Diagnostic and Prognostic Values of Admission Procalcitonin Levels in Community-Acquired Pneumonia in an Intensive Care Unit

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Abstract

Background: Measurement of procalcitonin (PCT) has been studied for several years in infectious diseases. Some studies have focused on community-acquired pneumonia (CAP) but only one was conducted in critically ill patients hospitalized in an intensive care unit (ICU).

Patients and Methods: To determine the diagnostic and prognostic role of PCT in patients admitted in an intensive care unit for severe CAP, 110 patients hospitalized in our unit were prospectively studied. Within 48 hours following ICU admission, PCT serum level was measured with a quantitative method above a threshold value of 0.5 ng/ml.

Results: Initially focusing on the diagnostic value of PCT, 20% of the patients had a serum PCT level < 0.5 ng/ml, 30% between 0.5 ng/ml and 2 ng/ml, and 50% ≥ 2 ng/ml. Serum PCT level was higher in microbiologically documented CAP (median = 4.9 ng/ml vs 1.5 ng/ml if no bacteria were found; p = 0.001), but was not predictive of any specific bacterial agent. Concerning the prognostic value, the serum PCT level was higher for bacteremic patients and/or septic shock patients (4.9 ng/ml vs 1.5 ng/ml; p = 0.0003). Moreover, PCT levels were increased in patients who developed, during their ICU stay, infection-related complications (septic shock, multiorgan dysfunction, acute respiratory distress syndrome and disseminated intravascular coagulation). Finally, the initial PCT level was significantly higher in patients who died during the ICU stay (5.6 ng/ml vs 1.5 ng/ml; p < 0.0001). Such a relationship was not found with C-reactive protein (CRP).

Conclusion: In ICU patients admitted for severe CAP, initial PCT values could be an interesting predictor for complications and mortality.

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Introduction

Numerous studies have been designed to identify sensitive and specific markers to differentiate inflammatory from infectious diseases and more specifically to separate bacterial from viral or fungal infections. According to several authors, procalcitonin (PCT) could be an interesting candidate. In healthy individuals, the serum PCT concentration is lower than 0.1 ng/ml but any infectious or inflammatory injury, inducing tumor necrosis factor and/or interleukin-6 release, increases the PCT serum level. Elevation of this peptide in inflammatory disorders has been known since 1975 [1], and the understanding of its pathophysiology has improved during the last three decades [2, 3]. In 1993, *Assicot* et al. [4] confirmed a potential PCT level relevance in the diagnosis and prognosis of infectious diseases. Animals as well as clinical studies have confirmed that procalcitonin is a potentially useful marker in the diagnosis of infectious diseases. Moreover, its level usually correlates with systemic involvement and prognosis [5–7]. However, only a few studies have focused on community-acquired pneumonia (CAP) [8–13], and among them, only one was performed in intensive care unit (ICU) patients [14]. We therefore decided to study the diagnostic and prognostic values of PCT, measured upon admission to the ICU, for patients admitted for severe CAP.

Patients and Methods

Study Location and Patient Selection

The study was conducted in the Intensive Care and Infectious Disease Unit of Tourcoing Hospital from January 1, 2001 to April 1, 2003. All consecutive patients exhibiting a severe CAP, for which the PCT level was determined within 48 h of ICU admission, were prospectively included in an observational cohort study.

CAP was defined by the following criteria observed at initial presentation or within 48 h following hospitalization: admission from home, presence of a new radiographic pulmonary infiltrate, acute onset of at least one "major" (cough, sputum production,

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fever) or two "minor" (dyspnea, pleuretic chest pain, altered mental status, pulmonary consolidation on physical examination, total leukocyte count >12,000/mm^3) clinical or biological findings suggestive of pneumonia. Patients hospitalized within 30 days prior to developing pneumonia, with radiographic abnormalities attributed solely to pulmonary embolus, lung carcinoma or congestive heart failure were excluded [15, 16].

The criteria for ICU admission were those defined by the American Thoracic Society by using a rule that required the presence of either two of three minor criteria (systolic blood pressure < 90 mmHg, multilobar disease, paO_2/FI_{O2} ratio < 250) or one of two major criteria (need for mechanical ventilation or septic shock) [17].

Data Collection and Definitions

For all patients, the following characteristics were prospectively collected upon ICU admission: age, gender, indication(s) of ICU admission, underlying clinical conditions, severity of illness, and vital sign abnormalities. The underlying clinical conditions were classified, according to the criteria proposed by *McCabe* and *Jackson* [18], as nonfatal, ultimately fatal or rapidly fatal. Immunosuppression was defined as a leukocyte count < 1,000/mm^3, recent use of systemic corticosteroids (> 10 mg/day of prednisone or equivalent for over 2 weeks), underlying malignancy, cytotoxic drugs, radiation treatment, or asplenia. Severity of illness was assessed by SAPS II [19] and organ system failure (OSF) scoring defined by *Knaus* [20] to which we added criteria for hepatic failure [21]. Neurological and mental status was stratified according to the Glasgow coma score [22]. Shock was defined as a sustained (> 1 h) decrease in the systolic blood pressure of at least 40 mmHg from baseline or a resultant systolic blood pressure < 90 mmHg after adequate fluid replacement and in the absence of any antihypertensive drug [23].

Within 48 h following ICU admission, we prospectively collected, at the same time, the following variables: temperature, leukocyte and platelet counts, C-reactive protein (CRP), and PCT values. PCT level was measured with a quantitative method using a monoclonal immunoluminometric assay (Lumitest PCT, Brahms Diagnostica, Berlin). Only values over the cutoff level set at 0.5 ng/ml were recorded.

Establishment of an etiologic diagnosis required isolation of bacteria in a significant quantity from a sample of lower respiratory tract secretions (endotracheal aspiration > 10^6 cfu/ml, protected brush catheter > 10^3 cfu/ml or bronchoalveolar lavage > 10^4 cfu/ml), or isolation of a definitive pathogen from a blood or pleural fluid culture [24]. These latter cultures were considered significant when the same organism was recovered from a respiratory secretion sample.

During the ICU stay, the occurrence of complications directly related to pneumonia was recorded. We distinguished infection-related complications (secondary septic shock, acute respiratory distress syndrome [ARDS], multiple organ failure [MOF], disseminated intravascular coagulation [DIC]) and hospital-acquired lower respiratory tract superinfections. MOF, ARDS, and DIC were defined according to the usual criteria [21, 25, 26]. In this study, MOF was defined by at least two organ failures, added to the initial respiratory distress. Patient mortality was evaluated at the ICU discharge.

Study Design and Statistics

To assess the diagnostic and prognostic values of PCT, we performed different sets of analyses. After a descriptive analysis of the entire population, we compared the patients based on the identification of a causative organism. Moreover, in patients with a positive bacteriological diagnosis, three groups were created according to the causal organism: *Streptococcus pneumoniae*, gram-negative bacilli, and other agents. To test the prognostic value of PCT, we compared patients on the occurrence of bacteremia, septic shock, infection-related complications and, finally, according to mortality.

In each analysis, PCT was considered as a numerical parameter allowing the comparison of mean or median. PCT values were then used to stratify the patients into three different classes according to the cutoffs recommended by the manufacturer: PCT < 0.5 ng/ml (probable exclusion of any bacterial infection), ≥ 2 ng/ml (probable diagnosis of bacterial infection) and ≥ 0.5 and < 2 ng/ml (no definitive conclusion).

Continuous variables were expressed as mean, standard deviation, median and quartiles. Categorical parameters were expressed as frequencies. Comparisons between groups were performed using the χ^2 test or Fisher's exact text for categorical parameters. Continuous variables were analyzed using t-test, analysis of variance, Kruskall-Wallis or Wilcoxon's tests, according to the normality of the parameter, the number of groups compared and the sample size of the groups. Differences between groups were considered to be significant for variables yielding a p-value ≤ 0.05. ROC curves were computed for PCT and CRP in order to assess the sensitivity and specificity to predict either a positive bacterial etiology or death. All analyses were performed using the SAS Software, V8.2 [27].

Results

Patients

A total of 110 patients with severe CAP were included. The mean age was 58.8 ± 16.3 years, and 64% were male. On ICU admission, SAPS II, Glasgow coma score and OSF score values were 43 ± 21.2, 12.5 ± 4, and 1.6 ± 1, respectively. According to the McCabe classification, ultimately and rapidly fatal underlying diseases were present in 57 and seven patients, respectively. The main organ dysfunctions on ICU admission are reported in Table 1. Among the 92 patients admitted with respiratory distress, 74 required mechanical ventilation: 65 were intubated and nine were treated with noninvasive ventilation. 42 patients (38.2%) developed septic shock: 16 were treated with dopamine, 14 with dobutamine, 12 with noradrenaline, and seven with adrenaline. For seven patients continuous hemofiltration was performed.

Diagnostic Value of PCT

The mean level of procalcitonin was 24 ± 80 ng/ml. The median value was 2 ng/ml, with a lower quartile at 0.6 ng/ml and an upper quartile at 8.6 ng/ml. Of the patients, 50% had a PCT level > 2 ng/ml, 30% had a level between 0.5 and 2 ng/ml, and 20% had a level < 0.5 ng/ml.

A causative organism was identified in 48 patients (43.7%). Predominant pathogens were *S. pneumoniae* (43.8%), gram-negative bacilli (37.5%), and *Staphylococcus aureus* (18.7%). In gram-negative bacilli, *Haemophilus influenzae* and *Escherichia coli* were frequently isolated. Median initial PCT level was higher when an etiologic

Table 1
Organ dysfunctions on admission.

	No.	%
Respiratory dysfunction	92	83.6
Hemodynamic dysfunction	37	33.6
Renal dysfunction	21	19.1
Hematologic dysfunction	6	5.5
Hepatic dysfunction	4	3.6
Neurologic dysfunction	14	12.7
Immunosuppression	14	12.7

Respiratory dysfunction: respiratory rate ≤ 5/min or ≥ 49/min, $PaCO_2$ ≥ 50 mmHg, $AaDO_2$ ≥ 350 mmHg or mechanical ventilation. Hemodynamic dysfunction: heart rate ≤ 54/min, mean blood pressure ≤ 49 mmHg, ventricular tachycardia or fibrillation or pH ≤ 7.24 with $PaCO_2$ ≤ 49 mmHg. Renal dysfunction: urine output ≤ 479 ml/24h, serum urea ≥ 100 mg/100 ml or serum creatinine ≥ 3.5 mg/100 ml. Hematologic dysfunction: leukocytopenia ≤ 1,000/mm³, thrombocytopenia ≤ 20,000/mm³ or hematocrit ≤ 20%. Hepatic dysfunction: serum bilirubin > 30 mg/l without hemolysis, ALAT > 2 × normal or hepatic encephalopathy. Neurologic dysfunction: Glasgow coma score < 6 without sedation

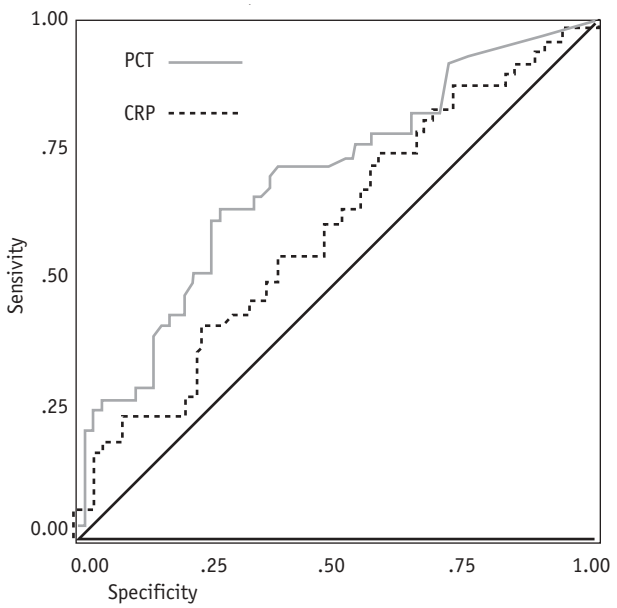

Figure 1. ROC curve: PCT, CRP and bacterial documentation.

agent was recovered (4.9 ng/ml [1.2–20.8] vs 1.5 ng/ml [0.4–4.9]; p = 0.0009). Median values of PCT according to the causative pathogen were as follow: *S. pneumoniae*: 6.5 ng/ml (3.5–37), gram-negative bacteria: 1.4 ng/ml (0.6–7.1), and *S. aureus*: 4.3 ng/ml (1.1–61). A PCT level ≥ 2 ng/ml was found in 81% of patients with pneumococcal CAP, in 43.8% of patients with CAP due to gram-negative bacilli, and in 72.7% of patients with CAP due to another agent (essentially *S. aureus*). In patients without any microbial documentation, a PCT level ≥ 2 ng/ml was observed in 37.1% of cases (Table 2).

The ROC analysis did not allow the identification of a specific threshold to differentiate positive from negative documented CAP based on PCT as well as CRP values: the areas under the curve were 0.597 for the CRP, and 0.685 for the PCT, respectively (Figure 1).

In the three groups of patients classified based on the PCT level, we determined the mean values of clinical and biological parameters collected on the day of PCT measure (Table 3). No significant relationship was found between PCT levels and body temperature or leukocyte count. In contrast, mean CRP values significantly increased with PCT levels (p = 0.04). However, the mean CRP value was already high (138 ± 140 mg/l) in the group of patients who had a PCT level < 0.5 ng/ml. Finally, the PCT level was inversely associated with platelet count (p = 0.001).

Prognostic Value of PCT

Ten patients exhibited bacteremia associated with CAP. Causative organisms were *S. pneumoniae* (n = 7), *E. coli* (n = 2), and *S. aureus* (n = 1). Procalcitonin level was > 2 ng/ml in nine patients exhibiting bacteremic CAP. In the remaining patient, the PCT level was 1.8 ng/ml. No patient with bacteremia had a PCT level < 0.5 ng/ml.

The PCT level significantly increased in the presence of septic shock (5.1 ng/ml [2.4–41] vs 1.4 ng/ml [0.6–5.4];

Table 2
PCT levels according to bacterial diagnosis[a].

Causative pathogen No. (%)	PCT < 0.5 ng/ml 22	0.5 ≤ PCT < 2 ng/ml 33	PCT ≥ 2 ng/ml 55	P-value[b]
None	18 (29)	21 (33.9)	23 (37.1)	0.003
Positive	4 (8.3)	12 (25)	32 (66.7)	–
- *Streptococcus pneumoniae*	2 (9.5)	2 (9.5)	17 (81)	–
- Gram-negative bacilli	2 (12.5)	7 (43.7)	7 (43.8)	–
- Other	0	3 (27.3)	8 (72.7)	–

[a] data are presented as no. (%); [b] comparison between all the groups

p = 0.0002) and increased with the number of organ dysfunction (no dysfunction: 1.4 ng/ml [0.4–2.1]; n = 21, 1 or 2 dysfunctions: 1.7 ng/m [0.6–7.6]; n = 70, and more than 2 dysfunctions: 12.3 ng/ml [2.5–125] n = 19; p = 0.0001). The PCT level was more often ≥ 2 ng/ml in patients exhibiting > 1 organ dysfunction (p = 0.0006) (Table 4).

A total of 41% of patients developed complications during their ICU stay: 17.3% a superinfection, 34.6% infection-related complications (ARDS: 22.7%, septic shock: 30%, MOF: 18.2%, DIC: 10.9%). In patients developing infection-related complications, initial PCT levels were significantly higher (5.4 ng/ml [1.8–18] vs. 1.3 ng/ml [0.4–5.7]; p < 0.001).

Of the patients who developed an infection-related complication during their ICU stay, 73% had a PCT value ≥ 2 ng/ml on admission, whereas only 5.3% of them had a value < 0.5 ng/ml (p = 0.0007). The relationship between an initial PCT level > 2 ng/ml and the ultimate occurrence of infection-related complications was found for any kind of complication (Table 5).

30 (27.3%) of the 110 patients died during their ICU stay. The median value of PCT for the survivors was 1.5 ng/ml (0.6–5.4) compared to 5.6 ng/ml (2.4–61) for the deceased (p < 0.0001). Mortality rate significantly increased according to the initial PCT level (Table 6). In patients exhibiting an initial PCT level > 2 ng/ml, mortality rate was 41.8% (23/55). This percentage dropped to 12.7% when PCT level was below 2 ng/ml (p = 0.0006).

In the survivors and deceased, mean values of CRP were 150 mg/l and 210 mg/l, respectively. We tried to find CRP and PCT cutoff values that were significantly related to mortality with a ROC curve (Figure 2). Sensitivity and specificity of these measures were insufficient to estimate survival (area under the curve: 0.57 for CRP, 0.723 for PCT).

Table 3
Diagnostic value of PCT compared with others infectious markers[a].

No.	PCT < 0.5 ng/ml 22	0.5 ≤ PCT < 2 ng/ml 33	PCT ≥ 2 ng/ml 55	P-value[b]
Temperature (°C)	38 ± 0.5	37.8 ± 1.4	38 ± 1.2	0.97
Leukocyte count (/mm³)	13,045 ± 3,930	15,045 ± 8,085	12,214 ± 6,920	0.3
CRP (mg/l)	138 ± 140	188 ± 124	223 ± 147	0.04
Platelet count (10³/mm³)	259 ± 99	263 ± 144	181 ± 114	0.001

[a] data are presented as no. or mean value ± SD; [b] comparison between all the groups

Table 4
Prognostic value of PCT according to organ dysfunctions and septic shock[a].

No.	PCT < 0.5 ng/ml 22	0.5 ≤ PCT < 2 ng/ml 33	PCT ≥ 2 ng/ml 55	P-value[b]
Bacteremia	0	1	9	0.03
Septic shock	1 (2.4)	11 (26.2)	30 (71.4)	0.0002
Organ dysfunction				0.0006
0 or 1	19 (31.1)	20 (32.8)	22 (36.1)	
> 1	3 (6.1)	13 (26.5)	33 (67.4)	

[a] data are presented as no. (%); [b] comparison between all the groups

Table 5
Prognostic value of PCT and complications[a].

No.	PCT < 0.5 ng/ml 22	0.5 ≤ PCT < 2 ng/ml 33	PCT ≥ 2 ng/ml 55	P-value[b]
Sepsis-related complications	2 (5.3)	8 (21)	28 (73.7)	0.0007
– ARDS	2 (8)	3 (12)	20 (80)	0.003
– Septic shock	2 (6.1)	7 (21.2)	24 (72.7)	0.005
– MOF	2 (10)	1 (5)	17 (85)	0.002
– DIC	0 (0)	1 (8.3)	11 (91.7)	0.009

[a] data are presented as no. (%); [b] comparison between all the groups

Table 6
Prognostic value of PCT and mortality[a].

No.	PCT < 0.5 ng/ml 22	0.5 ≤ PCT < 2 ng/ml 33	PCT ≥ 2 ng/ml 55	P-value[b]
Deceased	3 (10)	4 (13.3)	23 (76.7)	0.003
Survivors	19 (23.7)	29 (36.3)	32 (40)	

[a] data are presented as no. (%); [b] comparison between all the groups

Discussion

Even if the admission mean PCT value is far above the critical cutoff threshold of 2 ng/ml (24 ± 80 ng/ml), 50% of the patients had values < 2 ng/ml, and 20% < 0.5 ng/ml. These results suggest that this marker is not an interesting tool to diagnose severe CAP. However, to assess CAP severity PCT appears to be a better indicator: a high level is associated with a high incidence of bacteremia, severe sepsis, infection-related complications, and finally, mortality.

During the last decade, the measurement of procalcitonin became a common tool in infectious diseases management, particularly in sepsis with bacteremia [29, 30, 38]. However, sensitivity and specificity of this parameter remain low in localized [5] or moderate infections [31, 32]. Studies evaluating PCT in CAP are sparse and, most of the time, with a limited number of patients. Studies focusing on patients with moderately severe CAP without sepsis demonstrated that the increase in PCT was not constant (60% of the patients) [8, 9], and moderate (usually < 0.5 ng/ml) [10, 11]. Only one study was performed in patients exhibiting severe CAP requiring ICU admission: the median PCT value was > 2 ng/ml [14]. Our data are consistent with this result; however, we must underline that, even if the mean PCT level on ICU admission was far over the cutoff value set at 2 ng/ml, only 50% of our patients had an initial PCT level ≥ 2 ng/ml. Moreover, for 20% of the patients, the PCT value < 0.5 ng/ml. Consequently, PCT does not appear as a significant marker for the positive diagnosis of CAP since a level < 0.5 ng/ml could not rule out the diagnosis and could delay the initiation of an empiric antibiotic treatment.

The role of PCT measurement to predict a causative organism incriminated in sepsis remains unclear. Most of the studies demonstrated that PCT levels appeared quite similar in sepsis due to gram-positive or gram-negative bacteria [28, 29]. In lower respiratory tract infections, PCT level is low when causative organisms are atypical pathogens or *Mycobacterium* spp. [8–10]. In the present study, PCT levels appeared significantly higher when a causative organism was identified (4.9 ng/ml vs 1.5 ng/ml; p = 0.0009). Although we found no precise relationship between a PCT level and a group of causative agents, we noticed that most patients with pneumococcal CAP (81%) had an initial PCT level > 2 ng/ml. This could be explained by the high frequency of bacteremia associated with pneumococcal CAP in our series (7/21 patients). In patients without identification of a causal organism, we found a high percentage (63%) of PCT levels < 2 ng/ml. A virus or intracellular bacteria could be involved. CAP diagnosis may also have been overestimated, even if the patient fulfilled all inclusion criteria.

When comparing PCT to other usual markers of infection, we noted a significant relationship between CRP and PCT. Consistent with other authors, CRP values were always higher than baseline, even in patients with a PCT value < 0.5 ng/ml [8, 31]. In fact, if PCT is a better marker of sepsis than CRP [28, 35], CRP appears to be more useful in localized infections. In respiratory tract infections, CRP levels are usually high, even in patients exhibiting a moderately severe CAP [12]. Nevertheless, CRP is not the best marker based on its kinetic properties, and its inflammation-related production. Consequently, we think these two measures must be interpreted carefully in the diagnosis of CAP.

In our series, ten patients (9%) were bacteremic; nine had an initial PCT level ≥ 2 ng/ml and none a level < 0.5 ng/ml. Several studies showed, in bacteremia, that the

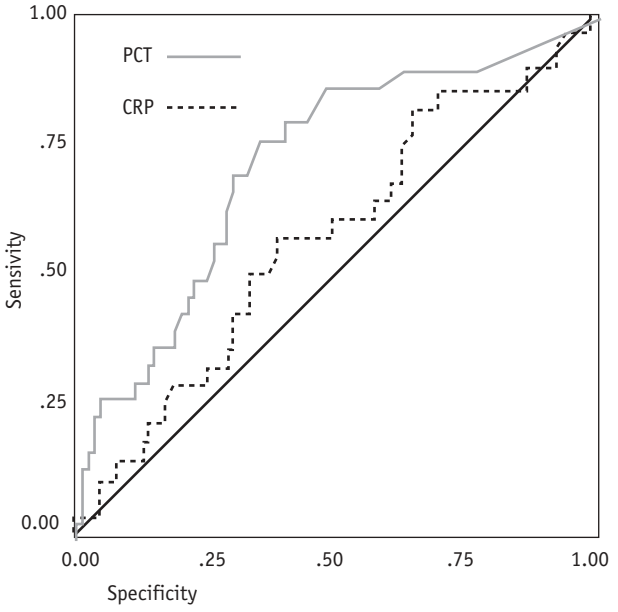

Figure 2. ROC curve: PCT, CRP and mortality.

initial PCT level was usually high [32, 33]. Some authors even proposed the use of specific cutoff values for bacteremia: a level < 0.5 ng/ml would suggest the absence of bacteremia and > 20 ng/ml would be in favor of a bacteremic episode [28, 34]. In our study, we never observed a PCT level < 0.5 ng/ml in bacteremia, supporting the exclusion of bacteremia in this case. On the contrary, a PCT level > 2 ng/ml did not appear to be such a good predictor of bacteremia since 46 of the 55 patients exhibited a high level without positive blood cultures. In spite of these results, we realize that the prognostic value for bacteremia is difficult to evaluate with only ten patients.

We found that the serum PCT level increased significantly with the severity of the sepsis, particularly when more than one organ failed, and when an infection-related complication such as ARDS, DIC, or septic shock occurred. This relationship between the PCT level and the severity of illness (systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock) has been previously reported [14, 30, 35, 36]. The PCT level increases with the number of organ failures [31, 37]. When compared to the other inflammatory markers (CRP, interleukin-6, interleukin-8, D-dimers, tumor necrosis factor), PCT always appears as the best indicator to assess the severity of sepsis [30, 31, 38]. Our results are in agreement with these data suggesting that PCT measurement is more interesting to estimate the severity of a CAP than to confirm a diagnosis.

Although we were unable to find a PCT level to predict mortality, a significant and positive relationship between the initial PCT level and the mortality rate was observed. In experimental studies, animals receiving PCT had, compared with controls, a higher mortality rate, whereby an injection of an antiserum directed against procalcitonin improved survival [38, 39]. In clinical studies, a correlation between mortality rate and PCT level on admission was reported in most publications including patients with severe sepsis or septic shock [28, 40]. Some authors even proposed to include the PCT level in scores assessing sepsis severity on ICU admission [41]. In a few studies, although a correlation between PCT level on admission and survival did not appear, an increase in PCT levels within the first 48 h following admission appeared as a risk factor of death, whereas a decrease was associated with a better outcome [30, 42]. In CAP, the initial PCT level was not so clearly related to prognosis. *Brunkhorst* et al. [14] studied 93 patients with severe CAP and ventilator-associated pneumonia in an ICU, the median initial PCT level was 2.3 ng/ml. PCT levels were measured daily during the first 5 days of hospitalization and never correlated with prognosis. However, the authors underlined that an increase in PCT levels at the end of the observation period was a poor prognostic factor. In a second study reporting 96 patients with moderately severe CAP, PCT was not correlated to mortality, but the median PCT level was 0.2 ng/ml and only two patients died [9].

Our study has several limitations: first, recent studies showed that the PCT level decreases rapidly after hospital admission for CAP [9, 14]. The blood samples were collected within the first 48 h after admission because of limited laboratory availability in our hospital; therefore, our results must be taken with caution. For the same reason, we did not perform repeated samples to evaluate PCT kinetics. Second, our method can only measure a PCT level > 0.5 ng/ml. It was recently shown in CAP that values from 0.1 to 0.5 ng/ml could help diagnose a bacterial origin and guide antibiotic treatment [13]. Some of our patients may have developed pulmonary diseases without any bacterial agent, even if they had criteria defined as severe CAP.

In conclusion, measurement of PCT appears as an interesting marker in the management of CAP, even if no particular level appears sensitive enough to be useful for the diagnosis. Consequently, it must always be used in association with the other usual infectious markers. The prognostic value of PCT seems to be more interesting: a PCT level > 2 ng/ml upon ICU admission is associated with an increased rate for the evolution of septic shock, multiorgan dysfunctions, and mortality. However, alone its value seems insufficient to classify the patients.

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