The role of Procalcitonin in Community Acquired Pneumonia: A Literature Review

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Abstract:

Community-acquired pneumonia (CAP) is a significant clinical and public health problem. Recently, attention has been paid to the potential for procalcitonin (PCT) both to differentiate the diagnosis and to indicate the prognosis of pneumonia. The purpose of this literature review was to evaluate the eligibility of PCT for defining typical bacterial infections and for predicting severity and mortality in trials for CAP. The literature review suggests that PCT has the ability to supplement clinical information to determine whether or not the cause of the infection is likely to be bacterial. In addition, PCT seems to be superior to the most prevalent inflammatory biomarker C-reactive protein and also demonstrates a significant correlation between the current clinical scoring systems and actual mortality.

Keywords: community-acquired pneumonia | procalcitonin

Article:

Pneumonia is the eighth leading cause of death across all age groups in the United States, accounting for 0.3% of deaths in 2004 (Minino, Heron, & Smith, 2006). There were 4.2 million ambulatory care visits for pneumonia in the United States (File & Marrie, 2010). A total of 1.2 million people were admitted to hospitals, and 55,477 people died of pneumonia in 2006 (Heron et al., 2009). Community-acquired pneumonia (CAP) is a significant burden. In the United States, the economic burden associated with CAP is more than $17 billion annually despite the availability of recommended treatment guidelines of CAP (File & Marrie, 2010). The mortality rate in patients with severe CAP is up to 50% worldwide (Rello, 2008). In addition, severe CAP is the largest single cause of infection-related disease in developed countries (Kaplan et al., 2003).

In light of this problem, the present diagnostic and prognostic tools for CAP have been challenging for the following two reasons. First, the current diagnostic gold standard for pneumonia includes evaluation of blood or sputum cultures. Both of these tests lack sensitivity and specificity (Schuetz et al., 2009) to distinguish a large number of microorganisms. Second,

clinicians must decide whether initial antibiotic therapy should treat a bacterial infection or nonbacterial infection (Donowitz, 2010). Traditionally, the use of antibiotics is determined by assessing clinical symptoms and chest radiographic evaluation. Neither of these distinguishes bacterial from nonbacterial infections because different agents can present similar symptoms and radiographic findings (Niederman, 2008). Therefore, selection of antibiotics for CAP is complicated. For example, the illness may be empirically diagnosed as a bacterial infection in some patients with nonbacterial pneumonia (viral illnesses or noninfective). However, treating nonbacterial causes with antibiotics is ineffective and contributes to the increasing prevalence of antibiotic resistance, health care cost, and toxicity along with allergic reaction risks (World Health Organization, 2000, as cited in Simon, Gauvin, Amre, Saint-Louis, & Lacroix 2004). Conversely, bacterial CAP can be misdiagnosed as noninfectious pneumonia because of negative or subtle clinical and radiographic findings (Niederman, 2008). Furthermore, initiating antibiotic therapy promptly is critical in bacterial CAP. In fact, an antibiotic treatment delay of greater than 4 hr can be associated with increased mortality (Fine et al., 1997, as cited in Christ-Crain et al., 2006).

Second, difficulty in estimating pneumonia severity and predicting its prognosis is a persistent problem in CAP (Brown & Dean, 2010). It is critical for clinicians to identify those patients who are at greater risk for deterioration with severe CAP progression so that clinicians can accurately and quickly intervene in the management of the patient. (Mira, Max, & Burgel, 2008). Most patients admitted to a hospital for CAP are initially cared for in the emergency department (ED; Yealy et al., 2004). The placement of patients inpatient at a hospital is a major clinical decision for emergency health care providers with great impact on patient outcome (Nazarian, Eddy, Lukens, Weingart, & Decker, 2009). Patients with CAP transferred from a floor to the intensive care unit (ICU) after hospitalization had a higher mortality than those patients admitted directly to the ICU (Mandell et al., 2007).

Currently, the Pneumonia Severity Index (PSI) is one of the clinical scoring systems used to stratify patients with CAP and to identify seriously ill patients (Mandell et al., 2007). However, the PSI is complicated to use and requires a computation program to score 20 variables. Validation for the instrument is best in the evaluation of patients with low versus high mortality (Lim et al., 2003). Given this diagnostic and prognostic uncertainty, a complementary tool, procalcitonin (PCT), has been studied for distinguishing typical bacterial pneumonia and predicting mortality from CAP. Biomarkers are useful in quantifying the presence of bacterial infection objectively and are more easily obtained than those data that are obtained from the clinical scoring systems. Among the various biomarkers, PCT has been suggested as the most promising biomarker (Brown & Dean, 2010). Procalcitonin, a precursor peptide of the hormone calcitonin, increases in microbial infections and inflammation (Whang et al., 1998). It can be released by an inflammatory process induced directly via microbial toxins or indirectly via a humoral or cell-mediated host response (Chris-Crain & Müller, 2007). This induction can be attenuated by cytokines in a viral infection or fastidious organisms (e.g., *Mycoplasma*, *Chlamydia*), which may be the reason that PCT is not more pronounced in atypical pathogen infections (Brown, 2009). Regardless, PCT seems to be an important serum marker for indicating a greater bacterial load or an excessive inflammatory response. Highly increased levels of PCT can imply adverse conditions within the host such as extensive

consolidation in the lungs or the development of septic shock (Brown & Dean, 2010). Therefore, an increased PCT level may correlate with mortality and condition severity.

Procalcitonin has great accessibility to the clinical staff regarding timing and cost. Its secretion begins within 4 hr after stimulation and peaks at 8 hr (Nijsten et al., 2000). Procalcitonin is stable in samples, the assay is relatively easy to perform, and the result is available within 1 hr (Riedel, Melendez, An, Rosenbaum, & Zenilman, 2011), with a moderate cost ($27–$30), (Arnold Huang at Thermo Fisher Scientific, written communication, April 13, 2012).

The goals of this article were to provide an overview of PCT as a diagnostic and prognostic biomarker in CAP and to evaluate the ability of PCT based on the recent published research studies. The primary purposes of the review were to determine (1) whether PCT can distinguish typical bacterial infection versus atypical pathogen infection in CAP; (2) whether PCT is a superior biomarker of inflammation for identifying typical bacterial infection in CAP; (3) whether PCT can assess the severity of CAP in accordance with the current clinical scoring systems; and (4) whether PCT level is related to mortality risk.

METHODS

The search strategy was designed to find literature related to PCT in CAP. MEDLINE (OVID) was reviewed as well as bibliographies from retrieved articles and relevant citations. Search terms consisted of “procalcitonin” and “pneumonia.” More than 163 studies were initially identified and screened by examining: reference with title and abstract, applying the inclusion and exclusion criteria listed later, and reference accessibility. A total of 10 empirical articles, comprising six prospective cohort studies and four retrospective cohort studies, were examined.

Selection of Studies and Data Extraction

Studies were included in the analysis if (1) PCT was used as a diagnostic or prognostic assessment measure of CAP, (2) participants had a diagnosis of CAP with the presence of symptoms (cough, sputum production, fever, and dyspnea) and a lung infiltrate seen on the radiograph, (3) the age of participants was older than 15 years and they were immunocompetent, and (4) published in English from 2000 to the time of the review conducted for this study. Studies were excluded from this literature review that met the following criteria: (1) whether the study participants consisted of an identical comorbidity with CAP (the purpose of study focused on the particular comorbidity rather than CAP) and (2) whether PCT was not used to evaluate either a diagnostic tool or a prognostic tool.

RESULTS

There have been numerous international efforts to study the relationship between PCT and CAP, including research carried out in Austria, France, Germany, Slovenia, Spain, Sweden, and the United States (Bellmann-Weiler, Ausserwinkler, Kurz, Theurl, & Weiss, 2010; Boussekey et al., 2005; Hedlund & Hansson, 2000; Huang et al., 2008; Jereb & Kotar, 2006; Krüger et al., 2008; Krüger, Ewig, Giersdorf, et al., 2010; Krüger, Ewig, Kunde, et al., 2010; Masiá et al.,

2005; Menéndez et al., 2009). In addition, the studies were conducted in various clinical settings such as general inpatient, outpatient, ICU, and ED.

Most of the studies (seven of 10 studies) used highly sensitive PCT assays, which are Kryptor PCT and Liasion PCT assays distributed by BRAHMS Diagnostica GmbH. The Kryptor PCT has a functional assay sensitivity of 0.06 mcg/L and assay time of 19 min, using 20–50 mcg/L of plasma or serum (Christ-Crain & Müller, 2007). The liaison PCT correlates very well with results obtained by Kryptor PCT; the maximum deviation is 20% (BRAHMS, n.d.). The remainder of the three studies used the LUMI test, which is a manual assay and has the relative sensitivity to detect a limit of 0.3–0.5 mcg/L (Christ-Crain & Müller, 2007). However, it is thought that this characteristic of LUMI test only limits its diagnostic accuracy in terms of detecting mildly elevated PCT levels. It would not have an effect on the prognostic accuracy because PCT is likely to be at least moderately elevated in severe CAP cases.

There are overlaps of studies in terms of investigating diagnostic and prognostic values of PCT. Among the total of 10 empirical studies, four studies focused on PCT as a diagnostic marker (Bellmann-Weiler et al., 2010; Hedlund & Hansson, 2000; Jereb & Kotar, 2006; Masiá et al., 2005), nine studies explored PCT as a prognostic marker (Bellmann-Weiler et al., 2010; Boussekey et al., 2005; Hedlund & Hansson, 2000; Huang et al., 2008; Krüger et al., 2008; Krüger, Ewig, Giersdorf, et al., 2010; Krüger, Ewig, Kunde, et al., 2010; Masiá et al., 2005; Menéndez et al., 2009), and three studies dealt with both aspects of PCT (Bellmann-Weiler et al., 2010; Hedlund & Hansson, 2000; Masiá et al., 2005). Therefore, the majority of the recent articles on PCT and CAP have investigated its role for assessing CAP severity and mortality. The four studies (diagnostic aspect of PCT) examined whether or not there was a significant difference in PCT level between typical bacterial infections and atypical pathogen infections in CAP. They discussed the superiority of PCT by comparing it with C-reactive protein (CRP), which is also frequently used in practice as a major inflammatory biomarker. The nine studies (prognostic aspect of PCT) explored the eligibility of PCT by using two different methods. First, several researchers examined the correlation with the clinical scoring systems (PSI, CURB-65, CRB-65, and APACHE II) and the level of PCT. Second, other researchers investigated the correlation with the actual mortality in CAP and PCT levels. All of them evaluated the performance of PCT by comparing other biomarkers.

DISCUSSION

Procalcitonin as a Diagnostic Marker

Procalcitonin as a Complementary Diagnostic Tool to Identify the Presence of Typical Bacterial Pneumonia

The causes of CAP have been divided into two major groups: typical bacterial pathogens and atypical pathogens. The major typical bacterial pathogens include *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Hemophilus influenzae*. The major atypical pathogens include viruses, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae* (Fang et al., 1990).

Three of four studies (Bellmann-Weiler et al., 2010; Hedlund & Hansson, 2000; Jereb & Kotar, 2006) showed that the PCT level was increased significantly in typical bacterial pneumonia compared with atypical pathogen pneumonia (see Table 1). Blood PCT level lower than 0.1 ng/ml indicates the absence of bacterial infection (BRAHMS, n.d.). First, Bellmann-Weiler et al. (2010) analyzed the records of 61 hospitalized patients with CAP caused by *S. pneumoniae* (typical agent) or *L. pneumophila* (atypical agent) to determine PCT levels for the differential diagnosis. *S. pneumoniae* pneumonia showed significantly increased PCT compared with *L. pneumophila* pneumonia (20.94 vs. 6.76 mcg/L; $p < 0.01$). Second, Hedlund and Hansson (2000) evaluated 96 hospitalized patients and found that typical bacterial pneumonia had increased PCT levels in contrast to atypical pathogen pneumonia (5.75 vs. 2.15 mcg/L; $p < 0.03$). Then, Jereb and Kotar (2006) assessed 30 hospitalized patients and discovered the difference in PCT level between typical bacterial pneumonia and atypical pathogen pneumonia (7.64 vs. 0.80 mcg/L; $p = 0.031$). However, Masiá et al. (2005) showed no significant difference when they examined the 185 CAP patients. They found that the highest PCT levels predicted bacterial cause only with low-risk classes (PSI I–II). Masiá et al. (2005) divided the causal group into four subgroups: classic bacterial pathogen, atypical pathogens, viruses, and mixed. The rest of the studies divided the causal group into two major groups. Therefore, it is possible that the four specified groupings could attenuate the statistical significance over the studies with two major groups. In addition, the sample size in some of the four etiologic groups was small, and the lack of statistical power might have prevented them from detecting significant differences among groups. Overall, the studies suggest that patients with very high levels of PCT are more likely to have a pneumonia caused by typical bacterial pathogens and patients with low levels of PCT are more likely to have a pneumonia caused by atypical pathogens.

The most effective cutoff value of PCT to distinguish typical bacterial pneumonia versus atypical pathogen pneumonia is not defined. The mean PCT levels for typical bacterial pneumonia (5.75–20.94 mcg/L) and for atypical pathogen pneumonia (2.15–6.76 mcg/L) were variable (Bellmann-Weiler et al., 2010; Hedlund & Hansson, 2000). Even though all the studies measured PCT level on Day 1 (admission), it is not clear whether they measured it before administration of antibiotics or not. The PCT concentration decreases rapidly in effectively treated bacterial infection with antibiotics (Al-Nawas, Krammer, & Shah, 1996).

However, two clinical trials and one systemic review show a cutoff value of PCT to be used with antibiotics. Clinicians were recommended not to prescribe antibiotics in patients with a procalcitonin level less than 0.1 mcg/L but were encouraged to administer antibiotics in patients with levels of more than 0.25 mcg/L. These cutoff values are consistent in the three studies (Christ-Crain et al., 2004, 2006; Schuetz, Chiappa, Briel, & Greenwald, 2011).

Procalcitonin as a Superior Diagnostic Marker

Among several markers of inflammation, primarily PCT and CRP have been studied to investigate their accuracy in detecting bacterial infections (Simon et al., 2004). Both PCT and CRP are acute-phase reactants that rapidly increase during inflammatory disease. These two markers have been recognized as more reliable indicators of infection than a pyrexia or raised white blood cell count (Brown, 2009).

Table 1. Description of individual studies examining PCT as differentiating between typical and atypical pathogens in CAP

Author	Year	Study sample size	Study design	Causal groups	PCT level difference between groups	CRP level difference between groups	PCT measuring time	Type of PCT assay
Bellmann-Weiler et al.	2010	61 hospitalized patients	Retrospective cohort study	*Streptococcus pneumonia* *Legionella pneumophila* (37 vs. 24)	$p < 0.01$** at Day 1	NS	Day 1 Day 5	Kryptor
Hedlund & Hansson	2000	96 hospitalized patients	Prospective cohort study	Classic bacteria[a] Atypical agents[b] (27 vs. 9)	$p < 0.03$* at Day 1	NS	Day 1 Day 4 Day 7 Day 10 8 weeks 6 months	Lumitest
Jereb et al.	2006	30 hospitalized patients	Prospective cohort study	Classic bacteria[a] Atypical agents[b] (20 vs. 10)	$p = 0.031$* at Day 1	NS	Day 1	Liaison
Masiá et al.	2005	144 hospitalized patients and 41 outpatients (total 185)	Prospective cohort study	Classic bacteria ($n = 39$) Atypical agents[b] ($n = 36$) Viruses ($n = 15$) Mixed agents ($n = 14$)	NS	Not checked	Not mentioned	Liaison

Note. CAP = community-acquired pneumonia; CRP = C-reactive protein; NS = not significant; PCT = procalcitonin.
[a]*Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Hemophilus influenzae*.
[b]*Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*.
*$p < 0.05$. ** $p < 0.01$. ***$p < 0.001$.

Three studies compared the superiority of PCT with CRP (Bellmann-Weiler et al., 2010; Hedlund & Hansson, 2000; Jereb & Kotar, 2006). They also suggested that the PCT marker was more accurate than the CRP marker in differentiating typical bacterial infection from atypical pathogen infection. The researchers did not find any difference in CRP levels between etiologic groups, and this finding agrees with that of Simon et al. (2004). Simon et al. (2004) reviewed 12 studies (a systematic review and meta-analysis) to evaluate the accuracy of serum PCT and CRP levels as markers of bacterial infection. The PCT level was more sensitive (92% vs. 86%) and more specific (73% vs. 70%) than the CRP level for differentiating bacterial from viral inflammation. In addition, the CRP level is attenuated by immunosuppressive medication (steroids); in contrast, the PCT level remained unaffected (Müller et al., 2002). Therefore, the PCT seems to have an advantage over the CRP because of its higher sensitivity, specificity, and unchanging characteristic from drugs.

Procalcitonin as a Prognostic Marker

Procalcitonin's Relationship to Severity

To determine whether PCT is related to severity, the pattern of PCT in CAP must be evaluated in conjunction with current clinical scoring systems. The clinical scoring systems include the PSI and the CURB-65 and CRB-65 scales. They have been developed to standardize initial assessment for the anticipated course of CAP (Rello, 2008). The PSI classifies patients into 5 categories on the basis of mortality risk. It recommends that patients in Groups I and II should be treated in outpatient department, those in Group III should be treated in an observation unit, and those patients who fall within Groups IV and V should be admitted (Fine et al, 1997, as cited in Nazarian et al., 2009). The effectiveness of PSI has been supported in a study that used the score to determine the need for hospitalization of patients with pneumonia; no adverse outcomes were noted (Aujesky et al., 2005). The CURB-65 scale has been proposed as a simpler alternative to the PSI. Criteria for this scale include confusion, urea (>7 mmol/L), respiratory rate more than 30 breaths per minute, low systolic (<90 mmHg) or diastolic blood pressure (≤60 mmHg), and age 65 years and older (Lim et al., 2003). The score ranges from 0 to 5; the higher the number, the more severe the condition. The CRB-65 is a simpler form of CRUB-65; urea is omitted. Finally, the Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system is a tool for assessing the severity of critically ill patients upon admission (Knaus, Draper, Wagner, & Zimmerman, 1985). All these severity tools have been used in studies testing the severity of illness as compared with PCT.

Procalcitonin showed positive correlation with the current severity index scales (Hedlund & Hansson, 2000; Krüger, Ewig, Giersdorf, et al., 2010; Masiá et al., 2005; Menéndez et al., 2009; see Table 2). Menéndez et al. (2009) investigated 453 hospitalized patients with CAP and demonstrated strong correlations between PCT levels and PSI ($p < 0.0001$), CURB-65 ($p < 0.0001$), and CRB-65 ($p < 0.0001$). Hedlund and Hansson (2000) investigated 96 hospitalized patients and concluded that the severity of disease measured by APACHE II score was strongly associated with levels of PCT at admission ($p = 0.006$). These results are consistent with the findings of Hirakata et al. (2008) that 93.3% of patients with mild CAP had lower values of PCT (<0.5 mcg/L). Consequently, adding PCT to the clinical scoring systems may improve the ability of clinicians to predict potential adverse outcomes or death.

Table 2. Description of individual studies examining PCT as correlation with the clinical scoring systems and mortality

Author	Year	Study sample size	Study design	Comparison group	Type of PCT assay	PCT correlation with mortality	PCT correlation with the clinical scoring systems
Bellmann-Weiler et al.	2010	61 hospitalized patients	Retrospective cohort study	Days 1 and 5 Survivors Dead (no. of patients were not mentioned)	Kryptor	Day 1 PCT 12.23 vs. 26.92 mcg/L $p = 0.08$* Day 5 PCT 1.42 vs. 20.12 mcg/L $p < 0.0001$***	Not checked
Boussekey et al.	2005	110 patients hospitalized in ICU	Prospective cohort study	Day 30 Survivors ($n = 80$) Dead ($n = 30$)	Lumitest	Day 30 PCT 1.5 vs. 5.6 mcg/L $p < 0.0001$***	Not checked
Hedlund & Hansson	2000	96 hospitalized patients	Prospective cohort study	6 months Survivors ($n = 88$) Nonsurvivors ($n = 6$)	Lumitest	6 month $p = 0.002$** (>0.1 vs. ≤0.1)	$p = 0.006$** with APACHE II
Huang et al.	2008	1,651 patients presenting to ED	Prospective cohort study	PCT tier I, II, III, and IV	Kryptor	Day 30 $p < 0.0001$*** Day 90 $p < 0.0001$***	Not mentioned
Krüger et al.	2008	1,113 hospitalized patients and 558 outpatients (total 1,671)	Retrospective cohort study	Day 28 Survivors ($n = 1,476$) Nonsurvivors ($n = 70$)	Kryptor	Day 28 PCT 0.88 vs. 0.13 mcg/L $p < 0.001$***	Not mentioned
Krüger, Ewig, Giersdorf, et al.	2010	728 hospitalized patients	Retrospective cohort study	Day 28 Survivors ($n = 710$) Death ($n = 18$) Day 180 Survivors ($n = 691$) Death ($n = 37$)	Kryptor	Day 28 PCT 0.10 vs. 0.36 mcg/L $p = 0.0135$* Day 180 PCT 0.10 vs. 0.23 mcg/L $p = 0.0273$*	$p < 0.0001$*** with CRB-65
Krüger, Ewig, Kunde, et al.	2010	1,740 patients (inpatient and outpatient)	Retrospective cohort study	Day 28 Survivors ($n = 1,658$) Dead ($n = 78$) Day 180 Survivors ($n = 1,565$) Dead ($n = 171$)	Kryptor	Day 28 PCT 0.83 vs. 0.10 mcg/L $p < 0.0001$*** Day 180 PCT 0.43 vs. 0.09 mcg/L $p < 0.0001$**	Not mentioned
Masiá et al.	2005	144 hospitalized patients and 41 outpatients (total 185)	Prospective cohort study	1 year PCT ≥0.5 ($n = 21$) PCT <0.5 ($n = 164$)	Liaison	1 year PCT ≥0.5 mcg/L 23.8% death PCT <0.5 mcg/L 2.4% death $p = 0.001$**	$p = 0.001$** with PSI
Menéndez et al.	2009	453 hospitalized patients	Prospective cohort study	Day 30 Survivors ($n = 417$) Dead ($n = 36$)	Liaison	Day 30 PCT 1.8 vs. 0.58 mcg/L $p = 0.002$**	$p < 0.0001$*** with PSI, CURB-65, and CRB-65

Note. ED = emergency department; ICU = intensive care unit; PCT = procalcitonin; PSI =Pneumonia Severity Index.
*$p < 0.05$. **$p < 0.01$. *** $p < 0.001$.

Procalcitonin as a Complementary Prognostic Tool to the Clinical Scoring Systems

Two studies (Huang et al., 2008; Krüger, Ewig, Giersdorf, et al., 2010) suggested that the PCT could add additional information to the current clinical scoring systems. Huang et al. (2008) analyzed 1,651 patients presenting to the ED to describe the pattern of PCT in CAP. They generated Kaplan-Meier plots of 30-day mortality by PCT tier (>0.1 or <0.1 mcg/L) and calculated test characteristics. The subjects in PCT Tier I (<0.1 mcg/L) had identical low 30-day mortality (1.5%). Patients with lower levels of PCT were at a low risk of death, regardless of PSI and CURB-65 severity. This finding is consistent with the results of Krüger, Ewig, Giersdorf, et al. (2010), who enrolled 728 patients and followed them for 28 days. They found that the patients with lower levels of PCT (≤0.2 mcg/L) had a lower risk of death regardless of CRB-65 score. It appears that PCT provides independent identification of patients at low risk of death. However, "dose–response mortality" was not observed as PCT level increased, which makes it difficult to conclude that a higher PCT level is associated with a high mortality (Huang et al., 2008, p. 55). In addition, the kinetics of the PCT are not yet fully understood. For these reasons, using PCT as an alternative tool to the clinical scoring systems requires further prospective study before widespread use can be recommended.

Procalcitonin's Relationship to Mortality

All of the nine studies reported that PCT level showed a statistically significant correlation with mortality in CAP (p values <0.05 were considered significant); each of the studies measured different days for mortality (Day 1 to 1 year) and the results were identical (see Table 2). This uniform result strengthens the conclusion that the use of PCT in concert with selected current clinical scoring systems may result in a stronger prognostic marker for CAP than any of it used separately.

However, using PCT alone to predict mortality has not been fully supported. Several researchers evaluated the ability of PCT as an independent prognostic tool. In a study by Huang et al. (2008), the investigators tested the sensitivity and specificity of PCT. Three studies calculated the areas under the curve of PCT for analyzing survival rate by receiver operating characteristic analysis. Huang et al. (2008) manifested the characteristics of PCT as 35% specificity, 92% sensitivity, 1.41 positive likelihood ratio, and 0.22 negative likelihood ratio, which suggest modest sensitivity and specificity. Similarly, the area under the curve of PCT for predicting mortality was 80% (Krüger et al., 2008), 65% (Krüger, Ewig, Giersdorf, et al., 2010), and 76% (Krüger, Ewig, Kunde, et al., 2010). These results suggest that the PCT should be used as a complementary tool rather than as a stand-alone biomarker.

Procalcitonin has been studied to facilitate the diagnosis of sepsis. There is no single test that immediately confirms the diagnosis of sepsis (Annane, Bellissant, & Cavaillon, 2005). However, PCT has been studied as diagnostic markers of active bacterial infection. As a result, a great deal of studies showed that PCT is a good biological diagnostic marker of sepsis. Procalcitonin concentrations increase significantly in patients with severe sepsis or septic shock (up to 1,000 ng/ml; Jacobs, Lund, Potts, Bell, & Habener, 1981). In addition, concentrations of PCT above 1.1 ng/ml are highly indicative for sepsis (92.8%; Giamarellos-Bourboulis et al., 2004) and PCT has a good negative predictive value for sepsis (98%; Riedel et

al., 2011). The cutoff value for sepsis has been set at 0.44–1.1 ng/ml in different studies (Charles et al., 2009; Clec'h et al., 2004; Giamarellos-Bourboulis et al., 2004). Finally, it is proposed that PCT should be included both in diagnostic guidelines for sepsis (Uzzan, Cohen, Nicolas, Cucherat, & Perret, 2006; Zahorec, 2001) and in the international definition of sepsis (Levy et al., 2003). Although PCT is a promising marker, it seems not to be sufficiently reliable as the sole or main diagnostic indicator. Therefore, clinicians should consider the overall clinical picture when making a clinical judgment.

Procalcitonin as a Superior Prognostic Biomarker

Three studies compared the performance of PCT with CRP (Bellmann-Weiler et al., 2010; Boussekey et al., 2005; Menéndez et al., 2009). Two studies (Bellmann-Weiler et al., 2010; Boussekey et al., 2005) proved that PCT levels more effectively predict mortality than CRP. The CRP level did not demonstrate any difference between survivors and nonsurvivors. However, Menéndez et al. (2009) described that high levels of CRP is an independent predictive value for predicting mortality at 30 days (21.9 vs. 14.4 mg/dl, $p = 0.0001$). In the study of Menéndez et al. (2009), there is a remarkable discrepancy between survivors and nonsurvivors. The deceased were older and had more neurological disease than survivors ($p = 0.0001$). Therefore, their results may not be generalizable.

Krüger, Ewig, Giersdorf, et al. (2010) and Krüger, Ewig, Kunde, et al. (2010) concluded that mid-regional proadrenomedullin (MR-pro ADM) and C-terminal proatrial vasopressin (CT-proAVP) may be better prognostic biomarkers than PCT. These two studies have several common points. First, several of the same authors conducted and analyzed both studies, which were based on results from the German Competence Network for the study of CAP. However, the results of both studies are debated by others. It is thought that comorbidity was a confounding factor in the study of Krüger, Ewig, Giersdorf, et al. (2010). Specifically, the nonsurvivors had higher congestive heart failure rates and more chronic renal disease than survivors ($p = 0.0002$). Krüger, Ewig, Kunde, et al. (2010) did not offer the basic characteristics of the patients, which made it impossible to determine whether the comparison groups were homogenous. Therefore, it is unreasonable to conclude that MR-pro ADM and CT-proAVP are more accurate prognostic biomarkers than PCT.

CONCLUSION

Procalcitonin has emerged as a potentially reliable diagnostic and prognostic marker for CAP. First, PCT has substantial usefulness as a diagnostic marker in CAP patients. The PCT marker has the ability to differentiate the typical bacterial infections from atypical pathogen infections. It can offer a possible guideline to determine the initiation of antibiotics. In addition, PCT may be a useful complimentary tool in some specific situations. These may include patients who have unremarkable symptoms (apyrexia, minimal cough, and sputum) at presentation and/or patients with underlying parenchymal lung disease that makes radiological evaluation of a new consolidation difficult (Brown, 2009). Procalcitonin has shown potential usefulness in the outpatient department in treating lower respiratory tract infections. Briel et al. (2008) investigated whether antibiotic therapy guided by PCT reduces the use of antibiotics without increasing the restrictions experienced by patients. The authors found that PCT testing

yielded a 72% decrease in antibiotic use, with no difference in ongoing symptoms or relapse at 28 days between groups.

Second, PCT has considerable value as a prognostic marker in CAP patients in that it does correlate well with selected current clinical scoring systems that test short- and long-term mortality. In addition, PCT showed potentially complementary diagnostic ability with the clinical scoring systems. Low PCT levels offer additional risk stratification in low-risk CAP patients, predicting low mortality regardless of the clinical scoring tiers. The findings of PCT as a prognostic tool may contribute in the improvement of the management of severe CAP by identifying the possibility of adverse outcomes early in the course of disease. Procalcitonin may provide a reliable standard tool for use in ED practitioner decisions related to initial hospitalization, direct admission to ICU, and the beginning of additional treatment.

However, caution should be exercised in the use of PCT in practice at this point. First, PCT cannot substitute for a careful history, thorough physical examination, and seasoned clinical diagnosis of common clinical patterns of infection. Second, the PCT level must always be evaluated within the clinical context. Third, PCT should not be used ever in isolation to make clinical decisions. In conclusion, the PCT can be best used in conjunction with the sound clinical evaluation by health care providers.

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