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Diagnostic accuracy of nucleic acid amplification based assays for tuberculous meningitis: A meta-analysis

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SUMMARY

Background: Numerous in-house and commercial nucleic acid amplification tests (NAAT) have been evaluated using variable reference standards for diagnosis of TBM but their diagnostic potential is still not very clear.

Methods: We conducted a meta-analysis to assess the diagnostic accuracy of different NAAT based assays for diagnosing TBM against 43 data sets of confirmed TBM ($n = 1066$) and 61 data sets of suspected TBM ($n = 3721$) as two reference standards. The summary estimate of the sensitivity and the specificity were obtained using the bivariate model. QUADAS-2 tool was used to perform the Quality assessment for bias and applicability. Publication bias was assessed with Deeks' funnel plot.

Results: Studies with confirmed TBM had better summary estimates as compared to studies with clinically suspected TBM irrespective of NAAT and index tests used. Among in-house assays, MPB as the gene target had best summary estimates in both confirmed [sensitivity:90%(83–95), specificity:97-%(87–99), DOR:247 (50–1221), AUC:99%(97–100), PLR:38.8-(6.6–133), NLR:0.11(0.05–0.18), $I^2 = 15\%$] and clinically suspected [sensitivity:69%(47–85), specificity:96%(90–98), DOR:62(16.8–232), AUC:94%(92–97), PLR:16.9(6.5–36.8), NLR:0.33(0.16–0.56), I^2:15.3%] groups. GeneXpert revealed good diagnostic accuracy only in confirmed TBM group [sensitivity = 57%(38–74), specificity = 98%(89–100), DOR = 62(7–589), AUC = 87%(79–96), PLR = 33.2(3.8–128), NLR = 0.45(0.26–0.68), $I^2 = 0\%$].

Conclusions: This meta-analysis identified potential role of MPB gene among in-house assays and GeneXpert as commercial assay for diagnosing TBM.

Introduction

Tuberculous meningitis (TBM) is the most debilitating clinical manifestation of tuberculosis occurring in approximately 10% of all tuberculosis [1] cases in developing countries with a global burden touching approximately 100,000 cases per year.[2,3] The disease is associated with distressing levels of neurological mortality and morbidity.[4,5] Survivors often suffer substantial neurological sequelae including developmental delay in children, seizures, motor deficits and cranial nerve palsies.[6] Appropriate early diagnosis and treatment can only improve prognosis and prevent long term neurological sequelae.[4,5] However, the disease remains a daunting diagnostic challenge due to non-specific symptoms and also because none of the available diagnostic assays are sufficiently sensitive and specific in diagnosing this paucibacillary disease in useful clinical time frame.[7]

The conventional gold standards for diagnosis, microscopy and conventional/automated *Mycobacterium tuberculosis* (MTB) cultures, are quite insensitive and time consuming to be helpful for clinical decision.[8] Recently, molecular diagnostic methods based on nucleic acid amplification tests (NAAT) are emerging as promising technologies for rapid diagnosis of TBM. Though these tests offer a faster, sensitive and specific diagnosis for respiratory specimens but literature about usefulness of these tests for diagnosing TBM is highly scattered for any meaningful interpretation.[9]

There are numerous detectable gene targets present in MTB genome and multiple type of in-house and commercial NAAT assays available for detection of MTB in TBM patients [10] but there is still no consensus as to which gene target and method is

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associated with diagnostic and clinical utility in TBM patients. Moreover, there is no single reference standard for diagnosing TBM and different studies have used different standards for evaluating NAAT. A few published meta-analysis concerning accuracy of nucleic acid amplification assay for diagnosing TBM have suffered from extreme heterogeneity due to (1) highly variable reference standard depending upon best available reference standard (2) inclusion of studies with very small number of patients leading to poor statistical power (3) pooling of all the gene targets, NAAT methodologies together.[11–13]

Although numerous detectable gene targets and large number of NAAT protocols have been evaluated in plethora of studies but the best gene target and NAAT methods for MTB detection in TBM patients which are less cumbersome, adaptable to any laboratory and are sensitive enough to enable the diagnosis of TBM are still not known. Here, we aimed to review the published literature to find out the overall diagnostic accuracy in patients with confirmed and clinically suspected TBM separately, to compare diagnostic accuracy of in-house and commercial NAAT, different gene targets so as to infer clinical utility for early detection of MTB in TBM patients, using stringent inclusion criteria and subgroup analysis.

Methods

Search strategy

We conducted database search using freely accessible Medline/Pubmed for all the studies published till March 25, 2017 using the following search terms: “Extra-pulmonary tuberculosis”, “Tuberculous meningitis”, “TBM”, “PCR”, “polymerase chain reaction”, “nucleic acid amplification”, “Mycobacterium tuberculosis”, “cerebrospinal fluid”, “diagnosis” using combination of the Boolean ‘OR’ and ‘AND’ operators with search string “(“Extra-pulmonary tuberculosis” OR “Tuberculous meningitis” OR “TBM”) AND (“PCR” OR “polymerase chain reaction” OR “nucleic acid amplification”) AND (“Mycobacterium tuberculosis” OR “cerebrospinal fluid” OR “diagnosis”)”. Cross references of previously published review articles and included articles were hand searched to find out any additional relevant study. Only articles written in English language were included in the study.

Eligibility criteria

The studies were screened for inclusion or exclusion based on the predetermined inclusion and exclusion criteria as follow:

Inclusion criteria

The present study included patients who were suspected to have TBM based on clinical features, including sub-acute or chronic fever and signs of meningeal irritation with or without other features of central nervous system (CNS) abnormality and at least one of the following criteria: (a) The cerebrospinal (CSF) findings showing increased protein levels, decreased glucose levels (CSF/blood glucose ratio), and pleocytosis with lymphocyte predominance; (b) demonstration of AFB by smear and/or cultures in CSF; (c) computed tomography (CT) and/or magnetic resonance imaging suggestive of tuberculosis; d) clinician decision to start on Anti tubercular treatment (ATT); e) active extra neural tuberculosis elsewhere.[14]

Exclusion criteria

The studies were excluded based on the following criteria: (a) CSF sample taken from patients suspected of having meningitis, tuberculosis or any other CNS disease but without detailed inclusion criteria to specify TBM; (b) ≤ 10 CSF samples reported; (c) data lacking for computation of sensitivity and specificity; (d) gene target not specified; (e) multiplex PCR without gene specific data; (f) specimen collection after initiation of ATT; (g) multiple samples from one patient without results of first sample.

None of the study was excluded on the basis of study design, diagnostic methodology or results obtained.

Index test

We included all PCR based NAAT as index test with both commercial and in-house assays.

Reference standard

The microbiologically confirmed TBM by cultures (definitive TBM) and clinically suspected TBM patients (both probable and possible TBM) were taken as two reference standards for comparison of index tests according to the criteria of Marais et al 2010.[14] The patients confirmed on the basis of autopsy/biopsy or NAAT itself were not included in confirmed diagnosis.

Study selection

After excluding all non-English articles, titles/abstract screening was done by two authors independently (RG and PT). Articles not excluded by any of the investigator were studied in detail and final decision was taken after consensus with two more investigators (SK and SK). Any duplicate data or publication was carefully removed.

Data extraction

Two investigators (PT and NJ) independently extracted and tabulated data into Microsoft excel 2007. The data of both the investigators were cross checked and discrepancies were resolved by discussion with two other investigators (PT and RG).

Quality assessment

The methodological quality of the studies was judged on the basis of Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[15]

Publication bias

We conducted publication bias analysis using Deek’s test in STATA software (version 13.1, College Station, TX).

Statistical analysis

The present meta-analysis was performed by segregating each study into different datasets based on NAAT assay and gene targets used. The numbers of true positives (TP), false negatives (FN), false positives (FP) and true negatives (TN) were accessed from each included study. Several diagnostic accuracy measures (the diagnostic odds ratio (DOR) and, the area under the summary receiver operating characteristics (SROC) curve (AUC)), summary estimates (Sensitivity, Specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), negative predictive value (NPV)) were calculated. The data were presented graphically on paired Forest plots and hierarchical SROC curves. The I^2 static ($< 40\%$) and Q-test ($p < 0.05$) was used to evaluate heterogeneity of overall test accuracy among included studies.[16,17] The details of the statistical parameters used are provided in the supplementary file 1. Subgroup analysis was conducted using several study characteristics separately and above

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