Diagnostic value of serum procalcitonin in patients with chronic renal insufficiency: a systematic review and meta-analysis

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Abstract

Background. The diagnostic value of procalcitonin (PCT) for patients with renal impairment is unclear.

Methods. We searched multiple databases for studies published through December 2011 that evaluated the diagnostic performance of PCT among patients with renal impairment and suspected systemic bacterial infection. We summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic (HSROC) curves, and bivariate random effects models.

Results. Our search identified 201 citations, of which seven diagnostic studies evaluated 803 patients and 255 bacterial infection episodes. HSROC–bivariate pooled sensitivity estimates were 73% [95% confidence interval (95% CI) 54–86%] for PCT tests and 78% (95% CI 52–92%) for CRP tests. Pooled specificity estimates were higher for both PCT and CRP tests [PCT, 88% (95% CI 79–93%); CRP, 84% (95% CI, 52–96%)]. The positive likelihood ratio for PCT [likelihood (LR)+ 6.02, 95% CI 3.16–11.47] was sufficiently high to be qualified as a rule-in diagnostic tool, while the negative likelihood ratio was not low enough to be used as a rule-out diagnostic tool (LR− 0.31, 95% CI 0.17–0.57). There was no consistent evidence that PCT was more accurate than CRP test for the diagnosis of systemic infection among patients with renal impairment.

Conclusions. Both PCT and CRP tests have poor sensitivity but acceptable specificity in diagnosing bacterial infection among patients with renal impairment. Given the poor negative likelihood ratio, its role as a rule-out test is questionable.

Keywords: bacterial infection; chronic renal insufficiency; procalcitonin

Introduction

Patients with end-stage renal disease (ESRD) are more susceptible to systemic bacterial infection with worse outcome [1–5]. Patients on peritoneal dialysis (PD) are susceptible to PD-related peritonitis and exit-site infection [1, 4, 6], while patients on hemodialysis (HD) are susceptible to exit-site infection, bloodstream infection, and catheter-related infection [2, 3]. Due to their compromised immune statuses, clinical signs for infection in these patients are often subtle and nonspecific, and the conventional laboratory markers are often influenced by uremia. Furthermore, patients on chronic HD or PD therapy may have chronic systemic inflammation stimulated by an incompatibility of the biomaterial of the dialysis procedures [7, 8]. It has been shown that leukocyte count, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) may increase nonspecifically in these patients without infection [7, 9, 10].

Procalcitonin (PCT), a 116-amino acid precursor protein of calcitonin, has been shown to be able to accurately distinguish bacterial from nonbacterial infections, or other sterile inflammation conditions [11–13]. PCT is constitutively produced in the C cells of the thyroid gland without hormone activity. It is rapidly produced and released to peripheral circulation in response to endotoxin and pro-inflammatory cytokines, such as IL-1β and TNF-α. Unlike CRP, PCT production is inhibited by interferon-gamma (IFN-γ), a cytokine that is produced during viral infections. PCT has not been extensively studied in patients with chronic renal insufficiency or ESRD. The few currently available studies are either relatively small in sample size or use unrepresentative populations [14–20]. Therefore, the relative merits of PCT testing in patients with chronic renal insufficiency remain unclear.

The aim of the study was to systemically and quantitatively assess the current evidence on the usefulness of PCT tests among patients with chronic renal insufficiency, using a novel bivariate analysis approach.

Materials and methods

Systemic meta-analysis guideline adherence

We adhered to the standard methods and procedures for systematic reviews and meta-analyses of diagnostic tests [21–23].

Literature search strategy

We performed a search on PubMed without language restrictions using the keyword ‘procalcitonin’ crossed with ‘kidney’, ‘renal insufficiency’, ‘end-stage renal disease’, ‘hemodialysis’, ‘peritoneal dialysis’ and ‘renal replacement’. Our search was limited to human studies published from inception to December 2011. A similar search strategy and similar search terms were used in EMBASE. PubMed and EMBASE searches were conducted independently by two authors. To ensure a comprehensive acquisition of literature, independent supplemental manual searches were performed on the reference lists of relevant articles and Cochrane
We included studies that met all of the following inclusion criteria: (i) evaluation of PCT alone or compared with other laboratory markers, such as CRP, to diagnose bacterial infection in patients with chronic renal insufficiency; and (ii) sufficient data to reconstruct a 2 × 2 contingency table for meta-analysis. Two authors independently assessed all titles/abstracts to determine whether inclusion criteria were satisfied. Full-text articles were retrieved if any of the reviewers considered the abstracts suitable. The two reviewers then independently assessed the full text of the retrieved studies for their suitability for inclusion. Discrepancies between the two reviewers were resolved by an additional reviewer assessing the full article. The decision regarding whether to include a particular article was made by consensus. The two original reviewers independently extracted data from each of the studies included. Among the pre-defined variables collected were year of publication, study design (prospective or retrospective, cross-sectional or case-control), number of patients included, age group (adults or children), setting, study population, outcome disease definition, timing of the PCT measurement, markers other than PCT, cutoff of the tested markers, and study results, including sensitivity and specificity. The quality of the selected studies was assessed by Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria [24]. When multiple pairs of sensitivity or specificity were reported in one study, we consistently used the data with the highest Youden index (sensitivity + specificity – 1) for meta-analysis.

Data preparation and statistical analysis

Because pooling sensitivity and specificity can separately produce biased estimates of test accuracy, we preferred to generate pooled estimates when both sensitivity and specificity were reported in a study. We used the bivariate random effects regression model for diagnostic meta-analysis to obtain weighted summary estimates of the sensitivity and specificity of PCT [25]. The bivariate approach assumes a bivariate distribution for the logit-transformed sensitivity and specificity. The bivariate model estimates and adjusts for the negative correlation between the sensitivity and specificity of the index test due to the threshold effect [25]. We also generated hierarchical summary receiver operating characteristic (HSROC) curves as a way to summarize the global test performance from different diagnostic studies [26]. HSROC curves differ from traditional receiver operating characteristic (ROC) curves in allowing random effects by each individual study. The HSROC curves generated the curve restricted by the observed range of sensitivity and specificity from the included studies. It does not extrapolate beyond the available data. Both bivariate model and HSROC methods are supported by the Cochrane Diagnostic Test Accuracy Working Methods group [23]. The multiple sources of heterogeneity frequently exist in diagnostic studies. In addition to visual assessment with the use of the forest plots, we formally quantified the extent of heterogeneity by calculating the inconsistency index (I² statistics) [27]. I² is a measure of the between-study variation that cannot be explained by the within-study variation [27]. Statistically significant heterogeneity was considered present at I² > 50%. When I² is >50%, we calculated pooled sensitivity and specificity estimates with the use of random effects modeling, which provides more conservative estimates than fixed effects modeling [27]. To explore the source of heterogeneity, we performed subgroup analysis by pre-specified clinical and study design characteristics. High-cutoff value was defined as the level of PCT >0.5 ng/mL, and low-cutoff value was defined as the level of PCT <0.5 ng/mL. We also performed a diagnostic odds ratio (OR) meta-analysis and plotted the forest plots for diagnostic OR. To test for possible publication bias, we used a linear regression of log ORs on the inverse root of effective sample sizes to test funnel plot asymmetry [28]. Statistical analyses were conducted using STATA 11.0 (Stata Corp., College Station, TX, USA), notably with the user-written ‘midas’ and ‘metandi’ programs for stata. All statistical tests were two-sided, and statistical significance was defined as a P-value <0.05.

Results

Identification of studies and their quality

Our initial search yielded 151 citations. After title and abstract exclusion, 14 potentially relevant articles were retrieved for full-text review. Of these, six articles were excluded because related diagnostic tests or outcomes were not reported [29–34], and one was excluded because the study made comparisons with the serum level of PCT in septic patients before and after hemofiltration [35]. We contacted the authors to retrieve data for analysis but could not get any response. Finally, a total of seven citations were included in the analysis (Figure 1). In total, we included 803 patients tested with PCT and 492 patients tested with CRP. The prevalence of bacterial infections was 255 of 803 (31.8%) and 84 of 330 (25.5%), respectively.

Study characteristics

Of the total studies, four studies included patients on PD [14, 16, 17, 19], two included patients with renal insufficiency [18, 20] and one included patients on HD [15]. The study settings included hospitalized patients (four studies) [14–17], ambulatory patients (two studies) [18, 19] and intensive care unit (ICU) patients (one study) [20]. The outcome definitions can be classified into two broad categories: microbiologically documented infections (MDIs) or MDIs and clinically documented infections (CDIs). The sensitivity and specificity of PCT or CRP tests are also presented in Table 1. The sensitivity of PCT in identifying bacterial infections ranged from 42 to 94%, and the specificities ranged from 67 to 100%. Five studies also looked into CRP testing, with sensitivities ranging from 40 to 98% and specificities ranging from 48 to 100%. Table 1 lists the characteristics of all seven included studies.

Of the included studies, all data collection was carried out prospectively, used the same reference standard for the outcome verification independent of the index test and provided clear descriptions of patient selection criteria and index tests. All patients received either blood culture tests or complete clinical evaluation as reference tests without differential disease ascertainment. None of the included studies provided any explanation for uninterpretable test results or participants’ withdrawal from the study. Incorporation bias is likely, since no studies provided descriptions of whether blinding to index testing affected the outcome verification. Figure 2 provides an overall picture of the methodological quality of studies as evaluated by the QUADAS tool.

Results of individual studies

The results of the meta-analysis showed that both PCT and CRP are more specific than they are sensitive in diagnosing bacterial infections among patients with renal impairment.

Bivariate pooled sensitivity and specificity estimates for PCT are 0.73 (95% CI 0.54–0.86) and 0.88 (95% CI 0.79–0.93), respectively (Figure 3A). Bivariate pooled
sensitivity and specificity estimates for CRP are 0.78 (95% CI 0.52–0.92) and 0.84 (95% CI 0.52–0.96), respectively (Figure 3B). The CIs for specificity were substantially smaller than those for sensitivity, because more patients turned out to be non-infected. The positive likelihood ratio for PCT testing was high enough to be
used as a rule-in test (LR+: 6.02; 95% CI 3.16–11.47), while the negative likelihood ratio was not sufficiently low to be used as a rule-out test (LR−: 0.31; 95% CI 0.17–0.57). A similar trend for likelihood ratio was observed for CRP testing. The positive likelihood ratio for CRP was high (LR+: 4.89; 95% CI 1.61–14.85), whereas the negative likelihood ratio was not low enough (LR−: 0.26; 95% CI 0.13–0.53). Figure 4 shows the forest plots of diagnostic OR for PCT (A) and CRP (B).

To compare the overall performance of the two biomarkers independent of the threshold effects, we calculated the global measures of test performance, area under the ROC (AUROC) and diagnostic odd ratio. HSROC showed an AUROC of 0.89 (95% CI 0.86–0.92) for PCT and an AUROC of 0.88 (95% CI 0.83–0.92) for CRP (Figure 4). The diagnostic OR for PCT was 19.4 (95% CI: 6.93–54.2) for PCT and 19.0 (95% CI: 8.9–40.4) for CRP. There is no evidence to show that PCT is a superior test to
CRP in this patient population. A substantial degree of heterogeneity was observed for PCT testing ($I^2$, 89.8%; 95% CI 54.2–89.3), but not for CRP testing ($I^2$, 0.0%; 95% CI 0.0–79.2).

**Subgroup analysis**

We performed subgroup analysis by restricting studies with similar cutoff values, study populations, and outcome definitions. For the three studies reporting test results with the use of a standard PCT cutoff value (0.5 ng/mL) [14, 17, 19], sensitivity decreased appreciably (0.62, 95% CI 0.48–0.99) and the specificity increased correspondingly (0.94, 95% CI 0.84–0.95). Five studies also reported diagnostic accuracy parameters on higher PCT cutoff values (0.79–2 ng/mL) [14–17, 20]. The specificity, positive likelihood ratio, AUROC, and diagnostic OR all improved accordingly. In contrast, subgroup analysis on parameters based on lower cutoff values (0.38–0.5 ng/mL) showed appreciably decreased performance in sensitivity, specificity, negative likelihood ratio, AUROC, and diagnostic OR compared with the overall estimates. There are four studies carried out on patients undergoing PD [14, 16, 17, 19]. These four studies used PCT testing to diagnose PD peritonitis. The pooled estimates showed a poor sensitivity (0.53, 95% CI 0.39–0.66) and reasonably high specificity (0.91, 95% CI 0.84–0.95). There is no evidence of publication bias on either overall or subgroup analysis. The diagnostic test accuracy indices for overall analysis and subgroup analysis are summarized in Table 2.

**Discussion**

Renal elimination is thought to be one of the major pathways for the elimination of PCT [36–38]. Previous studies showed that the urine levels of PCT were significantly reduced in patients with severe renal dysfunction. Despite decreased renal elimination, the plasma clearance rate...
Procalcitonin test for diagnosis of patients with chronic renal insufficiency

Table 2. Summary of subgroup analysis of the included studies by different study characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of studies</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR− (95% CI)</th>
<th>AUROC (95% CI)</th>
<th>Diagnostic efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analysis [14–19]</td>
<td>7</td>
<td>0.73 (0.54–0.86)</td>
<td>0.88 (0.79–0.93)</td>
<td>6.02 (3.16–11.47)</td>
<td>0.21 (0.17–0.25)</td>
<td>0.89 (0.86–0.91)</td>
<td>0.89 (0.86–0.91)</td>
</tr>
<tr>
<td>High-cutoff value [14, 17, 20]</td>
<td>5</td>
<td>0.68 (0.31–0.91)</td>
<td>0.94 (0.84–0.96)</td>
<td>3.98 (2.83–6.20)</td>
<td>0.94 (0.84–0.96)</td>
<td>0.88 (0.83–0.92)</td>
<td>19.0 (8.9–40.4)</td>
</tr>
<tr>
<td>Low-cutoff value [14, 17, 19]</td>
<td>4</td>
<td>0.53 (0.36–0.69)</td>
<td>0.94 (0.84–0.96)</td>
<td>3.98 (2.83–6.20)</td>
<td>0.53 (0.36–0.69)</td>
<td>0.88 (0.83–0.92)</td>
<td>19.0 (8.9–40.4)</td>
</tr>
<tr>
<td>Cutoff = 0.5 ng/mL [14, 17, 19]</td>
<td>3</td>
<td>0.78 (0.52–0.92)</td>
<td>0.84 (0.62–0.96)</td>
<td>4.89 (1.61–14.85)</td>
<td>0.73 (0.54–0.92)</td>
<td>0.88 (0.83–0.92)</td>
<td>19.0 (8.9–40.4)</td>
</tr>
<tr>
<td>PD peritonitis [14, 16, 17, 19]</td>
<td>4</td>
<td>0.53 (0.36–0.69)</td>
<td>0.94 (0.84–0.96)</td>
<td>3.98 (2.83–6.20)</td>
<td>0.53 (0.36–0.69)</td>
<td>0.88 (0.83–0.92)</td>
<td>19.0 (8.9–40.4)</td>
</tr>
<tr>
<td>CRP</td>
<td>Overall analysis [14, 15, 17–19]</td>
<td>5</td>
<td>0.78 (0.52–0.92)</td>
<td>0.84 (0.62–0.96)</td>
<td>4.89 (1.61–14.85)</td>
<td>0.26 (0.13–0.53)</td>
<td>0.88 (0.83–0.92)</td>
</tr>
</tbody>
</table>

PCT, procalcitonin; CRP, C-reactive protein.

aHigh-cutoff value: greater than 0.5 ng/mL.
bLow-cutoff value: less than 0.5 ng/mL.

correlated only weakly with renal dysfunction, and clinical decisions based on PCT may not be influenced [36–38]. The results of this meta-analysis confirmed a comparable diagnostic accuracy for PCT testing in severely renal impaired patients compared with patients with normal renal function. In our analysis, which included 803 patients with normal renal insufficiency, we showed that PCT testing has diagnostic accuracy similar or even superior to the results on normal adult populations (AUROC: 0.84, 95% CI: 0.75–0.89; sensitivity: 0.76, 95% CI: 0.66–0.84; specificity: 0.70, 95% CI: 0.60–0.79) reported in previous meta-analysis [11]. By adapting the threshold from 0.5 to between 0.8 and 2 ng/mL, the AUROC can be further enhanced, with most improvement coming from the positive likelihood ratio. In contrast to previous findings, we did not find consistent evidence showing PCT to be a more accurate test than CRP in diagnosing systemic infections among patients with renal insufficiency. However, we observed that CRP may complement PCT in diagnosing PD peritonitis. Subgroup analysis showed that CRP is a more sensitive but less specific test than PCT. It is therefore interesting to know whether combining the diagnostic value of two biomarkers may further enhance the diagnostic performance.

The overall positive likelihood ratio (LR+: 6.02, 95% CI: 3.16–11.47) for PCT testing was high enough to be used as a reliable rule-in tool for the diagnosis of systemic infections in patients with renal insufficiency. In a population with a 30% prevalence (pretest probability) of systemic infection, a positive likelihood ratio of 6.02 translates into a positive predictive value (posttest probability) of 72.3% [39]. In other words, approximately two of three patients with positive PCT test results can be expected to have either clinically or microbiologically confirmed systemic infection. The diagnostic value for PCT to rule out systemic infection in patients with severe renal dysfunction performed as well as its rule-in value. In the same population with a 30% prevalence of systemic infection, a negative likelihood ratio of 0.31 translates into 88% negative predictive value. In other words, only 1 in 8 patients with negative PCT results may turn out to have either clinically or microbiologically confirmed systemic infection. However, considering the huge social and medical costs for the missed diagnoses of systemic infection, we do not recommend that PCT testing be used as a standalone test. Instead, we recommend that medical treatment decisions be based on an algorithm that integrates the clinical information and PCT results as shown in several clinical trials using PCT information to guide antibiotics treatment. Otherwise, we recommend the repeated measurements of PCT in clinically suspected cases to further reduce the false negative rate.

We did a subgroup analysis on studies using PCT to predict peritonitis in patients undergoing PD [14, 16, 17, 19]. Results show that PCT has a poor sensitivity (0.53, 95% CI: 0.39–0.66) but a reasonably high specificity (0.94, 95% CI: 0.84–0.95) in predicting PD peritonitis. PD peritonitis is still considered the most important complication of PD, with high mortality and morbidity. No major progress has been made in improving the diagnosis of PD peritonitis since the introduction of the
microbiological culture system in PD effluent [1, 40]. Microbiological cultures are the gold standard for diagnosis but suffer from delayed reporting and high false negative rates. In this regard, the use of PCT testing can greatly shorten the turnaround time of laboratory reports, but the results should be interpreted in light of its acceptable rule-in value and suboptimal rule-out value.

Our study has both strengths and weaknesses. For the strengths, we used bivariate models to derive pooled sensitivity and specificity estimates, which greatly reduced the influence of threshold effects caused by different cutoff values used in the included studies. Furthermore, by performing subgroup analysis on PD patients, our results provide more clinical implications to the clinicians involved in the care of patients undergoing PD. For the weaknesses, our study suffered from high between-study heterogeneity, owing to the use of different criteria to define renal dysfunction and systemic infection and from enrolling patients in different settings. We used a more conservative random effect model to derive diagnostic accuracy parameter estimates, but it cannot be excluded that residual heterogeneity remained and played some role in the observed parameter estimates. Furthermore, our study lacks accuracy parameter estimates on the HD population, another important population among patients with severe renal dysfunction. Previous study demonstrated that HD patients without infection had higher PCT levels than PD patients without infection [41]. The study also did not show better diagnostic accuracy over the PD populations [41]. Limited by the number of studies, we could not perform a subgroup comparison to confirm the previous finding. Lastly, the cutoff values for both PCT and CRP varied greatly between the selected studies. Despite the adjustment by bivariate model, we cannot exclude the possibility of residual influence on the pooled estimates for diagnostic accuracy parameters.

In conclusion, our study shows that PCT can be a useful test in identifying patients with systemic infections among patients with severe renal dysfunction and may also be helpful in diagnosing PD peritonitis among patients undergoing PD. Although PCT performs as well in patients with renal dysfunction as for patients with normal renal function, use of a raised cutoff value may further enhance accuracy. Compared with PCT, CRP is not inferior in the diagnosis of systemic infection in patients with impaired renal function. It is also important that PCT is far from being a ‘gold standard’ test. Additional studies are needed to determine how to best combine the diagnostic values of PCT with other biomarkers or clinical diagnostic scoring systems to enhance the overall diagnostic accuracy.

Conflict of interest statement. None declared.

References


Prevalence and associations of limited health literacy (HL) in chronic kidney disease: a systematic review

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Abstract

Background. Health literacy (HL) is important in chronic disease. This review aimed to evaluate the literature evidence on prevalence and associations of limited HL in chronic kidney disease (CKD).

Methods. Seven databases were searched using terms for CKD and HL. Studies were included that ascertained the prevalence of limited HL using a validated tool in adults with CKD of any stage. The primary outcome was an objectively measured prevalence of limited HL in a population with CKD. The secondary outcome was associations of limited HL. Two reviewers assessed study inclusion and quality. Prevalence values were combined using a random-effect model to give overall prevalence.

Results. Eighty-two studies were identified from searching, of which six met the inclusion criteria. The total number of people in all studies was 1405. Five studies were in dialysis or transplant populations, and all were from the USA. There was a significant heterogeneity in the prevalence of limited HL [9–32% (median 25%, inter-quartile range 16%)]. The pooled prevalence of limited HL in all studies was 22.7% (95% confidence interval 20.6–24.8%), but study heterogeneity limited the generalizability of this combined prevalence. The review identified associations between limited HL and socio-economic factors (lower education attainment, lower income), and certain process and outcome measures (lower likelihood of referral for transplant, higher mortality).

Conclusions. Limited HL is common among people with CKD and independently associated with socio-economic factors and health outcomes. It may represent an important determinant of inequality in CKD.

Keywords: chronic kidney disease; health literacy; inequalities; prevalence

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