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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.

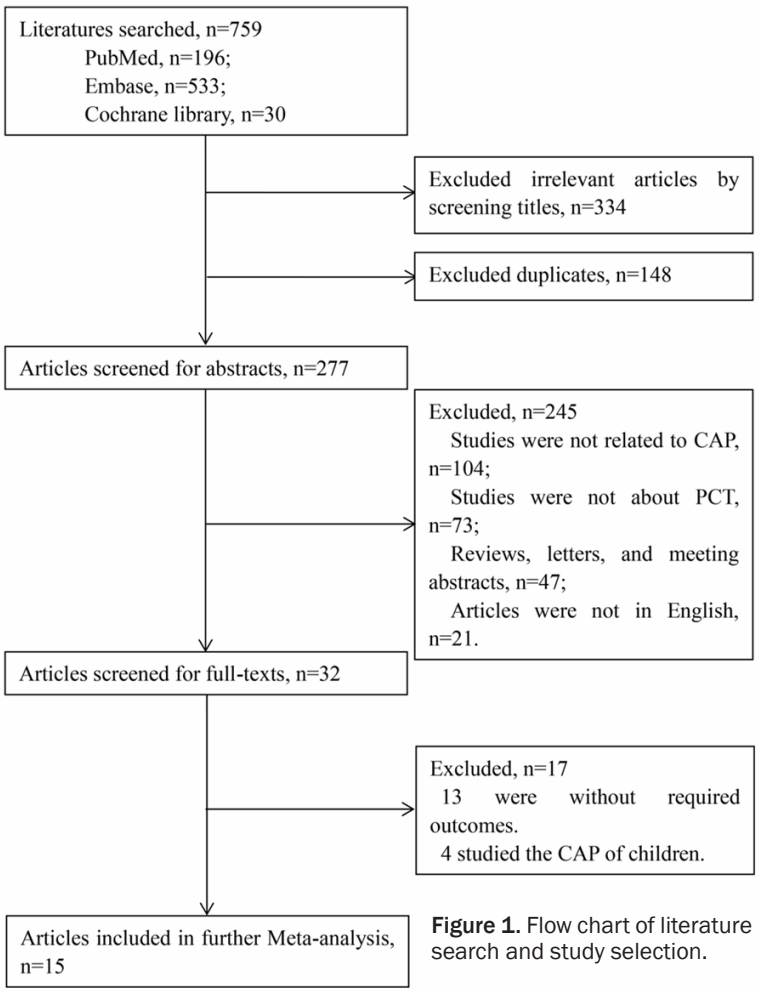

Figure 1. Flow chart of literature search and study selection.

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

Table 1. Characteristics of the included articles

Author, year	Country	Study period	Participants	CAP score	Measuring method of PCT	No. (M/F)	Age, year (mean ± SD)	Severity of illness	Quality assessment
Andrijevic, 2014	Serbia	2010.01-2012.12	Age >18 y, established diagnosis of CAP.	PSI, MEWS, CURB-65	VIDAS BRAHMS PCT assay on VIDAS system	101 (76/25)	63.7±11.8	Mixed	7
Boussekey, 2005	France	2001.01-2003.04	Patients with severe CAP	SAPS II, OSF	Monoclonal immunolumino-metric assay	110 (70/40)	58.8±16.3	Severe	7
España, 2012	Spain	2006.05-2007.06	Patients with non-severe CAP	CURB-65	Sandwich immunoanalysis based on the TRACE	344 (196/148)	53.49±18.82	non-severe CAP	7
Hedlund, 2000	Sweden	1992	patients, 50 to 85 years of age, with CAP	APACHE II	Monoclonal immunolumino-metric assay	96 (46/50)	Mean: 72	Mixed	9
Hirakata, 2008	Japan	2004.11-2006.01	Patients diagnosed with CAP.	NA	Fully automated chemilumi-nescent enzyme immunoassay	88 (60/28)	67.0±15.9	15-severe; 43-mod-erate; 30-mild	7
Huang, 2008	USA	2001.11-2003.11	>18 years and had a clinical and radiologic diagnosis of pneumonia	PSI, CURB-65	Time-resolved, amplified cryptate emission assay	1651 (860/791)	65.0±18.5	Mixed	7
Masiá, 2005	Spain	1999.10-2001.10	Patients had a clinical and a chest radiologic diagnosis of pneumonia.	PSI	Monoclonal immunolumino-metric assay	240 (150/90)	59 (15-93)[1]	Mixed	9
Menéndez, 2012	Spain	2004.11-2009.05	Hospitalized patients with CAP	NA	Immunoluminometric tech-nique	685	NA	Mixed	7
Müller, 2010	Switzerland	2006.12-2008.03	Patients with radiologic -confirmed CAP	PSI, CURB-65	Time-resolved amplified cryptate emission technology assay	925 (546/379)	73 (59-82)[2]	Mixed	8
Okimoto, 2009	Japan	2007.03-2009.01	Patients with CAP	A-DROP	NA	162 (102/60)	70.8±18.8	39-mild; 81-moder-ate; 37-severe; 5-super severe	6
Pereira, 2013	Portugal	2008.12-2013.01	Patients with severe CAP admitted to ICU	PSI	Highly sensitive immunoas-say based on enzyme-linked fluorescent assay technique	108 (68/40)	61±16	Severe	9
Ramírez, 2011	Spain	2003.01-2005.10	Age ≥16 hospitalized with a diag-nosis of CAP	PSI	Immunoluminometric tech-nique	Non-ICU: 627 (411/216); ICU: 58 (34/24)	Non-ICU: 67±17; ICU: 64±17	Mixed	8
Tamura, 2014	Japan	2009-2011	Patients with CAP and treated in the department	PSI, A-DROP	Elecsys BRAHMS PCT auto-mated immunoassays	122 (82/40)	74 (64-79)[2]	Mixed	9
Ugajin, 2014	Japan	2010.08-2012.10	Age >18 y with CAP	PSI, A-DROP, CURB-65	Immunochromatographic semi- quantitative procalcito-nin test kit	213 (127/86)	median (IQR) 82 (74–88)	Mixed	9
Zhydkov, 2014	Switzerland	2006.12-2008.03	Age ≥18 y and diagnosis of CAP	CURB-65	Highly sensitive time-resolved amplified cryptate emission technology assay	875 (544/331)	73 (59-82)[2]	Mixed	9

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).

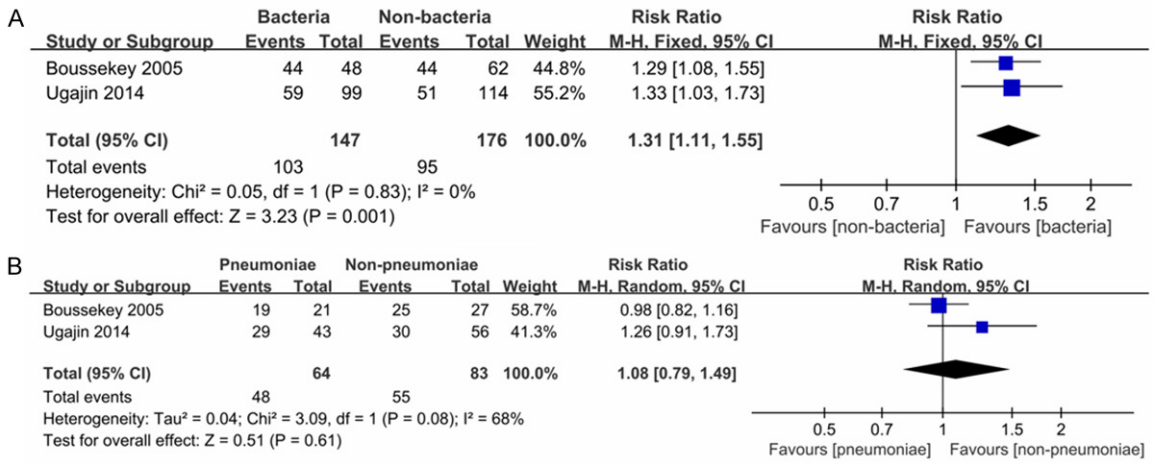

Figure 2. A: Identification of pathogen in PCT>0.5 ng/ml; B: Identification of *Streptococcus pneumonia* in PCT>0.5 ng/ml.

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, Span, 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 6scores, 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

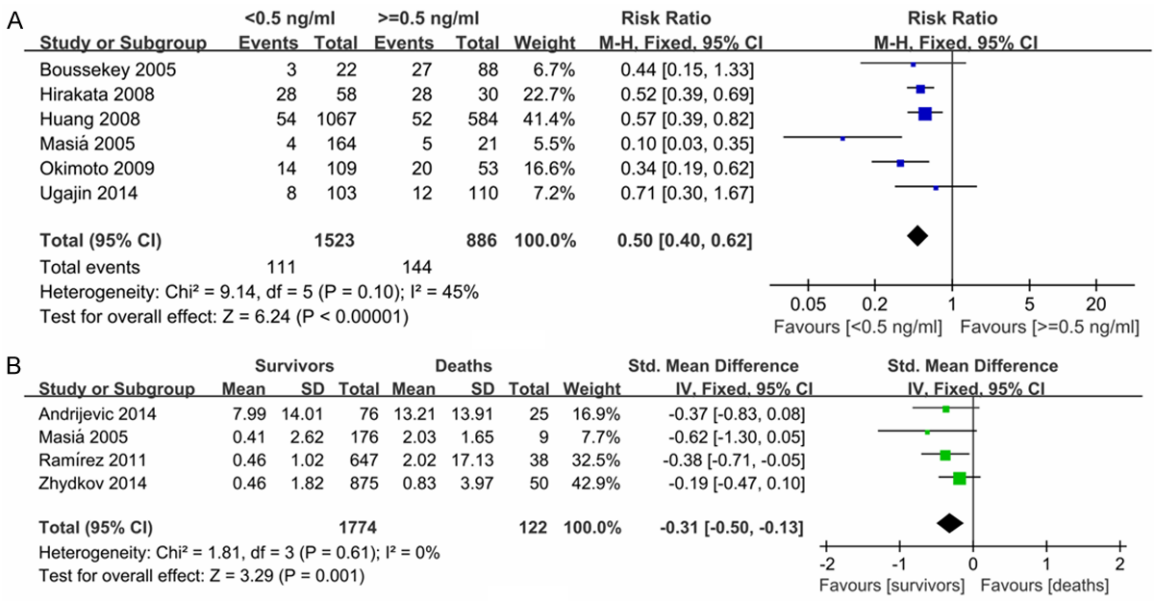

Figure 3. A: Comparison of the mortality between PCT<0.5 ng/ml and PCT≥0.5 ng/ml; B: Comparison of PCT levels between survival cases and death cases.

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 use to explain the probability of identification of *Streptococcuspneumonia* (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 I^2 = 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, I^2 = 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

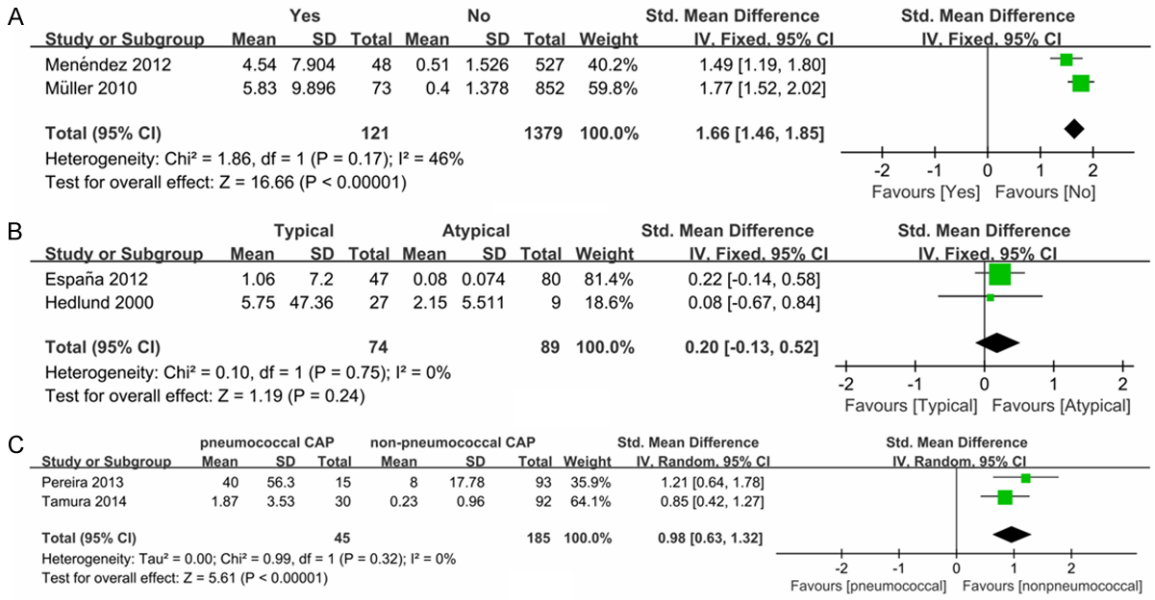

Figure 4. A: Comparison of the PCT levels between patients that bacteria could be detected and patients that could not be; B: Comparison of the PCT levels between patients of typical bacteria and patients of atypical bacteria; C: Comparison of the PCT levels between patients of pneumococcal CAP and patients of non-pneumococcal 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 patients 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 present 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 these 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-pneu-

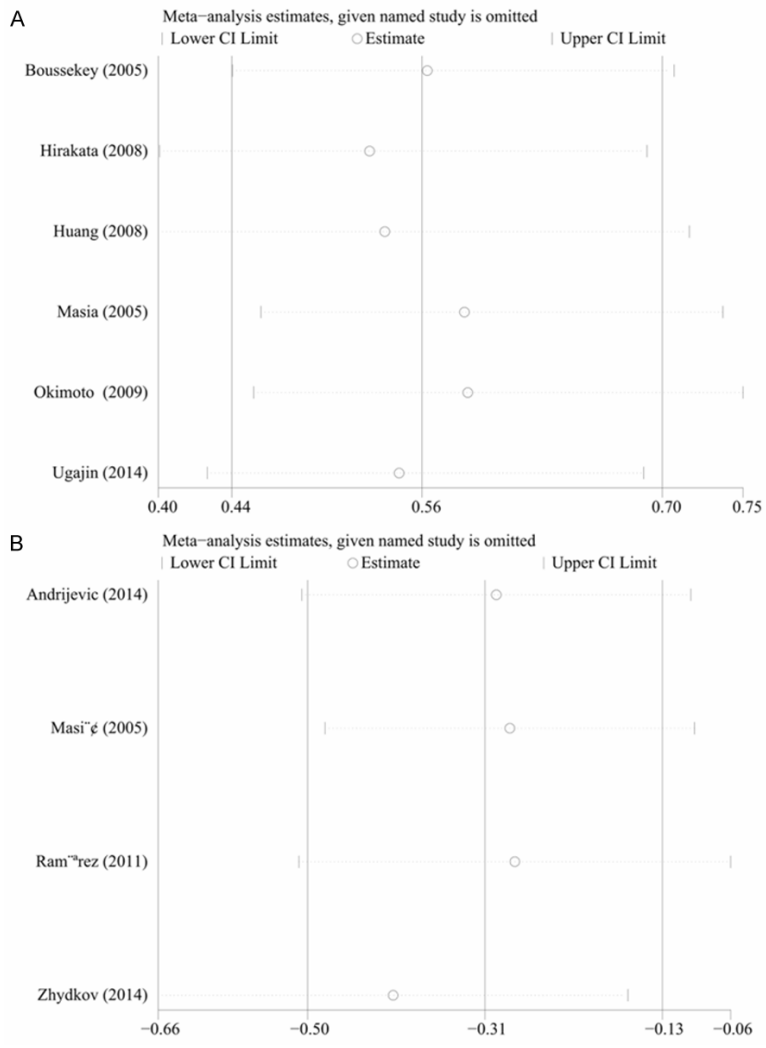

Figure 5. Sensitivity analysis. A: Sensitivity analysis of morality; B: Sensitivity analysis of PCT levels (survivors *vs* deaths).

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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References

[1] Martin SW and Al-Haddad M. Community-acquired pneumonia. Anaesthesia & Intensive Care Medicine 2013; 14: 457-459.

[2] Bartlett JG and Mundy LM. Community-acquired pneumonia. N Engl J Med 1995; 333: 1618-1624.

[3] Lim W, Macfarlane J, Boswell T, Harrison T, Rose D, Leinonen M and Saikku P. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 2001; 56: 296-301.

[4] Ruiz M, Ewig S, Torres A, Arancibia F, Marco F, Mensa J, Sanchez M and Martinez JA. Severe community-acquired pneumonia: risk factors and follow-up epidemiology. Am J Respir Crit Care Med 1999; 160: 923-929.

[5] Whicher J, Bienvenu J and Monneret G. Procalcitonin as an acute phase marker. Ann Clin Biochem 2001; 38: 483-493.

[6] Nijsten MW, Olinga P, de Vries EG, Koops HS, Groothuis GM, Limburg PC, Henk J, Moshage H, Hoekstra HJ and Bijzet J. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. Crit Care Med 2000; 28: 458-461.

[7] Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, Jäger L and Reinhart K. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. J Lab Clin Med 1999; 134: 49-55.

[8] Karzai W, Oberhoffer M, Meier-Hellmann A and Reinhart K. Procalcitonin-a new indicator of the systemic response to severe infections. Infection 1997; 25: 329-334.

[9] Gendrel D and Bohuon C. Procalcitonin, a marker of bacterial infection. Infection 1997; 25: 133-134.
[10] Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C and Schild U. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009; 302: 1059-1066.
[11] Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, Périat P, Bucher HC and Christ-Crain M. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Arch Int Med 2008; 168: 2000-2007.
[12] Jones AE, Fiechtl JF, Brown MD, Ballew JJ and Kline JA. Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. Ann Emerg Med 2007; 50: 34-41.
[13] Meisner M, Tschaikowsky K, Palmaers T and Schmidt J. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. Crit Care 1999; 3: 45.
[14] Hedlund J and Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. Infection 2000; 28: 68-73.
[15] Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M and Muller B. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006; 174: 84-93.
[16] Masiá M, Gutierrez F, Shum C, Padilla S, Navarro JC, Flores E and Hernández I. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. Chest J 2005; 128: 2223-2229.
[17] Polzin A, Pletz M, Erbes R, Raffenberg M, Mauch H, Wagner S, Arndt G and Lode H. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. Eur Respir J 2003; 21: 939-943.
[18] Brunkhorst F, Al-Nawas B, Krummenauer F, Forycki Z and Shah P. Procalcitonin, C-reactive protein and APACHE II score for risk evaluation in patients with severe pneumonia. Clin Microbiol Infect 2002; 8: 93-100.
[19] Boussekey N, Leroy O, Georges H, Devos P, d'Escrivan T and Guery B. Diagnostic and Prognostic Values of Admission Procalcitonin Levels in Community-Acquired Pneumonia in an Intensive Care Unit. Infection 2005; 33: 257-263.
[20] Wells GA, Shea B, O'connell D, Peterson JEA, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2000.
[21] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557.
[22] Collaboration C. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre 2014.
[23] StataCorp L. Stata version 12.0. College station. TX: StataCorp LP 2011.
[24] Andrijevic I, Matijasevic J, Andrijevic L, Kovacevic T and Zaric B. Interleukin-6 and procalcitonin as biomarkers in mortality prediction of hospitalized patients with community acquired pneumonia. Ann Thorac Mede 2014; 9: 162-7.
[25] Espana P, Capelastegui A, Bilbao A, Diez R, Izquierdo F, De Goicoetxea ML, Gamazo J, Medel F, Salgado J and Gorostiaga I. Utility of two biomarkers for directing care among patients with non-severe community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2012; 31: 3397-3405.
[26] Hirakata Y, Yanagihara K, Kurihara S, Izumikawa K, Seki M, Miyazaki Y and Kohno S. Comparison of usefulness of plasma procalcitonin and C-reactive protein measurements for estimation of severity in adults with community-acquired pneumonia. Diagn Microbiol Infect Dis 2008; 61: 170-174.
[27] Huang DT, Weissfeld LA, Kellum JA, Yealy DM, Kong L, Martino M, Angus DC; GenIMS Investigators. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. Ann Emerg Med 2008; 52: 48-58, e42.
[28] Menéndez R, Sahuquillo-Arce JM, Reyes S, Martínez R, Polverino E, Cillóniz C, Córdoba JG, Montull B and Torres A. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. Chest J 2012; 141: 1537-1545.
[29] Müller F, Christ-Crain M, Bregenzer T, Krause M, Zimmerli W, Mueller B and Schuetz P. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest J 2010; 138: 121-129.
[30] Okimoto N, Hayashi Y, Ishiga M, Nanba F, Kishimoto M, Yagi S, Kurihara T, Asaoka N and Tamada S. Procalcitonin and severity of community-acquired pneumonia. J Infect Chemother 2009; 15: 426-427.
[31] Pereira JM, Teixeira-Pinto A, Basílio C, Sousa-Dias C, Mergulhão P and Paiva JA. Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia? J Crit Care 2013; 28: 970-974.
[32] Ugajin M, Yamaki K, Hirasawa N and Yagi T. Predictive values of semi-quantitative procalci-

tonin test and common biomarkers for the clinical outcomes of community-acquired pneumonia. Respir Care 2013; 59: 564-73.

[33] Ramírez P, Ferrer M, Martí V, Reyes S, Martínez R, Menendez R, Ewig S and Torres A. Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia*. Crit Care Mede 2011; 39: 2211-2217.

[34] Zhydkov A, Christ-Crain M, Thomann R, Hoess C, Henzen C, Zimmerli W, Mueller B, Schuetz P; ProHOSP Study Group. Utility of procalcitonin, C-reactive protein and white blood cells alone and in combination for the prediction of clinical outcomes in community-acquired pneumonia. Clin Chem Lab Med 2015; 53: 559-566.

[35] Tamura M, Watanabe M, Nakajima A, Kurai D, Ishii H, Takata S, Nakamoto K, Sohara E, Honda K and Nakamura M. Serial quantification of procalcitonin (PCT) predicts clinical outcome and prognosis in patients with community-acquired pneumonia (CAP). J Infect Chemother 2014; 20: 97-103.

[36] Nylen ES, Whang KT, Snider RH, Steinwald PM, White JC and Becker KL. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. Crit Care Med 1998; 26: 1001-1006.

[37] Wagner KE, Martinez JM, Vath SD, Snider RH, Nylén ES, Becker KL, Müller B and White JC. Early immunoneutralization of calcitonin precursors attenuates the adverse physiologic response to sepsis in pigs. Crit Care Med 2002; 30: 2313-2321.

[38] Cheval C, Timsit J, Garrouste-Orgeas M, Assicot M, De Jonghe B, Misset B, Bohuon C and Carlet J. Procalcitonin (PCT) is useful in predicting the bacterial origin of an acute circulatory failure in critically ill patients. Intensive Care Med 2000; 26: S153-S158.

[39] Pettilä V, Hynninen M, Takkunen O, Kuusela P and Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Med 2002; 28: 1220-1225.

[40] Harbarth S, Holeckova K, Froidevaux CL, Pittet D, Ricou B, Grau GE, Vadas L, Pugin J; Geneva Sepsis Network. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 2001; 164: 396-402.

[41] Claeys R, Vinken S, Spapen H, ver Elst K, Decochez K, Huyghens L and Gorus FK. Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates. Crit Care Med 2002; 30: 757-762.

[42] Moulin F, Raymond J, Lorrot M, Marc E, Coste J, Iniguez J, Kalifa G, Bohuon C and Gendrel D. Procalcitonin in children admitted to hospital with community acquired pneumonia. Arch Dis Child 2001; 84: 332-336.