reported for the same CRP serum threshold level. Moreover, Smith and Lipworth¹³ measured serum CRP concentrations by fluorescent polarization immunoassay during the first day of hospital admission and found higher values in patients with CAP than in patients with nonpneumonic bronchial infection (217 vs 18 mg/L). In a study by Castro-Guardiola et al¹⁰ on CAP diagnosed at the hospital emergency department, mean serum CRP levels of 181 mg/L in cases of confirmed CAP were found, with mean levels of 88 mg/L found in false-positive cases. In this study, the multivariate analysis identified serum CRP level as the best marker for differentiating these two clinical conditions, with a sensitivity of 70% and specificity of 96% for a cut point of 100 mg/L (OR, 17.5).

It should be taken into account that CRP level is a nonspecific marker of acute-phase inflammation and, therefore, is subject to the influence of other factors. General characteristics of patients, such as age and sex, may strongly influence serum CRP values and, consequently, predefined cut point levels. In agreement with the study of Hutchinson et al,²⁰ the present findings suggest important differences in CRP concentrations according to age and sex groups, although statistically significant differences were not reached due to the small number of patients in some of the categories. It is also well-known that a large variety of pathologic conditions causing tissue damage may be an important stimulus for the hepatic synthesis of CRP. It should be noted that in our study the number of concurrent illnesses (*ie*, diabetes and immunosuppressive or debilitating diseases) as well as alcohol use and smoking status were determinant factors of serum CRP levels. The observation of higher CRP levels in ex-smokers than

in smokers or never-smokers may be explained by a higher severity of pneumonia in ex-smokers compared to the other groups, as shown by a significantly higher percentage of patients aged > 75 years, as well as more patients with debilitating disorders, immunosuppressive diseases, two or more comorbid conditions, and need of inpatient care. The results of multivariate analysis showed that a cut point of 33 mg/L is useful in discriminating between confirmed and unconfirmed CAP, maintaining a sensitivity of 83% and increasing specificity to 62.5%.

An etiologic diagnosis was reached in 44.8% of patients, even though sputum culture and/or lower respiratory tract secretion sampling was not used in all patients. *S pneumoniae* and *C pneumoniae* were the most common causative agents in our geographic area,² which is similar to the findings of Macfarlane et al²¹ in a community-based study of lower respiratory tract infections. When serum CRP values in different etiologic groups were studied, infections caused by *S pneumoniae* and *L pneumophila* caused a greater host response to infection, characterized by more important increases of CRP.^{22–25} In a recent study²⁶ 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 (25 vs 15 mg/L, respectively; $p = 0.0003$), and the authors raised the question of whether *L pneumophila* triggers more (or different) inflammatory pathways than other atypical microorganisms. On the other hand, the higher levels of CRP observed in patients with CAP produced by *S pneumoniae* and *L pneumophila* could be due to the fact that these etiologic agents more commonly produce severe CAP. However, this finding has little usefulness for the management of patients as *Legionella* usually does not respond to β -lactam agents and requires the addition of other antibiotics to a treatment regimen.

The median serum CRP level in patients with pneumococcal pneumonia was 166 mg/L, and significantly higher than median levels found in the remaining patients. These findings have been also emphasized by other authors.^{11,12,25,27} In addition, it has been stressed there is a higher increase in CRP in CAP with pneumococcal bacteremia.¹¹ Median CRP levels in the group of 21 patients with *C pneumoniae* was 137.7 mg/L. These results are consistent with those reported by Kauppinen et al²⁷ in the comparison of hospitalized patients with CAP due to *S pneumoniae* and *C pneumoniae*. The lowest levels were found in patients with negative microbiologic findings, as well as in those with infection caused by *C burnetii* and in patients with viral infection. Macfarlane et al¹⁸ 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. This is in contrast to the reasoning of other authors who have argued for the presence of *S pneumoniae* when the etiologic diagnosis is not reached,²⁸ in which case a higher CRP level might be expected. In this respect, Kerttula et al⁸ found that 19% of patients with CAP without etiologic diagnosis showed serum CRP levels that were similar to those found in patients with pneumococcal disease.

Finally, the most outstanding result was the higher increase in serum CRP values in patients with CAP in whom the clinical condition was considered to be severe and about whom a decision for in-hospital care was made. In addition, 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 in CRP level according to the site of treatment suggest the possibility of using serum CRP level at the time of diagnosis of CAP as a criterion of severity. In this respect, sensitivity and specificity values for the best cut points in men (106 mg/L) and women (110 mg/L) are adequate enough to be used as an additional criterion for deciding on the necessity for in-hospital care. It is important, however, to consider the usefulness of the CRP value and the relative cut points in the context of the average age of our population (*ie*, < 60 years), which is related to the fact that patients from residential care facilities were excluded. Higher age and some comorbidities (*eg*, malignant neoplasm and neurologic disease) commonly found in patients with CAP should be evaluated in the future before validating the conclusions of this study for other populations with CAP. In previously published series,^{11,13,18,20,29,30} a relationship between CRP levels and the site of care could not be assessed, given that studies were performed in hospitalized patients or in small study populations, although a trend toward higher severity of illness and greater serum CRP levels was observed. Stauble et al³⁰ have related the need for hospitalization with high serum CRP levels even in low risk patients (*ie*, classes I to III in Fine et al¹⁴). Seppä et al,³¹ in patients > 65 years of age, reported a higher risk for death at 30 days when the initial serum CRP level was > 100 mg/L.

We conclude that in adult patients with suggestive symptoms of CAP, a serum CRP level > 33 mg/L is a useful marker for differentiating patients with true alveolar infection from patients with lower respiratory tract infection other than pneumonia. In patients with radiographic evidence of pneumonia, serum CRP levels are greater when *S pneumoniae* or *L pneumophila* are the causative pathogens. In these

cases, serum CRP levels of > 106 mg/L seem to predict severity of illness, which can be useful in deciding on the appropriate site of care.

If the present results are confirmed in other studies, CRP assay by rapid and simple techniques, such as reactive strips in capillary blood, will be a highly useful tool in the primary care setting for patients with suggestive clinical features of CAP.

ACKNOWLEDGMENT: The authors are grateful to Silvia Argilaga for statistical analysis, Cristina Mas for her administrative tasks, and Marta Pulido, MD, for editing the manuscript and editorial assistance.

APPENDIX: MEMBERS OF THE COMMUNITY-ACQUIRED PNEUMONIA MARESME STUDY GROUP

Primary Care Centers

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