BMJ Open

Diagnostic validity of MRI for central nervous system tuberculosis: protocol for a systematic review and meta-analysis

Yanqin Shen, Liwei Yao, Jinjuan Zhang, Huihong Lin

To cite: Shen Y, Yao L, Zhang J, *et al*. Diagnostic validity of MRI for central nervous system tuberculosis: protocol for a systematic review and meta-analysis. *BMJ Open* 2023;**13**:e075745. doi:10.1136/bmjopen-2023-075745

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-075745).

Received 17 May 2023
Accepted 19 September 2023

Department of Nursing, Hangzhou Red Cross Hospital, Hangzhou, Zhejiang, China

Correspondence to
Dr Huihong Lin;
linhuihtb@163.com

ABSTRACT

Introduction Central nervous system tuberculosis (CNSTB) is a severe condition, sometimes associated with a poor prognosis. Early diagnosis of CNSTB remains challenging, considering that conventional methods lack sensitivity or might lead to certain side effects. Herein, we presented a protocol for a systematic review and meta-analysis to assess the diagnostic efficacy of MRI for CNSTB.

Methods and analysis SinoMed, Wanfang database, China National Knowledge Infrastructure, Embase, the Cochrane Library and PubMed will be searched to identify studies reporting on the use of MRI in the diagnosis of CNSTB from database inception to December 2023. The following keywords will be applied: 'Intracranial tuberculosis', 'Cerebral tuberculosis', 'Central nervous system tuberculosis', 'Spinal tuberculous arachnoiditis' and 'Magnetic Resonance Imaging'. Studies that evaluate the diagnostic accuracy of MRI for the diagnosis of CNSTB and report clear reference criteria will be included. Studies from which full true positive, false positive, false negative and true negative values cannot be extracted, those published in languages other than English or Chinese, abstracts not reporting the full text, and case reports will be excluded. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) will be used to evaluate the methodological quality of each included study. Stata V.15.0 and RevMan V.5.3 will be used to perform a meta-analysis and generate forest plots and summary receiver operating characteristic curves. In case of significant heterogeneity between studies, possible sources of heterogeneity will be explored through subgroup and meta-regression analyses.

Ethics and dissemination This research is based on public databases and does not require ethical approval. Results will be submitted for publication in a peer-reviewed journal.

PROSPERO registration number CRD42023415690.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is prospectively registered in the PROSPERO database; Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) reporting guidelines were used to guide the reporting of this protocol and PRISMA-Diagnostic Test Accuracy guidance for the reporting of systematic reviews and meta-analyses of diagnostic test accuracy will be used when reporting the results.
⇒ The literature search includes both Chinese and English databases.
⇒ Rigorous methods and robust analyses allow minimal study bias and more standardised data reporting.
⇒ There may be significant heterogeneity in studies, resulting in less reliable results.

INTRODUCTION

Tuberculosis (TB) is one of the major public health threats worldwide.[1] In 2020, 9.87 million new TB cases and about 1.5 million deaths have been reported globally, with TB being the main cause of death from a single source of infection.[1 2] Depending on the site of *Mycobacterium tuberculosis* (MTB) infection, TB can be classified into pulmonary TB and extrapulmonary TB.[3] One of the catastrophic manifestations of EPTB is the affection of the central nervous system (CNS). Central nervous system tuberculosis (CNSTB) incidence is low, accounting for only 1–5% of new cases.[4] Most patients with CNSTB respond well to medical treatment alone; however, patients with tuberculous meningitis (TBM) have poor prognoses.[4] The main cause of serious adverse outcomes in this group of patients is the lack of available early and valid diagnostic methods,[5] resulting in delays in diagnosis and treatment.

CNSTB mainly includes TBM, intracranial tuberculoma and spinal arachnoiditis.[6] CNSTB diagnosis usually requires invasive procedures to obtain specimens, the most common being a lumbar puncture that is used to obtain cerebrospinal fluid (CSF) specimens.[7] Invasive procedures carry certain risks and require patient cooperation. CSF testing has substantial diagnostic significance

for TBM, while its diagnostic significance for cerebral TB that does not invade the meninges is limited.[8] The risk of puncture of the brain parenchyma is very high; thus, this method is used less frequently.[9 10] On the other hand, the MTB content in CSF is low, and the sensitivity of the commonly used acid-fast bacilli smear and MTB culture is still poor, failing to meet the need for early, effective diagnosis.[11] Even with the use of CSF for nucleic acid amplification tests (NAATs) to improve the diagnostic efficacy of TBM, the results are still unsatisfactory.[12] Rapid and effective diagnosis is the cornerstone of accurate treatment. Therefore, a safe and effective rapid diagnostic tool for CNSTB is urgently needed to improve the prognosis.

Imaging, especially MRI, is the most commonly used test for CNS lesions.[9] MRI is a non-invasive and radiation-free approach that can show the entire CNS lesions. Previous studies have shown that MRI is useful in diagnosing CNSTB,[13 14] including both intracerebral TB and TBM.[15–17] However, the diagnostic accuracy of MRI for CNSTB is not known. Therefore, this systematic review and meta-analysis aimed to assess the diagnostic accuracy of MRI for CNSTB in order to further inform the role of MRI in the diagnosis of CNSTB.

METHODS AND ANALYSIS

Design and registration

We will perform a systematic review and meta-analysis of the efficacy of MRI for the diagnosis of CNSTB. The study has been registered on PROSPERO.[18] We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Diagnostic Test Accuracy (PRISMA-DTA) guidelines to report this research.[19] The requirement for ethical approval was waived as this is a systematic review and meta-analysis based on published data. The PRISMA-Protocols reporting guidelines were used to guide the reporting of the present study protocol.

Information sources

Several commonly used Chinese and English databases (SinoMed, Wanfang database, China National Knowledge Infrastructure (CNKI), Embase, the Cochrane Library and PubMed) will be searched from database inception to December 2023 to identify relevant studies on MRI diagnosis of CNSTB. We will conduct an updated search before the study is completed. References from relevant reviews and meta-analyses will also be searched by hand to identify potentially eligible studies.

Search strategy

The two researchers will develop an effective search strategy through consultation. The English database will be searched in English and the Chinese database will be searched in Chinese. We will not restrict time during the search process. The search strategy of PubMed is presented in table 1. The other databases will use a similar search strategy (online supplemental file 1).

Eligibility criteria

Study type

Studies that evaluate the diagnostic efficacy of MRI for the diagnosis of CNSTB will be included, regardless of the type of study.

Table 1 Search strategy for PubMed

#1	"Intracranial tuberculosis" OR "cerebral tuberculosis" OR "central nervous system tuberculosis" OR "CNS tuberculosis" OR "brain tuberculomas" OR "brain tuberculosis" OR "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 achymeningitides" OR "Spinal tuberculous arachnoiditis" OR "Spinal arachnoiditis" OR "intracranial tuberculoma"
#2	"Magnetic Resonance Imaging"(MeSH) OR "Imaging, Magnetic Resonance" OR "NMR Imaging" OR "Imaging, NMR" OR "Tomography, NMR" OR "Tomography, MR" OR "MR Tomography" OR "NMR Tomography" OR "Steady-State Free Precession MRI" OR "Steady State Free Precession MRI" OR "Zeugmatography" OR "Imaging, Chemical Shift" OR "Chemical Shift Imagings" OR "Imagings, Chemical Shift" OR "Shift Imaging, Chemical" OR "Shift Imagings, Chemical" OR "Chemical Shift Imaging" OR "Magnetic Resonance Image" OR "Image, Magnetic Resonance" OR "Magnetic Resonance Images" OR "Resonance Image, Magnetic" OR "Magnetization Transfer Contrast Imaging" OR "MRI Scans" OR "MRI Scan" OR "Scan, MRI" OR "Scans, MRI" OR "Tomography, Proton Spin" OR "Proton Spin Tomography" OR "fMRI, Functional" OR "Functional MRI" OR "Functional MRIs" OR "MRIs, Functional" OR "Functional Magnetic Resonance Imaging" OR "Magnetic Resonance Imaging, Functional" OR "Spin Echo Imaging" OR "Echo Imaging, Spin" OR "Echo Imagings, Spin" OR "Imaging, Spin Echo" OR "Imagings, Spin Echo" OR "Spin Echo Imagings"
#3	#1 AND #2

MeSH, Medical Subject Headings.

Participants

Studies assessing untreated CNSTB participants, both children and adults, regardless of race and gender, will be included.

Index tests

MRI will be considered as the index test.

Comparator test

Comparative tests (not the reference standard) will not be mandatory in this study as long as the study reports the diagnostic efficacy of MRI for the diagnosis of CNSTB, whether single-arm or two-arm.

Outcomes

Diagnostic accuracy will mainly consist of the following parameters: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the areas under summary receiver operating characteristic (SROC) curves (AUC). These parameters are the target values that can be calculated in the study. Therefore, these parameters will be used as the primary outcomes to evaluate the diagnostic accuracy of MRI for CNSTB.

Reference standard

Culture or a composite reference standard (CRS) will be considered as the reference standard. The CRS comprises symptoms (such as headaches, vomiting and impaired consciousness), radiographic features (such as tuberculoma, hydrocephalus, basal meningitis and infarcts), cerebrospinal fluid biochemistry (such as elevated protein and white blood cell counts, and decreased sugar and chloride), MTB smear, MTB culture, NAATs and the effectiveness of anti-TB treatment combined with a clinical scoring system for diagnosing TBM.[20 21] Except for microbiological evidence (MTB smear, culture and NAATs) that can be singularly diagnostic of CNSTB, other parameters need to be evaluated in combination for a final diagnosis.

Target conditions

Original studies that meet the eligibility criteria and report clear reference criteria for compliance with this protocol will be included. In the original study, the true positive (TP), false positive (FP), false negative (FN) and true negative (TN) values for the MRI diagnosis of CNSTB will be extracted directly or obtained by calculation. If sufficient data were not reported in the original studies to obtain these values, we will contact the authors of the original studies to obtain additional information. Studies for which full TP, FP, FN or TN values cannot be extracted, studies published in languages other than English or Chinese, abstracts that do not report the full text and case reports will be excluded.

Literature screening and selection

EndNote V.9.2 will be used to manage the original study obtained by searching each database. The literature will be screened based on criteria for inclusion and exclusion criteria identified in this protocol. Two independent researchers (YS and LY) will conduct literature screening by carefully reading the title, abstract and full text to confirm whether the studies meet the inclusion criteria. They will be cross-checked to ensure consistency of results; in case of disagreement, a third investigator (HL) will be used for resolution.

Data extraction

After identifying the included studies, relevant information from the included studies, including general characteristics of the studies and information related to the diagnosis of CNSTB using MRI, will be extracted. The general study characteristics will include the name of the first author, year of study publication, the country where the study was conducted, type of study design, type of patient selection, sample size and type of CNSTB. Relevant data for the diagnosis of CNSTB using MRI will include TP, FP, FN, TN values, type of MRI (enhanced or not), type of MRI parameters and MRI presentation (hydrocephalus, basal meningitis, infarcts). As in the literature screening phase, two independent researchers will extract relevant data and inconsistencies will be resolved through discussions with a third investigator.

Methodological quality assessment

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) will be used to evaluate the methodological quality of each included study.[22] This revised assessment tool includes four domains (patient selection, index test, reference standard and flow and timing). The two independent investigators will conduct the methodological quality evaluation of each included study and will perform cross-checking. Also, disputed areas will be resolved through discussion with a third investigator. Egger's test and funnel plots will be used to carry out a formal assessment of publication bias.

Data synthesis and statistical analysis

The TP, FP, FN and TN values obtained from the original studies to diagnose CNSTB using MRI will be used to calculate the pooled sensitivity, specificity, PPV, NPV and their corresponding 95% CIs. I^2 statistics will be applied to assess heterogeneity between included studies: an I^2 value of 0% indicates no heterogeneity between studies, and an I^2 value >50% indicates significant heterogeneity between studies.[23] In case of significant heterogeneity between studies, we will explore possible sources of heterogeneity through subgroup analysis and meta-regression analysis if a sufficient number of studies are included. Subgroup analysis and meta-regression analysis will be conducted on different types of study designs, types of patient selection, types of CNSTB, types of MRI, types of MRI parameters and MRI presentation. Sensitivity analysis will be used to evaluate the robustness of the correlation analysis. Also, we will calculate the combined AUC and the corresponding 95% CI Stata V.15.0 (StataCorp, College Station, Texas, USA) with the *midas* command[24] and RevMan V.5.3 (Cochrane Collaboration, Oxford, UK) will

be used to perform a meta-analysis and generate forest plots and SROC curves. A p value<0.05 will be considered statistically significant for the relevant statistical analyses.

Evidence evaluation

Grading of Recommendations Assessment, Development and Evaluation guidelines will be used to assess the quality of evidence.[25] Based on the assessment, the quality of evidence will be classified into high, moderate, low and very low levels.[25]

Patient and public involvement

None.

Contributors YS, JZ and HL conceived of the study and initiated the study design. YS and LY designed search strategies. YS wrote original draft. LY and HL review and edit the draft. JZ supervised. All authors contributed to the refinement of the study protocol.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Huihong Lin http://orcid.org/0009-0002-5038-6207

REFERENCES

1 World Health Organization. *Global Tuberculosis Report 2021*. Geneva: World Health Organization, 2021.
2 Yu G, Shen Y, Xu X, *et al*. Nucleic acid amplification techniques for rapid diagnosis of Nontuberculous mycobacteria: A protocol of systematic review and meta-analysis. *PLoS One* 2021;16:e0250470.
3 Zheng H, Zhong F, Yu G, *et al*. Comparison of the diagnostic efficacy of the Capitalbio Mycobacterium real-time polymerase chain reaction detection test and Xpert MTB/RIF in smear-negative pulmonary tuberculosis. *Eur J Clin Microbiol Infect Dis* 2021;40:969–77.
4 Shen Y, Yu G, Zhao W, *et al*. Efficacy of Xpert MTB/RIF ultra in diagnosing tuberculosis meningitis: A systematic review and meta-analysis. *Medicine (Baltimore)* 2021;100:e26778.
5 Sheu JJ, Yuan RY, Yang CC. Predictors for outcome and treatment delay in patients with tuberculous meningitis. *Am J Med Sci* 2009;338:134–9.
6 Leonard JM. Central nervous system tuberculosis. *Microbiol Spectr* 2017;5.
7 Schaller MA, Wicke F, Foerch C, *et al*. Central nervous system tuberculosis: etiology, clinical manifestations and Neuroradiological features. *Clin Neuroradiol* 2019;29:3–18.
8 Katrak SM. Central nervous system tuberculosis. *J Neurol Sci* 2021;421:117278.
9 Chaudhary V, Bano S, Garga UC. Central nervous system tuberculosis: an imaging perspective. *Can Assoc Radiol J* 2017;68:161–70.
10 Davis AG, Rohlwink UK, Proust A, *et al*. The pathogenesis of tuberculous meningitis. *J Leukoc Biol* 2019;105:267–80.
11 Yu G, Wang X, Zhu P, *et al*. Comparison of the efficacy of Metagenomic next-generation sequencing and Xpert MTB/RIF in the diagnosis of tuberculous meningitis. *J Microbiol Methods* 2021;180:106124.
12 Donovan J, Thu DDA, Phu NH, *et al*. Xpert MTB/RIF ultra versus Xpert MTB/RIF for the diagnosis of tuberculous meningitis: a prospective, randomised, diagnostic accuracy study. *Lancet Infect Dis* 2020;20:299–307.
13 Parry AH, Wani AH, Shaheen FA, *et al*. Evaluation of intracranial Tuberculomas using diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS) and susceptibility weighted imaging (SWI). *Br J Radiol* 2018;91:20180342.
14 Di Napoli A, Cristofaro M, Romano A, *et al*. Central nervous system involvement in tuberculosis: an MRI study considering differences between patients with and without human immunodeficiency virus 1 infection. *J Neuroradiol* 2020;47:334–8.
15 Dian S, Hermawan R, van Laarhoven A, *et al*. Brain MRI findings in relation to clinical characteristics and outcome of tuberculous meningitis. *PLoS One* 2020;15:e0241974.
16 Uysal G, Köse G, Güven A, *et al*. Magnetic resonance imaging in diagnosis of childhood central nervous system tuberculosis. *Infection* 2001;29:148–53.
17 Janse van Rensburg P, Andronikou S, van Toorn R, *et al*. Magnetic resonance imaging of Miliary tuberculosis of the central nervous system in children with tuberculous meningitis. *Pediatr Radiol* 2008;38:1306–13.
18 Shen Y, Yao L, Zhang J, *et al*. Diagnostic validity of magnetic resonance imaging for central nervous system tuberculosis: A protocol of systematic review and meta-analysis. PROSPERO 2023 CRD42023415690, Available: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023415690
19 McInnes MDF, Moher D, Thombs BD, *et al*. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA* 2018;319:388–96.
20 Thwaites GE, Chau TTH, Stepniewska K, *et al*. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet* 2002;360:1287–92.
21 Wilkinson RJ, Rohlwink U, Misra UK, *et al*. Tuberculous meningitis. *Nat Rev Neurol* 2017;13:581–98.
22 Whiting PF, Rutjes AWS, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
23 Yu G, Shen Y, Ye B, *et al*. Diagnostic accuracy of Mycobacterium tuberculosis cell-free DNA for tuberculosis: A systematic review and meta-analysis. *PLoS One* 2021;16:e0253658.
24 Yu G, Zhong F, Ye B, *et al*. Diagnostic accuracy of the Xpert MTB/RIF assay for lymph node tuberculosis: A systematic review and meta-analysis. *Biomed Res Int* 2019;2019:4878240.
25 Schünemann HJ, Oxman AD, Brozek J, *et al*. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336:1106–10.