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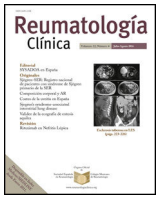

Original article

Performance of adenosine deaminase in synovial fluid for the diagnosis of tuberculous arthritis: A systematic review and meta-analysis

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ABSTRACT

Objectives: Adenosine deaminase (ADA) activity has shown good performance in diagnosing pleural, peritoneal, and meningeal tuberculosis. This meta-analysis aimed to evaluate the performance of measuring ADA activity in synovial fluid for the early diagnosis of joint tuberculosis.
Methods: We searched published information in MEDLINE, Embase, Cochrane Library, Web of Science, and MedRxiv databases, as well as unpublished information in the American College of Rheumatology and European League Against Rheumatism for conference abstracts (2012–2021). We also scanned the reference lists of articles. Two reviewers independently applied the criteria for selection, assessed quality, and extracted data (PROSPERO number CRD42021284472).
Results: Seven independent studies ($N = 305$ subjects) that compared ADA activity in synovial fluid with a composite reference diagnostic method for tuberculosis were included. Overall, the risk of bias was judged low. Studies were classified as high quality ($n = 3$; 148 subjects) and low quality ($n = 4$; 157 subjects). Pooled sensitivity and specificity of ADA activity was 94% (95% confidence interval [CI], 0.89–98; $I^2 = 23\%$) and 88% (95% CI, 83–92; $I^2 = 83\%$), respectively. The random-effects model for pooled diagnostic Odds ratio was 67.1 (95%CI, 20.3–222.2; $I^2 = 30\%$). The receiver operating characteristic curve area was 0.96 (95% CI, 0.92–0.99). Meta-regression did not identify the quality of the study, country of publication, or the type of assay as a source of heterogeneity.
Conclusions: Measuring ADA activity in synovial fluid demonstrates good performance for the early diagnosis of joint tuberculosis.

Rendimiento de la adenosina desaminasa en el líquido sinovial para el diagnóstico de la artritis tuberculosa: una revisión sistemática y metaanálisis

Palabras clave:
Tuberculosis
Adenosina desaminasa
Líquido sinovial
Sensibilidad y especificidad

RESUMEN

Objetivos: La actividad de la adenosina desaminasa (ADA) ha mostrado un buen desempeño en el diagnóstico de la tuberculosis pleural, peritoneal y meníngea. Este metaanálisis tuvo como objetivo evaluar el rendimiento de la medición de la actividad de la ADA en el líquido sinovial para el diagnóstico precoz de la tuberculosis articular.
Métodos: Se realizaron búsquedas de resúmenes de congresos en la información publicada en las bases de datos MEDLINE, Embase, Cochrane Library, Web of Science y MedRxiv, así como en información no publicada en el *American College of Rheumatology* y la *European League Against Rheumatism* (2012-2021). También se escanearon las listas de referencias de los artículos. Dos revisores aplicaron de forma independiente los criterios de selección, evaluaron la calidad y extrajeron los datos (número PROSPERO CRD42021284472).

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Resultados: Se incluyeron siete estudios independientes (n = 305 sujetos) que compararon la actividad de la ADA en el líquido sinovial con un método diagnóstico compuesto de referencia para la tuberculosis. En general, el riesgo de sesgo se consideró bajo. Los estudios se clasificaron como de alta calidad (n = 3; 148 sujetos) y de baja calidad (n = 4; 157 sujetos). La sensibilidad y la especificidad agrupadas de la actividad de la ADA fueron del 94% (intervalo de confianza [IC] del 95%: 0,89-98; I^2 = 23%) y del 88% (IC 95%: 83-92; I^2 = 83%), respectivamente. El modelo de efectos aleatorios para el odds ratio diagnóstico agrupado fue de 67,1 (IC 95%: 20,3-222,2; I^2 = 30%). El área de la curva característica de operación del receptor fue de 0,96 (IC 95%: 0,92-0,99). La metarregresión no identificó la calidad del estudio, el país de publicación o el tipo de ensayo como fuente de heterogeneidad.
Conclusiones: La medición de la actividad de ADA en el líquido sinovial demuestra un buen rendimiento para el diagnóstico precoz de la tuberculosis articular.

Introduction

Bone and joint tuberculosis may account for up to 35 percent of cases of extrapulmonary tuberculosis. Skeletal tuberculosis most often involves the spine, followed by tuberculous arthritis in weight-bearing joints and extraspinal tuberculous osteomyelitis.[1] An early and correct diagnosis of tuberculosis is critical to reducing disability since a delay in the diagnosis can lead to joint destruction, joint deformity, and even paraplegia. In joint tuberculosis, conventional synovial fluid analysis and traditional protocols for diagnosis are time-consuming procedures with low sensitivity.[2] Recently, commercial automated molecular tests have been incorporated as rapid diagnostic tools. As an example, the Xpert MTB/RIF assay (Cepheid, CA, USA) is a nucleic acid amplification test targeting the IS6110 that simultaneously detects Mycobacterium tuberculosis complex and resistance to rifampin (RIF) in less than 2 h.[3] However, nucleic acid amplification techniques require instrumentation and power requirements of polymerase chain reaction not always available in low-resource settings. Adenosine deaminase, referred to as ADA (EC 3.5.4.4), is a key enzyme in purine metabolism, which catalyzes the irreversible deamination of adenosine (deoxyadenosine) to inosine (deoxyinosine). A laboratory determination of ADA activity is simple, quick, and relatively cheap.[4] The activity of ADA is indirectly related to the subsets of T cell lymphocytes activated by the inflammatory response induced by tuberculosis. Several studies have confirmed the diagnostic potential of ADA for patients with suspected pleural, peritoneal o meningeal tuberculosis.[5–7] The most commonly used cut-off values for ADA were ≥40 IU/L for pleural and peritoneal tuberculosis, and ≥10 IU/L for meningeal tuberculosis. However, the clinical performance of measuring the activity of ADA in the synovial fluid has received less attention. Considering the small number of studies analyzing the current role of ADA as a diagnostic tool for synovial tuberculosis, we conducted a systematic review of the literature and a meta-analysis to determine the usefulness of ADA levels in diagnosing tuberculous arthritis.

Methods

The present meta-analysis was performed according to the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) (Supplementary file) statement and with methods recommended by the Cochrane Diagnostic Test Accuracy Working Group.[8,9] The protocol for this meta-analysis is registered with PROSPERO (number CRD42021284472).

Data sources and search strategy

We performed a systematic literature search using electronic datasets (i.e., PubMed, Embase, Cochrane Central, Web of Science, and MedRxiv databases) for adenosine deaminase as a tool for diagnosing synovial tuberculosis. We also screened for references from original articles, previous systematic reviews, and conference abstracts from the American College of Rheumatology and the European League Against Rheumatism to identify eligible trials until October 2021. The search strategy used was Adenosine Deaminase AND Tuberculosis AND Synovial fluid. No language restriction. Publication period: January 1986 to October 2021. References cited in the included articles and reviews were further explored for possible candidate studies.

Inclusion criterials

We included full-text original studies that assessed the diagnostic accuracy of adenosine deaminase activity for synovial tuberculosis. Reference standards were well-defined and appropriate to the studies. The articles directly provided true positive, false positive, false negative, and true negative values for the assay or included the data necessary to calculate these measures. We excluded case reports, articles written in languages other than English and Spanish, and studies with <10 samples.

Reference standard

The reference standard was a composite of clinical symptoms, radiographic features, biochemical test results, smears, culture, histopathology, and response to antituberculosis drugs or a mycobacterial culture as it was defined in the original paper. Some or all of the factors with positive results were considered positive tuberculous arthritis. Cases were considered non-tuberculosis if all the results were negative. We used the composite reference standard as defined in the original paper.

Literature screening and selection

1Two investigators (JCC-Q, JAB) independently assessed the candidate articles by reviewing their titles and abstracts, followed by the full text, for inclusion. Discrepancies between the two investigators were resolved by discussion with a third investigator (JR, JE).

Data extraction

We extracted data including author name; year; country; patient selection method, adenosine deaminase assay, true positive, false positive, false negative, and true negative values. The same two investigators independently extracted the necessary information from each of the included articles; we crosschecked the information they obtained. Discrepancies in the two data sets were settled by a discussion with a third investigator, similar to that used during the literature selection phase.

Assessment of study quality

Two investigators independently used a revised tool for Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to assess

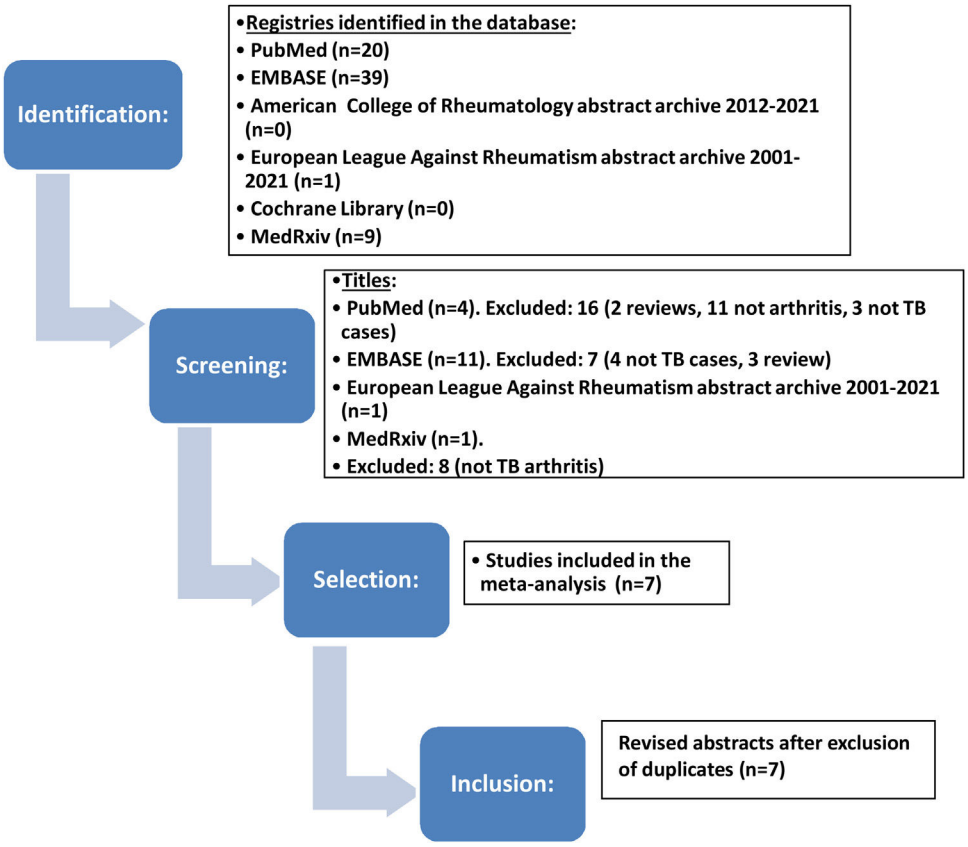

Fig. 1. Process of selection of studies included in the meta-analysis. Revised abstracts after exclusion of duplicates ($n = 7$).

study quality separately.[10] We chose not to formally assess publication bias, as the available methods such as funnel plots are not considered valid for diagnostic accuracy reviews.[10]

Data synthesis and statistical analysis

We first obtained the values corresponding to True Positive, False Positive, False Negative, and True Negative in each included study. We calculated the estimated pooled sensitivity and specificity of adenosine deaminase activity in synovial fluid associated with the 95% confidence interval (CI), against the composite reference standard or culture, using bivariate random effects models. Forest plots for sensitivity and specificity were generated for each study. The areas under the summary receiver operating characteristic (SROC) curves (AUC) were subsequently calculated. I^2 statistics were used to assess heterogeneity across the studies. While 0% indicated no observed heterogeneity, values greater than 50% were considered to imply substantial heterogeneity.[11] We explored different patient selection methods, assay methods, and quality of study as potential sources of heterogeneity, using subgroup and metaregression analyses. MetaDisc 1.4 (HRC, Madrid, Spain) generated forest plots of sensitivity and specificity with 95% CI for each study and carried out meta-analyses and meta-regression analyses.[12]

Results

Identification of studies and study characteristics

Through our search strategy, we identified candidate articles from relevant databases, and seven articles with a total of 305 patients met the inclusion criteria (Fig. 1).[13–19] Four studies were conducted in India, and one study each was conducted in Korea, Thailand, and Spain (Table 1). The assay to measure the activity of ADA was carried out using the Galanti–Giusti method in five studies. There were three prospective studies, three retrospective studies, and one ambispective study. Six articles were written in English and one in Spanish.

Study quality

The methodological quality of the included studies, using the QUADAS2 tools is summarized in Fig. 2. The risk of bias was below 50% and it was mainly due to patient selection and the reference standard; flow and timing from the index test were judged with low risk of bias. Overall, the applicability concern was low. Based on the risk of bias, prospective studies were classified as high-quality and retrospective–ambispective as low quality. Adenosine deaminase activity in tuberculous arthritis. The activity of ADA in synovial fluid was measured using the colorimetric method of Galanti–Giusti in 5 studies,[13,19] one study used an enzymatic spectrophotometric method,[17] and one study used a commercial assay (ADA-N kit; Denka Seiken Co Ltd, Japan).[18] The values of ADA activity in patients with tuberculous joint infection varied across studies even in those publications using the same methodology. The cut-off values of ADA for diagnosing tuberculosis ranged from 15 to 60 IU/L, being the median value between 40 and 50 IU/L. Compared with other etiologies, patients with tuberculous joint infection had greater values of adenosine deaminase activity in every study, but there was some overlap in cases with septic arthritis (Table 2).

Diagnostic accuracy of adenosine deaminase for tuberculous arthritis

The sensitivity of adenosine deaminase in synovial fluid ranged from 86% (95% CI, 64–97) to 100% (95% CI, 86–100). The pooled

Table 1
Characteristics of studies included in the meta-analysis.

Author [ref.]	Year	Country	Type of study	N° of subjects included	N° of subjects analyzed	ADA assay method	ADA cut-off point	TB cases (%)	TP	FP	FN	TN
Telenti[13]	1991	Spain	Retrospective	15	15	Galanti–Giusti	ND	1 (7)	1	0	0	15
Kumar[14]	1994	India	Retrospective	95	75	Galanti–Giusti	10 μm/L	25 (33)	25	0	0	50
Gupta[15]	2010	India	Prospective	30	30	Galanti–Giusti	40 U/L	21 (70)	18	3	3	6
Foocharoen[16]	2011	Thailand	Prospective	40	36	Galanti–Giusti	31 U/L	6 (17)	6	0	1	28
Sharma[17]	2015	India	Prospective	122	83	Enzymatic method	51 U/L	53 (64)	51	9	2	21
Sohn[18]	2021	South Korea	Retrospective	43	43	ADA N kit	60 U/L	9 (21)	9	8	0	26
Kawle[19]	2021	India	Ambispective	36	23	Galanti–Giusti	15 U/L	8 (35)	7	2	1	13

ND: not described. TP: true positive. FP: false positive. FN: false negative. TN: true negative.

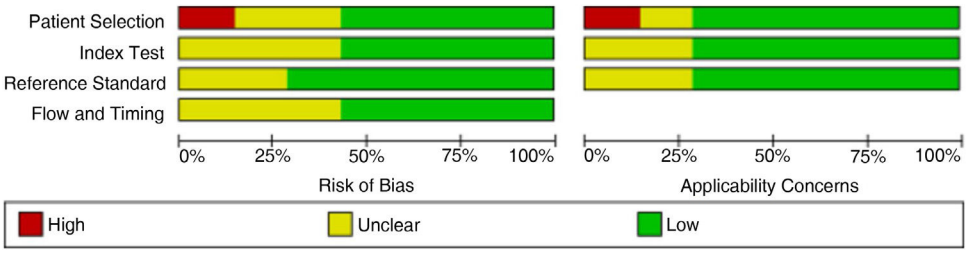

Fig. 2. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

Table 2
Adenosine deaminase activity (U/L), mean ± SD or median [range], in synovial fluid according etiology.

Studies included in meta-analysis	Tuberculosis arthritis	Septic arthritis	Rheumatoid arthritis	Crystal-induced arthritis	Osteoarthritis	Post-traumatic arthritis	Miscellaneous arthritis
Telenti[13]	91	30.5 [28–33]	ND	25 [17–37]	16	21.2 [16–26]	ND
Kumar[14,a]	14.0 ± 2.3	3.9 ± 0.25	8.9 ± 0.69	ND	5.5 ± 0.74	4.9 ± 0.23	ND
Gupta[15]	88 [46–156]	ND	ND	ND	ND	ND	27.2 [25–32.6]
Foocharoen[16]	35.7 ± 10.4	23.7 ± 5.9	16.8 ± 11.7	15.0 ± 12.1	ND	ND	ND
Sharma[17]	146.5 ± 116.7	ND	ND	ND	ND	ND	55.0 ± 48.4
Sohn[18]	108 [76–150]	119.8 [23–250]	ND	ND	ND	ND	31.5 [11–60]
Kawle[19]	17 [11–35]	ND	ND	ND	ND	ND	8 [3–12]

ND: not determined.
[a] Adenosine deaminase activity in μm/L.

sensitivity was 94% (95% CI, 89–98; I^2 = 23.2%) and the specificity ranged from 67% (95% CI, 30–93) to 100% (95% CI, 93–100) (Fig. 3a). The pooled specificity of adenosine deaminase was 88% (95% CI, 83–92; I^2 = 83%) (Fig. 3b). There was substantial heterogeneity of specificity but not of sensitivity. The AUC of the SROC was 0.96 (95% CI, 0.92–0.99) (Fig. 4). We explored the heterogeneity among studies using subgroup and meta-regression analyses on predefined subgroups of quality of the study (High = 1 vs Low = 0), type of assay (Galanti–Giusti = 1 vs. another type of assay = 0), and country of study (India = 1 vs. another country = 0). We did not find heterogeneity among the studies according to the predefined subgroups.

Discussion

Our meta-analysis included 7 studies (305 patients) quantifying adenosine deaminase in synovial fluid with comparisons to the clinical reference standard for the diagnosis of tuberculous arthritis.[13–19] The Galanti–Giusti method,[20] was used to assess adenosine deaminase activity in most studies. However, the cut-off point of adenosine deaminase activity for the diagnosis of tuberculosis varied across the publications, being 40–50 IU/L the median value. The pooled sensitivity and specificity were 94% (95% CI, 89–98) and 88% (95% CI, 82–92), respectively. The meta-analysis showed homogeneity for pooled sensitivity but significant heterogeneity for the specificity of the test.

Regarding specificity, the activity of adenosine deaminase in synovial fluids is also elevated in other conditions besides tuberculosis. We found a decreasing gradient in adenosine deaminase activity from arthritis caused by tuberculosis and bacterial infections through rheumatoid arthritis, crystal arthritis, and finally osteoarthritis. We found in some cases of overlap of adenosine deaminase activity between tuberculosis and septic arthritis[13,19]; therefore it is necessary to routinely include biochemical analysis and culture as part of the diagnostic procedures.

We analyzed the possible sources of heterogeneity in the analysis of the specificity of the adenosine deaminase test. Some of the studies were prospectively conducted and others were retrospective, which could have an impact on the selection of patients. Also, the reference standard could have varied among the articles included. Most studies used a composite of clinical, histological, microbiological, and response to therapy criteria, but the proportion of cases with a confirmed infection by microbiological methods was unknown. Publication bias was not assessed since at present there is no recognized and accepted statistical method for quantifying the potential publication bias in diagnostic studies.[21] The direction of the study, variations in the components of the clinical reference standard, and publication bias could explain some sources of heterogeneity. To assess the origin of heterogeneity we carried out subgroup and meta-regression analyses focused on the quality of the study, country, and type of assay. After carrying out metaregression analysis according to the aforementioned subgroups we could not identify the source of heterogeneity. The availability of data in the publications did not permit the analysis of other potential sources of heterogeneity.

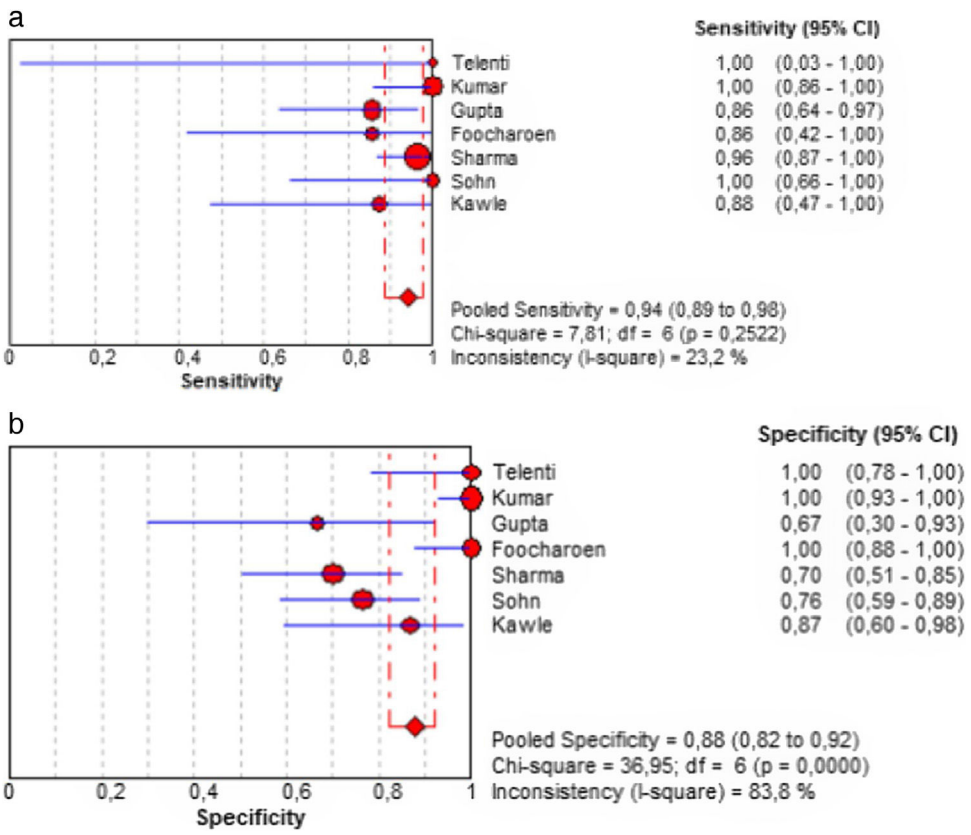

Fig. 3. (a) Pooled sensitivity. (b) Pooled specificity.

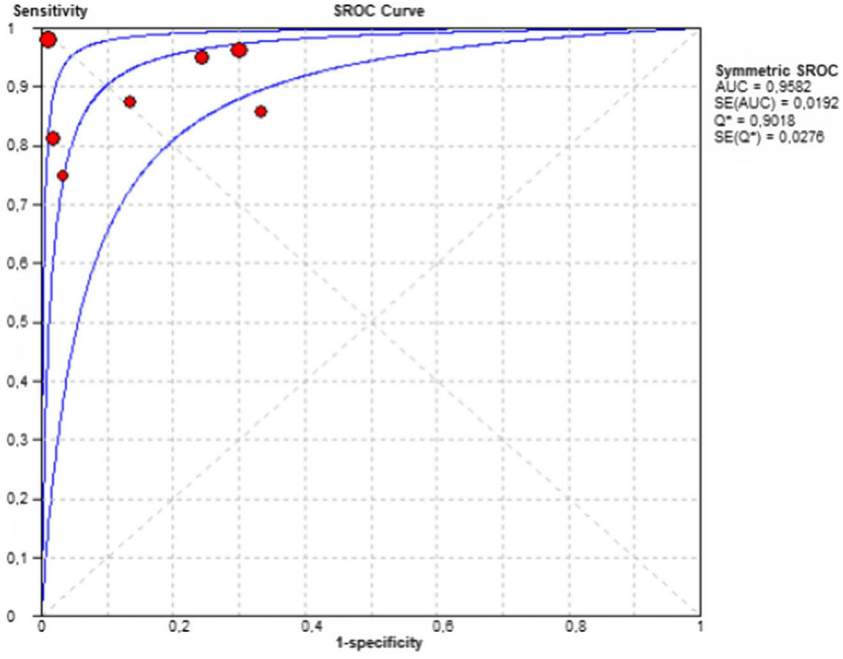

Fig. 4. Area under the receiver operating characteristic of synovial ADA for tuberculous arthritis detection compared with a composite reference standard.

There are no direct comparisons between the diagnostic performances of adenosine deaminase and Xpert MTB/RIF in synovial fluid for the diagnosis of tuberculosis joint infection. In the meta-analysis carried out by Shen et al., the pooled sensitivity and specificity of Xpert MTB/RIF were 81% and 99%, respectively.[22] In our study adenosine deaminase showed slightly better sensitivity of 94% with some poorer specificity of 88%. Compared with Xpert MTB/RIF, adenosine deaminase assessment has the disadvantage of not providing information on the susceptibility of Mycobacterium tuberculosis to rifampin in case of a positive result.

Besides Xpert MTB/RIF, other nucleic acid amplification techniques are targeting the mpb64 and IS6110 genes. Combining the

results of IS6110 RT PCR and mpb64 RT PCR improved the overall sensitivity and hence mpb64 can be used as an additional target for diagnosis of extrapulmonary tuberculosis.[23] However, due to the simplicity and availability of adenosine deaminase assays they can be used as complementary information to nucleic acid amplification techniques.

In summary, measuring the activity of adenosine deaminase in synovial fluid is easy, cheap, and available in areas with poor resources. Adenosine deaminase activity values above the cut-off point add significant diagnostic information to start empirical treatment against tuberculosis while waiting for synovial fluid Lowenstein culture results. Adenosine deaminase activity in synovial fluid can be used as an additional tool for the diagnosis of tuberculosis joint infection in cases of negative results from nucleic acid amplification methods.

Authors' contributions

This manuscript is co-authored by JCCQ, JB, JR, and JE (conception and design, analysis and interpretation of data, and writing of manuscript). All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval consent was waived. All the data presented in this review is from previously published studies.

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Conflict of interest

They authors declare that they have no conflict of interest.

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