Sequential measurements of procalcitonin in diagnosing ventilator-associated pneumonia

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ABSTRACT

We evaluated the utility of procalcitonin to improve the accuracy of clinical and microbiological parameters in diagnosing ventilation-associated pneumonia (VAP).

Sequential measurement of procalcitonin and C-reactive protein, and the calculation of the simplified Clinical Pulmonary Infection Score (CPIS) were done in 44 mechanically-ventilated patients >48 hours without active infection at admission until the end of mechanical ventilation or suspicion of VAP. Patients who developed extrapulmonary infection were excluded.

Twenty cases were suspected of having VAP and diagnosis was microbiologically-confirmed in 9. In patients with confirmed VAP, procalcitonin levels were higher that those without VAP (p<0.001). C-reactive protein and CPIS were lower in patients without suspected VAP (p=0.004 and <0.001, respectively) but could not discriminate confirmed and non-confirmed suspicion of VAP. The best sensitivity and specificity (78% and 97%, respectively) corresponded to procalcitonin. The CPIS resulted in the same sensitivity, but had a lower specificity (80%). C-reactive protein had the worst sensitivity (56%), but a good specificity (91%). CPIS ≥6 combined with serum levels of procalcitonin ≥2.99 ng/mL did not improve the sensitivity (67%) but resulted in 100% specificity.

Procalcitonin might be useful in the diagnosis of VAP. Combined values of CPIS and procalcitonin below the cutoff points excluded false positive diagnoses of VAP.
INTRODUCTION

Ventilator-associated pneumonia (VAP) is an important problem in daily practice in intensive care medicine since it is associated with more prolonged hospital stay and greater mortality [1,2]. However, the diagnosis of VAP continues to be difficult [3]. The classical clinical criteria, the appearance of infiltrates on chest x-ray, purulence of respiratory secretions, variations in body temperature or the number of circulating leukocytes have a low specificity for the diagnosis of VAP. Microbiological confirmation takes 24-72 hours and the frequent previous use of antibiotics may give false negative information. The lack of consensus between the different authors and the poor accuracy in the diagnostic criteria used demonstrate the diversity between the values published and the incidence of VAP [1-3]. In this context, the determination of biological markers may aid in the diagnostic algorithm of VAP. One of these markers is procalcitonin, which is secreted by the organism as part of the systemic inflammatory response but only when this is triggered by infection [4]. Procalcitonin has been successfully applied in different diseases to determine the presence of an active infectious process [5]. Nonetheless, few studies have analyzed the behavior of procalcitonin when the infection is in the lung [6-9]. Furthermore, there are even fewer studies aiming to establish a diagnostic cutoff value of procalcitonin in VAP and their results are discordant [10-12].

Our hypothesis is that serum procalcitonin values may aid in the diagnosis of VAP. We performed a cohort study with sequential measurement of procalcitonin in patients receiving mechanical ventilation in our unit with the aim of determining the utility of procalcitonin in the diagnosis of VAP and
establishing a cutoff point while attempting to eliminate all interference due to extrapulmonary infections.

METHODS

Design and inclusion criteria

We performed a prospective, observational study in the intensive care unit (ICU) of a tertiary university-teaching hospital from September 2004 to February 2006. The ICU has 21 beds and attends medical patients. This study was approved by the Ethical Committee of the hospital and informed consent was obtained from the families of the patients studied.

We included patients receiving mechanical ventilation expected to continue more than 48 hours. Exclusion criteria were active infection at admission and previous diagnosis of small cell lung cancer or medullar cancer of the thyroid. Patients developing nosocomial infection other than VAP during hospitalization were excluded on diagnosis of these infections.

Data collection protocol

The following data were collected on study inclusion: sex, comorbidities, severity scores prior to intubation, including the Glasgow Coma Scale, the Acute Physiology Score (APS), the Acute Physiology and Chronic Health Evaluation Score-II (APACHE-II) [13], the Sepsis-related Organ Failure Assessment (SOFA) [14], the simplified Clinical Pulmonary Infection Score (CPIS) [15], the presence or not of the Systemic Inflammatory Response Syndrome (SIRS) [16], the causes of the initiation of mechanical ventilation, and the use of antibiotics the week prior to inclusion in the study.
Daily evaluation of the patients included calculation of the severity scores: APS, APACHE-II and SOFA, evaluation of SIRS, calculation of the simplified-CPIS, evaluation of the clinical diagnostic criteria of VAP, the presence of other infections [17] and the use of systemic antibiotics.

The day of study inclusion we determined procalcitonin and C-reactive protein (CRP). These determinations were repeated every 48 hours until the end of the study.

In cases with clinical suspicion of VAP, samples were collected to determine procalcitonin and CRP in serum and in bronchoalveolar lavage (BAL). These evaluations were repeated 72 hours after case confirmation.

The follow up of patients included in the study continued until the end of mechanical ventilation or until the appearance of the first episode of suspicion of VAP.

Definitions

The suspicion of VAP was established if patients met either: a) classical clinical criteria, the appearance of a new pulmonary infiltrate on chest x-ray or progression of an existing infiltrate together with two of the following criteria: temperature greater than 38 ºC, leukocytosis greater than 12,000/mm³ or purulent respiratory secretions [18]; or b) simplified-CPIS score greater than 5 points [15].

The confirmation of VAP was defined by the quantitative culture of BAL with $\geq 10^4$ colony forming units per milliliter [19] of a potentially pathogenic microorganism. At this time, blood and urine were also collected [20] to discard the presence of other nosocomial infections [17]. Patients were classified into three groups based on their evolution with regard to the appearance of VAP: a)
without suspicion of VAP and absence of pulmonary infiltrates; b) with non-confirmed VAP (with initial suspicion of VAP not confirmed microbiologically); and c) with VAP confirmed microbiologically. An effort was made to find an alternative diagnosis in those patients from group b).

**Evaluation of the evolution of VAP**

Cases confirmed with VAP were evaluated at 72 hours. Non responders were considered to be cases in which at least one of the following criteria were present: a) absence of improvement in PaO₂/FiO₂, b) persistence of fever (≥ 38°C) together with purulent respiratory secretions, c) increase in the respiratory infiltrate on chest x-ray of >50%, or d) the development of septic shock or multiorgan failure [21].

**Study of inflammatory markers**

The blood samples taken for determination of inflammatory markers were centrifuged (1,500 rpm, 10 min.) and the supernatant was frozen at -20°C. Procalcitonin was measured by TRACE (Time-Resolved Amplified Cryptate Emission) technology in a Kryptor analyzer (Brahms Diagnostica, Berlin, Germany). Measurement of CRP was performed with an immunoturbidimetric method using a commercial kit (Tina-quant CRP, Roche Diagnostics, Mannheim, Germany).

**Statistical analysis**

Categorical variables were compared using the Chi-square and the Fisher's exact tests when appropriate. Comparison of numerical and categorical variables was performed with the Student’s t or the Mann-Whitney U tests when the second was dichotomous and the ANOVA analysis of variance or the Kruskal-Wallis H test were carried out for variables with more than 2 categories. The
sensitivity, specificity and positive and negative predictive values of procalcitonin, CRP and CPIS were determined comparing patients with confirmed VAP and those without pneumonia (non-confirmed suspicion and no suspicion). Receiver operating characteristic (ROC) curves were made to determine the optimal cutoff values and to evaluate the general discriminative capacity of these indices. The optimal cut off values were obtained from the best sensitivity/specificity ratios. The results were expressed as median with interquartile (25%-75%) range in parenthesis. Statistical analysis was performed with the SPSS v.10 computer program.

RESULTS

Description of the population

All patients receiving mechanical ventilation were screened during the study period (Figure 1), and 52 patients were included in the study. Eight of the patients initially included were excluded: in 5 cases mechanical ventilation was used for less than 48 hours and in 3 cases active infection was diagnosed after the time of inclusion. No patient developed nosocomial infection other than VAP.

The reason for admission to the ICU was cerebral vascular accident in 30 cases (68%), cardio-respiratory failure followed by reanimation in 9 cases (20.5%), coma of another etiology in 2 cases (4.5 %), one acute respiratory failure of neuromuscular origin, one cardiogenic shock secondary to acute myocardial infarction and one exacerbation of chronic respiratory insufficiency. The most common co-morbidities were diabetes mellitus (20,5%), smoking (11,4%), systemic steroids (4,5%) and COPD (2,3%).
Twenty patients were suspected of having VAP throughout their stay in the ICU. Microbiological analysis of the BAL confirmed the presence of VAP in 9 cases. The causative microorganisms of the confirmed cases of VAP were *Staphylococcus aureus* in 3 cases, *Acinetobacter baumanii* in 3 cases, *Klebsiella pneumoniae* in 2 cases and *Streptococcus pneumoniae* in one case. After 72 hours of evolution 2 patients were classified as responders and 4 as non responders, while the remaining 3 could not be evaluated because of death due to brain injury before 72 hours.

The non-microbiologically confirmed cases (11) were not considered as having VAP. Only in three of these patients there was a positive culture of BAL, all of them with less than $10^3$ colony forming units per millimeter of *Acinetobacter baumanii*, coagulase-negative *Staphylococcus* species and *Haemophilus influenzae*. In 18% of these patients an antibiotic treatment was in use.

Table 1 shows the characteristics of the patients at the time of study inclusion. No statistically significant differences were found in any of the variables studied.

Table 2 describes the characteristics of the three groups the day on which VAP was suspected. In the patients not suspected of having VAP the characteristics of day 4 were used (median of day of evolution in which VAP was suspected in the other two groups). The administration of systemic antibiotic treatment on the days prior to suspicion of VAP was similar in the three groups. No differences were found in regard to the presence of SIRS, APACHE-II, APS, temperature and leukocyte count. The SOFA score and simplified-CPIS scale were greater, and the PaO$_2$/FiO$_2$ ratio was lower, in the
groups with confirmed and non-confirmed suspicion of VAP compared to the group without clinical suspicion of VAP.

**Results of C-reactive protein and procalcitonin in the diagnosis of VAP**

The differences in the plasma levels of procalcitonin and CRP among the three groups the day of VAP suspicion were statistically significant, especially in regard to procalcitonin ($p<0.001$), with the highest values corresponding to patients with microbiological confirmation of VAP (Table 2). When comparing patients with VAP and non-confirmed VAP, only procalcitonin was significantly higher in patients with VAP ($p=0.001$), while CRP was not significantly different.

Analysis of procalcitonin in BAL did not show differences between the group with VAP and the group with non-confirmed VAP (Table 2). A non-significant trend to higher BAL levels of CRP were shown in patients with confirmed VAP ($p=0.091$).

**Diagnostic value of serum levels of procalcitonin and CRP and the CPIS scale**

Table 3 shows the optimal cutoff values of procalcitonin, CRP and simplified-CPIS to calculate the operative indices, as well as the general discriminative capacity of these indices to differentiate between the presence and the absence of VAP, assessed by the area under the ROC curve (Figure 2). The best sensitivity and specificity (78% and 97%, respectively) corresponds to procalcitonin. The simplified-CPIS resulted in the same sensitivity, but had a lower specificity (80%). C-reactive protein had the worse sensitivity (56%), but a good specificity (91%).
The use of simplified-CPIS ≥ 5 points in combination with serum levels of procalcitonin ≥ 2.99 ng/mL did not improve the sensitivity (67%) but resulted in 100% specificity.

The diagnostic capacity of procalcitonin, CRP and the simplified-CPIS score were maintained on comparing all patients with clinical suspicion of VAP (with and without microbiologic confirmation) versus the group without suspicion of VAP. The area under the ROC curve was 0.785, 0.782 and 0.970 for procalcitonin, CRP and the simplified-CPIS, respectively. However, on comparing the group with confirmed VAP versus the group with non-confirmed VAP, the discriminative capacity only remained with procalcitonin (the area under the ROC curve was 0.828), while in the other variables, the area under the ROC curve fell to 0.544 and 0.651 for CRP and the simplified-CPIS, respectively.

DISCUSSION

The results of this study show that serum procalcitonin is useful in the diagnosis of VAP. The simplified CPIS scale has a similar sensitivity but lower specificity than serum procalcitonin. Combining the clinical data, assessed by the CPIS scale, and serum procalcitonin excluded false positive diagnoses of VAP in our population.

Currently, the diagnosis of VAP is still established by the presence of some clinical criteria together with a positive quantitative culture of a representative respiratory sample. Nonetheless, the incidence of VAP in patients receiving mechanical ventilation varies widely from one study to another (9% – 27%). This discordance may lay in the lack of consensus
regarding the diagnostic criteria which, in turn, is due to the inaccuracy of the criteria used. The sensitivity and specificity of the classical clinical criteria are deficient. One study in post mortem pulmonary biopsies reported that the combination of new and persistent infiltrates on chest x-ray and two or three of the following criteria: fever (> 38 °C), leukocytes (>12,000/mm³) or purulent tracheal secretion, had a sensitivity of 69 % and a specificity of 75 % (3). With regard to microbiological confirmation, the problems are the delay in obtaining culture results (48 – 72 hours), the variability of the cut-off of colony forming units used and the potential interference of antibiotic use. In this context the determination of biological markers, such as procalcitonin, CRP and soluble triggering receptor expressed on myeloid cells (sTREM-1), might be of help in the diagnostic process of VAP [12].

Procalcitonin is secreted as part of the systemic inflammatory response to infection. Serum values of procalcitonin vary greatly based on the type and severity of infection [4,5]. Few studies have analyzed the behavior of procalcitonin in lung infection [6-9]. However, the use of procalcitonin for the diagnosis of VAP has not been established.

In the present study we have evaluated the relationship between procalcitonin and VAP and we have established a diagnostic cutoff point of 2.99 ng/mL that provides the best sensitivity and specificity. This finding is of particular importance to distinguish infectious from non-infectious etiologies in patients with pulmonary infiltrates, which is a current dilemma in the clinical practice. The differences in the cutoff point of PCT found in other diseases (f.e. CAP) could be due explained by the increased and complex inflammatory response in critically ill mechanically ventilated patients.
Our results are different from those obtained by Oppert et al. (cutoff point 1 ng/mL) [10]. However, it seems that the diagnostic criteria of VAP used by these authors differed greatly from those currently accepted. Duflo et al. found a diagnostic cutoff point 3.9 ng/mL with a sensitivity of 41% and a specificity of 100% [11]. However, they only included patients with suspicion of VAP and they did not control for extrapulmonary infections as we did in our study. Similar to the study by Duflo et al, we did not find any differences in alveolar PCT values among different groups. PCT mainly forms part of the systemic response to infection and consequently alveolar values are lower compared to serum ones.

Gibot et al. analyzed the behavior of procalcitonin in pneumonia (community and ventilator-acquired) and concluded that there were no differences between the groups with and without pneumonia [12]. However, a high percentage of patients with pneumonia had other infections which increased the serum procalcitonin values.

The results of this study indicate that, although CRP may have a certain utility in the diagnosis of VAP, procalcitonin was better than CRP as a biological marker of bacterial infection. In a previous metaanalysis performed by Simon et al. [5], procalcitonin was also superior to CRP in different types of bacterial infections. Povoa et al. recently studied the role of CRP to detect infections in critically ill patients. In this study, CRP was a reasonable marker of bacterial infection when combined with body temperature [23]. However, the groups studied were very heterogeneous and then conclusions for specific groups have to be made cautiously, since CRP values are not only influenced by infections but also by any pro-inflammatory circumstance of non infectious nature [23,24].
The simplified CPIS scale, as used by Luna et al., has shown to be useful in the diagnosis and prognosis of VAP, and our results are in agreement with previous publications [15]. In this study, 100% patients with VAP had a score greater than 5 points, as we observed in our patients with confirmed VAP. Combining both the simplified CPIS and procalcitonin for the initial diagnosis of VAP we obtained a 100% specificity. The major advantage of this combination is in avoiding false positive results. This can be very useful in order to restrict unnecessary antibiotic treatments. However, the risk of undertreatment has to be taken into account.

By contrast, in a recent preliminary report, crude levels of procalcitonin did not result in good diagnostic accuracy for VAP (25). The explanation for this is the population selected without avoiding extrapulmonary infections.

Procalcitonin is a good prognostic marker in patients with VAP, as it has been demonstrated by Luyt et al. [26]. Due to the small number of responders and non responders after 72 hours of evolution in our study, we could not evaluate the utility of procalcitonin for the assessment of antibiotic treatment response.

The main limitations of our study are the small sample size and the selection of the type of patients. These limitations are the consequence of avoiding the multiple confounding factors usually present in critically ill patients for these type of studies. To avoid the interferences of extrapulmonary infections in the determination of procalcitonin values, it was necessary to exclude patients who had active infection at the time of initiating mechanical ventilation. Likewise, we excluded patients who developed extrapulmonary infection during follow-up. Therefore, we can confirm that the variations
observed in the plasma procalcitonin values were only due to the presence or absence of VAP. Another limitation is that despite we used quantitative microbiology to confirm VAP, it is important to keep in mind the potential false-positive and false-negative results of using quantitative cultures. Obviously this could have influenced our PCT results.

In conclusion, the measurement of serum procalcitonin might be a reliable marker for the diagnosis of VAP. Combining this marker with the simplified CPIS scale we obtained 100% specificity and therefore this would avoid unnecessary antibiotic treatments by excluding false positive diagnoses of VAP. However, we recognize that this is a pilot study with several limitations and despite the promising results PCT is not yet a tool to be used in the routine practice to diagnose VAP. The next step is the validation of our results in an independent population representative of a medical ICU.
LEGENDS TO THE FIGURES

**Figure 1.** Screening of patients undergoing mechanical ventilation during the study period.

**Figure 2.** Receiver-operator-characteristic (ROC) curves for procalcitonin (PCT), C-reactive protein, the simplified Clinical Pulmonary Infection Score (CPIS) and the combination of PCT + CPIS.

AUC = area under the ROC curve. CI = confidence interval. The optimal cutoff points for the 3 variables are shown in Table 3.

REFERENCES


Table 1. Characteristics of the patients on the day of study inclusion (at start of mechanical ventilation) *

<table>
<thead>
<tr>
<th></th>
<th>Non-suspected VAP</th>
<th>Non-confirmed VAP</th>
<th>Confirmed VAP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>63 (52-72)</td>
<td>66 (53-73)</td>
<td>61 (45-74)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>16</td>
<td>5</td>
<td>6</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>ICU stay (days)</strong></td>
<td>10 (5.5-16.5)</td>
<td>16 (10-18.5)</td>
<td>7 (6-14)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Hospitalization (days)</strong></td>
<td>11.5 (6.5-25)</td>
<td>16 (10-25.5)</td>
<td>7 (6-14)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>GCS prior to intubation</strong></td>
<td>6 (3-8)</td>
<td>6 (3-7.5)</td>
<td>4 (3-5)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Previous antibiotics(days)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Presence SIRS</strong></td>
<td>19 (79%)</td>
<td>9 (82%)</td>
<td>9 (100%)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>APACHE-II</strong></td>
<td>20 (16.5-24)</td>
<td>18 (15.5-23)</td>
<td>20 (18-24)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>APS</strong></td>
<td>14.5 (11.5-16.5)</td>
<td>13 (11-19)</td>
<td>18 (13-21)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>SOFA</strong></td>
<td>6 (5-8)</td>
<td>6 (5.5-7.5)</td>
<td>7 (6-7)</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>CPIS</strong></td>
<td>3 (1.5-3)</td>
<td>2 (1.5-4)</td>
<td>2 (1-4)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Temperature (ºC)</strong></td>
<td>37.5 (36.3-37.9)</td>
<td>37.0 (36.0-38.5)</td>
<td>38.0 (36.0-38.5)</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Leucocytes, 10⁹/L</strong></td>
<td>11.1 (8.3-15.5)</td>
<td>11.1 (7.6-13.5)</td>
<td>14.5 (9.3-15.2)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>PaO₂/FiO₂ (mmHg)</strong></td>
<td>298 (229-349)</td>
<td>290 (255-382)</td>
<td>274 (141-409)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>CRP (mg/dl)</strong></td>
<td>3.9 (1.5-6.4)</td>
<td>4.3 (1.2-6.4)</td>
<td>3.1 (1.2-7.7)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Procalcitonin (ng/ml)</strong></td>
<td>0.15 (0.10-0.73)</td>
<td>0.33 (0.17-1.90)</td>
<td>0.46 (0.22-1.17)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Results are expressed as median (interquartile ranges), unless specified. ICU = Intensive Care Unit. GCD = Glasgow Coma Score. SIRS = Systemic Inflammatory Response Syndrome. APACHE = Acute Physiology And Chronic Health Evaluation Score. APS = Acute Physiology Score. SOFA = Sepsis-related Organ Failure Assessment. CPIS = Clinical Pulmonary Infection Score. CRP = C-reactive protein.
Table 2: Characteristics of patients on day of VAP suspicion *

<table>
<thead>
<tr>
<th></th>
<th>No suspected VAP</th>
<th>Non-confirmed VAP</th>
<th>Confirmed VAP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n: 24</td>
<td>n: 11</td>
<td>n: 9</td>
<td></td>
</tr>
<tr>
<td>Previous antibiotics, days</td>
<td>2 (0-3)</td>
<td>2 (0-2.5)</td>
<td>1 (0-2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Presence of SIRS</td>
<td>15 (62.5%)</td>
<td>9 (81.8%)</td>
<td>9 (100%)</td>
<td>0.072</td>
</tr>
<tr>
<td>APACHE II</td>
<td>17 (11.5-20.5)</td>
<td>17 (14.5-22)</td>
<td>21 (20-24)</td>
<td>0.18</td>
</tr>
<tr>
<td>APS</td>
<td>11.5 (8-17)</td>
<td>14 (10-19)</td>
<td>16 (15-19)</td>
<td>0.078</td>
</tr>
<tr>
<td>SOFA</td>
<td>5 (3-7.5)</td>
<td>7 (6-9.5)</td>
<td>9 (8-10)</td>
<td>0.003</td>
</tr>
<tr>
<td>CPIS</td>
<td>2 (1-4)</td>
<td>6 (5-7)</td>
<td>7 (6-8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.4 (36.5-38)</td>
<td>38.3 (38-38.4)</td>
<td>37 (36-39.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>Leucocytes, 10⁹/L</td>
<td>9.7 (8.0-13.4)</td>
<td>10.4 (7.5-14.0)</td>
<td>12.4 (10.3-17.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>PaO₂/FiO₂, (mmHg)</td>
<td>291 (211-373)</td>
<td>210 (181-284)</td>
<td>200 (166-229)</td>
<td>0.042</td>
</tr>
<tr>
<td>Serum CRP (mg/dl)</td>
<td>7.8 (5.2-11.8)</td>
<td>13.3 (11.7-17.1)</td>
<td>19.69 (11-20.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum procalcitonin (ng/ml)</td>
<td>0.21 (0.09-0.50)</td>
<td>0.76 (0.31-0.93)</td>
<td>3.86 (2.99-11.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BAL CRP (mg/ml)</td>
<td>-</td>
<td>0.42 (0.18-1.03)</td>
<td>1.9 (1.67-2.22)</td>
<td>0.091</td>
</tr>
<tr>
<td>BAL procalcitonin (ng/ml)</td>
<td>-</td>
<td>0.08 (0.04-0.19)</td>
<td>0.07 (0.04-0.13)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* Results are expressed as median (interquartile ranges), unless specified.

SIRS = Systemic Inflammatory Response Syndrome. APACHE = Acute Physiology And Chronic Health Evaluation Score. APS = Acute Physiology Score. SOFA = Sepsis-related Organ Failure Assessment. CPIS = Clinical Pulmonary Infection Score. CRP = C-reactive protein. BAL = Bronchoalveolar Lavage.
Table 3: Diagnostic value of serum levels of procalcitonin and C-reactive protein, and the Clinical Pulmonary Infection Score

<table>
<thead>
<tr>
<th></th>
<th>Optimal cutoff</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>≥19.69 mg/dl</td>
<td>0.714</td>
<td>56%</td>
<td>91%</td>
<td>89%</td>
<td>62.5%</td>
</tr>
<tr>
<td></td>
<td>≥2.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procalcitonin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPIS</td>
<td>≥6</td>
<td>0.873</td>
<td>78%</td>
<td>97%</td>
<td>94%</td>
<td>87.5%</td>
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<td></td>
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<td></td>
<td>80%</td>
<td>93%</td>
<td>50%</td>
</tr>
<tr>
<td>Procalcitonin +</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPIS *</td>
<td></td>
<td></td>
<td>67%</td>
<td>100%</td>
<td>92%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* For values of both procalcitonin and CPIS above their optimal cutoff. AUC = area under the ROC curve. CRP = C-reactive protein. CPIS = Clinical Pulmonary Infection Score. NPV = negative predictive value. PPV = Positive predictive value.
420 patients receiving mechanical ventilation

Ventilation foreseen <48 h (103 patients)

317 patients

Active infection (262 patients)

55 patients

Missing (3 patients)

52 patients

Excluded (8 patients)

44 patients
AUC: 0.870
95% CI: 0.712 – 1.027

AUC: 0.714
95% CI: 0.515 – 0.914

AUC: 0.873
95% CI: 0.757 – 0.989

AUC 0.961
95% CI: 0.905 - 1.016