

Original Article

Evaluation of adenosine deaminase in the diagnosis of pleural tuberculosis: a Brazilian meta-analysis*

Avaliação da adenosina desaminase no diagnóstico da tuberculose pleural: uma metanálise brasileira

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Abstract

Objective: To evaluate Brazilian studies by summarizing the accuracy of adenosine deaminase in the diagnosis of the pleural tuberculosis, with the objective of lending support to the movement to make the test part of the routine in the investigation of pleural effusions.

Methods: A search for Brazilian studies related to the determination of adenosine deaminase levels in the pleural liquid was carried out. These studies were evaluated and included in this study. The data were analyzed using summary receiver operating characteristic (SROC) curves, which enabled the studies to be collected and evaluated regarding the accuracy of the diagnosis. As for the global values of sensitivity and specificity, the Bayes' theorem was applied to calculate the post-test probabilities in different prevalences of the disease. **Results:** Twenty-five studies dating from 1987 to 2005 and including enough information to be used in the meta-analysis were identified. After evaluation, nine studies were included, totaling 1674 patients. According to the SROC curve, a sensitivity of 91.8% (95% CI: 89.8-93.6%) and a specificity of 88.4% (95% CI: 86.0-90.5%) were found, with an area of 0.969 below the curve. The overall odds ratio was 112.0 (95% CI: 51.6-243.2). Considering a prevalence of tuberculosis of 50% (considered neutral), the post-test probability was 88.7% for a positive test and 91.5% for a negative test. **Conclusion:** Despite the differences found among studies, it is possible to conclude that the determination of adenosine deaminase levels has high accuracy in the diagnosis of the pleural tuberculosis and should be used as a routine test in its investigation.

Keywords: Pleural effusion; Tuberculosis; Diagnosis; Adenosine deaminase; Meta-analysis.

Resumo

Objetivo: Avaliar trabalhos brasileiros resumindo a acurácia da adenosina desaminase no diagnóstico da tuberculose pleural, com o intuito de contribuir para a concretização do exame como rotina na investigação dos derrames pleurais. **Métodos:** Depois de realizada uma busca por trabalhos brasileiros referentes à dosagem da adenosina desaminase no líquido pleural, estes foram avaliados e incluídos no estudo. A análise dos dados foi feita por meio da curva *summary receiver operating characteristic* (SROC) que possibilitou a reunião dos estudos quanto a acurácia para o diagnóstico. Com os valores globais de sensibilidade e especificidade foi aplicado o teorema de Bayes para calcular as probabilidades pós-teste em diferentes prevalências da doença. **Resultados:** Entre 1987 e 2005 foram encontrados 25 estudos contendo informações suficientes que poderiam ser utilizadas na metanálise. Após avaliação, foram incluídos nove estudos, totalizando 1.674 pacientes. De acordo com a curva SROC, foi encontrada uma sensibilidade de 91,8% (IC95%: 89,8-93,6%) e uma especificidade de 88,4% (IC95%: 86,0-90,5%), com uma área abaixo da curva de 0,969. O *odds ratio* global foi de 112,0 (IC95%: 51,6-243,2). Considerando uma prevalência da tuberculose pleural de 50% (considerada neutra), a probabilidade do diagnóstico pós-teste positivo é de 88,7% e sua exclusão após resultado negativo de 91,5%. **Conclusões:** Apesar das diferenças encontradas entre os estudos, é possível concluir que a adenosina desaminase possui alta acurácia no diagnóstico da tuberculose pleural, devendo ser utilizada de rotina em sua investigação.

Descritores: Derrame pleural; Tuberculose; Diagnóstico; Adenosina desaminase; Metanálise.

Introduction

According to the World Health Organization, 9 million people developed tuberculosis in the year 2004. Of those, 3.9 million were cases of active tuberculosis, and 741,000 were co-infected with HIV. In Brazil, the prevalence of the disease is approximately 77 cases per 100,000 inhabitants.⁽¹⁾

In Brazil, tuberculosis is the principal cause of exudative pleural effusion, and the extrapulmonary form is the form most commonly seen in adults.⁽²⁻⁴⁾ The methods currently considered the gold standards in the diagnosis of tuberculosis in the pleural fluid have many problems: low positivity

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rates in the direct testing for acid-fast bacilli (AFB), with sensitivity ranging from 0 to 30%⁽⁵⁾; low sensitivity (20 to 30%); and delay in the results of the *Mycobacterium tuberculosis* culture in the fluid.⁽⁶⁻⁸⁾ The combination of pleural biopsy culture with the histopathological examination has higher sensitivity than do the other methods (50 to 80%), although the pleural biopsy it is more invasive.⁽⁵⁻⁸⁾

In this context, the need to search for new methods that facilitate the diagnosis of pleural tuberculosis arose. Among the many methods which have been studied, the determination of adenosine deaminase (ADA) levels stands out as one of the tests with better yield and lower costs.⁽⁵⁾

An enzyme that participates in the metabolism of purines, ADA is also related to the proliferation of lymphocytes during the cellular response.⁽⁹⁻¹¹⁾ In addition to being a method with low operational cost, the determination of ADA levels is simple and demands little technical training, as well as using affordable reagents, glassware and equipment common to most medium-sized laboratories.^(8,12) Despite the good results of the determination of ADA levels in the pleural fluid already described in the literature,^(2,13-15) it must be borne in mind that ADA levels can be elevated in cases of pleural involvement caused by rheumatoid arthritis, in some types of lymphomas and in most empyemas, as well as in cases of tuberculous effusion.^(7,8,16-18)

The number of publications involving the determination of ADA levels as a diagnostic test for pleural tuberculosis has increased. Therefore, it is necessary to transform this increasing amount of information into knowledge through the collection, organization, critique and analysis of the results. To that end, we adopted the meta-analysis strategy, which allows the findings of individual studies to be extrapolated, evaluating each one of them and increasing the accuracy of the results, thus improving the precision.⁽¹⁹⁾

The aim of this study was to evaluate Brazilian studies, summarizing the accuracy of the determination of ADA levels as a diagnostic test for pleural tuberculosis, with the objective of making the test the test part of the routine investigation of pleural effusion in the Brazilian population.

Methods

The articles were selected after a search of the Latin American and Caribbean Health Sciences

Literature, Scientific Electronic Library Online and Medline databases using the following search string: 'adenosine deaminase' AND 'tuberculosis' AND 'pleural'. We selected studies carried out in Brazil and published in any language. The initial selection criteria were place of publication, language, country of author residence, author affiliation (institution), or, when necessary, all of the above. In addition, the term 'adenosine' was searched in the Lattes platform database (a compilation of researcher resumé, including scientific production, hosted by the Brazilian National Council for Scientific and Technological Development) in order to find the articles related to the criteria above by author. The temporal starting point was as far back as possible according to the availability of each database.

The studies related to the determination of ADA levels in the pleural fluid with the objective of diagnosing tuberculosis in Brazil were selected, reviewed independently by the authors of this study and compared. After listing all of the studies, the ones included were those which provided the quantitative of true positives (TPs), true negatives (TNs), false positives (FPs) and false negatives (FNs), or those which presented the sensitivity and specificity values and the quantitative of the positive or negative diagnosis of pleural tuberculosis, together with the ADA cut-off value used.

Studies published only in abstract form were excluded, as were multiple studies by the same author, only the one with the greatest number of cases being considered, due to the possibility of patient overlap.⁽²⁰⁾ We opted to include as many articles as possible, as long as they meet the eligibility criteria described, because the adoption of rigid criteria in relation to the selection of patients would limit the number of studies. Since there is evidence that ADA levels are not influenced by gender or age, and that ADA levels in the pleural fluid are no different in immunocompromised patients, including HIV-infected individuals, than in immunocompetent individuals,^(4,21) such variables were not considered criteria for exclusion, nor were individuals presenting such factors treated as a specific sub-group.

After the reading, data related to the relevant variables of each study, such as the author and date of the study, were obtained, and the characteristics of the methodology, such as the studied population, type of selection, technique employed to determine

ADA levels, diagnostic criteria and statistical analysis, were noted. When available, these data, together with the cut-off value used, as well as the sensitivity and specificity values, with their respective confidence intervals (CIs), were added to a table. Another table was constructed apart for the observed values of TPs, TNs, FPs and FNs in each study. When the results expressed by the authors did not allow direct extraction of the values mentioned (TPs, TNs, FPs, FNs), these were calculated based on data provided in the text.⁽²²⁻²⁴⁾

As for the analysis of the quality of the selected studies and their grouping in the meta-analysis, it was necessary to evaluate their similarities and to validate them based on three pre-established, multi-faceted criteria:

- appropriate, consecutive selection of the sample, the absence of any bias related to this selection and to the clinic and demographic description of the sample, as well as (for articles published after 1996) the approval of the ethics in research committee of the institution
- appropriate description of the criteria for the gold standard in the diagnosis of pleural tuberculosis, including the presence of histopathological examination, AFB testing or culture, the application of these criteria in all cases and the independent comparison of ADA levels
- results presented in detail with the presence of appropriate statistical treatment, 95% CI or p value, in addition to sensitivity, specificity, cut-off value used, FP values and FN values.⁽²²⁾

In order to make this meta-analysis, studies which met the three criteria, even if only partially, were used. Those that did not meet the criteria were excluded in order to decrease the variability of the sample.

The joint analysis of the different studies was made through the combination of the sensitivity and specificity values of each one, constructing a summary receiver operating characteristic (SROC) curve, which is distinguished from a ROC curve by the fact that each point in the graphic represents a study, rather than the individual values evaluated. Each point in the graphic is constructed with the TP (sensitivity) and FP (or 1 – specificity) values described in each article. To demonstrate the performance of the diagnostic test as a whole,

the area under the SROC curve was calculated. In order to highlight the accuracy of the studies, the Q value, which represents the intercept between the ROC curve and a diagonal line running from the lower right corner to the left upper corner of the graphic, corresponding to the highest common value of sensitivity and specificity, was calculated. Another indicator obtained to evaluate the quality of the test was the odds ratio, calculated on the basis of the sensitivity and specificity values.⁽²²⁻²⁴⁾

The overall sensitivity and specificity values, together with their respective 95% CIs, were also found through the SROC curve. Using these values, we calculated the post-test probability for various, randomly determined prevalences of tuberculosis.

Spearman's correlation coefficient was used to study the influence that the ADA cut-off value used in the different studies had on accuracy.

The choice of the meta-analytic approach depends, in part, on the variability (heterogeneity) observed in the results. When the sensitivity and specificity values are used as points to construct the SROC curve for this method of analysis, some random differences are to be expected. However, the influence of other factors such as patient selection and study design can increase this variability. To evaluate the existence of variability in the sample, each odds ratio, together with its 95% CI, was calculated individually. Each study received a different weight and was evaluated using the chi-square test, values of $p < 0.05$ being considered statistically significant.⁽²²⁾

The data were analyzed using the Meta-DiSc program, version beta 1.1.1 (freeware)⁽²⁵⁾ and the Medcalc program, version 9.0.1.1 (MedCalc Software, Mariakerke, Belgium).

Results

The search of the electronic databases identified twenty-five Brazilian studies in which ADA levels were determined in pleural fluid. All twenty-five were published between 1987 and 2005. Of those, four were excluded for being review articles and not presenting their own data which could be incorporated into this study. Ten were excluded for being by the same authors, due to the possibility of patient overlap, and one was excluded for not meeting the quality criteria adopted. One study was not evaluated due to a lack of access to the full

text. The nine remaining studies allowed the collection of all information necessary for their inclusion. Their principal data are summarized in Table 1, and the accuracy as a diagnostic test is described in Figure 1.^(2,4,21,26-31)

The sum of the studies comprises a sample of 1674 patients. Of those, 857 (51.2%) had tuberculosis, and 817 (48.8%) had effusion of other etiologies. The sensitivity values varied from 68.8 to 100% with a mean of 91.8% (95% CI: 89.8-93.6%) and the specificity varied from 75.8 to 96.9% with a mean of 88.4% (95% CI: 86.0-90.5%). As shown in Table 1, the ADA level cut-off values for the diagnosis of pleural tuberculosis ranged from 30 to 60 U/L, with a mean of 40.7 U/L.

In relation to the quality of the selected studies, only two of the nine rigorously met all three criteria. The others were included because they met partially or completely each of the criteria. Of the nine, three fully met criterion 1 (related to sample selection), six fully met criterion 2 (related to methodology), and eight fully met criterion 3 (related to the presentation of the results). In three of the articles, it was necessary to use other data obtained from the text in order to calculate the TP, FP, TN and FN values, which were then used in constructing the SROC curve.

Figure 2 shows the result of the SROC curve constructed based on the nine studies. Three curves are shown. The central curve corresponds to the true SROC curve, and the peripheral curves to its 95% CIs. The area under the curve was 0.9696, and the Q value was 91.9%. The odds ratio, together with its respective 95% CI and weight, was calculated for each study (Table 2). The overall odds ratio was 112.0 (95% CI: 51.6-243.2).

The test of heterogeneity evaluated through the odds ratio revealed significant variance among the studies ($p < 0.05$). Spearman's correlation coefficient ($R_s = 0.333$) for the ADA cut-off value showed a weak association that was not statistically significant ($p = 0.376$).

As shown in Figure 3, Bayes' theorem was used to calculate the post-test probability of an individual having or not having the disease, presenting a result considered positive or negative, respectively, in relation to different prevalences (pre-test probability). Considering prevalences of pleural tuberculosis of 5, 25, 50 and 85% (understood as very low, low, intermediate and high), respectively, the post-test probability of being diagnosed with pleural tuberculosis and presenting a positive ADA result was 29.4, 72.5, 88.7, 97.8%, whereas that of presenting a negative ADA result and not having pleural tuberculosis was 99.5, 97.0, 91.5 and 65.5%.

Discussion

Due to the high prevalence of tuberculosis in Brazil,^(1,3) and to the difficulties that still exist in diagnosing pleural tuberculosis, it is necessary to investigate new methods that are rapid, efficient, present a favorable cost-benefit ratio and can be performed anywhere in Brazil without great investment.^(5,7,8)

The determination of ADA levels has already been studied in various parts of the world, and nearly all of the authors recommend it as a useful diagnostic test in the investigation of pleural tuberculosis, principally in areas where there is a high prevalence of tuberculosis.^(6,8) Even in countries where the prevalence of the disease is low, the test has been

Table 1 – List of selected articles, according to year of publication, with the principal values evaluated.

Authors	Year	Cut-off (U/L)	TP/FN	FP/TN	Sensitivity (%)	Specificity (%)	Method
Filho FC ⁽²⁹⁾	1987	40	46/0	15/47	100	75.8	Giusti
De Oliveira HG ⁽³⁰⁾	1994	40	51/3	31/191	94.4	86.0	Giusti
Chalhoub M ⁽²⁷⁾	1996	40	140/10	4/58	93.3	93.5	Giusti
Bottini PV ⁽²⁸⁾	1996	45	16/0	2/62	100	97.0	Giusti
De Melo FAF ⁽²⁶⁾	1997	30	251/17	8/141	93.7	94.6	Giusti
Silva Junior CT ⁽³¹⁾	2000	38	97/23	13/82	80.8	86.3	Giusti
Kaisemann MC ⁽²⁴⁾	2004	35	77/6	1/27	92.8	96.4	Giusti
Neves DD ⁽²⁾	2004	39	98/6	19/92	94.2	82.9	Giusti
Bem AF ⁽²³⁾	2005	60	11/5	2/22	68.8	91.6	Giusti

TP: true positive; TN: true negative; FP: false positive; and FN: false negative.

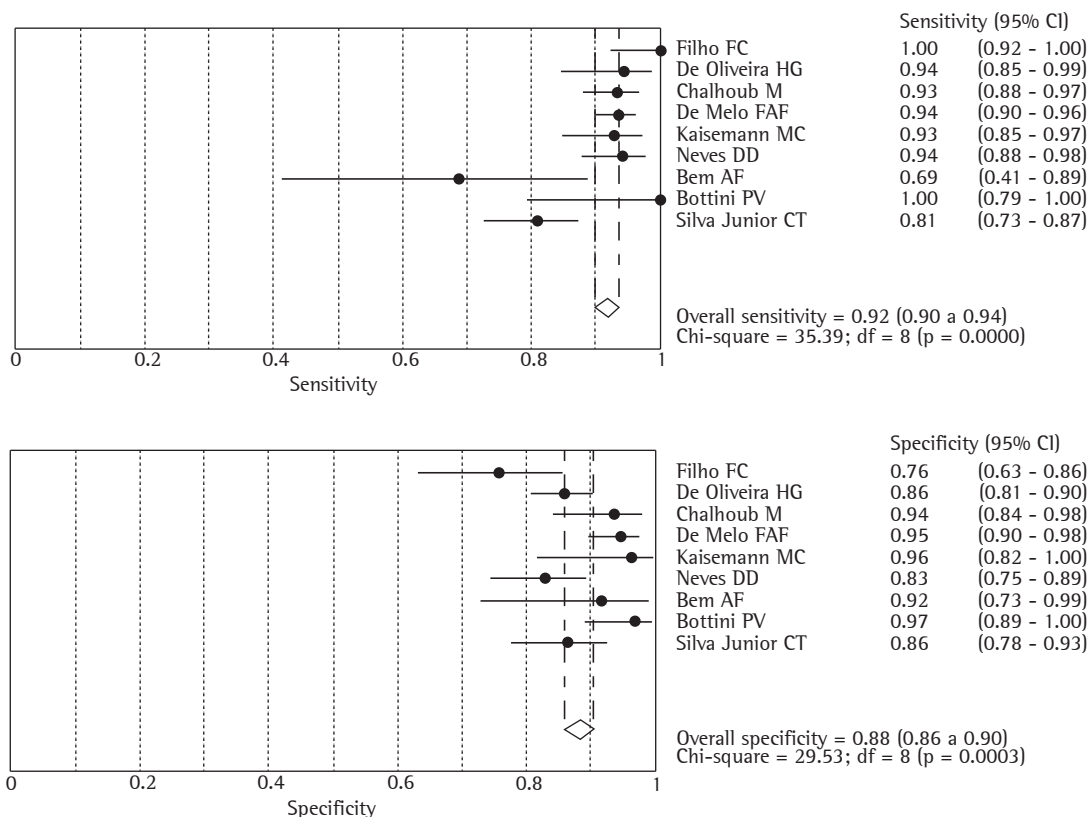


Figure 1 – Sensitivity and specificity values, with confidence intervals.

useful to rule out the diagnosis of tuberculosis and has presented high accuracy for the diagnosis, when compared to other tests employed in the routine investigation.⁽⁸⁾

Many studies regarding the accuracy of determining ADA levels have been carried out in various states in Brazil. However, to date, the determination of ADA levels is not routinely used in Brazil. The present study gathered data from nine Brazilian articles, resulting in this analysis, through which 1674 cases of pleural effusion were evaluated. Of those, 51.2% were caused by tuberculosis. The objective of the study was to promote better understanding of the use of this method in our population.

Due to random factors, the variability among the study results was greater than expected. This can be explained by the differences in methodology, principally in relation to the eligibility criteria (especially the inclusion or exclusion of patients with purulent effusion) and the gold standard chosen (broader or

narrower) for the diagnosis of tuberculosis. However, this variation is not influenced by the cut-off value chosen in the different studies, since only a strong correlation found using Spearman's test would indicate this effect on the overall accuracy of the test.

The variability observed should not be seen as an impediment to the analysis of the results, since the tests of heterogeneity have limitations and must be analyzed carefully, taking into consideration that the variabilities - clinical, methodological and statistical - can still exist even with a judicious selection of the studies. In addition, studies being conducted in distinct circumstances, differing in relation to the type of population, diagnostic criteria, etc., can lead to conflicting results. However, more than being a problem in relation to the homogeneity of the data, the inconsistent results, when analyzed systematically, can provide relevant data regarding the behavior of the test in clinical practice. In order to test the possible interactions of these variables and their influence on accuracy, a study with this objec-

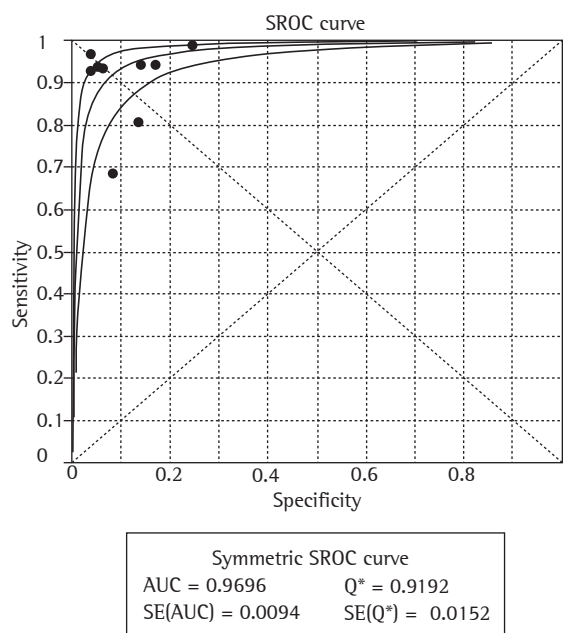


Figure 2 - Summary receiver operating characteristic (SROC) curve constructed using the nine studies selected.

tive and an appropriate design should be carried out.

The SROC curve constructed with the studies included in this meta-analysis proves that ADA is an excellent biochemical marker of pleural tuberculosis. The 0.97 area under the SROC curve (the closer this value is to one, the better the diagnostic test is) and the 112.06 odds ratio (with a small confidence interval) show the reliability of the diagnostic test.

The ADA cut-off value of 40 U/L, in addition to being recommended by the Brazilian Consensus on Tuberculosis, corresponds to the mean obtained from the evaluated studies, and should immediately

be implemented. There is a tendency to use a lower cut-off value (approximately 30 U/L), which would increase sensitivity. From this perspective, a negative result practically rules out the possibility of pleural tuberculosis, and the values considered negative would have to be accompanied by other evidence or test results in order to confirm the diagnosis.

The sensitivity and specificity values (91.8 and 88.4%, respectively) calculated by pooling the data from the analyzed studies, proved the high accuracy of the determination of ADA levels as a diagnostic test, and, consequently, its usefulness in clinical practice. The small 95% CI (less than 5%) obtained for sensitivity and specificity alike shows the sufficiency of the number of evaluations employed in order to make such a statement.

Since the predictive values of a diagnostic test vary according to the prevalence of the disease (or of the pre-test probability), it is important to determine the probability of effusion being secondary to tuberculosis given a certain value of ADA. The predictive values for different randomly chosen prevalences were described to illustrate the accuracy of determining ADA levels in various situations.

The Bayes' theorem analysis indicated that, when the prevalence of the disease (pre-test probability) is lower than 25%, the chance of an FN result is so low (due to high sensitivity) that only the result of the determination of the ADA level would be sufficient to rule out, until proven, the tuberculous etiology, with negative predictive values above 97%.

In areas where the pre-test probability is approximately 50% (as in Brazil) the positive post-test probability is 88.7% and the negative post-test probability is 91.5%, both of which are considered high. It is noteworthy that, in these cases, the inclu-

Table 2 - Odds ratios for each study with the respective 95% CIs and weights.

Study	Odds ratio	95% CI	Weight %
Filho FC ⁽²⁹⁾	285.00	16.567 - 4902.7	5.35
De Oliveira HG ⁽³⁰⁾	104.74	30.779 - 356.45	12.97
Chalhoub M ⁽²⁷⁾	203.00	61.189 - 673.48	13.15
De Melo FAF ⁽²⁶⁾	260.23	109.54 - 618.21	15.48
Kaisemann MC ⁽²⁴⁾	346.50	39.884 - 3010.3	7.70
Neves DD ⁽²⁾	79.08	30.254 - 206.75	14.81
Bem AF ⁽²³⁾	24.20	4.031 - 145.30	9.47
Bottini PV ⁽²⁸⁾	825.00	37.748 - 18030.8	4.75
Silva Junior CT ⁽³¹⁾	26.60	12.680 - 55.808	16.32
Overall	112.06	51.61 - 243.29	

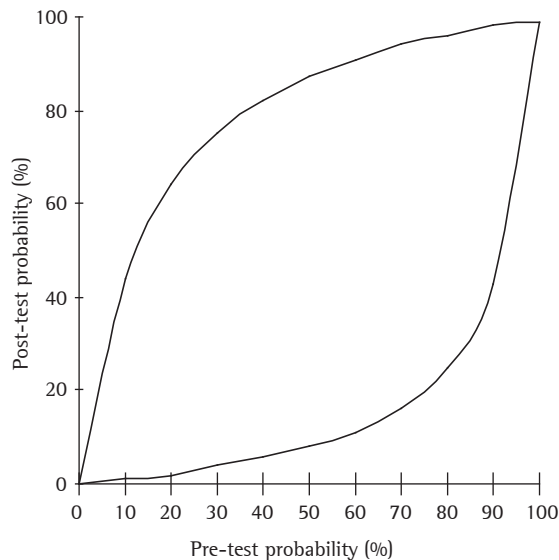


Figure 3 – Variation of probability of having tuberculosis (post-test probability) in relation to different prevalences (pre-test probability).

sion of certain variables, such as clinical history and percentage of lymphocytes, as recommended by many studies, increases the capacity to diagnose or rule out pleural tuberculosis.^(14,17,28,30) We should bear in mind that the most common causes of FP results on the test employed to determine ADA levels are complicated parapneumonic effusions and empyemas.^(6,13,14)

Despite its high accuracy, the determination of ADA levels should not be considered a substitute for the attempt to isolate the bacillus through culture. Although culture presents low positivity, it is the only way in which the diagnosis can be confirmed and drug susceptibility tests can be conducted, is the latter being an important aspect to be considered, since the number of cases involving multidrug-resistant bacteria is increasing.⁽¹⁸⁾ However, the determination of ADA levels provides results more rapidly than does culture and is less invasive than is histopathological examination (biopsy), which is also not a bacteriological exam.^(6,12,14)

This meta-analysis allowed us to summarize and group the Brazilian results found in individual studies and to determine more precisely the performance of determining ADA levels as a diagnostic test for pleural tuberculosis in the Brazilian

population. The results found are similar to those described in the world literature, which reinforces the recommendation of making the determination of ADA levels a routine in the diagnosis of tuberculosis in Brazil.^(10,12,14)

We can conclude that the determination of ADA levels in the pleural fluid could facilitate the diagnosis of tuberculosis in Brazil. Determining ADA levels is easy, rapid, reproducible, low cost and highly accurate. It can decrease the interval between symptom onset and specific treatment, as well as decreasing the costs involved in performing time-consuming, invasive (and often unnecessary) exams. It can also avoid inappropriate treatments. That makes it essential in a public health care system, in which resources are becoming scarcer and the number of individuals seeking medical treatment increases daily.

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