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Developing a Scoring System in the Diagnosis of Tuberculous Pleural Effusion

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Abstract
Pleural effusion occurs in approximately 5% of patients with tuberculosis. Since tuberculous pleural effusion is paucibacillary in nature, demonstration of AFB bacilli will not be possible in most of the cases, which makes the diagnosis difficult. None of the available pleural fluid tests are confirmatory for the diagnosis.
Aim of the study: *To develop a scoring system for the diagnosis of TB pleural effusion based on clinical features & tests that are easier to perform & inexpensive.*
Methodology: *The study was conducted as prospective Diagnostic tests evaluation. All cases of pleural effusion attending Department of Pulmonary Medicine, Medical College, Thiruvananthapuram were subjected to blood investigatiuons, chest xray, mantoux test and pleural fluid analysis in addition to detailed clinical history. A scoring system was developed using appropriate statistical methods for diagnosis of tuberculosis.*
Results: *Score less than 7, TB pleural effusion unlikely; 7 -10 TB pleural effusion probable; 11 – 16, TB pleural effusion most probable and score greater than 16 TB pleural effusion definite*
Keywords: *Pleural effusion, Tuberculosis, Scoring system.*

Introduction

Tuberculosis (TB) is a leading cause of preventable morbidity and mortality from an infectious agent worldwide. The interaction of HIV with Mycobacterium tuberculosis has lead to its resurgence in developed nations and has increased the burden of TB cases in developing countries [(1,2)]. Tuberculous pleuritis is a common manifestation of extra pulmonary tuberculosis, second to TB lymphadenitis. The frequency of TB as a cause of pleural effusion depends on the prevalence of TB in that particular population [(3)]. Pleural effusion occurs in approximately 5% of patients with TB [(4)]. Pleural TB occurs as a result of a TB antigen entering the pleural space, usually through the rupture of a sub pleural focus, followed by a local, delayed hypersensitivity reaction mediated by CD4+ cells [(5)]. This process may occur during primary or re-activation TB and may or may not involve viable bacilli entering the

pleural space [6]. This paucibacillary nature makes the diagnosis of TB pleural effusion a real challenge.

Although an untreated TB pleural effusion resolves spontaneously, in 43 to 65% cases active pulmonary or extra pulmonary TB occur over next several years [7,8]. Thus, the long – term prognosis is determined by prompt recognition & early initiation of effective therapy, which lowers the risk of subsequent disease [9].

Conventional diagnostic tests for pleural TB such as microscopic examination of the pleural fluid for acid-fast bacilli, mycobacterial culture of pleural fluid, sputum or pleural tissue, and histopatho-logical examination of pleural tissue for granulomatous inflammation have its own recognized limitations for clinical use.

Limitations of conventional tests

- Pleural fluid AFB smear positive: yield < 5%(10,11)
- Pleural fluid AFB culture positive: yield 24 -58 % (7,11)
- Pleural biopsy : invasive, yield & complication dependent on skill of operator
- Pleural fluid/ tissue AFB culture results: available only after 6 – 8 wks
- Spontaneous sputum or gastric lavage for AFB culture: yield 0 – 30% (yield depending on parenchymal lesion)(12)
- Induced sputum : 52 % sensitivity (13)

Due to these limitations several newer pleural fluid tests have been developed such as nonspecific inflammatory & immune response markers; ADA, IFN-γ, lysozyme , IL – 2 ,TNFα ;Specific markers of immune response like IGRA and nucleic acid amplication tests (NAATs)

Among nonconventional tests, ADA and IFN-γ have the best sensitivity and specificity, but they are biomarkers of the inflammatory process in the pleural space and do not confirm the etiologic agent. NAATs is not approved for the diagnosis of pleural effusion. Limited evidence is available for other novel tests and biomarkers.

Combinations of tests seem to perform better than any single test, especially combinations that include adenosine deaminase, but only a few studies have evaluated scoring system. In this scenario, taking into account of the clinical features & certain simple, inexpensive, rapid & sensitive pleural fluid tests, this study aims at developing a scoring system that can yield a diagnosis of TB pleural effusion with a high predictive value.

Aim of study

- To develop a scoring system for the diagnosis of TB pleural effusion based on clinical features & tests that are easier to perform & inexpensive.

Study design

Diagnostic tests evaluation.

Study population and setting

All cases of pleural effusion attending Department of Pulmonary Medicine, Medical College, Thiruvananthapuram.

Study period

January 2009 –January 2010.

Inclusion criteria

- All patients with exudative pleural effusion were included in the study.

Exclusion criteria

- Age<12 years
- Empyema
- Hydropneumothorax

Sample size

Calculated as 60 positive cases, using a software developed by CMC Vellore -> nMaster 1.0 LNK

Assuming sensitivity of new test 80%, sensitivity of reference test 95%, power 80%, alpha error 5%; one sided test

Methodology

Total 120 patients were included in the study, 60 each in the TB and Non TB group. Detailed clinical history and physical examination done.All patients were subjected routine blood, RBS, Sputum AFB, Chest Xray. Severity of effusion

graded as massive (fluid level above 2nd rib),moderate(fluid level below 2nd rib). Mantoux test (interpretation done according to the CDC recommendation).Thoracocentesis & Pleural fluid sent for TC, DC, cytology for malignant cells, ADA, protein, sugar, AFB smear, gram stain, Culture& Sensitivity& pleural biopsy done in feasible situations.

Based on a Departmental consensus 65 patients with probable tuberculous etiology were started on CATEGORY I ATT, to make the treatment uniform as there were 3 HIV positive & 6 sputum positive pulmonary TB patients in the study group and rest of the patients with alternate diagnosis treated accordingly. Follow up was done every month & response to treatment assessed clinically & radiologically and those not responding were further evaluated. Thus of the 65 TB patients, 5 did not respond to ATT & on evaluation were found to be malignant. Documented response to ATT was taken as gold standard. At the end of the study by backward logistic regression model, significant variables were selected .Standard beta of the regression analysis is used for calculation of the score. The results of this study are analyzed & presented in the following pages. Statistical analysis was performed using SPSS statistical software.

Percentage distribution of the sample according to diagnosis

Table: 1

Diagnosis	Count	Percent
Tuberculosis	60	50.0
Malignancy	37	30.8
Parapneumonic	15	12.5
Others(SLE,RA)	8	6.7

Table: 2 Association between occurrence of TB and Mantoux test

Mantoux	Group				p#	OR
	TB (N=60)		Non-TB(N=60)			
	Count	Percent	Count	Percent		
Positive	44	74.6	6	11.54	0.0001	22
Negative ®	15	25.4	46	88.46		

: Fisher's Exact Test, ® :- Reference category

Table: 3 Comparison of sample based on ADA

ADA	TB		Non-TB		χ^2	p
	Count	Percent	Count	Percent		
<30	6	10	51	85.0	71.48**	0.0001
30-50	12	20	6	10.0		
50-70	18	30.0	2	3.3		
70+	24	40.0	1	1.7		

Table: 4 Regression analysis for the prediction of TB

Variables	B	SE	P
Fever (Yes)	6.24	2.62	0.017
Lymphocytic & Malignant cells negative	4.63	2.42	0.055
Mantoux (Positive)	5.00	2.89	0.043
ADA	0.14	0.06	0.010
constant	-12.84	4.89	0.009

Four variables came significant in the final step of regression

Table: 5 Assigning scoring by regression coefficient

Variable	Score	Proportionate simplified score
Fever (Yes)	6	4
Lymphocytic & Malignant cells negative	4.5	3
Mantoux (Positive)	5	3
ADA (30-49)	5.5	4
ADA (50-69)	8.5	6
ADA (>70)	10	7

Table : 6 Distribution of cases based on Scoring System

Score	TB		Non TB	
	Count	Percent	Count	Percent
<7	0	0.0	47	78.3
7 - 10	12	20.1	9	15.0
11 - 16	37	61.6	4	6.6
>16	11	18.3	0	0.0

Results & Discussion

After the final step of regression, four variables came significant; fever, positive mantoux, pleural fluid which is lymphocyte predominant & malign-ant cells negative and ADA. Scores were assigned according to the regression coefficient (β).

Cases were recorded for the 4 variables and total score computed & ROC curve plotted.

Total score at a cut off of:

6.5 : sensitivity 100% & specificity 78%

9.5 : sensitivity 92% & specificity 93%

15 : sensitivity 30% & specificity 100 %

Two models of scoring system developed by PORCEL & VIVES had sensitivity of 95 and 97%, respectively and specificity of 94 and 91%, respectively for discriminating TB from malignant effusions. (14)

When the distribution of cases in the study group was assessed based on the constructed score, majority (61.6%) of TB pleural effusion cases had a total score between 11 and 16(sensitivity 18 - 80%, specificity 93 -100%); 20.1% had a score between 7 and 10; sensitivity 80 -100%, specificity 88 – 93%); 18.3% had a score >16(sensitivity 18%, specificity 100%); none had a score<7.

None of the patients in the non TB group had a score >16. Majority (78.3%) of non TB group had a total score <7. Based on this data, the scoring system was formulated as

- <7 : TB pleural effusion unlikely;
- 7 -10 : TB pleural effusion probable ;
- 11 – 16 :TB pleural effusion most probable
- >16 : TB pleural effusion definite

Conclusions

- The diagnosis of TB pleural effusion remains a challenge.
- Due to the limitations of individual tests, combinations of tests seem to perform better than any single test, especially combinations that include ADA.
- In this scoring system, a total score of >9.5 has a sensitivity of 92%, specificity of 93% and positive likelihood ratio 13.8.
- Specificity is 100% when the total score is >15.
- Score 7-10,TB pleural effusion probable;11-16:TB pleural effusion most probable;>16 ,TB pleural effusion definite.

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