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The role of procalcitonin in the identification of invasive fungal infection—a systemic review and meta-analysis☆,☆☆

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ABSTRACT

We aimed to summarize evidence on the accuracy of procalcitonin (PCT) test in differentiating fungal infection from other causes of infection. We searched electronic database for original researches that reported diagnostic performance of PCT alone or compare with other biomarkers to diagnose invasive fungal infection (IFI). We included 8 qualifying studies studying 474 episodes of suspected fungal infection with 155 (32.7%) probable or proven IFIs. Four studies compared IFI to bacterial sepsis, in which the pooled positive likelihood ratios and negative likelihood ratios were 4.65 (95% confidence interval [CI], 2.46–8.79) and 0.15 (95% CI, 0.05–0.41), respectively. Another 4 studies compared IFI to uninfected individuals, in which the pooled positive likelihood ratios and negative likelihood ratios were 4.01 (95% CI, 2.04–7.88) and 0.23 (0.07–0.77), respectively. The existing literature suggests good diagnostic accuracy for the PCT test for discrimination between IFIs and bacterial infection or noninfectious conditions. Given the high heterogeneity, medical decisions should be based on both PCT test results and clinical findings.

1. Introduction

The incidence of fungal infections has markedly increased over the past 2 decades. Several factors have contributed to this increase. These include greater use of immunosuppressive drugs; prolonged use of broad-spectrum antibiotics; widespread use of indwelling catheters; and the acquired immunodeficiency syndrome (Ascioglu et al., 2002). Fungal infections have emerged as a leading cause of sepsis in critically ill patients. The case fatality rate of invasive fungal infection is higher than that of bacterial sepsis, reported to be as high as 40–60% (Lin et al., 2001).

Early recognition of invasive fungal infection allows for early antifugal therapy with improved outcome, but early diagnosis is hampered by a lack of a reliable diagnostic tool. The clinical manifestation of fungal infection is usually nonspecific and cannot be differentiated from that of bacterial infection. Microbiological cultures, although specific, are time consuming and suffer from low sensitivity even in case of disseminated infection (Bassetti et al., 2010). Newer diagnostic tools such as polymerase chain reaction are promising but still suffer from contamination, restricted spectrum of species detected, and increased laboratory workload issues (Khot and Fredricks, 2009).

Procalcitonin (PCT) is a precursor of calcitonin and consists of the N-terminal end, calcitonin, and catacalcin, including 116 amino acids in total. In healthy subjects, it is less than 0.1 ng/mL, while in cases of infection, it is rapidly produced by extrathyroid cells, such as neuroendocrine lung cells and monocytes. It has been shown to differentiate accurately between systemic bacterial infection and noninfectious inflammatory states and can guide the decision and adjustment of duration of antibiotics in intensive care unit (ICU) patients (Assicot et al., 1993).

To date, there are only a limited number of studies investigating the diagnostic role of PCT in invasive fungal infection. However, these studies were inconclusive because of limited sample sizes and different PCT cut-off values employed. To summarize the current evidence on the value of PCT as a marker of invasive fungal infection, we conducted this systemic review and meta-analysis (Charles et al., 2006, 2009; Distefano et al., 2004; Eloy et al., 2001; Martini et al., 2010; Montagna et al., 2013; Petrikkos et al., 2005; Zeglen et al., 2009).

2. Methods

The review was conducted in accordance with the standard guidelines for reporting diagnostic tests meta-analysis (Leeflang et al., 2008).

3. Search strategy

We searched 3 electronic databases (Medline, Embase, and Cochrane databases) for studies published through December 2012

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with PCT and combined with the following MeSH terms and free text: fungi, candidiasis, aspergillosis, mycoses, and mold. We did not set any time or language restrictions for these searches. Reference lists of relevant systematic reviews and included articles were reviewed for further relevant articles. Non-English language studies were translated. Selection was performed independently by 2 reviewers. Discrepancies between the reviewers were resolved by a consensus meeting with the third or fourth coauthor.

4. Selection criteria

The title and abstract of the studies were screened in the first round, and potentially relevant articles were retrieved for full-text review in the second round. For inclusion, the studies had to fulfill the following criteria: 1) include results of a PCT test, 2) use invasive fungal infection (IFI) defined by the European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG) criteria or comparable ones as the primary endpoint, and 3) include calculations of sensitivity and specificity or have sufficient data to construct a 2×2 contingency table. Both prospective and retrospective cohort and case-control studies were included. We excluded case reports, case series, review articles, editorials, and clinical guidelines. Two authors independently assessed all titles and abstracts to determine whether the inclusion criteria were satisfied. Full-text articles were retrieved if any of the reviewers considered the abstract suitable. The study inclusion and exclusion process is summarized in Fig. 1.

5. Quality assessment

The methodological quality of the selected studies was evaluated independently by 2 reviewers with a validated tool for the quality assessment of diagnostic accuracy studies (Quality Assessment of Diagnostic Accuracy Studies, QUADAS) (Whiting et al., 2003, 2011). Discrepancies were resolved by a consensus meeting with the third and fourth. Data were extracted by 1 reviewer using a standardized data extraction form and verified by a second independent reviewer. Data extracted included study characteristics (title, authors, journal), study design (cross-sectional or case-control), study population (adult or pediatric), comparison group (bacterial infection or noninfectious controls), type and manufacturer of index test, timing of biomarker measurement, reference standard for IFI, and the sensitivity and specificity of the biomarkers.

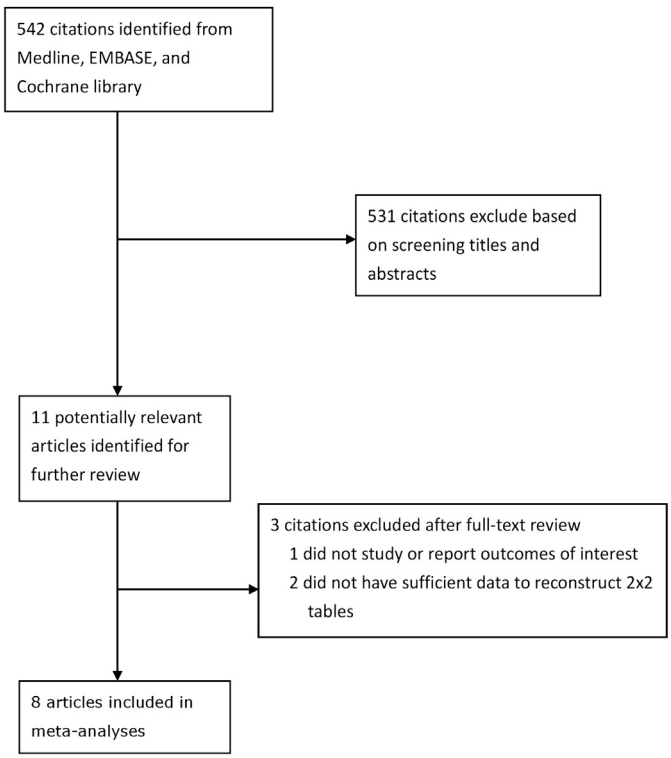

Fig. 1. Flow chart of study identification and inclusion.

6. Data synthesis and analysis

We calculated the mean sensitivity, specificity, and likelihood ratios by using the bivariate model (Reitsma et al., 2005). The bivariate model assumes a bivariate distribution for the logit-transformed sensitivity and specificity and adjusts for the negative correlation between the sensitivity and specificity of the index test that may arise from the different thresholds used in different studies. To compare the overall discrimination between 2 biomarkers, we constructed hierarchical summary receiver operating characteristic (HSROC) curve and calculated the area under the curve (AUC) (Jones and Athanasiou, 2005). In addition, we calculated another global measure, diagnostic odds ratio (DOR). The DOR compares the odds of positive test results between individuals with and without the disease. The mean DOR was estimated by fixed or random effect pooling methods depending on whether heterogeneity was present. To deal with zero observations in 2×2 contingency tables, we performed continuity correction by adding one-half to the cell with zero count, thereby reducing the small study bias. Diagnostic accuracy studies are expected to show considerable heterogeneity. Heterogeneity was assessed by means of the test of inconsistency (I^2). The inconsistency index (I^2) describes the variation of effect estimate that is attributable to heterogeneity across studies (Lijmer et al., 2002). We prespecified several additional analyses to examine the potential effects of different methodological quality factors, adjust for covariates, and assess the robustness of our results. Funnel plots were generated to allow visual inspection for publication bias, and tests for rank correlation and for regression asymmetry (Egger's test) were used to detect asymmetry (Song et al., 2002). Statistical analyses were conducted using STATA 11.0 (Stata Corp, College Station, TX, USA). All statistical tests were 2 sided, and statistical significance was defined as a *P*-value of less than 0.05.

7. Results

In total, 542 studies (excluding duplicates) were identified using the search strategy outlined earlier (Fig. 1). After the first round screening of tile and abstracts, 531 nonrelevant studies, case reports, or reviews were excluded. Eleven potential relevant studies were retrieved for full-text evaluation, of which 3 further studies were excluded for varying reasons at this stage, leaving 8 that met the inclusion criteria.

These studies included 474 episodes of suspected infection with 155 (32.7%) confirmed systemic fungal infection episodes. Table 1 presents summaries of the characteristics of the included studies and patients. The number of subjects with systemic fungal infection in each study was 27 to 91. Two studies were done in the neonate population, and the remaining was done in the adult population. Four studies used candidemia as the primary outcome, and the rest included all kinds of systemic fungal infection. Causative organisms isolated were *Candida albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, *Aspergillus* spp., and *Penicillium* zygomycetes. Measurements of serum PCT levels were performed by 3 different types of assays: Immunoluminometric LUMI test (Brahms Diagnostica, Berlin, Germany) in 5 studies, TRACE (time resolved amplified cryptate emission) technology Kryptor test (Brahms Diagnostica, Berlin, Germany) in 1 study, and