

ORIGINAL ARTICLE

Adenosine deaminase and tuberculous meningitis—A systematic review with meta-analysis

FELIPE FRANCISCO TUON^{1,2}, HERMES RYOITI HIGASHINO¹, MAX IGOR BANKS FERREIRA LOPES¹, MARCELO NÓBREGA LITVOC¹, ANGELA NAOMI ATOMIYA¹, LEILA ANTONANGELO³ & OLAVO MUNHOZ LEITE¹

From the ¹Department of Infectious and Parasitic Diseases, Hospital das Clínicas, School of Medicine, University of São Paulo, SP, ²Division of Infectious and Parasitic Diseases, Hospital Universitário Evangélico de Curitiba, PR, and ³Microbiology and Cytology Laboratories, Division of Central Laboratory, LIM 03, Department of Pathology, University of São Paulo, Medical School, São Paulo, SP, Brazil

Abstract

Tuberculous meningitis (TBM) is a severe infection of the central nervous system, particularly in developing countries. Prompt diagnosis and treatment are necessary to decrease the high rates of disability and death associated with TBM. The diagnosis is often time and labour intensive; thus, a simple, accurate and rapid diagnostic test is needed. The adenosine deaminase (ADA) activity test is a rapid test that has been used for the diagnosis of the pleural, peritoneal and pericardial forms of tuberculosis. However, the usefulness of ADA in TBM is uncertain. The aim of this study was to evaluate ADA as a diagnostic test for TBM in a systematic review. A systematic search was performed of the medical literature (MEDLINE, LILACS, Web of Science and EMBASE). The ADA values from TBM cases and controls (diagnosed with other types of meningitis) were necessary to calculate the sensitivity and specificity. Out of a total of 522 studies, 13 were included in the meta-analysis (380 patients with TBM). The sensitivity, specificity and diagnostic odds ratios (DOR) were calculated based on arbitrary ADA cut-off values from 1 to 10 U/l. ADA values from 1 to 4 U/l (sensitivity >93% and specificity <80%) helped to exclude TBM; values between 4 and 8 U/l were insufficient to confirm or exclude the diagnosis of TBM ($p = 0.07$), and values >8 U/l (sensitivity <59% and specificity >96%) improved the diagnosis of TBM ($p < 0.001$). None of the cut-off values could be used to discriminate between TBM and bacterial meningitis. In conclusion, ADA cannot distinguish between bacterial meningitis and TBM, but using ranges of ADA values could be important to improve TBM diagnosis, particularly after bacterial meningitis has been ruled out. The different methods used to measure ADA and the heterogeneity of data do not allow standardization of this test as a routine.

Introduction

Tuberculous meningitis (TBM) is an important and common central nervous system infection, particularly in developing countries [1]. In these countries, TBM accounts for more than 20% of community-acquired meningitis in adults [2]. TBM is associated with high rates of death and neurological disability, particularly in children and in immunocompromised patients [3–5]. More accurate and rapid diagnostic tests are necessary to prevent delays in specific treatment and to prevent sequelae.

A positive mycobacterial culture in the cerebrospinal fluid (CSF) remains the gold standard in TBM diagnosis. CSF acid-fast bacilli are identified in less than

10% of cases, and mycobacteria culture positivity ranges from 50% to 75% after 8 weeks, an unacceptable length of time for the diagnosis of tuberculosis [6]. Despite the advantages of the automated mycobacteria culture systems, the mean recovery time remains too long for making treatment decisions [7].

The neurological symptoms and signs are quite non-specific, varying from few or no clinical signs of meningitis to stupor or coma with systemic toxicity and gross paresis or paralysis. The characteristic CSF abnormalities in TBM are similar to those accompanying a variety of meningeal processes, such as partially treated bacterial meningitis, fungal meningitis, syphilitic meningitis, and vasculitis. Bacterial meningitis and TBM may have similar characteristics in developing

countries and aseptic meningitis may also need to be ruled out. Thus, the decision of whether or not to treat a patient as a TBM patient is a relatively common one in clinical practice. Abnormalities include a moderate lymphocytic pleocytosis with moderately elevated spinal fluid protein and moderate hypoglycorrhachia [1,8,9].

Due to the difficulty of establishing the diagnosis of TBM using clinical, radiological (magnetic resonance imaging or computed tomography), cytological, biochemical and even microbiological approaches, additional tests have been developed. These include indirect and direct products from *Mycobacterium tuberculosis*, such as adenosine deaminase (ADA) activity, radioactive bromide partition test, tuberculostearic acid assay, antibodies against mycobacterial antigens and nucleic acid amplification reactions. The use of ADA is increasing because it is simple and affordable. Consequently, many studies have been published that have evaluated the performance of ADA [2].

ADA is an enzyme required for the conversion of adenosine to inosine and is found in many tissues, particularly in T-lymphocytes from the lymphoid tissue [10]. High ADA levels in tuberculosis appear to be related to the subset of activated T-lymphocytes in response to tuberculous antigens [11].

The usefulness of ADA in the diagnosis of pleural, peritoneal and pericardial tuberculosis is not well established, although some meta-analyses justify its use. This test is hardly ever used without confirmation of the diagnosis by culture [12–14]. Nevertheless, several cut-offs for ADA in TBM have been proposed by different studies, and thus, there is a lack of standardization in the ADA cut-off value for diagnosing TBM. The sensitivity, specificity and positive and negative predictive values for ADA depend on the selected cut-off value, the control group and the local prevalence of tuberculosis. The reported sensitivity has varied from 40% to 100%, and the specificity from 70% to 100% [15,16]. Even though several studies have demonstrated the value of ADA as a diagnostic test, others have published discordant results. To our knowledge, there have been no meta-analyses on the utility of the ADA test for TBM diagnosis. The goal of this systematic review was to evaluate the ADA test as a diagnostic test for TBM.

Materials and methods

Search strategy

A systematic search of the medical literature was performed using the databases of MEDLINE, EMBASE, Web of Science, Cochrane Library and

LILACS (January 1966–May 2007). The search terms used were ‘tuberculo*’, ‘meningit*’ and ‘adenosine deaminase’ (*denotes the inclusion of all words with the preceding radical). Other search terms used were: ‘tuberculous meningitis’, ‘tubercular meningitis’, ‘meningotuberculosis’ and ‘central nervous system tuberculosis’. References from the primary studies were reviewed to search for additional studies that were missed in the systematic electronic search [17].

Study selection

The studies were initially selected by 2 authors (F.T. and H.H.) independently. Disagreements were resolved by consensus. There was no language restriction. The inclusion criteria were: (1) the ADA values from each patient with TBM (case) and controls (diagnosed with other types of meningitis) were present and could be extracted for calculation of sensitivity and specificity (see Data extraction); (2) to avoid measurement bias, only papers evaluating total ADA were considered; and (3) cases of TBM were defined according to standardized criteria specified below.

TBM was defined by the presence of at least 1 of the following diagnostic criteria: (1) *M. tuberculosis* in CSF culture; (2) meningitis and presence of acid-fast bacilli on CSF smear; (3) meningitis associated with tuberculosis in another organ; or (4) clinical and/or laboratory evidence of TBM, with improvement after empirical treatment for tuberculosis [16]. Patients with other types of infectious meningitis (viral, bacterial or fungal) as well as neoplasms were included as controls in the calculations. Patients with normal CSF were excluded.

Data extraction

The ADA value of each patient was collected and classified according to the confirmed diagnoses: (1) tuberculosis, (2) meningitis other than tuberculosis, and (3) bacterial meningitis. We then calculated the sensitivity, specificity, diagnostic odds ratios, and positive and negative likelihood ratios for the different cut-offs. The patients included as controls for these calculations were diagnosed with either bacterial meningitis or other non-tuberculous meningitis.

Statistical analysis

To guarantee quality, as well as good article selection and data extraction [18,19], we conducted several tests of the validity in this meta-analysis. A Chi-squared test was performed to determine the variability between studies (heterogeneity), and statistical significance was defined as $p < 0.001$. In addition, the quality

of the articles was classified as 1, 2 or 3 according to criteria previously described and modified for TBM [14].

The sensitivity, specificity and diagnostic odds ratio (DOR) of each study were calculated along with 95% confidence intervals (CI). A graph of the summary receiver operating characteristic (SROC) curve was constructed from the sensitivity and specificity data of each article [20]. Positive likelihood ratios (LR+) and negative likelihood ratios (LR-), using a certain pre-test probability, were included to help evaluate the utility of ADA in clinical investigations. The possibility of publication bias was analyzed using the Egger test [21]. The software program Meta-DiSc 1.4 was used in the calculations, graph construction and determination of heterogeneity [22].

Results

Description of studies included

We found 522 studies and excluded 424 after the first screening (Figure 1). Of the 98 remaining articles, 67 were deemed inadequate for further analysis. Eighteen articles did not provide sufficient data for sensitivity and specificity calculations. Thus, 13 studies were included in the meta-analysis, with a total of 380 patients with TBM [11,15,16,23–32].

Study validity and data quality

Four prospective studies and 9 retrospective studies were included. Three studies included fewer than

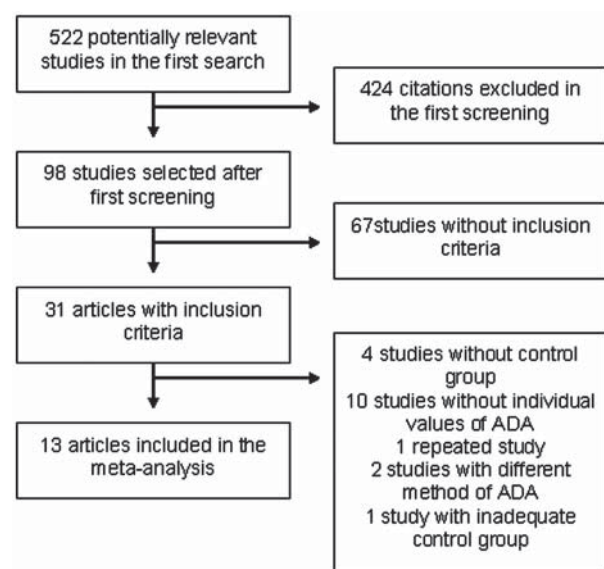


Figure 1. Selection of studies included in a meta-analysis of the use of adenosine deaminase activity in the diagnosis of tuberculous meningitis.

10 patients with TBM. The technique used for ADA measurement was not described in 3 studies. Three studies reported that ADA measurements were performed, but they did not report any clinical data. Two studies included evaluation of patients with HIV infection [26,32]. Five studies were classified as group 1 (low quality) and 5 studies were classified as group 2 (moderate quality). Most of the studies included adult patients and 2 studies evaluated only children (Table I).

The heterogeneity in the results for sensitivity, specificity, LR+, LR- and DOR in the diagnosis of TBM using the cut-off from each study and the cut-offs of 4, 8 and 10 U/l (the most common values among all studies), was tested. For the first part of this study, the control group included all those with any meningitis except for TBM (i.e., bacterial, viral or fungal meningitis or neoplasm). The variables showed significant dispersion ($p < 0.001$), except for the sensitivity of using ADA with the cut-off value of 4 U/l ($p = 0.091$) and for the LR- with the ADA cut-off value of 8 U/l (Table II).

Results of the variables

The sensitivity, specificity and DOR with ADA cut-offs of 4, 8 and 10 U/l and the cut-offs determined by the authors of each study were plotted (Figure 2). There was a significant difference in sensitivity using the different cut-offs (Table II).

Next, the sensitivity, specificity, LR+, LR- and DOR using the ADA cut-offs from 1 U/l to 20 U/l for TBM and other meningitis (non-bacterial and bacterial) were determined (Table III). Values from 1 to 4 U/l showed sensitivities of 93% to 100% and specificities that were lower than 80% to exclude TBM ($p < 0.001$). The ADA values between 4 and 8 U/l were insufficient to diagnose the presence of TBM ($p = 0.07$). Values higher than 8 U/l showed a specificity that was higher than 96% but a sensitivity that was lower than 59% ($p < 0.001$).

Based on the SROC curve, the ideal ADA cut-off was 5.30 U/l, which was associated with a sensitivity and a specificity of 84%. The area under the curve in the SROC curve was close to 1 (0.9065), but had a wide standard deviation (SD) (Figure 3).

None of the variables were sufficient to allow the discrimination between TBM and bacterial meningitis. The mean ADA from patients with TBM was 11.50 U/l (SD = 7.90) and in patients with bacterial meningitis was 11.80 U/l (SD = 10.70). The mean ADA from patients with meningitis other than bacterial types was 3.00 U/l (SD = 4.2). The DOR of ADA with a cut-off of 10 U/l for TBM compared with bacterial meningitis was 1.10 (95%CI = 0.65–1.84). The DOR of ADA with a cut-off of 10 U/l for TBM compared with other non-bacterial meningitis was

Table I. Brief description and classification of the articles included in the meta-analysis of adenosine deaminase activity in the cerebral spinal fluid for the diagnosis of tuberculous meningitis.

| Author, y, country | N | Weight of each study | Age | Prospective/retrospective | Consecutive/random sample | >10 patients with TB | ADA measurement assay and cut-off | Blind test | Aetiology of control group ^a | Criteria of control group ^b | Probable TB by outcome | HIV patients | Quality |
|-----------------------------|------|----------------------|----------|---------------------------|---------------------------|----------------------|-----------------------------------|------------|---|--|------------------------|--------------|---------|
| Blake, 1982, South Africa | 109 | 10% | All ages | R | C | Yes | Unknown 6.00 U/l | No | V+B+N+F | No | No | No | 1 |
| Mann, 1982, South Africa | 60 | 5% | Children | R | C | Yes | Unknown 5.00 U/l | No | V+B | No | No | No | 1 |
| Malan, 1984, South Africa | 96 | 9% | All ages | R | C | Yes | Giusti 6.00 U/l | No | V+B | Yes | Yes | No | 2 |
| Donald, 1986, South Africa | 160 | 15% | All ages | R | C | Yes | Giusti 6.00 U/l | no | V+B | Yes | Yes | No | 2 |
| Ribera, 1987, Spain | 96 | 9% | Unknown | P | R | Yes | Giusti 9.00 U/l | Yes | V+B | Yes | Yes | No | 3 |
| Pettersson, 1991, Finland | 56 | 5% | Adults | R | C | No | Giusti 20.00 U/l | No | V+B | No | No | No | 1 |
| Kaur, 1992, India | 52 | 5% | Adults | P | R | No | Giusti 10.00 U/l | Yes | V+B | Yes | Yes | No | 3 |
| Lopez-Cortes, 1995, Spain | 141 | 13% | All ages | P | R | Yes | Giusti 10.00 U/l | No | V+B | Yes | Yes | Yes | 3 |
| Baro, 1996, Chile | 27 | 2% | Adults | R | C | Yes | Giusti 7.10 U/l | No | V+B | No | No | No | 1 |
| Zapata, 1996, Chile | 35 | 3% | Adults | R | C | No | Giusti 9.00 U/l | No | V+B+N+F | No | No | Yes | 1 |
| Mishra, 1996, India | 56 | 5% | Children | R | R | Yes | Giusti 5.00 U/l | No | V+B | No | No | No | 2 |
| Schutte, 2001, South Africa | 26 | 2% | Adults | P | C | Yes | Unknown 10.00 U/l | Yes | B | Yes | No | No | 2 |
| Choi, 2002, Korea | 178 | 16% | Adults | R | C | Yes | Giusti 10.00 U/l | No | V+B | Yes | Yes | No | 2 |
| Total | 1092 | 100% | | | | | | | | | | | |

N, number of patients; TB, tuberculosis; ADA, adenosine deaminase; HIV, human immunodeficiency virus.

^aV, viral; B, bacterial; N, neoplasm; F, fungal.

^bDescription of the best available technique for the diagnosis.

Table II. Sensitivity, specificity, diagnostic odds ratio, and positive and negative likelihood ratios (LR+ and LR-) with 2 cut-off values and heterogeneity of the adenosine deaminase activity in the cerebral spinal fluid for the diagnosis of tuberculous meningitis.

| Property | Measure (95% CI) | Heterogeneity |
|-------------------------------|---------------------|-------------------|
| ADA cut-off 10 U/l | | |
| Sensitivity | 49.5 (43.6–55.4) | $p < 0.001^{a,b}$ |
| Specificity | 90.7 (88.5–92.7) | $p < 0.001$ |
| LR+ | 4.72 (2.73–8.13) | $p < 0.001$ |
| LR- | 0.61 (0.50–0.74) | $p = 0.002$ |
| DOR | 11.06 (5.07–23.70) | $p < 0.001$ |
| ADA cut-off used by the study | | |
| Sensitivity | 74.3 (69.0–79.2) | $p < 0.001^a$ |
| Specificity | 87.4 (84.9–89.7) | $p < 0.001$ |
| LR+ | 5.61 (3.10–10.30) | $p < 0.001$ |
| LR- | 0.30 (0.18–0.47) | $p < 0.001$ |
| DOR | 24.22 (9.23–63.64) | $p < 0.001$ |
| ADA cut-off 8 U/l | | |
| Sensitivity | 63.0 (57.1–68.6) | $p < 0.001$ |
| Specificity | 84.8 (82.1–87.3) | $p < 0.001$ |
| LR+ | 4.29 (2.56–7.10) | $p < 0.001$ |
| LR- | 0.49 (0.40–0.60) | $p = 0.083$ |
| DOR | 11.66 (5.52–24.64) | $p < 0.001$ |
| ADA cut-off 4 U/l | | |
| Sensitivity | 92.7 (89.1–95.4) | $p = 0.091^b$ |
| Specificity | 72.3 (69.0–75.4) | $p < 0.001$ |
| LR+ | 3.44 (2.25–5.28) | $p < 0.001$ |
| LR- | 0.14 (0.09–0.21) | $p < 0.001$ |
| DOR | 29.85 (14.91–59.74) | $p < 0.001$ |

ADA, adenosine deaminase; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio.

^aSignificant difference in sensitivity of ADA cut-off 10 U/l and ADA cut-off used by the study, $p < 0.05$.

^bSignificant difference in sensitivity of ADA cut-off 10 U/l and ADA cut-off 4 U/l, $p < 0.05$.

112 (95% CI = 88.87–145.77). Studies with adults or children showed similar results.

Publication bias

The Egger test was used to evaluate the possibility of publication bias, and significant findings ($p < 0.05$) indicated the presence of publication bias. The funnel graph showed the studies to be above the line of the summary DOR, confirming a publication bias that included only articles showing favourable results in studies with few cases.

Discussion

There was some enthusiasm for the use of ADA in CSF diagnosis of tuberculosis 20 y ago. No one has managed to present persuasive evidence that it is a real practical addition in making clinical decisions and most centres have abandoned it.

This systematic review with some calculus used as meta-analysis, showed that CSF ADA was not a valid test, with inadequate sensitivity and specificity using established cut-offs. Based on the ROC curve, the ideal cut-off was 5.3 U/l (84% sensitivity and specificity). A higher specificity could be achieved with

a cut-off of 20 U/l (100%); however, the sensitivity dropped to 16%. Nevertheless, an ADA value of 3.0 U/l presented a sensitivity of 98% and specificity of 72% in excluding TBM. Based on these findings, the one best ADA cut-off value could not be determined; however, using ADA values in set ranges could aid in the reinforcement or discarding of a TBM diagnosis. Nevertheless, we believe that this 'ideal' cut-off maximizes both sensitivity and specificity and therefore assumes that equal value is placed on ruling in and ruling out the diagnosis. This is unlikely to be true in clinical practice. Stratification was thus performed to improve the diagnosis of TBM. Obviously, these values could be dependent on the pre-test probability. Thus, a patient with clinical signs and CSF analysis suggestive of TBM, who has an ADA value higher than 8 U/l, has an increased probability of having TBM. Nevertheless, an ADA value lower than 3 U/l could exclude a TBM diagnosis.

The utility of using different cut-offs of ADA can be better understood by evaluating the positive and negative likelihood ratios. An ADA level of 10 U/l was associated with a LR+ of 23.18, while an ADA level of 3 U/l was associated with a LR- of 0.03. These data, when transferred to a Bayesian nomogram, demonstrate the value in the diagnosis of TBM with ADA activity ≥ 10 U/l in the post-test probability.

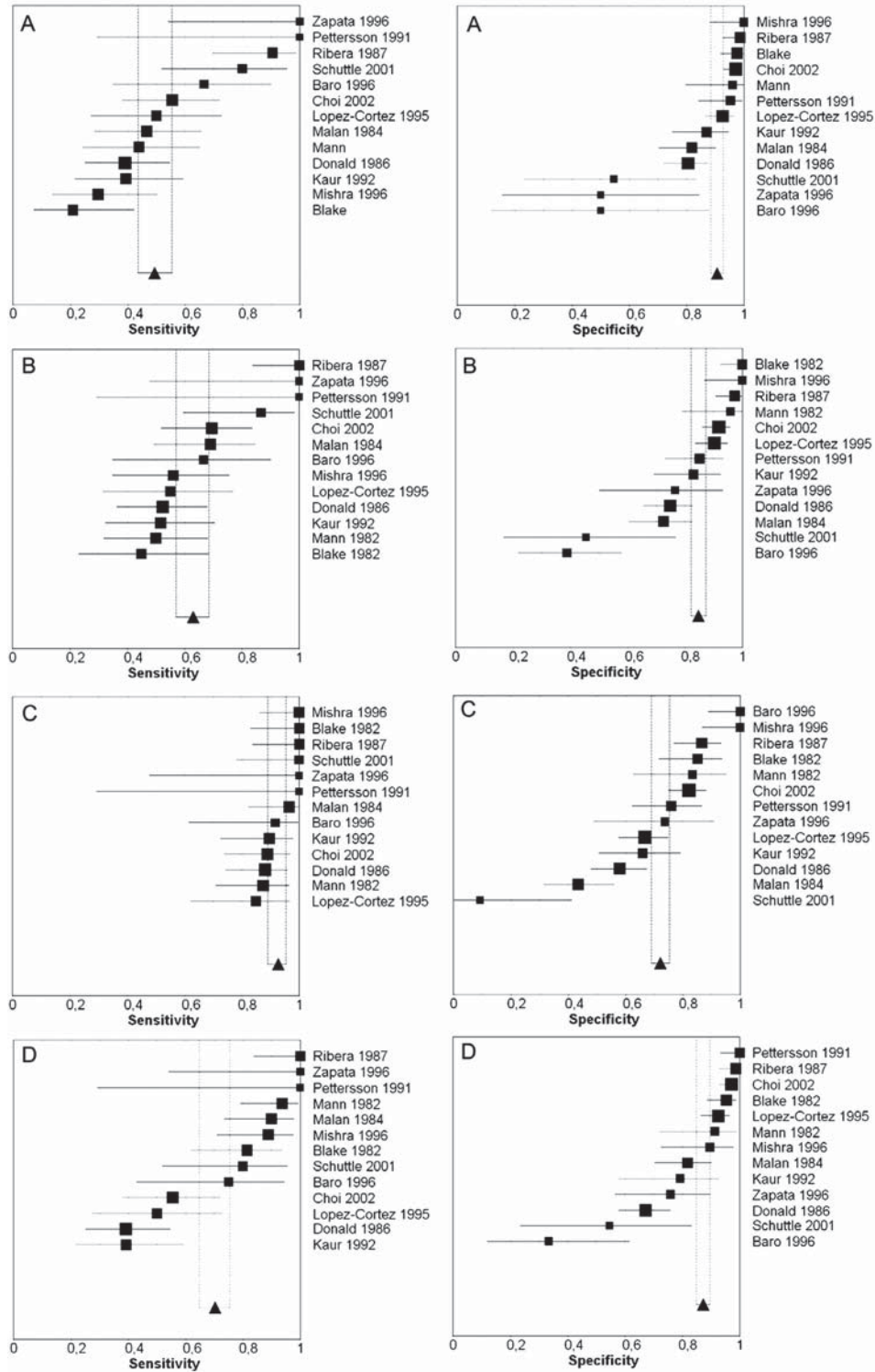


Figure 2. Sensitivity and specificity plotted on Forest graphs for adenosine deaminase activity (ADA) in cerebral spinal fluid for the diagnosis of tuberculous meningitis. The central point determines the mean, and the lines determine the 95% confidence interval (CI). The triangle represents the sum of the studies and the respective 95% CI. (A) ADA cut-off of 10 U/l; (B) ADA cut-off of 8 U/l; (C) ADA cut-off of 4 U/l; (D) ADA cut-off determined by the authors of each article.

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Table III. Adenosine deaminase sensitivity, specificity, diagnostic odds ratio, and positive and negative likelihood ratios (LR+ and LR-) in the diagnosis of tuberculous meningitis considering different cut-offs (ranging from 1 to 20 U/l) with different control groups (all non-tuberculous meningitis and bacterial meningitis).

| Tuberculous meningitis versus other meningitis | | | | | | |
|--|-------------|-------------|-------|------|--------|-------------|
| ADA cut-off (U/l) | Sensitivity | Specificity | LR+ | LR- | DOR | |
| Low probability of TB | | | | | | $p < 0.001$ |
| 1.0 | 100% | 6% | 1.06 | 0.03 | 31.45 | |
| 2.0 | 98% | 55% | 2.19 | 0.03 | 65.13 | |
| 3.0 | 98% | 72% | 3.49 | 0.03 | 112.67 | |
| 4.0 | 93% | 80% | 4.67 | 0.09 | 52.89 | |
| Indefinite TB | | | | | | $p = 0.07$ |
| 5.0 | 88% | 86% | 6.38 | 0.14 | 46.24 | |
| 6.0 | 80% | 91% | 9.00 | 0.22 | 40.88 | |
| 7.0 | 73% | 93% | 11.19 | 0.29 | 38.57 | |
| High probability of TB | | | | | | $p < 0.001$ |
| 8.0 | 59% | 96% | 13.71 | 0.42 | 32.36 | |
| 9.0 | 52% | 97% | 15.41 | 0.50 | 41.87 | |
| 10.0 | 46% | 98% | 23.18 | 0.55 | 45.59 | |
| 15.0 | 31% | 99% | 31.66 | 0.69 | 48.04 | |
| 20.0 | 16% | 100% | 40.52 | 0.84 | | |
| Tuberculous meningitis versus bacterial meningitis | | | | | | |
| ADA value (U/l) | Sensitivity | Specificity | LR+ | LR- | DOR | |
| <4 | 92% | 19% | 1.1 | 0.4 | 2.74 | $p = 0.5$ |
| >8 | 60% | 46% | 1.1 | 0.8 | 1.31 | |

ADA, adenosine deaminase; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio; TB, tuberculosis.

Indeed, collecting clinical and laboratory information together has been considered as standard procedure for TBM diagnosis. Thwaites et al. demonstrated the efficacy of the combination of these findings in TBM diagnosis, using a newly proposed score [9]. The ADA was not included in their score; however, in the setting of their study, the ADA test would have been useless because the diagnosis of TBM was compared with the diagnosis of bacterial meningitis, a common problem in Asian developing countries. Our study also demonstrated that ADA could not differentiate between bacterial meningitis and TBM, independent of the ADA cut-off used. In bacterial meningitis, there are several diagnostic tests, there is a faster clinical evolution and there is a faster treatment response to antibiotics (less than a week). However, the clinician faces a problem when diagnosing lymphocytic meningitis, which requires differentiating between viral, fungal and TBM, as well as partially treated bacterial meningitis.

In India, TBM represents more than 20% of all meningitis cases, and the main alternative diagnosis is bacterial aetiology, which decreases the usefulness of ADA in that country. Nevertheless, in Brazil, tuberculosis accounts for 3% of meningitis cases in the emergency room, and the main alternative diagnosis is viral aetiology. Thus, ADA could be used in countries where the incidence of tuberculosis is low.

Another useful test is a polymerase chain reaction (PCR) amplifying *M. tuberculosis* DNA [33]. PCR

shows a higher DOR than ADA for TBM but the high cost and specialized laboratories needed make it difficult to include PCR as a routine test in resource-limited areas, and it would be difficult to maintain quality control of the results for this technically very demanding test.

Our study had many limitations. There was great heterogeneity observed between studies. Some explanations for this are: (1) different in-house methods used by various clinical laboratories, (2) different patterns of immune response in the CSF resulting in different ADA results, and (3) different regional incidences of tuberculosis [34,35]. The method for measuring ADA was not detailed in the studies. This test is not standardized and we need more details on the ADA test methods. Some studies used a method measuring U/ml at 265 nm in the spectrophotometer and others made their measurements at 630 nm (data not shown). The values are very different depending on the wavelength used for readings. Thus, comparing and combining results on the basis of U/ml does not make sense.

Also, the differences in the composition of the control groups could explain the variability in the ADA cut-offs used. These studies do not explain how patients were recruited into the study or the prevalence of TBM in the setting, and what tests were performed prior to the use of the ADA and the reference test. These characteristics are important when considering the generalizability of the results.

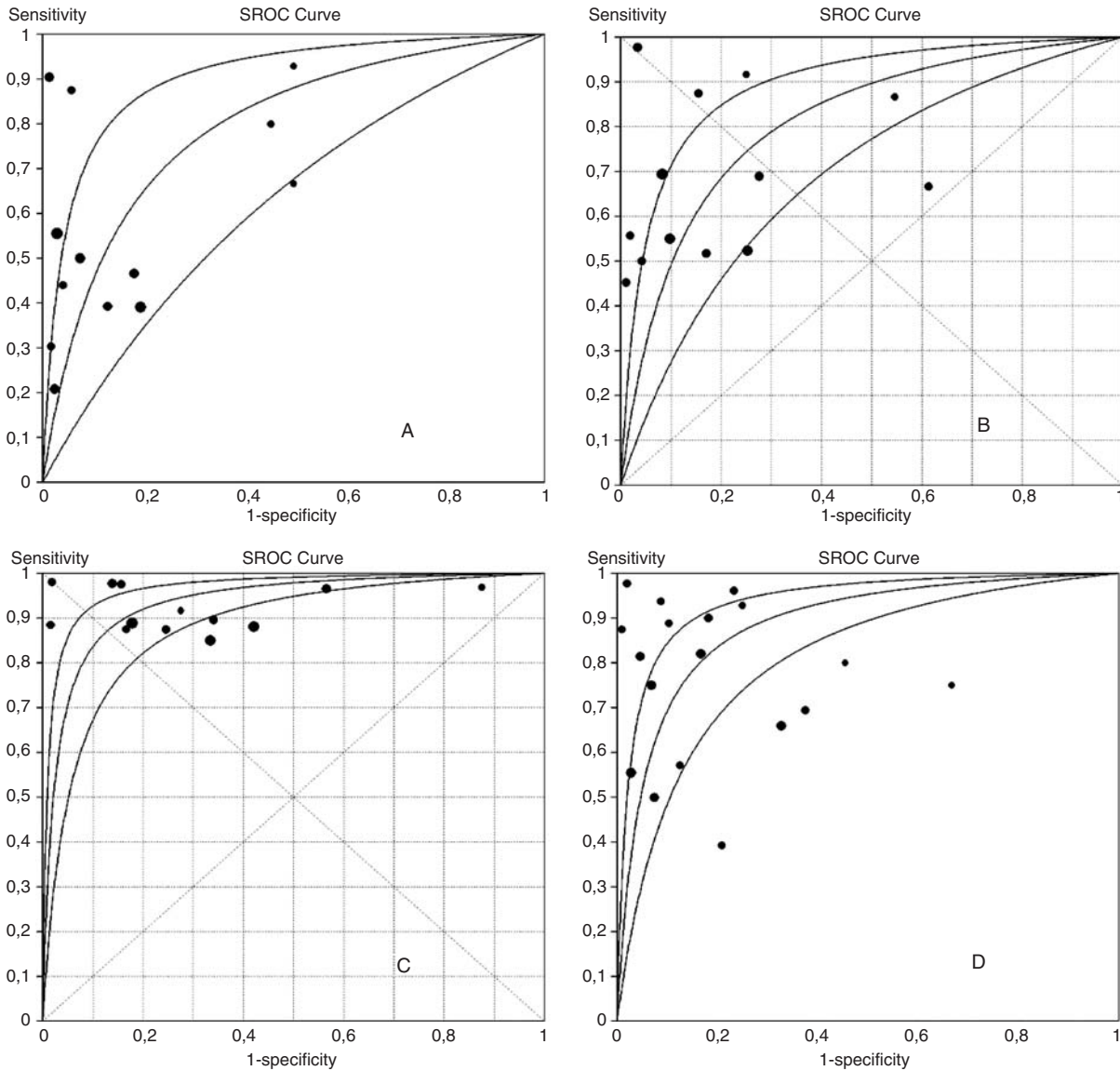


Figure 3. Summary receiver operating curve (SROC) for adenosine deaminase in the cerebral spinal fluid in the diagnosis of tuberculous meningitis.

Another problem of this review was publication bias, where there appeared to be a tendency of articles that show ADA to be a useful test being published. More studies of the utility of the ADA test are needed to exclude these biases. The last criterion of TBM we used ('clinical and/or laboratory evidence of TBM, with improvement after empirical treatment for tuberculosis') is controversial and may lead to biased results. Viral meningitis (also lymphocytic) is often self-limiting with or without treatment and may show similar laboratory findings in CSF.

The studies included in this analysis demonstrated poor correlation in the results and they were similar in terms of the number of patients and controls. Heterogeneity was present in some calculus, making these findings invalid. Because the methods used for

ADA measurement were not described in almost all studies, measurement biases were amplified.

Two studies evaluated patients with HIV infection. Lopez-Cortes et al. considered ADA unreliable for the diagnosis of TBM in HIV-infected patients. Unfortunately the number of patients did not allow a significant analysis [26]. Several studies have shown no differences in ADA expression among HIV-infected patients with extrapulmonary tuberculosis [14,36–40].

In summary, the present study demonstrated difficulties in the use of the ADA test, although it is a simple and affordable test that can be included in routine CSF analyses after lumbar puncture in an emergency room. The utility of this strategy alone or in combination with more expensive and laborious tests, such as PCR, has not yet been assessed in

epidemiological studies. ADA cannot distinguish between bacterial meningitis and TBM, but using ranges of ADA values could be important to improve TB diagnosis, particularly after bacterial meningitis has been ruled out.

Declaration of interest: (1) None of the authors have commercial relationships or other associations that might pose a conflict of interest (e.g., pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding). (2) There was no financial support for this study.

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