

Predictive Risk Factors of Pleural Tuberculoma Occurrence on Patients with Pleural Tuberculosis

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Research article

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Abstract

Background: Pleural tuberculoma (PTM) had been observed more and more frequently on patients with pleural tuberculosis (PT). The occurrence of PTM is not favorable for the treatment outcome of PT. However, its predictive risk factors had not been clarified. This study was to explore the predictive risk factors of PTM occurrence on the patients with PT.

Methods: From January 2017 to June 2018, patients diagnosed as PT were enrolled prospectively into the study. All clinical characteristics and pleural changes during the chemotherapy were recorded and adenosine aminase (ADA) □ lactate dehydrogenase (LDH) □ glucose and protein of pleural fluid were quantified. Interferon-gamma (IFN- γ) □ transforming growth factor -beta (TGF- β), plasminogen activator inhibitor type-1 (PAI-1) and tissue plasminogen activator (t-PA) of pleural fluid were tested before chemotherapy by enzyme-linked immunosorbent assay (ELISA).

Results: A total of 162 patients with PT were enrolled. 82 patients (51.3%, 82/162) developed PTM during chemotherapy. We found the probability of PT to develop PTM reached 99.5% when the patients with pleural thickness, packaged plural effusion, LDH>461.5 IU/L , ADA>62.9 IU/L , GLU<4.75 mmol/L and age>32.5 years old. The probability to develop PTM was as low as 1.4% when these 6 indices were in the opposite trend to the conditions list above. Using tested cytokines in pleural fluid from 76 cases, the probability of PTM if patients satisfied 3 indexes including increased TGF- β (>15.235 μ g/L) , increased PAI-1(>180.720 μ g/L) and decreased t-PA(<2.875 μ g/L) was 78%, and the probability to develop PTM was only as low as 2.7% when these 3 cytokines were in the opposite trend.

Conclusions: Age, pleural thickness, packaged pleural fluid, increased ADA, LDH, TGF- β , PAI-1 and decreased glucose and t-PA might be predictive risk factors of developing PTM for patients with PT, clinicians should take deep consideration if patients had above factors.

Background

Tuberculosis (TB) remains one of leading infectious diseases in the world. There were estimated 10.0 million new cases of TB worldwide in 2017 [1]. Pleural tuberculosis (PT) ranked the second most common form of extra-pulmonary tuberculosis [2,3]. In recent years, pleural mass or nodules had been observed in patients with PT, several published literatures reported its occurrence during the chemotherapy of PT and it was called as pleural tuberculoma (PTM) which was confirmed pathologically, bacterially or clinically [4–7]. PTM were observed by Chest CT with shown in figure 1(A, B, C and D). Figure 1A showed the chest CT with right pleural effusions when the patients admitted to hospital; Figure 1B showed the right pleura was clear after drainage of pleural fluid and chemotherapy; Figure 1C revealed the right pleural mass diagnosed as PTM after 4 months of standard first line anti-TB chemotherapy; Figure 1D indicated absorption of PTM after adjusting anti-TB regimen. In our study, PTM was referred as the pleural mass or nodules confirmed to be tuberculous granuloma by pathological examination with or without mycobacterium tuberculosis within lesions.

Hundreds of patients with similar radiological characteristic were found in clinics in China. However, published studies were limited in few case reports and all of them were reported in Asian countries or regions with high TB burden. There had no unified treatment regimen for patients with PTM currently. In china, we found PTM occurrence frequently, predominant in the course of chemotherapy of PT [5,8]. We think that PTM might be the origin of anti-TB treatment failure or relapse because mycobacterium tuberculosis complex (MTC) were mostly found in the pleural mass proved pathologically although patients have finished part course of chemotherapy with first-line anti-TB drugs. However, few studies were published with regard to the reasons of its occurrence and there had no unified treatment regimen for PTM, how to get further treatment and prevent its occurrence remains elusive.

In this study, we tried to find out the predictive risk factors of PTM at the initiation of anti-TB chemotherapy when patients had pleural effusion without pleural mass or nodule in order to prevent its occurrence.

Because of few studies referred to the reason and mechanism of PTM, we hypothesized Tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type-1 (PAI-1) might be involved into the development of PTM. t-PA and PAI-1 are vital cytokines of fibrinolytic system and played an important role in activation and inhibition in coagulation system [9]. Previous studies showed that imbalance of PAI-1 and t-PA in pleural spaces may lead to fibrin deposition and pleural inflammation [10,11]. Another cytokine, transforming growth factor -beta (TGF- β), a superfamily regulates tissue regeneration can also induce epithelial-mesenchymal transition (EMT) [12,13]. TGF- β might increase the levels of PAI-1 [14,15]. Therefore, we designed the prospected study including testing PAI-1, t-PA, TGF- β and Interferon-gamma (IFN- γ) in pleural effusion then observing the pleural changes during the chemotherapy, trying to find out the underlying predictive risk factors of PTM occurrence.

Materials And Methods

Patients

Between January 2017 and June 2018, patients diagnosed as PT with pleural effusion were admitted to Shanghai Pulmonary Hospital. Inclusive criteria were patients newly diagnosed as PT, pleural fluid could be available, and had no pleural mass or nodules before chemotherapy. All individuals tested were negative for human immunodeficiency virus (HIV) and had no history of anti-TB treatment. Patients were undergoing corticosteroid therapy, or had history of malignant tumor, or complicated by rheumatoid arthritis, or other pulmonary diseases were excluded.

Patients were diagnosed as PT according to the WHO guideline, if there was at least one of the following criteria [16,17]: (1) the identification of MTC in pleural fluid by acid-fast bacilli (AFB) smear; (2) the detection of MTC in pleural fluid by culture; (3) typical pathological findings of a pleural biopsy; and (4) the MTB positive results in sputum and chest X rays or chest CT scanning finding abnormal lesions of pleura compatible with lung TB; (5) clinical diagnosed as PT and had satisfied outcome under anti-TB treatment during follow up for one year.

The diagnostic criteria of PTM were patients satisfied the following conditions: (1) patients were diagnosed as PT clinically; (2) Chest CT scan showed pleural effusion before chemotherapy, no pleural mass or nodule were found after drainage of pleural effusion before chemotherapy of TB and then solitary or multiple pleural nodule were found by CT scan after chemotherapy which was confirmed as granulomatous lesions pathologically through pleural biopsies.

Clinical Sample Selection and Data Collection

Suspected PT patients underwent a percutaneous transthoracic puncture to collect pleural effusion. 10 ml pleural effusion of 162 patients was sent to the clinical laboratory for clinical test and another 10 ml of 76 patients was frozen in the refrigerator at -20°C . All clinical characteristics including name, included number, age, symptoms, complications, final diagnosis, pleural thickness, the diameter of pleural nodule, the history of diagnosis were recorded completely. Pleura thickness > 2 mm was considered as plural thickness [18]. Follow-up period was one year since starting the chemotherapy.

Laboratory analysis

Biomedical indicators of adenosine deaminase (ADA), lactate dehydrogenase (LDH), protein and glucose were tested in pleural fluid. IFN- γ , PAI-I, t-PA and TGF- β in pleural fluid were tested by enzyme-linked immunosorbent assay (ELISA) kit (eBioscience Corp, San Diego, CA). ELISA were detected on the reader with 450nm wavelength within 30 minutes after the end of operation. All procedures were carried out in strict accordance with the operating procedures of the product specification.

Ethical Approval

This study was approved by the ethics committee of Shanghai Pulmonary Hospital, Tongji University School of Medicine (K16–131). Written informed consent was obtained from all enrolled participants.

Statistics

The statistical analysis and data visualizing were performed using SPSS statistics version 25.0 (SPSS, Inc., Chicago, IL, USA), R 3.5.3 software (The R Foundation for Statistical Computing) and Stata/MP 14.0. All the abnormal distributed data sets are presented as median (range) which tested by Kolmogorov-Smirnov test. Continuous variables were compared using Mann-Whitney U tests. Variables displayed as percentages were compared with a χ^2 test. Differences with $P < 0.05$ were considered significant. The diagnostic value of each biomarker was calculated with the area under ROC curve (AUC) of receiver operation curve (ROC), best cutoff value was found at the point where Youden Index is the largest (Youden Index = Sensitivity + Specificity – 1). Pre-test and post-test possibility were used to evaluate the predictable ability of the biomarkers. The Fagan's nomogram was used to present pre-test probability and post-test probability which derived from Stata module (FAGAN: Stata module for Fagan's Bayesian

nomogram). Alluvial Diagrams was used to present the study cohort's frequency at the study items with levels which derived from R package (ggalluvial: Alluvial Diagrams in 'ggplot2').

Results

Clinical Characteristics

162 patients diagnosed as PT were finally enrolled in the study, 111 patients were male (68.5%), 51 were female (31.5%). The median age of them was 34 years old, range from 24–55 years old. 64.8% of them had pulmonary tuberculosis comorbidity. 53.7% (87/162) of 162 cases had pleural thickness, the diameter of pleural thickness was 0.75 ~ 7.26 cm. 82 cases (50.6%, 82/162) developed PTM during the chemotherapy.

Analysis of clinical characteristics and biochemical markers of pleural fluid in patients with PTM

In 82 PTM patients, 53 (64.7%) of them had a single pleural nodule, 22 cases (26.8%) had 2 nodules, only 7 patients (8.5%) had 3 and more than 3 nodules. 62.2% of PTM were observed to shrink in less than 6 months. 28 cases of PTM shrank obviously under changing anti-tuberculous regimen when diagnosed as being complicated with PTM during the chemotherapy. The characteristics of PTMs was presented in Table 1

Patients with PTM were found to be younger (29 years old *vs.* 42 years old, $p < 0.05$) than those who didn't developed PTM. The percentage of pleural thickness and packaged pleural effusion checked by ultrasound was significantly higher in PTM group compared to that in patients without PTM (80.5% *vs.* 26.3%, 50.0% *vs.* 18.8%, $p < 0.05$). And also, levels of lactate dehydrogenase (LDH) (530 IU/L *vs.* 318 IU/L, $p < 0.05$) and adenosine deaminase (ADA) (69.55 IU/L *vs.* 56.1 IU/L, $p < 0.05$) were higher in PTM, glucose level (4.7 mmol/L *vs.* 4.9 mmol/L, $p < 0.05$) in pleural fluid was statistically lower in PTM group than that in patients without PTM. Positive rate of mycobacterium tuberculosis complex (MTC) culture in both pleural effusion and sputum were similar low in both PTM and non-PTM group ($P > 0.05$). Data were shown in Table 2.

Changes of cytokines' levels of pleural fluid in patients with PTM

Cytokines of IFN- γ , TGF- β , PAI-1 and t-PA in pleural effusion were tested in 76 patients with PT at the initiation of chemotherapy. Among these patients, 34 cases developed PTM while 42 cases did not during the follow-up. We found IFN- γ was similar in both groups while TGF- β and PAI-1 were statistically higher in PTM patients than those in patients without PTM (20.021 $\mu\text{g/L}$ *vs.* 16.386 $\mu\text{g/L}$, 241.014 $\mu\text{g/L}$ *vs.* 187.152 $\mu\text{g/L}$, $P < 0.05$). Whereas t-PA was lower in PTM patients than that in patients without PTM (1.733 $\mu\text{g/L}$ *vs.* 3.025 $\mu\text{g/L}$, $P < 0.05$). Detailed data were presented in Table 3.

Predictive risk factors including clinical characteristics, biochemical indexes and cytokines for PTM occurrence

ROC curve was used to find the best cutoff value of biochemical indexes and cytokines. The value of AUC, best cutoff, sensitivity, specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), positive predictive value (PPV) and negative predictive value (NPV) of age, glucose, ADA, LDH, protein, TGF- β , PAI-1 and t-PA were shown in Table 4.

We use Fagan's nomogram to further evaluate the prognostic capacity of clinical characteristics, biochemical indexes and cytokines. From 162 patients, we found the probability of PT to develop PTM reached 99.5% when the patients with pleural thickness, packaged plural effusion, LDH>461.5IU/L, ADA>62.9IU/L, GLU<4.75mmol/L and age>32.5 years old. The probability to develop PTM was as low as 1.4% when these 6 indices were in the opposite trend to the conditions list above. Using tested cytokines in pleural fluid from 76 cases, the probability to occur PTM if patients had satisfied 3 indexes including increased TGF- β (>15.235 μ g/L), increased PAI-1(>180.720 μ g/L) and decreased t-PA(<2.875 μ g/L) was 78%, and the probability to develop PTM was as low as 2.7% when TGF- β , PAI-1 indexes were under their best cutoff value and t-PA were higher than its best cutoff value. The prior probabilities of these indexes were shown in Figure 3 and Figure 4.

Discussion

Recent years PTM had been more and more observed in Chinese clinics—most physicians failed to know how to get further treatment, especially for most cases without pleural nodule or mass on the initiation of anti-TB chemotherapy. These nodules or mass were mostly confirmed to be PTM which were granulomatous lesions, caseous necrosis with or without acid-fast bacillus (AFB) within the lesions. PTM might be single or multiple, its occurrence will bring patients unfavorable outcome, high cost and might be origin of treatment failure or relapse [19]. Therefore, exploring the predicted factors of PTM is essential for physicians to prevent its occurrence.

For underlying clinical predicative factors, according to the results in present study, pleural thickness and packaged pleural effusion might be risk predictive factors of PTM. These severe statuses sometimes need surgical operation [20,21]. Pleural thickness was reported to be the predictor for PT, Ruiz reported [22] that PT with pleural thickness were more common in men, elderly people, however, other studies showed that age, symptoms and pleural thickness were not related with PT [18], therefore, although existed controversial conclusions, combined with above results, pleural thickness might be closely related to the occurrence of PTM because the location of PTM is accompanied by local pleural thickness [23].

It was been reported that the occurrence of PTM was related to nonstandard anti-TB treatment, delayed treatment and no use of corticosteroid [8]. However, this study did not find these risk factors associated with the occurrence of PTM. It showed that patients younger than 32.5 years old were easier to have PTM, the reason might be associated with stronger allergic reaction in pleura.

For biochemical markers in pleural effusion, our results showed ADA and LDH in pleural effusion were higher in PTM patients and glucose was lower than patients without PTM. It had been reported that LDH of pleural fluid and the LDH ratio of pleural fluid to blood were higher in patients with pleural thickness than those in patients without pleural thickness [22]. Meanwhile another study found that pleural thickness may be related to lower glucose and higher ADA in pleural effusion [24–26]. Therefore, our findings in this study that higher ADA, LDH and lower glucose in pleural fluid associated with PTM might be reasonable.

For cytokines tested in pleural effusion, their change of expression had been associated with immune response in patients with PT. With the development of immunological reaction in host, the immune factors in pleural effusion might be predictors of pleural thickness, packaged pleural effusion which could be quantitatively analyzed [23,27,28]. According to Chung [9], it was reported that the **fibrinolytic activity** was depressed in packaged pleural effusions compared with free-flowing effusions. We found PTM patients were more common with packaged pleural effusion. Other studies showed that high levels of IFN- γ , TGF- β and lower glucose in pleural effusion were correlated with the occurrence of pleural thickness in PT [29], and they thought that pleural thickness and loculation of pleural effusion were related to local pleural immune response associated with cytokines. Other researchers found pleural thickness was related to the imbalance of PAI-1 and t-PA in pleural effusion and PAI-1 increased, the t-PA decreased in PT patients with pleural thickness while decreased PAI-1, increased t-PA was found in patients with sufficient drainage of pleural effusions, therefore, PAI-1 and t-PA may be predictors of pleural thickness in PTM [9,18,27,29]. Our study had proved these changes of PAI-1 and t-PA in PTM patients.

In order to figure out whether these indexes were valuable in predicting occurrence of PTM, we compared cytokines' level in PTM and non-PTM patients. Comparing four cytokines of pleural effusion in PTM and non-PTM groups, higher TGF- β (20.021 $\mu\text{g/L}$ vs 16.386 $\mu\text{g/L}$), higher PAI-1 (241.014 $\mu\text{g/L}$ vs 187.152 $\mu\text{g/L}$) and lower t-PA (1.733 $\mu\text{g/L}$ vs 3.025 $\mu\text{g/L}$) were found in PTM group. There was no statistical difference of IFN- γ between two groups. Increased TGF- β , PAI-1 and decreased t-PA were the predictors of PTM in PT patients. We further analyzed these indexes which were recognized to have statistical differences between PTM and non-PTM group using ROC curve to find the best cutoff value of these indexes, and calculated the posterior probability of these indexes. Our study showed that combination of six indexes including pleural thickness, LDH, package of pleural effusion, ADA, glucose and age can increase probability of developing PTM to 99.5%, on the contrast, the probability to develop PTM was as low as 1.4% if these indices were in the opposite trend. Estimating 3 cytokines indexes of pleural effusion, the probability to develop PTM was 78% when TGF- β , PAI-1 were above the best cutoff value and t-PA was below the best cutoff value. The posterior probability was only 2.7%, when these 3 cytokines were in the opposite trend. It demonstrated that these 9 indicators, including clinical characteristics, biochemical indexes and cytokines, may become the predictive factors of PTM in PT patients. Combined analysis of these indices in predicting development of PTM in PT patients could predict occurrence of PTM. In further study, it is necessary to verify by expanding sample size.

In our study, there was no significant correlation between bacterial positive rate of MTC culture in pleural effusion and occurrence of PTM. Authors believed that lower sensitivity of pleural effusion bacteria culture detection maybe related to fiber encapsulation of lesions on the pleural and MTC cannot released to pleural effusion. Further study should be done in the future.

In summary, clinicians should take deep consideration when PT patients have the following characteristics: younger than 32.5 years old, pleural thickness, packaged pleural effusion, increased ADA, LDH, TGF- β , PAI-1 and decreased level of glucose and t-PA in pleural effusion in order to prevent PTM occurrence.

List Of Abbreviations

TB: Tuberculosis

MTC: Mycobacterium tuberculosis complex

PT: Pleural tuberculosis; PTM: Pleural tuberculoma

ADA: Adenosine deaminase

LDH: Lactate dehydrogenase

IFN- γ : Interferon-gamma

ELISA: Enzyme-linked immunosorbent assay

TGF- β : [Transforming growth factor-beta](#)

t-PA: Tissue plasminogen activator

PAI-1: Plasminogen activator inhibitor type-1

EMT: Epithelial-mesenchymal transition

CT: Computed tomography

AFB: Acid-fast bacilli

ROC: Receiver operation curve

AUC: Area under receiver operation curve

PPV: Positive likelihood ratios

NPV: Negative likelihood ratios

PLR: Positive likelihood ratios

NLR: Negative likelihood ratios

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical guidelines of the institutional review board of Shanghai Pulmonary Hospital, Tongji University (project approval No. K16–131). All participants gave written consent for use of their clinical information and tissue samples for research purposes. Specimens were anonymized.

Consent for publication

All authors have read the final version of the manuscript and agreed with the content and have agreed to be a co-author on this manuscript.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors have stated that they have no conflicts of interest.

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Author's contributions

L. F. and C. W. designed the research; Z. D. wrote the article. Z. D. and L. F. collected the clinical data. L. F. interpreted the clinical data. W. Z. and Z. D. analyzed the data.

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Tables

Table 1 clinical characteristics of Pleural Tuberculomas

Element	N [82]	Percentage [%]
Number of pleural nodules		
1	53	64.7
2	22	26.8
3	6	7.3
5	1	1.2
Time elapsed between starting chemotherapy and appearing of pleural nodules, mo		
<2	32	39.0
2-4	40	48.8
4-6	10	12.2
Time elapsed between appearing and shrinking of pleural nodules, mo		
<6	51	62.2
6-12	26	31.7
Treatment after a year's chemotherapy		
Continue chemotherapy	24	29.3
Surgery	4	4.9
Follow-up	54	65.9

Table 2 Clinical factors between PTM (n=82) patients and non-PTM patients (n=80)

Demographic indices	Pleural tuberculoma [82]	No pleural tuberculoma [80]	P Value
Age, y	29(22-47)	42(27-59)	0.001*
Men	59[72]	52(65.0)	0.341
With plural thickness	66[80.5]	21[26.3]	0.001*
With pulmonary tuberculosis comorbidity	57[69.5]	48[60.0]	0.108
MTC culture positive of pleural effusion	9[11.0]	4[5.0]	0.247
MTC culture positive of sputum	8[9.8]	7[8.8]	0.825
Package of pleural effusion	41[50.0]	15[18.8]	0.001*
ADA of pleural effusion (UI/L)	69.55(60.075-83.675)	56.1(44.625-64.700)	0.001*
LDH of pleural effusion (UI/L)	530(359.75-715.5)	318(248-419.75)	0.001*
Glucose of pleural effusion (mmol/L)	4.7(3.4-5.8)	4.9(4.625-6.200)	0.008*
Protein of pleural effusion (g/L)	50(45-54)	47.0(42-53.75)	0.126

PTM= Pleural tuberculoma

MTC=Mycobacterium tuberculosis complex

* $P < 0.05$

Table 3 Cytokines Associated with PTM in pleural effusion($\mu\text{g/L}$)

Cytokines	PTM[n=34]	Non-PTM[n=42]	P Value ^a
INF- γ	3.918(0.992-5.491)	2.458(0.958 -5.669)	0.806
TGF- β	20.021(15.777-26.265)	16.386(14.363-23.423)	0.044*
PAI-1	241.014(191.213-320.184)	187.152(134.645-297.537)	0.048*
t-PA	1.733(1.069-2.876)	3.025(1.832-4.852)	0.024*

* $P < 0.05$

Table 4 Value of clinical and laboratory indexes of pleural effusion in predicting PTM

	AUC	Best Cutoff	Sensitivity	Specificity	PLR	NLR	PPV	NPV
Age*	0.651	32.5(y)	0.622	0.662	1.840	0.571	0.654	0.631
Glucose*	0.621	4.75(mmol/L)	0.524	0.737	1.992	0.646	0.672	0.602
ADA*	0.710	62.9(UI/L)	0.671	0.738	2.561	0.446	0.724	0.686
LDH*	0.745	461.5(UI/L)	0.659	0.775	3.295	0.426	0.771	0.696
TGF- β #	0.635	15.235($\mu\text{g/L}$)	0.912	0.381	1.473	0.231	0.544	0.842
PAI-1#	0.632	180.720($\mu\text{g/L}$)	0.824	0.476	1.573	0.370	0.560	0.770
t-PA#	0.651	2.875($\mu\text{g/L}$)	0.765	0.595	1.889	0.3950	0.605	0.529

* n=162

n=76

Figures

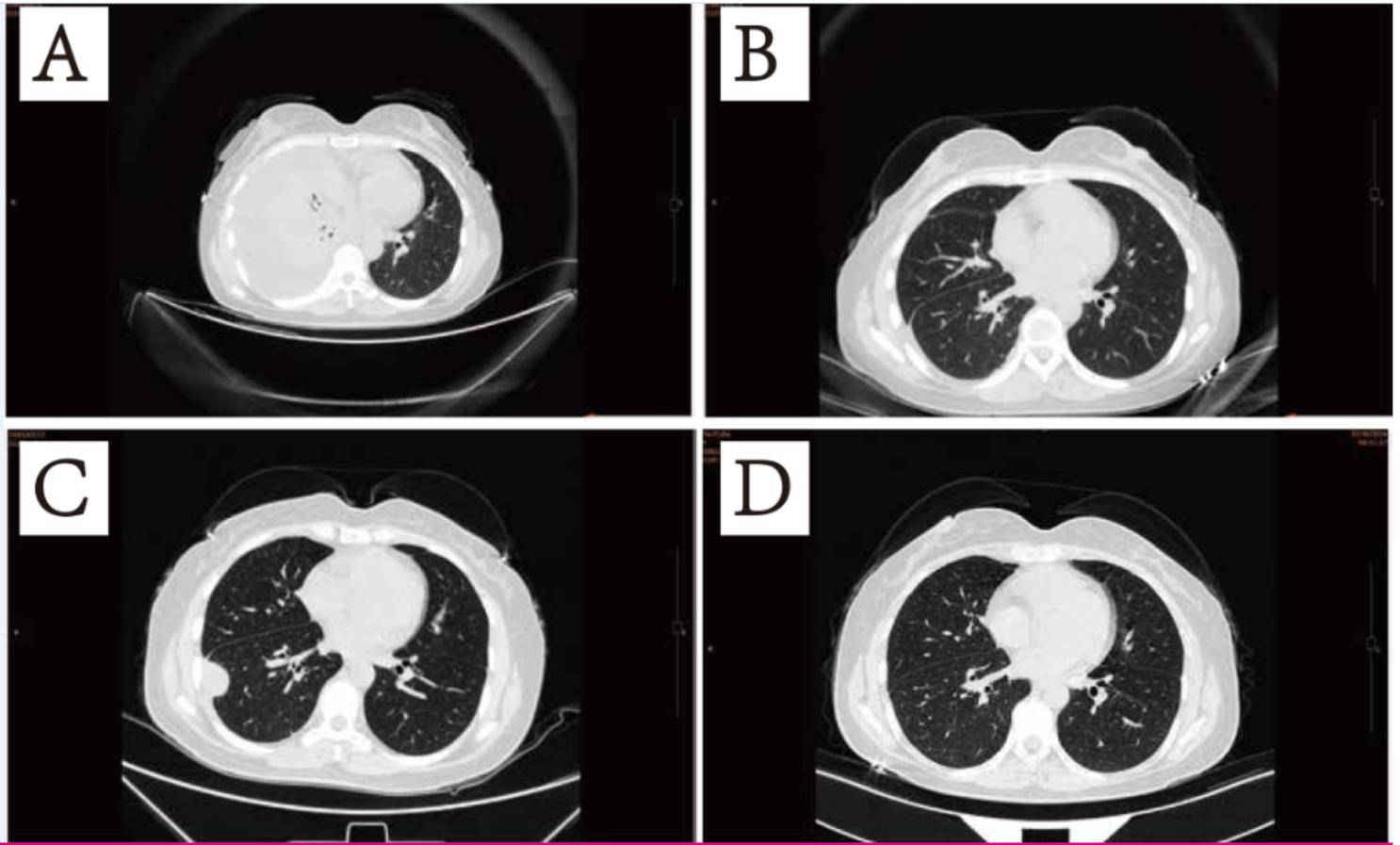


Figure 1

The occurrence and development of PTM was observed by Chest CT. A CT showed large amount of pleural effusion in right thorax. B The right pleura was clear after the drainage of pleural fluid and chemotherapy. C CT revealed the right pleural mass after 4 months of standard first line anti-TB chemotherapy. D CT indicated absorption of PTM after adjusting anti -TB regimen.

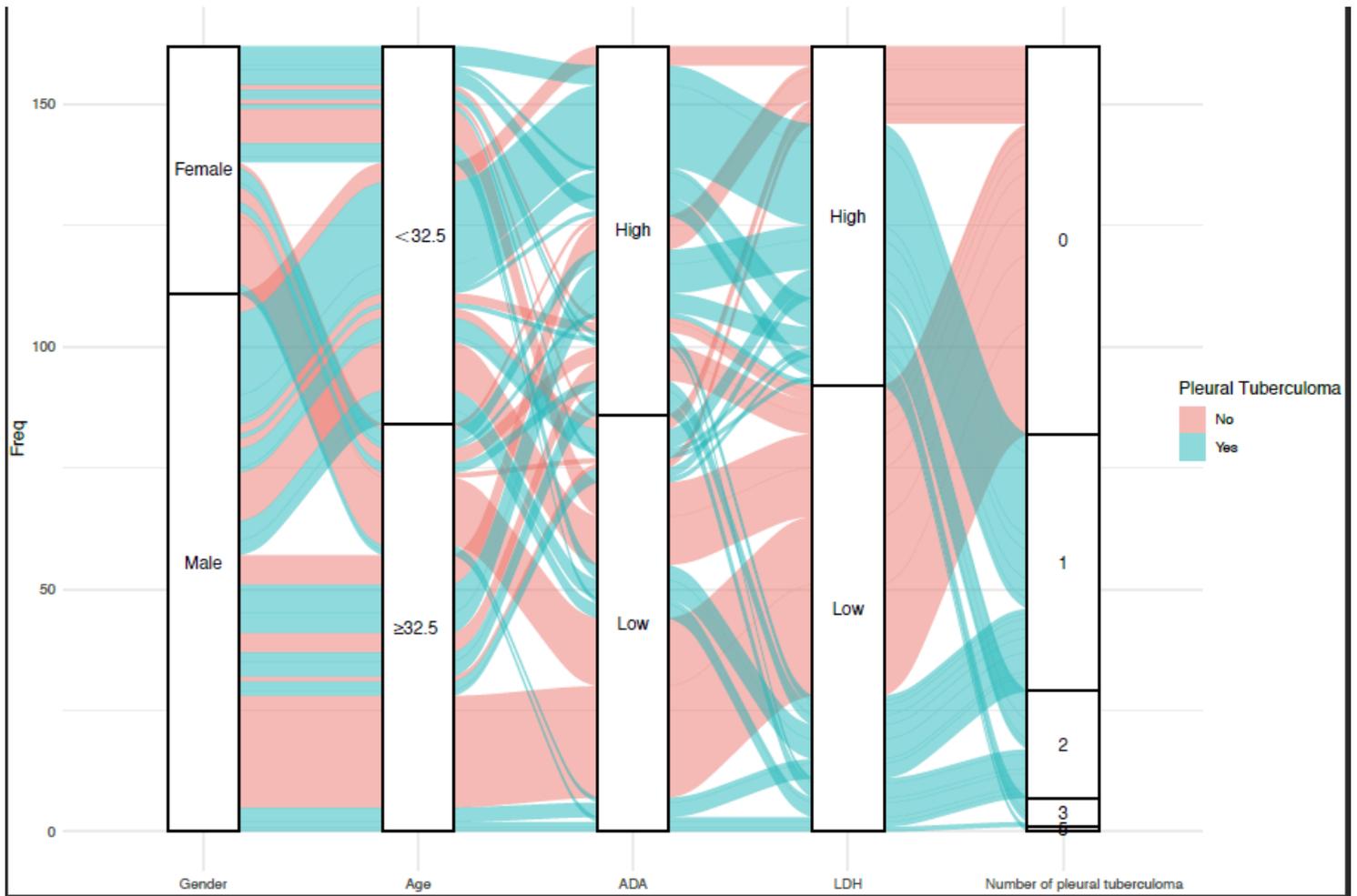


Figure 2

Alluvial Diagrams of the PT cohort. The variables involved in are gender, age, separation package of pleural effusion and number of PTM.

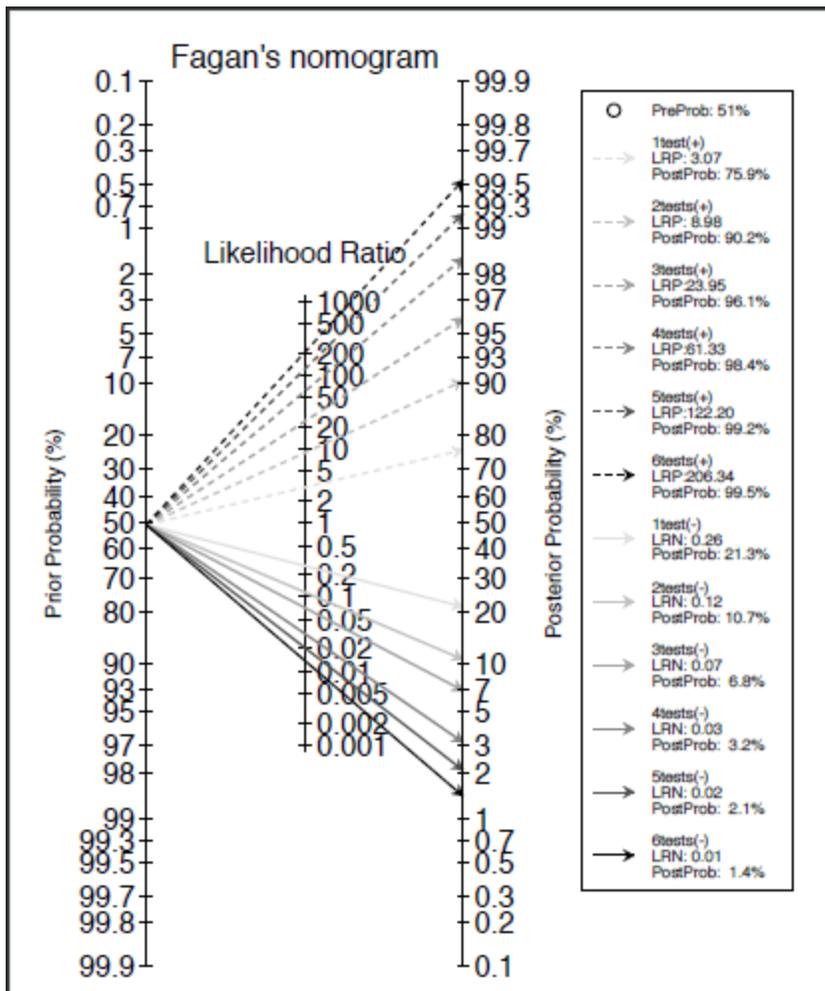


Figure 3

Fagan's nomogram for the 6 tests of 162 cohort which take in sequence of plural thickness, LDH, packaged plural effusion, ADA, glucose and age.

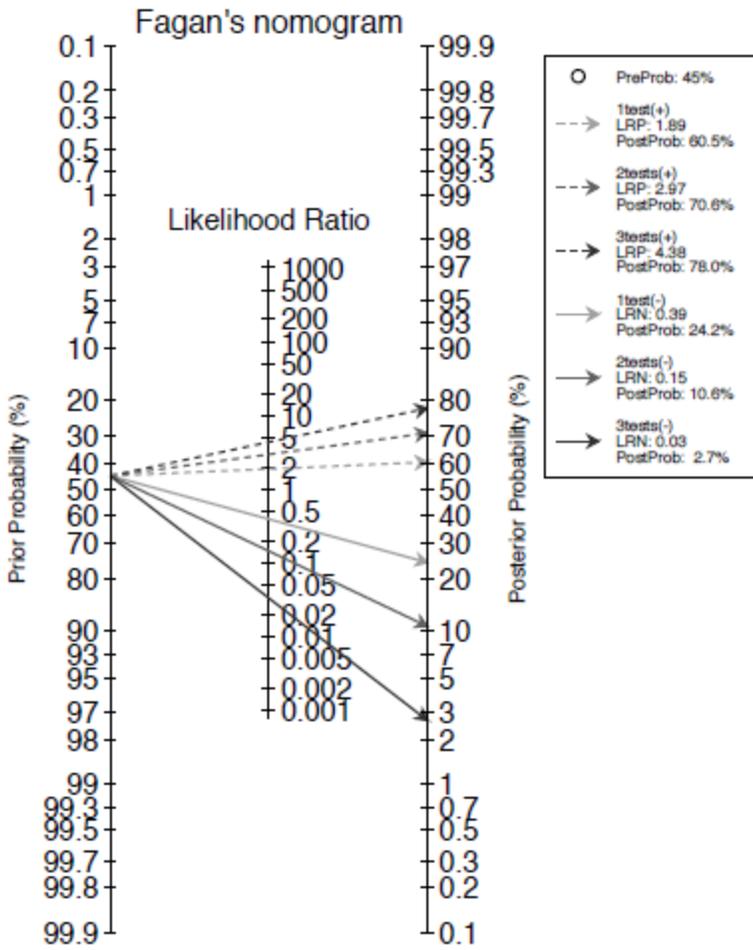


Figure 4

Fagan's nomogram for the 3 tests of 76 sub-cohort which take in sequence of t-PA, TGF- β , PAI-I.