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Diagnostic Accuracy of Ascitic Fluid IFN-γ and Adenosine Deaminase Assays in the Diagnosis of Tuberculous Ascites

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ABSTRACT

In this study, we evaluated the diagnostic accuracy and cost-effectiveness of ascitic fluid interferon-γ (IFN-γ) and adenosine deaminase (ADA) assays in the diagnosis of tuberculous ascites. Ascitic fluid from patients with proven tuberculosis (TB) ($n = 31$) and non-TB ascites ($n = 88$) was analyzed for IFN-γ and ADA levels. Areas under the receiver operative characteristic (ROC) curves (AUCs) for the two biologic markers were compared. Levels of ascitic fluid IFN-γ, median (range): 560 (104–1600) pg/mL vs. 4.85 (0–320) pg/mL ($p < 0.001$), and ADA, median (range): 58 (16–331) IU/L vs. 10 (0–59) IU/L ($p < 0.001$), were significantly different between TB and non-TB groups. IFN-γ and ADA assays showed equal sensitivity (0.97) and differed marginally in specificity (0.97 vs. 0.94). Difference in AUCs was not significant (0.99 vs. 0.98, $p = 0.62$). For differentiating TB from non-TB ascites, optimal cutoff points were 112 pg/mL for IFN-γ and 37 IU/L for ADA. The accuracy of the ADA assay was similar to that of the IFN-γ assay in differentiating of TB from non-TB ascites. Because both material and human costs of the ADA assay are far less than those of the IFN-γ assay, the former is probably the most appropriate diagnostic test for analysis of peritoneal fluid in resource-limited settings.

INTRODUCTION

TUBERCULOSIS (TB) REMAINS ONE of the major killers in the developing world. As the HIV epidemic continues to expand and as global initiatives aimed at treating sputum-positive pulmonary TB become more effective, extrapulmonary TB (EPTB) has grown, in both relative and absolute terms.[1] EPTB accounts for 15%–20% of the total TB cases in the HIV-negative population, whereas the EPTB proportion increases to >50% in the HIV-positive population. Abdominal TB constitutes about 3% of EPTB cases.[2] TB ascites is one of the clinical signs of abdominal TB, which is the sixth most common forms of EPTB.[3] It carries a high fatality rate if not detected early and adequately treated with antituberculosis treatment (ATT).[4,5] Unfortunately, laboratory diagnostic modalities for this disease are limited, and its varied clinical presentation makes the diagnosis difficult.[3] Thus, a large proportion of TB ascites goes undetected until it reaches an advanced and difficult to treat stage.[3] Evaluation of existing technologies and development of new ones are urgently required to control this epidemic.

Demonstration of *Mycobacterium tuberculosis* in ascitic fluid by microscopy or culture is inconclusive and can delay the diagnosis.[6] Histologic studies have been shown to be more sensitive than microscopy or culture,[7] but these may not be available at all health care facilities and have an associated risk of complications. Easily measurable markers in ascitic fluid obtained from the relatively simple procedure of paracentesis are, therefore, of great interest but have been understudied. Here, we directly compare the efficacy of two such markers, adenosine deaminase (ADA) and interferon-γ (IFN-γ), in the diagnosis of TB ascites. ADA is an enzyme of the purine salvage pathway that plays an important role in the proliferation of lymphocytes during the cellular immune response.[8] The enzyme levels in the pleural fluid are often used to diagnose TB pleural effusion.[9,10] Raised ADA levels in pericardial and cerebrospinal

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fluids may be a marker of TB pericarditis[11] and TB meningitis,[12] respectively. Elevated ADA level in ascitic fluid have been found to be helpful in the diagnosis of TB ascites.[13–17]

In response to infection by *M. tuberculosis*, the body initiates an immunologic cascade involving secretion of various cytokines and recruitment of Th1 lymphocytes. Following recruitment of these cells in high numbers at the morbid site, levels of various cytokines, including IFN-γ, are markedly elevated.[18–20] Several studies from different parts of the world have demonstrated the efficacy of IFN-γ in the diagnosis of TB pleural[21,22] and pericardial effusions,[23] and its diagnostic efficacy in TB pleural effusion has been compared with that of ADA in terms of cost-effectiveness.[24] There are fewer studies evaluating the role of IFN-γ in the diagnosis of TB ascites.[25–27] These studies compare its diagnostic efficacy with that of ADA in the diagnosis of TB ascites, but there are no studies to compare the cost-effectiveness of the two markers.

Among these studies, there is no concordance in the cutoff levels for diagnosis of TB ascites. This has been attributed to a variable cytokine response in patients with TB, possibly owing to malnutrition,[28] associated asymptomatic parasitic infestations,[29] and the severity of the disease.[30] Also, there is a lack of studies evaluating the diagnostic efficacy of IFN-γ in patients from the developing world. These areas are unique because of the high prevalence in the population of poor nutritional state. It is, therefore, imperative to conduct a study among TB ascites patients from resource-limited countries to determine the diagnostic efficacy and appropriate cutoff levels of IFN-γ in ascitic fluid. This study aims at assessing the diagnostic efficacy and cost-effectiveness of ascitic fluid IFN-γ and ADA levels among TB patients.

MATERIALS AND METHODS

The study was conducted at the All India Institute of Medical Sciences (AIIMS), a large tertiary care hospital in Delhi, India. This was a cross-sectional study designed to prospectively evaluate consecutive patients with ascites who came to the general medical outpatient department or were admitted to the inpatient medical wards of AIIMS during the period from November 2003 to May 2005. Informed written consent was obtained from each patient prior to their participation in the study.

One hundred forty-eight consecutive patients with evidence of ascites on clinical examination or ultrasonography were screened. To avoid any presumed confounding effect of comorbid conditions and to have a uniformity among the study subjects, 24 patients were excluded from study: 11 patients had received ATT for more than 2 weeks before coming to our hospital, 5 patients were receiving corticosteroids or immunosuppressive drugs for various indications, 6 patients showed evidence of liver failure, and 2 patients had renal failure. Additionally, 5 patients were excluded because *M. tuberculosis* could not be demonstrated in various clinical samples despite a successful response to ATT started after a possible clinical diagnosis of TB. Following all exclusions, 119 of the original 148 patients (80.4%) were entered into the evaluation phase.

Each patient was evaluated in detail by eliciting the relevant clinical history and performing a thorough physical examination. Anthropometric data, including body mass index (BMI), triceps skin-fold thickness, and midarm circumference, were recorded for all patients. Complete hemogram, serum total protein and albumin determination, chest radiographs, and sputum smear examination for *M. tuberculosis* were performed. A Mantoux test was done using an intradermal injection of 5 tuberculin units (TU) of purified protein derivative (PPD), assessed using standard measures at 48 h. Serologic tests for HIV were performed for all patients using ELISA, as described previously.[31]

Paracentesis was done in all patients, and ascites fluid was analyzed for albumin and sugar levels, cytology, gram stain and bacterial culture, Ziehl-Neelsen (ZN) staining, and culture for *M. tuberculosis.* Based on the results of paired serum and ascites fluid albumin levels, patients were classified as having low gradient ascites (serum/ascitic fluid albumin gradient [SAAG] <1.1g/dL) or high gradient ascites (SAAG ≥ 1.1g/dL) and were subjected to further diagnostic workup to determine the etiology depending on clinical suspicion.[32] In patients with concurrent pleural effusion, pleural fluid smear and culture for *M. tuberculosis* were performed to look for evidence of TB in the chest.

Diagnosis of TB ascites was based on one or more of the following: (1) demonstration of *M. tuberculosis* in centrifuged peritoneal fluid or biopsy specimen of peritoneum or peripheral lymph node by ZN staining, (2) positive culture of *M. tuberculosis* from peritoneal fluid, (3) demonstration of caseating granulomas in the peritoneal biopsy or lymph node biopsy specimens, and (4) low gradient ascites along with evidence to prove the presence of TB in other organs by positive sputum/pleural fluid smear or culture for *M. tuberculosis*, demonstrated by ZN staining.

Diagnosis in the non-TB group was based on peritoneal fluid cytology, biochemical analysis of ascites fluid, ultrasonography or CT scan of the abdomen, upper gastrointestinal endoscopy, liver biopsy, or diagnostic laparoscopy.

Ascitic fluid samples were analyzed for IFN-γ levels using ELISA, following the manufacturer's instructions (Predicta Human Cytokine ELISA plates, Genzyme Diagnostics, Cambridge, MA), which are described elsewhere.[33] Briefly, solid-phase enzyme immunoassay was employed using the multiple antibody sandwich principle. ELISA plates precoated with antibody by the manufacturing company were used. ADA levels were estimated using the method originally described by Guisti.[34] All determinations were carried out by a trained technician who was blinded to the patients' clinical profile at presentation as well as the eventual diagnosis. The principal investigator responsible for recruitment of patients was also blinded to the results of the IFN-γ and ADA assays.

Statistical analysis

All the data were recorded electronically and analyzed using STATA 7.0 (intercooled version, Stata Corporation, Houston, TX) statistical software. All entries were double-entered by separate data technicians. Data were described using the mean with standard deviation (SD) for normally distributed variables. Median with range was used to summarize ADA as well as IFN-γ levels, as they were not normally distributed. The

TABLE 1. CHARACTERISTICS OF PATIENTS IN THE STUDY

Variable	*TB group* (n = *31*)	*Non-TB group* (n = *88*)
Age (years)[a]	35.0 ± 14.5	45.8 ± 14.3
Sex (male/female)	11/20	65/23
Body mass index (kg/m2)[a]	19.5 ± 3.9	19.1 ± 3.9
Midarm circumference (cm)[a]	21.5 ± 3.5	22.5 ± 3.8
Triceps skin-fold thickness (mm)[a]	7.4 ± 1.2	7.8 ± 2
Mantoux test (>10 mm), *n* (%)	13 (41.9)	13 (14.7)
Ascitic fluid ADA (IU/L)[b]	58 (16–331)	10 (0–59)
Ascitic fluid IFN-γ (pg/ml)[b]	560 (104–1600)	4.85 (0–320)

[a]Variables shown as mean ± SD.
[b]Variables shown as median (range).

study group was divided into TB and non-TB patients on the basis of the etiology of ascites. To test for significance, independent sample *t*-tests were applied for normally distributed variables, whereas the Mann-Whitney U-test was applied for variables having nonnormal distributions. Sensitivity and 1-specificity were plotted for various cutoff levels of ADA and IFN-γ to construct the receiver operative characteristic (ROC) curve. The areas under the ROC curves (AUCs) were used to compare the diagnostic efficacy of ADA and IFN-γ levels. The proportion of subjects identified correctly as well as incorrectly by both the assays was computed using AUCs, and these proportions were compared using Pearson's chi-square test. Statistical significant was considered at $p < 0.05$.

Cost assessment

For the cost assessment, cost of reagents and kits of ADA and IFN-γ were determined from their supply source. Human resource and laboratory equipment costs were not estimated owing to their complexity. This biased the cost-effectiveness calculation in favor of IFN-γ, which requires greater baseline laboratory and human resource capacity.

RESULTS

All patients were seronegative for HIV. Of 119 patients included in the study, 31 were found to have TB. All 31 TB patients had low gradient ascites (SAAG < 1.1 g/dL). Of 31 TB patients, 5 had positive peritoneal fluid culture for *M. tuberculosis*, 6 had peritoneal biopsy, and 10 had peripheral lymph node biopsy specimens showing *M. tuberculosis* and caseating granulomas. Ten patients had evidence of TB in other organs, with *M. tuberculosis* in the sputum smear in 9 patients and in both sputum and pleural fluid smears in 1 patient.

Among the 88 patients who did not have TB, 68 were diagnosed with chronic liver disease secondary to chronic hepatitis B or C viral infection or chronic alcoholism, 13 with malignancy, and another 7 with ascites from various miscellaneous causes, such as nephrotic syndrome (4 patients), acute pancreatitis (1 patient), acute Budd-Chiari syndrome (1 patient), and congestive heart failure (1 patient).

Table 1 compares the clinical and demographic profiles, as well as the ascitic fluid ADA and IFN-γ levels, between the TB and non-TB groups. Patients with TB ascites were significantly younger than those of the other group ($p = 0.001$). The male/female ratio of the TB group was significantly lower than that of the non-TB group ($p = 0.001$). Between TB and non-TB groups, significant differences in the levels of IFN-γ, median (range): 560 (104–1600) pg/mL vs. 4.85 (0–320) pg/mL ($p < 0.001$), and ADA, median (range): 58 (16–331) IU/L vs. 10 (0–59) IU/L ($p < 0.001$), were observed.

Figure 1 shows ROC curves to compare ADA and IFN-γ levels in the two groups of patients. The AUCs for both of the markers were quite high, although the AUC of IFN-γ (0.991, 95% CI 0.98–1.00) was marginally greater than that of ADA (0.975, 95% CI 0.95–0.999) ($p = 0.62$). The best cutoff was taken at the point where the curve sharply angulated. It was found to be 112 pg/mL for IFN-γ and 37 IU/L for ADA. At the set threshold level for the studied population, true and false positive as well as negative rates and the related statistics on the predictive value of these markers are detailed in Table 2. For the best cutoff value, both the markers had a sensitivity of 0.97, whereas IFN-γ showed a specificity of 0.97, which was higher than that of ADA, which was 0.94.

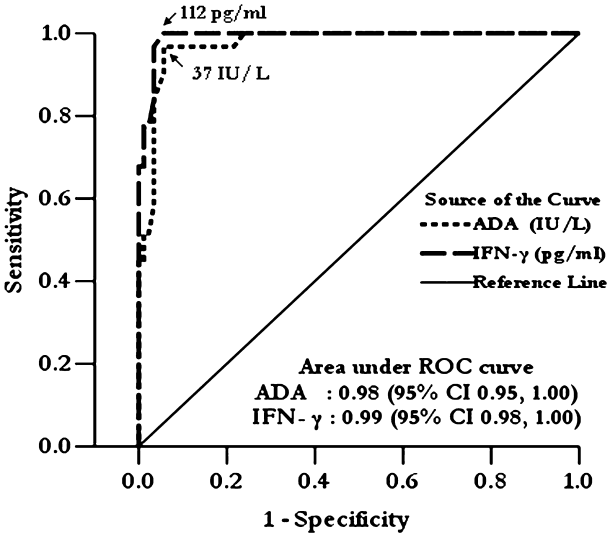

FIG. 1. ROC curves for ascitic fluid ADA and IFN-γ levels in the diagnosis of TB ascites. Arrows denote the cutoff values.

Table 2. Diagnostic Utility of ADA and IFN-γ Estimation in Differentiating TB vs. non-TB Ascites

Characteristic	*ADA*	*IFN-γ*
True negative	83	85
True positive	30	30
False positive	5	3
False negative	1	1
Sensitivity (95% CI)	96.8 (90.6, 100)	96.8 (90.6, 100)
Specificity (95% CI)	94.3 (89.5, 99.2)	96.6 (92.8, 100)
Positive predictive value (95% CI)	85.7 (74.1, 97.3)	90.9 (81.1, 100)
Negative predictive value (95% CI)	98.8 (96.5, 100)	98.8 (96.6, 100)
Accuracy (95% CI)	94.9 (91.0, 98.9)	96.6 (93.4, 99.9)
Area under ROC curve (95% CI)	0.975 (0.950, 0.999)	0.991 (0.980, 1.000)

As both the tests showed equal sensitivity of 0.97, there was no difference in terms of number of true positives detected. However, the ADA assay led to the detection of two more false positives than did the IFN-γ assay. This resulted in the higher specificity of the IFN-γ assay (0.97) compared with that of the ADA assay (0.94); this difference was marginal, however.

The cost of each test for the ADA assay was found to be about Rs. 20 (US$0.45), whereas that for one IFN-γ assay was around Rs. 900 (US$20.45).

DISCUSSION

We observed the ascitic fluid ADA assay to be a good diagnostic tool for TB ascites, in accordance with previous studies.[13–15,35–37] It was equivalent to the IFN-γ assay in terms of sensitivity, specificity, and AUC. Because the performance characteristics do not significantly differ and the ADA assay is far cheaper, this should be the test of choice in most clinical scenarios in resource-limited settings. Without compromising diagnostic accuracy, the ADA test can deliver timely results at a fraction of the cost.

Even in resource-poor settings, however, there may be instances in which the IFN-γ assay is particularly useful. In this study, the IFN-γ assay was marginally more specific, although not significantly so. If higher specificity is demonstrated in larger studies with higher power, there may be settings in which the IFN-γ assay should be used in spite of the cost. This may be particularly relevant to patients with occult malignancy, for whom a wrong diagnosis of TB ascites can cause a devastating delay in therapy. Such a clinical scenario is quite common in India, where the clinical suspicion for TB is high, and a single standard test confirming the presumed diagnosis of TB may be sufficient to start ATT, especially if the preliminary workup for malignancy is unrevealing. In addition to bearing the cost of ATT, patients with false diagnoses of TB may be exposed to undue risk of ATT-induced side effects, such as hepatotoxicity, peripheral neuropathy, hyperuricemia, and thrombocytopenia.

In addition to the actual material costs involved in the IFN-γ assay, there are many other factors that can make the difference in cost between IFN-γ and ADA assays more significant. The ADA assay requires a simple spectrophotometer, whereas the IFN-γ assay requires an ELISA reader, which is a sophisticated and much costlier instrument than the former. The IFN-γ assay also requires greater technical expertise than does the ADA assay. These factors render the difference in cost difficult to standardize, but the existing difference is likely to be even more than the material costs presented in this study. Such costs could be offset if the IFN-γ test were found to be much more specific than the ADA test. Comprehensive anti-TB care requires huge monetary and human resources and has potentially toxic effects. More operational research is required in this subject area. The results of this study, however, indicate that in most cases the ADA assay will be the diagnostic test of choice.

A modified method of IFN-γ assay has recently become available, which involves coating the ELISA plates with antibodies in the laboratory instead of using the manufacturer's precoated ELISA plates. Using this method, the cost of one IFN-γ assay comes out to be Rs. 100 (US$2.3) which is nine times less than the previous method. Although the manpower and the expertise required using this method are greater than when using precoated ELISA plates, the ADA assay cost remains five times less than that of the IFN-γ assay. If we take the new cost into account, the difference between two biologic markers in terms of cost-effectiveness units becomes marginal. Thus, if the cost of the IFN-γ assay can be reduced further, this may prove to a valuable as well as cost-effective tool in the diagnosis of TB ascites, especially in developing nations, which carry an increased burden of the disease.

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