

INPLASY PROTOCOL

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None.

Metagenomic Next-Generation Sequencing for diagnosis of tuberculosis Meningitis: A protocol of systematic review and meta analysis

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Review question / Objective: This study aims to evaluate the diagnostic accuracy of Metagenomic Next-Generation Sequencing against composite reference standard (CRS) for tuberculosis Meningitis (TBM) using meta analysis method.

Condition being studied: TBM is the most lethal form of TB infection, accounting for approximately 1%–5% of all new cases and causes severe disability or death in half of those infected. The most critical cause of this serious outcome is the failure to diagnose and treat TBM in the early stages. Therefore, there is an urgent need to improve early and rapid diagnosis of TBM to avoid most TBM-related deaths.

Information sources: We will search PubMed, Embase, the Cochrane Library, the Wanfang database, and China National Knowledge Infrastructure (CNKI) for studies evaluating the diagnostic accuracy of mNGS for TBM. References cited in the included articles and reviews will be further explored for possible candidate studies.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 July 2020 and was last updated on 22 July 2020 (registration number INPLASY202070100).

INTRODUCTION

Review question / Objective: This study aims to evaluate the diagnostic accuracy of Metagenomic Next-Generation Sequencing against composite reference standard (CRS) for tuberculosis Meningitis (TBM) using meta analysis method.

Rationale: Mngs may have advantages in the diagnosis of TBM, but it is still controversial.

Condition being studied: TBM is the most lethal form of TB infection, accounting for approximately 1%–5% of all new cases and

causes severe disability or death in half of those infected. The most critical cause of this serious outcome is the failure to diagnose and treat TBM in the early stages. Therefore, there is an urgent need to improve early and rapid diagnosis of TBM to avoid most TBM-related deaths.

METHODS

Search strategy: The search strategies will be conducted by Guoacn Yu and Wuchen Zhao. There will be no language restrictions on our search. Search strategy of PubMed will be as follows: #1 "Tuberculosis, Meningeal"[Mesh] OR "Meningeal Tuberculoses" OR "Meningeal Tuberculosis" OR "Tuberculoses, Meningeal" OR "TB Meningitis" OR "TB Meningitides" OR "Tubercular Meningitis" OR "Meningitides, Tubercular" OR "Meningitis, Tubercular" OR "Tubercular Meningitides" OR "Meningitis, Tuberculous" OR "Meningitides, Tuberculous" OR "Tuberculous Meningitides" OR "Tuberculous Meningitis" OR "Tuberculosis Meningitis" OR "Meningitides, Tuberculosis" OR "Meningitis, Tuberculosis" OR "Tuberculosis Meningitides" OR "Tuberculous Hypertrophic Pachymeningitis" OR "Hypertrophic Pachymeningitides, Tuberculous" OR "Hypertrophic Pachymeningitis, Tuberculous" OR "Pachymeningitides, Tuberculous Hypertrophic" OR "Pachymeningitis, Tuberculous Hypertrophic" OR "Tuberculous Hypertrophic Pachymeningitides" OR "Extrapulmonary tuberculosis" OR "Extrapulmonary tuberculosis" OR "Meningitis"[Mesh] OR Meningitides OR Pachymeningitis OR Pachymeningitides OR "Cerebrospinal Fluid"[Mesh] OR "Cerebrospinal Fluids" OR "Fluid, Cerebrospinal" OR "Fluids, Cerebrospinal" OR "Cerebro Spinal Fluid" OR "Cerebro Spinal Fluids" OR "Fluid, Cerebro Spinal" OR "Fluids, Cerebro Spinal" OR "Spinal Fluid, Cerebro" OR "Spinal Fluids, Cerebro" #2 "Metagenomic Next-Generation Sequencing" OR mNGS #3 #1 AND #2.

Participant or population: Patients with TBM.

Intervention: Metatagenomic Next-Generation Sequencing.

Comparator: Comparator is not a obligatory criteria (single arm study can be enrolled if P, I, O is satisfied because this study will measure the diagnostic accuracy of nucleic acid amplification tests for abdominal tuberculosis).

Study designs to be included: Any types of studies can be enrolled.

Eligibility criteria: Full-text original researches that assessed mNGS for TBM will be included. Clear and appropriate reference standards are defined in researches. True positive (TP), false positive (FP), false negative (FN), and true negative (TN) values for the assay can be extracted or calculated directly from the studies. We will exclude case reports, articles written in languages other than Chinese and English, researches with < 10 specimens, conference reports, and abstracts without full articles.

Information sources: We will search PubMed, Embase, the Cochrane Library, the Wanfang database, and China National Knowledge Infrastructure (CNKI) for studies evaluating the diagnostic accuracy of mNGS for TBM. References cited in the included articles and reviews will be further explored for possible candidate studies.

Main outcome(s): Sensitivity, specificity, the area under summary receiver operating characteristic (SROC) curve (AUC) and their respective 95% confidence intervals (CIs).

Data management: Primary search records will be imported into ENDNOTE X9.2 literature management software, according to eligibility criteria. Two investigators (Guoacn Yu and Wuchen Zhao) will independently assess the candidate articles by reviewing their titles and abstracts, followed by the full text, for inclusion. Discrepancies between the two investigators will be resolved by discussion

with a third investigator (Hong Zheng). We will extract data including first author name; publication year; country; TP, FP, FN, and TN values for the assay; reference standard; patient selection method; specimen type; sample pretreatment method; and condition along with other parameters. The same two investigators will independently extract the necessary information from each of the included articles; we will cross-check the information they obtained. Discrepancies in the two data sets will be settled by a discussion with a third investigator, similar to that used during the literature selection phase.

Quality assessment / Risk of bias analysis:

The two investigators will use a revised tool for Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to assess study quality separately and the discrepancy between reviewers will be solved by discussion with a third investigator (Hong Zheng).

Strategy of data synthesis: We will first obtain the values corresponding to TP, FP, FN, and TN in each included study, and calculated the estimated pooled sensitivity and specificity of mNGS associated with the 95% confidence interval (CI), against CRS, using bivariate random-effects models. Forest plots for sensitivity and specificity will be generated for each study. The areas under summary receiver operating characteristic (SROC) curves (AUC) will be subsequently calculated. I² statistics will be used to assess heterogeneity between the studies. While 0% will indicate no observed heterogeneity, values greater than 50% will be considered to imply substantial heterogeneity. We will explore different patient selection method, sample conditions, and sample pretreatment method as potential sources of heterogeneity, using subgroup and meta-regression analyses. At least four published studies will be required to perform the meta-analysis for predefined variable types. Data from studies against CRS and culture will be analyzed separately. Stata version 15.0 (Stata Corp., College Station, TX, USA) with the midas

command packages will be used to generate forest plots of sensitivity and specificity with 95% CI for each study and carry out meta-analyses and meta-regression analyses.

Subgroup analysis: If the necessary data are available, subgroup analyses will be done to evaluate the diagnostic accuracy of mNGS for TBM.

Sensibility analysis: If applicable, sensitivity analysis will be used to explore the source of heterogeneity when the heterogeneity is obvious.

Language: No.

Country(ies) involved: China.

Keywords: Metatagenomic Next-Generation Sequencing, diagnosis, tuberculosis Meningitis, systematic review, meta analysis.

Contributions of each author:

Author 1 - Guocan Yu - The author drafted the manuscript, searched databases, selected literatures, managed data and assessed quality.

Author 2 - Wuchen Zhao - The author searched databases, selected literatures, managed data and evaluated quality.

Author 3 - Yanqin Shen - The author drafted and revised the manuscript.

Author 4 - Pengfei Zhu - The author revised the manuscript.

Author 5 - Hong Zheng - The author provided statistical expertise, read, feedback and approved the final manuscript.