Procalcitonin kinetics and nosocomial pneumonia in older patients

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Abstract

**Background** Early identification of treatment failure (TF) of nosocomial pneumonia (NP) remains a major challenge. To test whether use of procalcitonin (PCT) kinetics could assess the clinical efficacy in older critically ill patients with NP.

**Methods** A prospective observational study was conducted in 60 patients (≥65 years) admitted to the intensive care unit with severe NP. Serum PCT was measured on day 0, day 3, day 7 and at the end of treatment (EOT). The PCT time course was analyzed according to the therapeutic efficacy.

**Results** PCT were elevated in all patients (n=60) on day 0 and the median levels (range) were 2.5 (0.85–42.7) µg/L. There were no differences between the improvement patients (n=41) and those without improvement (n=19) in PCT on day 0 (p>0.05). However, lower PCT on days 3, 7 and at the EOT (all p<0.05) as well as greater rate of PCT decline between day 0 and day 3 (ΔPCT\(_{D3}\)% ) (29.5 ± 10.8% vs 15.1 ± 5.9%, p = 0.009) were found in the improvement patients than in those without improvement. ΔPCT\(_{D3}\)% was the best single predictor of efficacy (area under the curve [AUC], 0.791, p < 0.001) and had a sensitivity of 75.7% and a specificity of 72.0% with threshold of 26.2%. By comparison, traditional parameters and absolute PCT failed to predict treatment response (p>0.05). Indeed, the combination of ΔPCT\(_{D3}\)% > 26.2% and modified clinical pulmonary infection score (mCPIS) < 6 points could improve the predictive value (AUC, 0.890; sensitivity, 81.3%; specificity, 86.5%) .

**Conclusions** PCT levels were not influenced by aging and PCT kinetics might help to identify TF. ΔPCT\(_{D3}\)% combined with CPIS have been shown to be an marker of clinical efficacy at an earlier stage.

**Keywords:** Nosocomial pneumonia (NP), procalcitonin (PCT), procalcitonin kinetics, therapeutic efficacy, modified clinical pulmonary infection score (mCPIS), older critically ill patients
Introduction

Older critically ill patients clearly face an increased risk for nosocomial infection. Nosocomial pneumonia (NP) remains one of the major causes of morbidity and mortality \([1,2]\). Reevaluation at 72 hours after treatment is crucial to detect the treatment failure (TF) as well as to prevent other complications \([1,4]\). Unfortunately, traditional parameters failed to assess the clinical efficacy at an earlier stage. For example, fever and leukocytosis are generally considered to lack of specificity \([5]\); sputum cultures are also limited due to time-consuming and difficulties in differentiating colonization from infection \([6]\); chest radiography also remains a challenge in older patients since inflammatory absorption, if any, often becomes evident until the late phase of infection as well as confused by non-infection factors (e.g. pulmonary edema) \([7]\). The lack of an effective measures to monitor therapeutic efficacy has led to efforts aimed at biomarkers.

Procalcitonin (PCT), a 116 amino acid polypeptide and a precursor of calcitonin, was first described by Assicot as marker of bacterial infection\([8]\). Resent studies \([9,11]\) have indicated that PCT is superior to other commonly used parameters in its specificity for bacterial infection and might help to guide antibiotic stewardship in lower respiratory tract infections (LRTI). However, its role for critically ill patients is still disputed \([12,14]\). Especially, little is known about the early time-dependent changes of PCT and its behaviors in older patients. Only a few studies at emergency department, in older patients with community associated pneumonia (CAP) or chronic obstructive pulmonary disease (COPD) exacerbation, are sparse and provide conflicting results \([15,18]\). To date, the utility of PCT for predicting therapeutic efficacy at an earlier stage has not been assessed in older patients admitted to the intensive care unit (ICU) and requires further study.

METHODS

Study setting and population

Older patients (aged \(\geq 65\) years) admitted to our 18-bed mixed medicosurgical ICU with suspected NP were eligible from January 2009 to June 2010. Patients were excluded if they had diagnosis of immunosuppression, non-infective induced agranulocytosis, confirmed nonbacterial infection or underwent concomitant infection at other sites on admission; if they had non-microbiologically confirmed NP, nonbacterial NP, progressive infection at other sites, or incomplete determination of PCT as well as uncertain therapeutic effects due to the duration of treatment less than 5 days or incomplete clinical data at the final analysis.
This study was approved by the ethics committee of our hospital and the board exempted informed consent because of non-intervention design and retrospectively group.

**Baseline assessment and data collection**

Recorded data concerned age, sex, comorbid condition, patient classification (medical or surgery), and prior hospitalization before ICU admission. The following data were obtained on days 0, 3, and 7, and at the end of treatment (EOT) (designated D₀, D₃, D₇, and Dₑ, respectively): white cell count (WCC); body temperature; the results of sputum culture; PCT; chest radiography and other laboratory tests required to calculate the modified clinical pulmonary infection score (mCPIS) [19], Acute Physiology and Chronic Health Evaluation (APACHE) II score [20], and Sequential Organ Failure Assessment (SOFA) score [21]; the presence or absence of infection at other sites, appropriate antimicrobial treatment (the drug had an *in vitro* activity against the isolated strain), duration of mechanical ventilation, ICU lengths of stay and 28-day ICU crude mortality.

**Study design**

This was a prospective observational study and treatment decisions were left up to clinicians. On admission, all patients were immediately applied empirical antimicrobial therapy. After that, the modifications were according to the culture results and the treatment response. The duration of treatment was continued for at least 8 days in patients with uncomplicated pneumonia, and for at least 2 to 3 weeks (decisions according to therapeutic response and severity of illness) in those with concomitant bacteremia or MDR infection (defined as resistance to ≥3 classes of antimicrobial agents, including cephalosporins, aztreonam, carbapenems, aminoglycosides, fluoroquinolones and so on) [24]. Mechanical ventilation and airway management were performed in accordance with a standard protocol [22].

**Microbiological processing and procalcitonin assay**

Respiratory samples were obtained by tracheal aspiration, bronchoalveolar lavage or sputum specimen. Only good-quality specimens (< 10 epithelial cells and > 25 WBCs per low-power field) were semiquantitative culture and more than 3+ of microbial culture growth was considered as positive [23]. PCT concentrations were measured using the commercially available immunoluminometric assay system (Brahms PCT LIA; Berlin, Germany). Functional assay sensitivity was defined as the lowest value with an interassay coefficient of
variance (CV) < 20% of 0.1 µg/L. Change rate in PCT (ΔPCT%) was calculated using the following formula:

$$ΔPCT_{DX}\% = \frac{PCT_{D0} - PCT_{DX}}{PCT_{D0}} \times 100$$

Its values >0 indicated decreasing PCT concentrations. Conversely, indicated unchanged or increasing PCT. All assays were performed according to the manufacturers’ instructions and standard microbiology guidelines [23, 24].

### Definitions and outcome measures

NP was suspected when a patient who was in hospital or residing in a long-term care facility (> 48 hours) or present < 7 days after a patient was discharged from the hospital with initial hospitalization of ≥ 3 days developed a new and persistent radiographic infiltrate plus 2 of the following: (1) body temperature > 38°C or < 36°C; (2) WCC > 11,000/mm$^3$ or < 4,000/mm$^3$; and (3) a macroscopically purulent tracheal aspirate [28].

Diagnosis of severe NP was defined using ATS guidelines [26] and met any one of the following conditions: (1) shock defined as systolic BP of < 90 mmHg or diastolic BP of < 60 mmHg; (2) respiratory failure (ie, mechanical ventilation or the need for a fraction of inspired oxygen of > 0.35 to maintain an oxygen saturation of > 90%; (3) requirement of vasopressor therapy for > 4 hours; (4) urine output of < 20 mL/h or total urine output of < 80 mL/h for > 4 hours, unless oliguria is present due to a condition other than infection/sepsis; (5) acute renal failure requiring dialysis; or (6) rapid radiographic progression, multilobar pneumonia, or cavitation of a lung infiltrate.

Clinical efficacy was assessed within the five days of EOT or the third weeks of antimicrobial treatment by investigators and categorized as clinical improvement (complete or partial resolution of signs and symptoms of pneumonia) and no improvement (deterioration or no improvement of signs and symptoms) [25]. Microbiologic responses were classified as eradication (including presumed microbiologic eradication) or persistence (including presumed microbiologic persistence) based on culture results and clinical responses.

### Statistical analyses

SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Normally distributed parameters were expressed as mean ± SD and compared using the Student’s t-test. Non-normally distributed parameters were expressed as median (ranges) and analyzed using the rank sum test. Unordered
categorical variables were expressed as percentages, and the difference was analyzed using the chi-square test. Logistic regression analysis was used to analyze the influential factors of clinical efficacy. The predictive ability was estimated by using receiver-operating characteristic curve (ROC). All tests were 2-tailed, and p values < 0.05 were considered statistical significance.

Results

Patients characteristics

During the study period, of 291 ICU patients (aged ≥65 years), 107 had suspected NP and 47 were excluded (the reasons for exclusion are listed in Figure 1). A total of 60 patients were included. The mean age was 70.7 ± 12.7 years. 71.7% were male and 38.3% were surgical patients. 41 were categorized as having clinical improvement and 19 as no improvement.

There are the following characteristics: 32 pre-ICU acquired cases of NP and 28 ICU acquired cases of NP; multilobar pneumonia in 25% of patients (n=15), concomitant bacteremia in 16.7% of patients (n=10), septic shock in 31.7% of patients (n=19) and dysfunction of more than two organs in 55.0% of patients (n=33). Invasive ventilation was used in 56 patients (93.3%) (20 diagnosed as having VAP). The APACHE II score and mCPIS were 15.8 ± 6.8 and 7.1 ± 1.5 on admission, respectively. The duration of antimicrobial treatment was 17.2 ± 5.5 days and 28-day ICU crude mortality was 8.3% (5 cases with MDR infections died). Variables are summarized in table 1.

Serum PCT concentrations and influential factors

PCT concentrations were measured in 365 samples taken from eligible patients and were analysed in 240 samples from enrolled patients. PCT were elevated (>0.5µg/L) in all patients on day 0 and the median levels (range) were 2.5 µg/L (0.85–42.7 µg/L). PCT were associated with appropriate empirical antibiotic therapy (r = 0.548, p = 0.045), age (r = 0.548, p = 0.045), septic shock (r = 0.780, p = 0.003), and organ dysfunction (r = 0.685, p = 0.005) as assessed by the SOFA score, but sex (r = 0.066, p = 0.595), serum creatinine concentration (r = 0.095, p = 0.890), surgery (r = 0.495, p = 0.071), MDR infection (r = 0.080, p = 0.721), the type of NP (e.g. VAP) (r = 0.158, p = 0.585), mixed bacterial infection (r=0.195, p=0.453), microbiologic eradication (r=0.211, p=0.265), therapeutic efficacy (r = 0.088, p = 0.775), or prognosis (r = 0.261, p = 0.425) were not.

Septic shock (odds ratio [OR] 5.1, 95% confidence interval [CI] 3.5–10.5, p = 0.01) and organ dysfunction
(OR 3.2, 95% CI 1.1–8.7, p = 0.03) were independent predictors of higher PCT at multivariable analysis.

**PCT kinetics and its role in predicting clinical efficacy**

There were no differences between the patients with improvement and those without improvement with regard to PCT on D₀ (3.8 ± 2.0 µg/L vs. 4.2 ± 2.3 µg/L, p = 0.289). However, PCT on D₁ (3.2 ± 0.7 µg/L vs. 4.0 ± 1.8 µg/L, p = 0.040), on D₃ (1.5 ± 0.6 µg/L vs. 3.7 ± 1.7 µg/L, p = 0.004) and at the EOT (0.6 ± 0.3 µg/L vs. 2.5 ± 1.3 µg/L, respectively, p = 0.001) were all lower in the patients with improvement. By comparison, the rate of PCT decline between day0 and day3 (ΔPCT₀₃%) was significantly faster in the patients with improvement than in those without improvement (29.5 ± 10.8% vs. 15.1 ± 5.9%, p = 0.009). In contrast, the trend toward leukocytosis, temperature, granulocyte percentage and mCPIS did not differ between 2 groups (Figure 2).

ΔPCT₀₃% had the closest correlation with therapeutic efficacy (AUC=0.791, 95% CI 0.696-0.895, p < 0.001) as compared to mCPIS on day 3 (0.683, 95% CI 0.529-0.719, p=0.048), WCC (0.238, p = 0.751), granulocyte percentage (0.429, p = 0.634), body temperature (0.452, p = 0.158) and absolute PCT concentration (0.540, p = 0.791). The ΔPCT₀₃% cutoff value of 26.2% had a sensitivity of 75.7% and a specificity of 72.0% for predicting clinical improvement. Combining the values for ΔPCT₀₃% (> 26.2%) and mCPIS (<6 points) together increased the AUC to 0.890, sensitivity to 81.3% and specificity to 86.5%, which was significantly better than ΔPCT₀₃% alone (p<0.05) (Figure 3).

**Serum PCT concentration and microbiological response**

A total of 75 strains of bacteria (45 MDR strains) were isolated: including 20 strains of *Acinetobacter baumannii* (18 MDR strains); 16 of *Pseudomonas aeruginosa* (10 MDR strains); 10 of methicillin-resistant *Staphylococcus aureus* (MRSA); 6 of *Stenotrophomonas maltophilia* (all of MDR); 5 of *Klebsiella pneumoniae* and *Escherichia coli*, respectively; 4 of *Serratia marcescens*; 3 of methicillin-sensitive *Staphylococcus aureus*; *Proteus mirabilis*, *Haemophilus influenzae*, and 2 of *Enterococcus faecalis* (repeated culture-positive from patients with recurrent aspiration, one MDR strains), respectively.

Patients in the microbiologic eradication group (n=15), as compared with the microbiologic persistence group (n=45), had a lower incidence of MDR infection [33.3% (5 patients) vs. 55.6% (25 patients), p = 0.003] and
lower PCT concentrations on D₃ (2.5 ± 1.3 µg/L vs. 4.1 ± 2.1 µg/L, p = 0.025), D₇ (0.9 ± 0.5 µg/L vs. 3.8 ± 1.8 µg/L, p = 0.001), and D₈ (0.3 ± 0.1 µg/L vs. 1.5 ± 1.1 µg/L, p < 0.001), but similar on D₀ (3.9 ± 1.8 µg/L vs. 4.3 ± 2.1 µg/L, p = 0.265). In the subgroup of microbiologic persistence, ΔPCT₃% were also clearly higher in the clinical improvement patients (n=26) than in the no improvement patients (n=19) (25.6% ±7.8% vs 15.1% ±5.9%, p = 0.015).

The influential factors of clinical efficacy

In contrast with the improvement group, no improvement patients were significantly older (75.1 ± 14.0 vs. 69.5 ± 7.3 years, p < 0.05) and had a higher SOFA scores (10.5 ± 7.3 vs. 9.5 ± 6.8, p < 0.05), prolonged antimicrobial treatment (18.5 ± 5.8 vs. 15.3 ± 4.7 days, p < 0.05) and duration of septic shock (7.1 ± 3.7 vs. 4.8 ± 2.5 days, p < 0.05), more frequent of underlying cardiac dysfunction (47.4% vs. 14.6%, p < 0.05), concomitant bacteremia (21.1% vs. 14.6%, p < 0.05), multilobar pneumonia (36.8% vs. 19.5%, p < 0.05), septic shock (36.8% vs. 24.5%, p < 0.05), dysfunction of ≥ 2 organs (68.4% vs. 48.8%, p < 0.05), and inappropriate antibiotic therapy (52.6% vs. 17.1%, p < 0.05). There were no differences among groups in terms of sex, prior hospitalization before ICU admission, mCPIS score, pro-albumin concentrations, body temperature, leukocyte, granulocyte percentage, mixed bacterial infection, and patient classification (p > 0.05 for each; table 1). In a multiple logistic regression analysis, underlying cardiac dysfunction (OR 5.3, 95% CI 2.1–9.8, p = 0.02), multilobar pneumonia (OR 3.4, 95% CI 1.3–7.5, p = 0.03), inappropriate empirical antibiotic therapy (OR 5.1, 95% CI 1.1–8.5, p = 0.02), concomitant bacteremia (OR 2.6, 95% CI 1.6–7.8, p = 0.03), dysfunction of ≥2 organs (OR 2.3, 95% CI 1.5–15.2, p = 0.03), and ΔPCT₃% < 26.2% (OR 8.2, 95% CI 3.3–11.75, p = 0.01) were independent predictors of TF.

Discussion

PCT and its kinetics as the way to assess the clinical efficacy at an earlier stage were addressed in older patients with NP. Our findings suggested that PCT kinetics within the first 72 hours of sepsis management may be a useful tool for predicting TF and might provide an opportunity to modify antibiotics and improve outcome.

First of all, elevated PCT were observed in all patients with severe bacterial NP and also observed to be
associated with severity of illness, whereas, the type of pneumonia, MDR infection or renal function were not. These findings suggested that PCT kinetics may not be influenced by aging and serve as an indicator of the severity of bacterial infection. PCT release mechanism may be one explanation for this: it originated from various tissues and cells (e.g., fat, liver, stomach, lung) and its level was strongly associated with the degree and extensity of sepsis, but specific bacterial strains or source of infection as well as impaired renal function were not [9,27,30]. Indeed, a relatively high PCT was used in comparison with study using a PCT of 0.38µg/L or more for diagnosis of bacterial infection in older patients [17]. Differences in the case mix (higher proportion of surgical patients were included) and critical severity (higher proportion of septic shock and higher SOFA scores) may contribute to higher PCT [31,33].

Second, PCT kinetics within the first 72 hours was also found to be significantly different, since a decrease ≥26.2% was expected in the patients with improvement, and was regarded as an independent predictor of clinical efficacy. As a result, patient management might be reassessed if PCT fell slowly (such as less than 26.2% between \( D_0 \) and \( D_3 \)). In such cases, modification to initial empirical therapy may be considered while the microbiological findings, if any, are still pending. On the contrary, absolute PCT failed to predict clinical efficacy due to the fact that it was affected by various factors, including concurrent infection at other sites, severity of infection, trauma or surgery [34]. Similarly, mCPIS is also not suitable for patients with trauma, surgery or acute respiratory distress syndrome [35,36], but better predictive ability was observed when combined with PCT kinetics.

Interestingly, PCT kinetics not serving as a marker of clinical efficacy, but indicating microbiologic eradication, could help to distinguish the improvement patients from those no improvement. This result was consistent with the experimental data: the PCT time course is thought to be closely dependent on bacterial load and the host response to microbial challenge [37]. PCT kinetics may offer a solution for the dilemma about positive sputum cultures (interpretation of colonization or infection) and guide appropriate duration of antibiotics.

In fact, a few studies conducted in ICU patients have demonstrated the relationship between early time-dependent changes of PCT and therapeutic efficacy. We found that the change rate of PCT in the improvement patients from \( D_0 \) to \( D_e \) [(90.1 ± 20.7)%] was similar to published data about PCT-guided
de-escalation algorithm (antibiotics were stopped if the PCT fell by more than 80% of its peak value)\textsuperscript{12,14}. Further studies are required to estimate the exact threshold of PCT for predicting therapeutic efficacy at an earlier stage.

**Limitations**

We are aware of the limitations of our study. First, the single centric study and small sample size may restrict further subgroup analysis (such as VAP, MDR infection). Second, the lack of gold standard for diagnosis NP and enrolled only patients with microbiologically confirmed NP may lead to selection bias. Third, we couldn’t determine whether the predictive value of $\Delta PCT_{D3}\%$ is equally applicable in very older individuals due to few patients > 90 years of age. Finally, whether the ideal strategy involves the use of the PCT kinetics to affect sepsis management in this crowd remains to be established.

**Conclusions**

Among older critically ill patients with NP, PCT and kinetics were not influenced by aging and might help to identify therapeutic efficacy at an earlier stage. The rate of PCT decline within the first 72 hours combined with CPIS have been shown to be an early marker of clinical efficacy. Further studies are needed to assess the utility of the daily monitoring of PCT in addition to clinical evaluation during the early management of sepsis.

**References**

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protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. Crit Care 1999, 3:45-50.


Figure Legends

Figure 1. Study design showing patient allocation.

Figure 2. Kinetics of clinical parameters and PCT concentrations in the improvement and no improvement groups from D₀ to D₆.
Solid line denotes improvement group, dotted line denotes no improvement group. Asterisk denotes statistical significance between groups. Results are expressed as median values with IQR (25–75%).

Figure 3. ROC curves for clinical efficacy.
Shown are the ROC curves for PCT kinetic within the first 72 hours of treatment (∆PCT₃₃%) and ∆PCT₃₃% combined with modified clinical pulmonary infection score (mCPIS) on day 3.
For ∆PCT₃₃% > 26.2% and mCPIS < 6 points, the AUC was 0.890; sensitivity, 81.3%; and specificity, 86.5%.
Table 1. Clinical characteristics of the 60 patients with confirmed bacterial nosocomial pneumonia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 60)</th>
<th>Improvement (n= 41)</th>
<th>No improvement (n = 19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male [n (%)]</td>
<td>43 (71.7%)</td>
<td>29 (70.7%)</td>
<td>14 (73.7%)</td>
<td>0.832</td>
</tr>
<tr>
<td>Age [years, mean ± SD]</td>
<td>70.7 ± 12.7</td>
<td>69.5 ± 7.3</td>
<td>75.1 ± 14.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Co-morbidities [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart function grade ≥3 (NYHA)</td>
<td>15 (25.0%)</td>
<td>6 (14.6%)</td>
<td>9 (47.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronic renal insufficiency (CKD stage &gt;3)</td>
<td>12 (20%)</td>
<td>8 (19.5%)</td>
<td>4 (21.1%)</td>
<td>0.851</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>18 (30.0%)</td>
<td>12 (24.5%)</td>
<td>6 (31.6%)</td>
<td>0.760</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>11 (18.3%)</td>
<td>8 (16.3%)</td>
<td>3 (15.8%)</td>
<td>0.915</td>
</tr>
<tr>
<td>Type of ICU admission [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>23 (38.3%)</td>
<td>17 (41.5%)</td>
<td>6 (31.6%)</td>
<td>0.155</td>
</tr>
<tr>
<td>Medical</td>
<td>37 (61.7%)</td>
<td>24 (58.5%)</td>
<td>13 (68.4%)</td>
<td>0.158</td>
</tr>
<tr>
<td>Prior hospitalization [days, median (range)]</td>
<td>6.9 (3–118)</td>
<td>6.8 (3–92)</td>
<td>7.1 (5–118)</td>
<td>0.814</td>
</tr>
<tr>
<td>Characteristics on admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score (mean ± SD)</td>
<td>15.8 ± 6.8</td>
<td>14.1 ± 5.3</td>
<td>15.9 ± 5.7</td>
<td>0.070</td>
</tr>
<tr>
<td>SOFA score (mean ± SD)</td>
<td>10.1 ± 5.7</td>
<td>9.5 ± 6.8</td>
<td>10.5 ± 7.3</td>
<td>0.042</td>
</tr>
<tr>
<td>Septic shock [n (%)]</td>
<td>19 (31.7%)</td>
<td>12 (24.5%)</td>
<td>7 (36.8%)</td>
<td>0.030</td>
</tr>
<tr>
<td>≥2 organ dysfunction [n (%)]</td>
<td>33 (55.0%)</td>
<td>20 (48.8%)</td>
<td>13 (68.4%)</td>
<td>0.005</td>
</tr>
<tr>
<td>mCPIS (mean ± SD)</td>
<td>7.1 ± 1.5</td>
<td>7.2 ± 1.7</td>
<td>7.1 ± 1.3</td>
<td>0.924</td>
</tr>
<tr>
<td>VAP [n (%)]</td>
<td>20 (33.3%)</td>
<td>13 (31.7%)</td>
<td>7 (36.8%)</td>
<td>0.213</td>
</tr>
<tr>
<td>Body temperature (°C, mean ± SD)</td>
<td>38.2 ± 0.9</td>
<td>38.3 ± 0.5</td>
<td>38.2 ± 0.7</td>
<td>0.401</td>
</tr>
<tr>
<td>WCC (10^9/L, mean ± SD)</td>
<td>11.32 ± 5.51</td>
<td>11.50 ± 5.69</td>
<td>10.73 ± 5.03</td>
<td>0.548</td>
</tr>
<tr>
<td>Granulocyte percentage (% , mean ± SD)</td>
<td>81.15 ± 17.55</td>
<td>81.25 ± 15.31</td>
<td>79.81 ± 11.47</td>
<td>0.680</td>
</tr>
<tr>
<td>Pro-albumin [mg/dl, median (range)]</td>
<td>195 (95–289)</td>
<td>201 (117–254)</td>
<td>198 (95-289)</td>
<td>0.917</td>
</tr>
<tr>
<td>Concomitant bacteremia [n (%)]</td>
<td>10 (16.7%)</td>
<td>6 (14.6%)</td>
<td>4 (21.1%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Mixed bacterial infection [n (%)]</td>
<td>15 (25.0%)</td>
<td>10 (24.4%)</td>
<td>5 (26.3%)</td>
<td>0.612</td>
</tr>
<tr>
<td>Multilobar pneumonia [n (%)]</td>
<td>15 (25.0%)</td>
<td>8 (19.5%)</td>
<td>7 (36.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Inappropriate empirical antibiotics [n (%)]</td>
<td>17 (28.3%)</td>
<td>7 (17.1%)</td>
<td>10 (52.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multidrug-resistant bacteria infection [n (%)]</td>
<td>30(50%)</td>
<td>20(48.8%)</td>
<td>10(52.6%)</td>
<td>0.657</td>
</tr>
<tr>
<td>Duration antibiotic treatment (days, mean ± SD)</td>
<td>17.2 ± 5.5</td>
<td>15.3 ± 4.7</td>
<td>18.5 ± 5.8</td>
<td>0.003</td>
</tr>
<tr>
<td>PCT on D0 (µg/L, mean ± SD)</td>
<td>4.1 ± 2.8</td>
<td>3.8 ± 2.0</td>
<td>4.2 ± 2.3</td>
<td>0.289</td>
</tr>
<tr>
<td>PCT on D1 (µg/L, mean ± SD)</td>
<td>3.5 ± 1.5</td>
<td>3.2 ± 0.7</td>
<td>4.0 ± 1.8</td>
<td>0.040</td>
</tr>
<tr>
<td>PCT on D2 (µg/L, mean ± SD)</td>
<td>2.9 ± 1.6</td>
<td>1.5 ± 0.6</td>
<td>3.7 ± 1.7</td>
<td>0.005</td>
</tr>
<tr>
<td>PCT on D3 (µg/L, mean ± SD)</td>
<td>1.2 ± 0.8</td>
<td>0.6 ± 0.3</td>
<td>2.5 ± 1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>∆PCTD0% (mean ± SD)</td>
<td>20.5 ± 9.4</td>
<td>29.5 ± 10.8</td>
<td>15.1 ± 5.9</td>
<td>0.001</td>
</tr>
<tr>
<td>∆PCTD3% (mean ± SD)</td>
<td>43.2 ± 23.4</td>
<td>70.5 ± 18.9</td>
<td>19.7 ± 9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆PCTD7% (mean ± SD)</td>
<td>73.5 ± 29.4</td>
<td>90.1 ± 20.7</td>
<td>49.7 ± 12.5</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>mCPIS on D1 (mean ± SD)</td>
<td>6.4 ± 1.7</td>
<td>6.1 ± 1.4</td>
<td>6.7 ± 1.4</td>
<td>0.354</td>
</tr>
<tr>
<td>ICU length of stay [days, median (range)]</td>
<td>14.5 (8–48)</td>
<td>12.7 (8–22)</td>
<td>18.5 (15–48)</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of septic shock [days, mean ± SD]</td>
<td>6.1 ± 2.8</td>
<td>4.8 ± 2.5</td>
<td>7.1 ± 3.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; mCPIS, Modified Clinical Pulmonary Infection Score; VAP, ventilator associated pneumonia; NYHA: New York Heart Association; CKD: chronic kidney disease; SOFA: sequential organ failure assessment; WCC, White cell count; PCT, procalcitonin; ΔPCT%, the rate of PCT decline.
**Figure 1**

Suspected nosocomial pneumonia in 107 of 291 patients over 65 years old

- 20 patients met the exclusion criteria at admission
  - 11 had previous diagnosis of immunosuppression
  - 9 had extrapulmonary infections

- 87 patients were eligible

- 27 patients met the exclusion criteria at final analysis
  - 8 had known infection at other sites
  - 5 had unavailable microbiologic culture data
  - 7 had confirmed non-bacterial infection
  - 3 had not completed PCT measurement
  - 4 had uncertain therapeutic effects

- 60 patients were finally enrolled

- 41 had improved (15 cured and 26 improved)
- 19 had no improved

- 5 died at 28 day in ICU

122x107mm (600 x 600 DPI)
Figure 2

105x129mm (96 x 96 DPI)