

OBJECTIVES

1. To determine the usefulness of Adenosine Deaminase (ADA) levels in synovial fluid (SF) in the diagnosis of tuberculous arthritis.
2. To obtain a diagnosis of joint tuberculosis early and correctly, in order to reduce disability, preventing a delay in diagnosis that can lead to joint destruction, joint deformity and even paraplegia.

METHODOLOGY

- **Type of study:** Meta-análisis
- **Literature search:** Studies published in databases (MEDLINE, Embase, Cochrane Library, Web of Science and MedRxiv) on ADA as a tool to diagnose synovial tuberculosis.
- **Publication period:** January 1986 - October 2021
- **Inclusion criteria:** Seven original full-text studies that assessed the diagnostic accuracy of ADA activity for synovial tuberculosis were included. Articles provided true positive, false positive, false negative, and true negative values or included the data needed to calculate them.
- **Data Synthesis and Statistical Analysis:** Estimated pooled sensitivity and specificity of ADA activity in SF associated with the 95% confidence interval (CI), versus culture or pooled reference standard, were calculated using bivariate random effects. Forest plots for sensitivity and specificity were generated with each study. Areas under summary receiver operating characteristic (SROC) were then calculated. I^2 statistics were used to assess heterogeneity between studies.

RESULTS

We included seven independent studies (N = 305 subjects) that compared ADA activity in SF with a composite reference diagnostic method for tuberculosis. In general, studies were classified as high quality (n = 3, 148 subjects) and low quality (n = 4, 157 subjects). The cut-off values of ADA for diagnosing tuberculosis ranged from 15 to 60 IU/L, being the median value between 40-50 IU/L. The pooled sensitivity and specificity of ADA activity measurement was 94% (95% CI, 89-98; $I^2=23\%$) and 88% (95% CI, 83-92; $I^2= 83\%$), respectively. The area under the ROC curve was 0.96 (95% CI, 0.92-0.99).

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

| Author | Year | Country | Type of study | No. of Subjects included | No. of subjects analyzed | ADA assay Method | ADA Cut-off point | TB cases, (%) | TP | FP | FN | TN |
|------------|------|-------------|---------------|--------------------------|--------------------------|------------------|-------------------|---------------|----|----|----|----|
| Telenti | 1991 | Spain | Retrospective | 15 | 15 | Galanti-Giusti | ND | 1 (7) | 1 | 0 | 0 | 14 |
| Kumar | 1994 | India | Retrospective | 95 | 75 | Galanti-Giusti | 10 µm/L | 25 (33) | 25 | 0 | 0 | 50 |
| Gupta | 2010 | India | Prospective | 30 | 30 | Galanti-Giusti | 40 U/L | 21 (70) | 18 | 3 | 3 | 6 |
| Foocharoen | 2011 | Thailand | Prospective | 40 | 36 | Galanti-Giusti | 31 U/L | 6 (17) | 6 | 0 | 1 | 28 |
| Sharma | 2015 | India | Prospective | 122 | 83 | Enzymatic method | 51 U/L | 53 (64) | 51 | 9 | 2 | 21 |
| Sohn | 2021 | South Korea | Retrospective | 43 | 43 | ADA N kit | 60 U/L | 9 (21) | 9 | 8 | 0 | 26 |
| Kawle | 2021 | India | Ambispective | 36 | 23 | Galanti-Giusti | 15 U/L | 8 (35) | 7 | 2 | 1 | 13 |

ND: Not described. TP: True positive. FP: False negative. FN: True negative

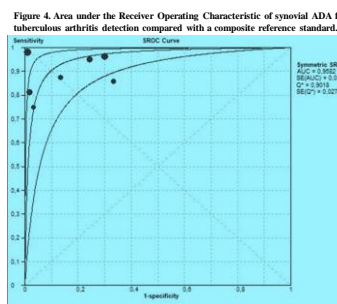
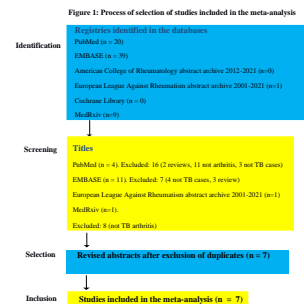


Figure 2: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

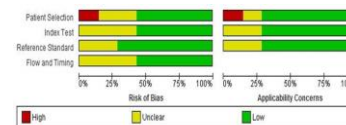


Figure 3a: Pooled sensitivity

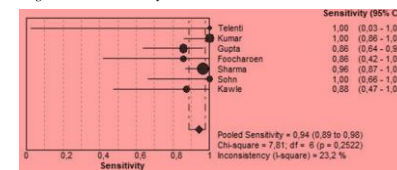
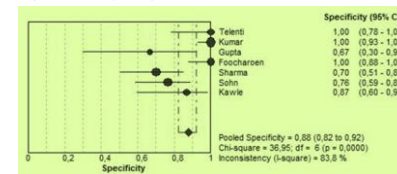


Figure 3b: Pooled specificity



CONCLUSIONS

1. Measuring adenosine deaminase (ADA) activity in synovial fluid (SF) is easy, inexpensive, and available in resource-poor areas.
2. ADA activity values above the cut-off point provide important diagnostic information to initiate empirical treatment of tuberculosis while awaiting the results of the Lowenstein culture of the SF..
3. ADA activity in the SF can be used as an additional tool for the diagnosis of tuberculous joint infection in cases of negative results of nucleic acid amplification methods.