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Review

The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis

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SUMMARY

Objective: Clinically, it is often difficult to differentiate between bacterial and viral aetiologies in adults with suspected meningitis. Several studies have demonstrated the potential use of serum procalcitonin (PCT) in making this differentiation. The aim was to pool these studies into a meta-analysis to determine the diagnostic accuracy of PCT.

Methods: Major electronic databases were searched for articles studying the use of serum PCT in the differentiation of bacterial and viral meningitis in adult patients. No date or language restrictions were applied. Data analysis was performed using Meta-DiSc 1.4 and MIX 2.0.

Results: Nine studies (n = 725 patients) were included in the meta-analysis. Serum PCT was found to be a highly accurate test for diagnosing meningitis. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) for PCT were 0.90 (95% confidence interval (CI) 0.84–0.94), 0.98 (95% CI 0.97–0.99), 27.3 (95% CI 8.2–91.1), 0.13 (95% CI 0.07–0.26), and 287.0 (95% CI 58.5–1409.0), respectively. PCT was found to be far superior to C-reactive protein, which had a pooled DOR of only 22.1 (95% CI 12.7–38.3).

Conclusions: Serum PCT is a highly accurate diagnostic test that can be used by physicians for rapid differentiation between bacterial and viral causes of meningitis in adults.

1. Introduction

Bacterial meningitis (BM) is a significant cause of morbidity and mortality worldwide, with 1.2 million cases per year, resulting in 135 000 deaths.[1] Due to the high mortality rate and potential neurological sequelae in survivors, there is an urgent need for rapid diagnosis with near 100% sensitivity.[2] Cerebrospinal fluid (CSF) analysis is the current gold standard for the diagnosis of BM, along with biomarkers such as C-reactive protein (CRP) and white blood cell count (WBC). However, none of these tests achieve 100% sensitivity and confer a high enough specificity to distinguish between bacterial and viral meningitis (VM).[2]

CRP has traditionally been used as the biomarker for inflammation. However, CRP may show a delayed increase during the course of bacterial infection, resulting in false-negative tests in the early stages of the disease.[3–6] CRP can also be elevated in viral infections, limiting its ability to discriminate between bacterial and viral aetiologies of meningitis.[7] Procalcitonin (PCT) is now considered to be the best candidate to replace CRP due to its high diagnostic accuracy in various infectious pathologies, including sepsis, acute infectious endocarditis, and pancreatitis.[8] Fibronectin, interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF-α) have also been proposed as potential biomarkers, but have not thus far been accepted widely for clinical use.[9]

Normal PCT levels in healthy individuals are <0.1 ng/ml, and levels increase dramatically in response to bacterial infection.[10] It has been hypothesized that this increase is due to the overexpression of the CALC-1 gene and increased release of PCT from various tissues in response to bacterial endotoxins and inflammatory cytokines such as TNF-α, IL-6, and IL-1β.[8,11,12] Unlike CRP, PCT has not been reported to be elevated in viral infections, thus conferring it the important ability to distinguish easily between bacterial and viral aetiologies.[13]

PCT also demonstrates utility in the early diagnosis of meningitis by rising after 4 h, peaking at 6 h, and remaining elevated over 24 h.[14,15] This is in contrast to CRP, which rises over 6–12 h and peaks at 24–48 h.[16,17] This delay in diagnosis, combined with the traditional 72-h wait for the results of Gram

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stains, often results in patients receiving empiric antibiotic therapy.[18,19] This can lead to potential adverse effects, increased health care costs, and an increased risk of nosocomial infection.[20–22]

Several studies have attempted to study the diagnostic accuracy of PCT in differentiating between BM and VM in adult patients.[23–31] The reported results of these studies are varied and a consensus has yet to be reached on the diagnostic value of PCT in meningitis.

The aim of this study was to pool and analyze the results of all the reported studies to determine the true diagnostic accuracy of PCT in adult patients with suspected meningitis.

2. Methods

2.1. Search strategy

In accordance with the PRISMA guidelines, a systematic literature search of the major electronic databases including PubMed, Scopus, EMBASE, Science Direct, Web of Science, and the Cochrane Library was performed to identify studies eligible for the meta-analysis. The search was specifically tailored to each of the electronic databases. Search terms included procalcitonin, PCT, S-PCT, ProCT, meningitis, and meningism. No date or language restrictions were set. Case reports, letters to the editor, and conference posters and abstracts were searched, but not included in the meta-analysis.

2.2. Selection of studies

Studies were eligible for inclusion in the meta-analysis if they (1) investigated the diagnostic accuracy of PCT in adult patients with suspected meningitis to distinguish between bacterial and viral aetiologies, (2) measured serum PCT on admission, and (3) reported data necessary to construct 2 × 2 tables (true-positives, false-positives, false-negatives, true-negatives). Studies were excluded if they (1) reported incomplete data or did not provide data necessary to construct 2 × 2 tables, (2) did not compare BM vs. VM, (3) had a poor methodological quality as determined using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, (4) studied exclusively paediatric populations, or (5) only measured the levels of PCT in CSF. Three authors (J.V., B.M.H., and P.K.R.) independently assessed each full-text article for inclusion in the analysis. Disagreements were resolved by a consensus among the authors. When necessary, articles were translated from their original text into English for further review by medical professionals who are native English speakers and fluent in the language of the original text.

2.3. Data extraction

Two authors (J.V. and J.R.) independently extracted data from the selected studies. Extracted data included sample size, mean age, PCT and CRP cut-offs, sensitivity, specificity, testing method, time of measurement, serum levels of PCT and CRP, and definitions of BM. Two by two tables were then constructed to calculate values of true-positives, false-positives, false-negatives, and true-negatives, to be pooled into the meta-analysis. In the case of studies that reported multiple cut-offs with sensitivities and specificities, the cut-off with the highest Youden's J statistic was used in the meta-analysis.[32] In the case of any discrepancies in the data, the authors were contacted by e-mail for clarification.

2.4. Quality assessment

Methodological quality was assessed with the QUADAS-2 tool.[33] This tool assesses risk of bias and applicability through a series of signalling questions related to methodological quality of the study. Risk of bias is assessed in four domains – patient selection, index test, reference standard, and flow and timing. Applicability is assessed by the first three of the aforementioned domains. Each domain was ranked as high risk, unclear risk, or low risk individually by two authors (J.V. and J.R.).

2.5. Statistical analysis

The statistical analysis was performed using Meta-DiSc 1.4 and MIX 2.0 by one of the authors (B.M.H.). Using a random-effects model, the pooled sensitivities, specificities, positive likelihood ratios (LR+), negative likelihood ratios (LR−), and diagnostic odds ratios (DOR) were calculated. Summary receiver operating characteristic (SROC) curves were generated and the area under the curve (AUC) and Q^* index (the point on the SROC curve where sensitivity and specificity are equal) were then calculated appropriately. Heterogeneity was assessed using the Higgins I^2 test, with values of 25%, 50%, and 75% indicating low, moderate, and high degrees of heterogeneity, respectively. The threshold effect was measured using Spearman's correlation coefficient.[34] In order to further explore heterogeneity, meta-regression was performed using a single covariate with logDOR as the dependent variable. To assess publication bias, an asymmetrical funnel plot was constructed. Due to the current lack of accurate and reliable tests for publication bias in diagnostic studies, no other assessments were performed.[35]

3. Results

3.1. Study identification

An overview of the study identification process is given in Figure 1. Through database searching, 2379 articles were initially

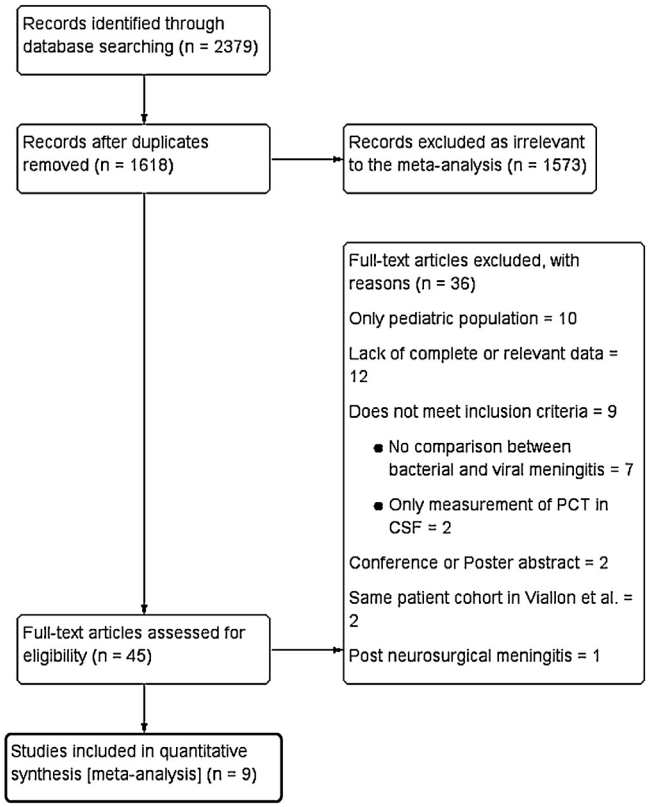

Figure 1. Flow chart of study identification, evaluation, and inclusion in the meta-analysis.