Original Article
Procalcitonin levels correlates with the pathogeny and severity of community acquired pneumonia: a meta-analysis

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Abstract: Background: The purpose of this study was to comprehensively evaluate the role of PCT (procalcitonin) in diagnosis and prognosis of community acquired pneumonia (CAP) by a meta-analysis. Methods: Two researchers independently performed a retrieve on the databases of PubMed, Embase and Cochrane published in English up to July 2015. The search strategy was (“community acquired pneumonia” OR CAP) AND procalcitonin. The risk ratio (RR) with 95% CI (confidence interval) was used for the analysis of dichotomous data. Standardized mean differences (SMD) and 95% CI were used to perform the analysis for continuous outcomes. All statistical analyses were performed by using RevMan (Review Manager) 5.3 software and Stata 12.0 statistical software package. Heterogeneity was analyzed with the Cochran Q test and $I^2$ test. Stata 12.0 was used to perform sensitivity analysis. Results: A total of 15 studies (6401 adult patients diagnosed with CAP) were selected in this meta-analysis. The number of patient mortality in PCT≥0.5 ng/ml was twice that of PCT<0.5 ng/ml (RR = 0.50 (95% CI: 0.40, 0.62)). The number of patients that pathogen could be detected was 1.31 times that of could not be detected (RR = 1.31 (95% CI: 1.11, 1.55)). PCT levels of death cases were significantly higher than those of survival cases (SMD = -0.31 (95% CI: -0.50, -0.13)). The sensitivity analysis showed that this meta-analysis result was stable. Conclusions: Serum PCT levels are significantly related with detection of CAP pathogen and severity of CAP cases.

Keywords: Meta-analysis, procalcitonin levels, community acquired pneumonia

Introduction
Community acquired pneumonia (CAP), the sixth leading cause of death in the United States, is a common lung inflammatory process that respond to infection with community (non-hospital) pathogens [1, 2]. It is estimated that about 83,000 CAP patients are admitted to hospital annually in the UK and 6% of these patients require admission to the ICU (intensive care unit) [3]. In addition, the mortality of ICU patients with CAP is more than 30% [3]. The risk factors for CAP include alcohol ingestion and the presence of prior ambulatory antimicrobial treatment [4]. Therefore, evaluation of the severity and prediction of the clinical outcomes are significantly important for the selection of therapeutic decision-making.

Procalcitonin (PCT), the prehormone of calcitonin [5], is produced by the liver and peripheral blood mononuclear cells [6, 7]. PCT levels are undetectable or low in serum of healthy individuals, but patients infected with severe generalized bacteria have an increase in PCT levels [8, 9]. It has been used as a marker for diagnosis and prognosis of pneumonia [10, 11], bacteremia [12] and sepsis [13]. Hedlund et al. indicate that measurement of PCT provides information for the severity of CAP [14]. Christ et al. suggest that PCT guidance can reduce antibiotic use in CAP [15]. Masiá et al. indicate that PCT levels are useful as a prognostic marker of CAP according to their research results [16]. However, some authors have not found the relationships between PCT levels and diagnosis of CAP [17, 18], and the results of Boussekey et al. suggest that PCT level is inclined to evaluate the severity of CAP compared with diagnosis of CAP [19]. Consequently, inconsistent opinions exist in the correlation of PCT and its role in diagnosis of CAP patients. It is necessary to evaluate the role of PCT in diagnosis of CAP with meta-analysis.
In our present study, we searched the databases of PubMed, Embase and Cochrane for studies published in English up to July 2015 and used meta-analysis to analyze the relationships between PCT levels and pathogeny and severity of CAP. We expected to evaluate the role of PCT levels in pathogen and severity of CAP.

**Materials and methods**

**Search strategy**

We studied publications that reported the correlation of PCT levels and pathogeny and severity of CAP. We searched the databases of PubMed, Embase and Cochrane for studies published in English up to July 2015. The key words used in this study were “procalcitonin” and “community acquired pneumonia”. The search strategy was (“community acquired pneumonia” OR CAP) AND procalcitonin.

**Study selection**

Two researchers reviewed titles, abstracts and full text independently. Disparities were resolved by discussion with the third researcher. The inclusion standards were as follows: English literature; literatures related with PCT levels of CAP; adults with CAP; the study contained at least one required outcome that this study aimed to pool.

The exclusion standards were as follows: Non-English literature; studies not related to CAP; studies not about PCT; articles such as reviews, letters and meeting abstracts; repeated publications; studies without required outcome.

**Data extraction and study quality assessment**

Data extraction and quality assessment were performed by two researchers independently. Disagreements were resolved through discussion with the third researcher. Extracted data include the first author, published year, study type, country, study period, contained clinical characteristics, evaluation standards of CAP’s severity, measuring method of PCT, numbers and age of contained cases, and outcome indicators of meta analyses.

The Newcastle-Ottawa Scale (NOS) [20] was used to assess the quality of the contained study.

**Statistical analyses**

The risk ratio (RR) and 95% CI (confidence interval) were used for the analysis of dichotomous data. Standardized mean differences (SMD) and 95% CI were used to perform the analysis for continuous outcomes. Heterogeneity was analyzed with the Cochran Q test and $I^2$ test [21]. If $P<0.05$ or $I^2>50\%$, which indicated that all the studies were heterogeneity, the random
# A meta-analysis of PCT levels and CAP

## Table 1. Characteristics of the included articles

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study period</th>
<th>Participants</th>
<th>CAP score</th>
<th>Measuring method of PCT</th>
<th>No. (M/F)</th>
<th>Age, year (mean ± SD)</th>
<th>Severity of Illness</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrijevic, 2014</td>
<td>Serbia</td>
<td>2010.01-2012.12</td>
<td>Age &gt;18 y, established diagnosis of CAP.</td>
<td>PCT, MEWS, CURB-65</td>
<td>VIDAS BRAHMS PCT assay on VIDAS system</td>
<td>101 (76/25)</td>
<td>63.7±11.8</td>
<td>Mixed</td>
<td>7</td>
</tr>
<tr>
<td>Boussekey, 2005</td>
<td>France</td>
<td>2001.01-2003.04</td>
<td>Patients with severe CAP</td>
<td>PCT, MEWS, CURB-65</td>
<td>Monoclonal immunolumino metric assay</td>
<td>110 (70/40)</td>
<td>58.8±16.3</td>
<td>Severe</td>
<td>7</td>
</tr>
<tr>
<td>España, 2012</td>
<td>Spain</td>
<td>2006.05-2007.06</td>
<td>Patients with non-severe CAP</td>
<td>PCT, MEWS, CURB-65</td>
<td>Sandwich immunoanalysis based on the TRACE technique</td>
<td>344 (196/148)</td>
<td>53.4±18.8</td>
<td>non-severe CAP</td>
<td>7</td>
</tr>
<tr>
<td>Hedlund, 2000</td>
<td>Sweden</td>
<td>1992</td>
<td>Patients, 50 to 85 years of age, with CAP</td>
<td>PCT, MEWS, CURB-65</td>
<td>Monoclonal immunolumimetric assay</td>
<td>96 (46/50)</td>
<td>Mean: 72</td>
<td>Mixed</td>
<td>9</td>
</tr>
<tr>
<td>Hirakata, 2008</td>
<td>Japan</td>
<td>2004.11-2006.01</td>
<td>Patients diagnosed with CAP.</td>
<td>PCT, MEWS, CURB-65</td>
<td>Fully automated chemiluminescent enzyme immunoassay</td>
<td>88 (60/28)</td>
<td>67.0±15.9</td>
<td>15-severe; 43-moderate; 30-mild</td>
<td>7</td>
</tr>
<tr>
<td>Huang, 2008</td>
<td>USA</td>
<td>2001.11-2003.11</td>
<td>&gt;18 years and had a clinical and radiologic diagnosis of pneumonia</td>
<td>PCT, MEWS, CURB-65</td>
<td>Time-resolved, amplified cryptate emission assay</td>
<td>1651 (860/791)</td>
<td>65.0±18.5</td>
<td>Mixed</td>
<td>7</td>
</tr>
<tr>
<td>Menéndez, 2012</td>
<td>Spain</td>
<td>2004.11-2009.05</td>
<td>Hospitalized patients with CAP</td>
<td>PCT, MEWS, CURB-65</td>
<td>Immunolumimetric technique</td>
<td>685</td>
<td>NA</td>
<td>Mixed</td>
<td>7</td>
</tr>
<tr>
<td>Okimoto, 2009</td>
<td>Japan</td>
<td>2007.03-2009.01</td>
<td>Patients with CAP</td>
<td>PCT, MEWS, CURB-65</td>
<td>A-DROP assay</td>
<td>162 (102/60)</td>
<td>70.8±18.8</td>
<td>39-mild; 81-moderate; 37-severe; 5-super severe</td>
<td>6</td>
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<tr>
<td>Pereira, 2013</td>
<td>Portugal</td>
<td>2008.12-2013.01</td>
<td>Patients with severe CAP admitted to ICU</td>
<td>PCT, MEWS, CURB-65</td>
<td>Highly sensitive immunoassay based on enzyme-linked fluorometric assay technique</td>
<td>108 (68/40)</td>
<td>61±16</td>
<td>Severe</td>
<td>9</td>
</tr>
<tr>
<td>Tamura, 2014</td>
<td>Japan</td>
<td>2009-2011</td>
<td>Patients with CAP and treated in the department</td>
<td>PCT, MEWS, CURB-65</td>
<td>Eleyes BRAHMS PCT automated immunoassays</td>
<td>122 (82/40)</td>
<td>74 (64-79)</td>
<td>Mixed</td>
<td>9</td>
</tr>
<tr>
<td>Ugajin, 2014</td>
<td>Japan</td>
<td>2010.08-2012.10</td>
<td>Age &gt;18 y with CAP</td>
<td>PCT, MEWS, CURB-65</td>
<td>Immunochromatographic semi-quantitative procalcitonin test kit</td>
<td>213 (127/86)</td>
<td>median (IQR) 82 (74-88)</td>
<td>Mixed</td>
<td>9</td>
</tr>
<tr>
<td>Zhydkov, 2014</td>
<td>Switzerland</td>
<td>2006.12-2008.03</td>
<td>Age ≥18 y and diagnosis of CAP</td>
<td>PCT, MEWS, CURB-65</td>
<td>Highly sensitive time-resolved amplified cryptate emission technology assay</td>
<td>875 (544/331)</td>
<td>73 (59-82)</td>
<td>Mixed</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: PCT: procalcitonin; CAP: community acquired pneumonia; PSI: the pneumonia severity index; MEWS: modified early warning score; CURB-65: the ‘confusion, urea, respiratory, and blood pressure’ (CURB) score, and CURB plus age >65; OSF: organ system failure; APACHE II: a modified version of the Acute Physiology and Chronic Health Evaluation; A-DROP: age, dehydration, respiratory failure, orientation disturbance, pressure scale; y: year; M: male; F: female; IQR: interquartile range; SD: standard deviation; NA: not available. 1 Data are shown as mean (range); 2 Data are shown as median (IQR).
A meta-analysis of PCT levels and CAP

A meta-analysis of PCT levels and CAP effects model was chosen. If not, the fixed effect model was selected. All statistical analyses were performed by using RevMan (Review Manager) 5.3 [22] software and Stata12.0 [23] statistical software package.

Sensitivity analysis

Stata 12.0 was used to perform sensitivity analysis. We trimmed one study at a time to assess the sensitivity of this analysis. The difference of pooled effects was compared before and after the trim. If the pooled results reversed after the trim, then it illustrated that the results was unstable.

Results

Study selection

A total of 759 articles were identified after the preliminary screening, with 196 from the PubMed, 533 from the Embase and 30 from the Cochrane library. After eliminating unrelated studies (334) and duplicate literatures (148), 277 studies remained. We obtained 32 studies for the full text screening after abstract screening, which eliminated non-English articles (21), summarizes, letters and conference excerpts (47), non-CAP studies (104) and non-PCT studies (73). Finally, after eliminating 4 studies of the CAP of children and 13 studies without required outcomes, a total of 15 studies were selected in this meta-analysis. The flow diagram of study selection for meta-analysis is shown in Figure 1.

Characteristics of the studies

Fifteen studies [14, 16, 19, 24-31] with 6401 adult patients diagnosed with CAP were included in this meta-analysis. The study period was 2000-2014 and the study samples came from several countries (France, Spain, and USA etc.). The characteristics of the included articles are shown in Table 1. The scoring standards for severity of CAP were PSI (the pneumonia severity index), CURB-65 (the “confusion, urea, respiratory and blood pressure” (CURB) score, and age >65) and A-DROP (age, dehydration, respiratory failure, orientation disturbance, pressure scale). The assay methods of PCT concentration in serum were monoclonal immunoluminometric assay, time-resolved, and amplified cryptate emission assay etc. Articles that scores got 6-9, indicating all included studies had higher quality. The research quality of Okimoto et al. [30] was relatively low with 6 scores, because the study lacked the comparison of baseline differences and the description of result’s assay method.

Identification of pathogen (PCT>0.5 ng/ml)

This analysis was use to show that whether the pathogen of CAP could be detected in PCT>0.5 ng/ml. A total of 2 studies [19, 32] reported probability of pathogen’s identification in PCT>0.5 ng/ml in which 147 patients’ pathogen could be detected and 176 could not. No prominent heterogeneity was found between studies with P = 0.83, I^2 = 0%. Therefore, the
fixed effect model was used and the pooled result was RR = 1.31 (95% CI: 1.11, 1.55). The results showed that the number of patients that pathogen could be detected was 1.31 times that of patients that pathogen could not be detected, and there was a statistical difference between patients that pathogen could be detected and patients that pathogen could not be detected (P = 0.001) (Figure 2A).

**Identification of Streptococcus pneumonia (PCT>0.5 ng/ml)**

This analysis was used to explain the probability of identification of Streptococcus pneumonia (one of the major pathogens of CAP) in PCT>0.5 ng/ml. There were 2 studies [19, 32] reported the probability of Streptococcus pneumonia's identification in PCT>0.5 ng/ml. A total of 147 patients were studied, including 64 pneumonia patients and 83 non-pneumonia patients. Prominent heterogeneity was found between studies with P = 0.08 and I² = 68%. Therefore, the random effects model was used and the pooled result was RR = 1.08 (95% CI: 0.79, 1.49). There was no statistical difference in the probability of Streptococcus pneumonia's identification between pneumonia patients and non-pneumonia patients (P = 0.61) (Figure 2B).

**Comparison of the mortality between PCT-positive and PCT-negative patients (PCT<0.5 ng/ml vs. PCT≥0.5 ng/ml)**

This comparison was used to explain the relationship between PCT levels and CAP severity (mortality). A total of 6 studies [16, 26, 27, 30, 32] reported mortality between PCT-positive (PCT<0.5 ng/ml, 1523 patients) and PCT-negative (PCT≥0.5 ng/ml, 886 patients). No prominent heterogeneity was found between studies with P = 0.10, I² = 45%. The fixed effect model was used and the pooled result was RR = 0.50 (95% CI: 0.40, 0.62). The results suggested that the number of patient mortality in PCT≥0.5 ng/ml was twice that of PCT<0.5 ng/ml and there was a statistical difference between PCT<0.5 ng/ml and PCT≥0.5 ng/ml (Figure 3A). The final result was RR = 0.43 (95% CI: 0.30, 0.62; P<0.01) after trimming a study which was a retrospective study [32].

**Comparison of the PCT levels between survival cases and death cases**

This comparison was also used to explain the relationship between PCT levels and CAP severity (survival cases and death cases). There were 4 studies [16, 24, 33, 34] reported the difference of PCT levels between survival cases and death cases.
A meta-analysis of PCT levels and CAP

and death cases, and 1774 survival cases and 122 death cases were included in this study. No prominent heterogeneity was present between studies with $P = 0.61$, $I^2 = 0\%$. Therefore, the fixed effect model was used and the pooled result was SMD = -0.31 (95% CI: -0.50, -0.13). It suggested that the PCT levels of survival cases were lower than those of death cases, and there was a statistical difference between survival cases and death cases ($P = 0.001$) (Figure 3B).

**Comparison of the PCT levels between patients that bacteria could be detected and patients that bacteria could not be detected.**

This comparison was used to explain the relationship between PCT levels and detection of pathogens. A total of 2 studies [31, 35] reported the difference of PCT levels between patients that bacteria could be detected and those that bacteria could not be detected. There were 121 cases that bacteria could be detected and 1379 cases that bacteria could not be detected in this study. No prominent heterogeneity was found between studies with $P = 0.17$, $I^2 = 46\%$. Therefore, the fixed effect model was used and the pooled results were SMD = 1.66 (95% CI: 1.46, 1.85; $P<0.001$). It suggested that the PCT levels of patients that bacteria could be detected were higher than those patients that bacteria could not be detected (Figure 4A).

**Comparison of the PCT levels between patients of typical bacteria and patients of atypical bacteria**

This comparison was used to explain the relationship between PCT levels and diagnosis of pathogens (typical bacteria or atypical bacteria). A total of 2 studies [28, 29] reported the difference of PCT levels between patients of typical bacteria and those of atypical bacteria, and 74 patients were included in typical bacteria group and 89 patients were included in atypical bacteria group. No prominent heterogeneity was found between studies with $P = 0.75$, $I^2 = 0\%$. Therefore, the fixed effect model was used and the pooled results were SMD = 0.20 (95% CI: -0.13, 0.52; $P = 0.24$). It indicated that the difference of PCT levels between typical bacteria group and atypical bacteria group was not significant (Figure 4B).

**Comparison of the PCT levels between patients of pneumococcal CAP and patients of non-pneumococcal CAP**

This comparison was also used to explain the relationship between PCT levels and diagnosis of pathogens (pneumococcal CAP or non-pneumococcal CAP).
A meta-analysis of PCT levels and CAP

mococcal CAP). Two studies [14, 25] reported the PCT levels between patients of pneumococcal CAP (45 patients) and patients of non-pneumococcal CAP (185 patients). No prominent heterogeneity was found between studies with $P = 0.32$, $I^2 = 0\%$. Therefore, the fixed effect model was used and the pooled results were SMD = 0.98 (95% CI: 0.63, 1.32; $P<0.01$). It indicated that the PCT levels of pneumococcal CAP group were higher than those of non-pneumococcal CAP group, and there was a statistical difference between two groups (Figure 4C).

Sensitivity analysis

The sensitivity analysis, in which one study was trimmed at a time, was used to judge the stability of the results. It showed that this meta-analysis result was stable (Figure 5A, 5B).

Discussions

This meta-analysis of 15 publications suggested that PCT levels were related with severity of CAP patients and detection and diagnosis of CAP pathogen. The present study showed that the number of patient mortality in PCT≥0.5 ng/ml was higher than that of PCT<0.5 ng/ml [16, 26, 27, 30, 32], PCT levels of death cases were significantly higher than those of survival cases [16, 24, 33, 34], PCT levels of cases that CAP pathogen could be detected were notably higher than those of cases that CAP pathogen could not be detected [31, 35], and PCT levels of pneumococcal cases were evidently higher than those of non-pneumococcal cases [14, 25].

Recently, some publications have studied the relationship between PCT levels and survival/mortality rate (severity) of CAP patients. In animal experiments, animals that injected with PCT have a higher mortality rate compared with controls, and injection of drugs that prevent PCT can improve survival [36, 37]. The correlations between PCT levels and survival/mortality rate of CAP patients have also been studied in clinical trials [38, 39]. Several studies showed that PCT levels’ increase was a risk factor of death within the first 48 hours on ICU admission, whereas a decrease had a better outcome [40, 41]. In this study, the number of CAP mortality rate in PCT≥0.5 ng/ml was twice that of PCT<0.5 ng/ml, and PCT levels of death cases were significantly higher than those of survival cases. Therefore, PCT levels were related with severity of CAP.

In our study, the number of CAP patients that pathogen could be detected was 1.31 times that of CAP patients that pathogen could not be...
detected in PCT>0.5 ng/ml, and the PCT levels of pneumococcal CAP group were higher than those of non-pneumococcal CAP group. One study shows that severe bacterial infections are related with increased PCT levels, whereas non-infectious inflammatory reactions or viral infections do not or moderately increase serum levels of PCT [8]. Based on 96 patients treated for CAP, Hedlund et al. suggest that measurement of PCT may help the physician to distinguish atypical bacterial etiology from typical etiology and its PCT threshold is 0.5 μg/l [14].

Besides, Moulin et al. indicate that PCT levels have greater predictive values in differentiation of bacterial infections and viral pneumonia with above a cut-off 1 μg/ml [42]. Therefore, PCT levels were related with diagnosis and detection of CAP pathogeny.

There were several strengths in this meta-analysis. Firstly, more comprehensive analyses were performed for diagnosis and detection of CAP pathogeny. Secondly, heterogeneity was relatively small. Finally, the results of this analysis were stable.

Despite these advantages, some limitations of this meta-analysis should be mentioned. We could not completely exclude the influence of heterogeneity, though the heterogeneity of this study was relatively small. Possible sources of heterogeneity were the difference of CAP severity, the difference in evaluation criterion of CAP severity and the difference of measuring method. Besides, there were limited number of studies included in this meta-analysis, so more subsequent clinical researches were needed to support our results.

This meta-analysis suggests that serum PCT levels are significantly related with diagnosis and detection of CAP pathogen and severity of CAP cases. Therefore, it can provide the basis for the clinical diagnosis of CAP. Because of some strengths and limitations of this study, rigorous research and large samples are needed to support our views.

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Disclosure of conflict of interest

None.

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