DIAGNOSTIC PREDICTION MODEL OF TUBERCULOUS PLEURAL EFFUSION

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ABSTRACT

Background: Percentage of TPE reach 20% of total EPTB cases. The diagnosis of TPE is difficult due to pleural biopsy procedure invasiveness and acid fast stain low sensitivity. Adenosine deaminase (ADA) can become reference test with high sensitivity and specificity but availability in primary health care is limited.

Objective: Analyze prediction model in diagnosis of tuberculous pleural effusion.

Methods: This study uses a cross-sectional method. The study was conducted at Cipto mangunkusumo Hospital. Independent variables consist of age, pleuritic chest pain, unilateral pleural effusion, glucose pleural fluid ≤70 mg/dL, exudative mononuclear pleural effusion, negative cytology malignancy, ultrasound characteristic and blood neutrophil-lymphocyte ratio. ADA ≥35 suggests TPE. The variaables analyzed bivariately, multivariately, ROC curve and Hosmer-Lemeshow.

Results: There were 91 subjects with characteristic of male 41 subjects (45,1%) and female 50 subjects (54,9%). Malignancy was the most frequent comorbid with 52 subjects (57,1%). Factors associated with TPE diagnosis are complex ultrasound characteristic OR 5,655 (CI 95% 1,700-18,812), pleural fluid glucose ≤70 mg/dL OR 11,262 (CI 95% 2,931-43,276) and exudative mononuclear dominant pleural effusion OR 8,567 (CI 95% 2,114-34,715). In ROC curve conclude AUC 0,841 with p<0,001 CI 95% (0,762-0,926). The result is a scoring system cut-off value ≥2 with probability 92,8%.

Conclusion: Predicted factors of TPE diagnosis are complex ultrasound characteristic, low pleural fluid glucose and exudative mononuclear dominant pleural effusion. The result is scoring system with cut-off value ≥2 with probability 92,8%.

Keywords: Tuberculous pleural effusion, ADA, complex ultrasound characteristic, exudative mononuclear dominant pleural fluid, pleural fluid glucose

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INTRODUCTION

Tuberculosis (TB) is one main cause of death in the world. In 2017, there were approximately 1,6 million of death in the world. Indonesia is the third most frequent country in terms of TB cases behind India and China with 8% of all world's cases.[1] Extrapulmonary TB (EPTB) cases in Southeast Asia is 15% of all world's cases. Tuberculous Pleural Effusion (TPE) is second most frequent EPTB cases behind tuberculous lymphadenitis with 20%.[2,3] Five region with the most frequent TB were Banten, Papua, West Java, Aceh and South Sumatera.[4]

Pleural effusion is the abnormal fluid accumulation in pleural space. The etiologic of pleural effusion must be recognized. TPE is one most common etiologic of pleural effusion. This is caused by infection of *Mycobacterium tuberculosis*. TPE often found in the epidemic country such as Indonesia. Problem in diagnosis of TPE are the low sensitivity of Acid Fast Stain (AFS) and culture examination and the invasiveness of thoracoscopy procedure. Pleural effusion only consists of 5-15% of cells, this is the reason that AFS and culture examination seldom shows positive result.[2,5]

TPE are hard to differentiated based on only clinical and radiological. This reason makes laboratory examination important. After thoracocinteces is being done, the pleural fluid is examined to reveal the etiology of pleural effusion. If the diagnosis is TPE then the management is easier. The pleural effusion is managed just as ordinary pleural effusion and also intiatiated of anti tuberculosis drugs.[6]

Incidence of TPE is approximately 20-45% in country like Indonesia. Problem in diagnosis of TPE are the low sensitivity of Acid Fast Stain (AFS) and culture examination and the invasiveness of thoracoscopy procedure. Based on this problems, we need test that has higher sensitivity and specificity like Adenosine Deaminase (ADA) to become the reference test. The used of ADA with cut off value ≥35 in terms of TPE diagnosis reaches 100% of sensitivity and 94% of specificity.[7] Beside TB, ADA can show high value in few condition such as Systemic Lupus Erythematosus (SLE), Lymphoma, Empyema and Rheumatoid Arthritis (RA).[8]

In this study, interpretation of thoracal ultrasound become a special characteristic. It has been stated that in TPE the complex ultrasound interpretation reach 90% of all cases.[9] The TPE patient is usually younger, approximately 76% of them are less than 40 years old.[10] The pleuritic chest pain is one most frequent symptoms that reach almost 75% of all cases.[11] The majority of TPE is unilateral (86%) and most of them is right sided (48%).[6] Pleural fluid glucose of TPE usually low, it related due to chronic inflammation.[12] Cytology examination is routinely done to rule out malignancy etiology.[13] Neutrophil-Lymphocyte ratio (NLR) is one inflammation marker tthat estimated to predict TB acivity.[14]

In previous literature, there are many prediction model of TB that being studied. Retrospective study of Kawkitinarong et al revealed sensitivity of 75% and specificity of 80%. This study has a specialty that include thoracal ultrasound as its variable.[15] Other studies were study of Valdes et al that revealed sensitivity of 95,4% and specificity of 94,3%, study of Porcel et al that revealed sensitivity of 95% and specificity of 91% and study of Neena et al that revealed sensitivity of 92% and specificity of 93%. Those last three studies have a common that include ADA as one of variables.[16,17,18] ADA is good test but it is still limited to be done in primary or secondary healthcare service in Indonesia.

This research studies about predicting factors of TPE. Then those factors related with TPE is developed to be scoring system. This research is hoped to add more information and can be beneficial in terms of faster and more efficient TPE diagnosis in secondary healthcare service with more simple data.

MATERIALS AND METHODS

Study site and population

This study is a cross-sectional study, with total

111 samples of primary data from Respirology and Critical Care Procedure Room, Cipto Mangunkusumo Hospital, Jakarta.

Inclusion and exclusion criteria

The inclusion criteria is subjects with pleural effusion that older than 18 years old. However, subjects with SLE, lymphoma, empyema and RA were excluded from this study.

Statistical analysis

Statistical analysis was conducted by using SPSS version 20.0. Bivariate analysis for categorical variables was performed with Chi-Square test. Furthermore, variables with $p < 0.25$ in the bivariate analysis will be included in the multivariate analysis. Multivariate analysis using logistic regression (backward method) was performed on all variables. The variables with $p<0.05$ included in final model. The Receiving Operator Characteristic (ROC) is performed to the final model and the cut-off value is set. The Hosmer-Lemeshow and bootstrapping is performed in order to validate the data.

RESULTS

Total 91 subjects were meet our inclusion and exclusion criteria, with mean age 51.7 years old and proportion of male 45.1% and female 54.9%. The proportion of TPE in this study was 25.3%. The etiology of non –TB pleural effusion were 57.4% malignancy, 22% cardiovascular impairment, 7.3% liver impairment, 5.8% renal impairment, 4.4% infection and 2.9% other. In this study the most frequent comorbid of these subjects was malignancy with 57.1%. The other characteristics of all subjects can be seen in table 1

The results of bivariate analysis using Chi-Square test showed factors related to TPE were pleuritic chest pain with a prevalence ratio of 1.731 (95% CI 0.865-3.3464), exudate mononuclear dominant with a prevalence ratio of 3.086 (95% CI 1.253-7.597), complex thorax ultrasound with a prevalence ratio of 3.455 (95% CI 1.501-7.956), and pleural fluid glucose ≤ 70 mg/dL with a prevalence ratio of 3.254 (95% CI 1.698-6.237). The results of the bivariate abalysis of each variable can be seen in full in table 2.

Variables that have a p value of < 0.25 in the bivariate analysis are then entered into a multivariate analysis with logistic regression, backward method. Variables with $p < 0.25$ from the bivariate analysis were pleuritic chest pain ($p=0.205$), exudate mononuclear dominant ($p=0.013$), complex thoracal ultrasound ($p=0.003$) and pleural fluid glucose ≤ 70 mg/dL ($p=0.002$). Final multivariate analysis found factors related to TPE were exudate mononuclear dominant, complex thoracal ultrasound and pleural fluid glucose ≤ 70 mg/dL. Full results can be seen in table 3.

In the analysis of scoring system each variable of exudate mononuclear dominant, complex thoracal ultrasound and pleural fluid glucose ≤ 70 mg/dL earn 1 point. Based on this, the maximal score of a subject was 3 (three) and the minimum score was 0 (null). Full results can be seen in table 4 and 5.

In the ROC analysis set the Area Under Curve (AUC) was 0.841 with $p<0.001$ (95% CI 0.762-0.926). This value was obtained at the best cut-off point ≥2 with sensitivity of 82.6% and sensitivity of 76.47%. Probability of TPE formula was -7,227 + 2,572 (Exudate mononuclear dominant) + 2,202 (Complex pleural effusion) + 2,413 (Pleural fluid glucose ≤ 70 mg/dL)Full results can be seen in table 4 and figure 1, 2.

In this study there were 19 subjects which had score ≥2 with probability of 92,8%. This can be seen in table 5 and 6.

This study used Hosmer –Lemeshow in terms of calibration and got $p=0.662$. After bootstrapping 1000 times this study resulted constant result of $p=0.662$. Value of $p>0.005$ suggest good calibration.

DISCUSSION

In this study the mean age of subjcts was 51.7 years old. This characteristic was different from Solari et al which had mean age 43.5 years old

in their study. The majority gender of this study was female with proportion of 54.9%. This was different result with the study of Solari et al.[19] Malignancy is the most frequent comorbid in this study with proportion of 57.1%. This is different with the study of Neves et al that malignancy had 19% proportion.[20] This differences may be because the status of Cipto Mangunkusumo Hospital as a tertiary healthcare facility that most of the cases were the complex cases that cannot be handled in primary or secondary healhcare facility such as malignancy.

The proportion of TPE in this study was 25.3%. This is suitable with other result which were 22.9% in Lampung and 30.84% in Solo.[21,22] Mean age of TPE group was 48.5 years old. This was different from Solari et al with 37.1 years old.[19] In this study most gender in TPE group was fenmale with proportion of 64%. This was in line with study of Amalia and Pradjoko with female proportion of 61.1%.[23]

Age relations with TPE

This research did not get a significant relationship between young age and TPE. The results of this study are not in line with the Solari study in Peru which found that age under 40 years was related to the incidence of TPE with OR 0.96 (95% CI 0.94 – 0.98). In those study, mean age of TPE was 37.1 years old, meanwhile mean age of TPE in this study was 43.5 years old. In high prevalence country, TPE usually occurred in young age patients.[19] This insignificant result is probably caused by differences of population and characteristic in this study that Cipto Mangunkusumo Hospital is tertiary healthcare facility that has geriatric healthcare facility.

Pleuritic chest pain relations with TPE

This research did not get a significant relationship between pleuritic chest pain and TPE after multivariate analysis. This result may be because the different of proportion between pleuritic chest pain and other (complex thoracal ultrasound, exudate mononuclear dominant and low pleural fluid glucose). This result is not in line with study of Maskell that pleuritic chest pain is 75% of TPE cases.[24] Pleuritic chest pain is caused by inflammation of parietal pleura and has various etiologies such as malignancy and infection. The role of Cipto Mangunkusumo Hospital as tertiary healthcare facility with high malignancy prevalence may be contribute to this insignificant result.

Unilateral pleural effusion relations with TPE

This research did not get a significant relationship between unilateral pleural efusion and TPE. This result is not in line with study of Neves that unilateral pleural effusion with Odds Ratio (OR) 2.75 (95% CI 0.8-10.6).[20] Bintcliffe stated that common unilateral pleural effusion etiologies were TB, malignancy and infection.[25] The role of Cipto Mangunkusumo Hospital as tertiary healthcare facility with high malignancy prevalence may be contribute to this insignificant result.

Low pleural fluid glucose relations with TPE

This study found a significant relationship between pleural fluid glucose ≤ 70 mg/dL with TPE with p=0.001 and OR 11.168 (95% CI 2.675-46.627). This result is in line with study of Gonzalez that has a meaningful relation with p<0.0001.[26] In other literature, Lee stated that complex pleural efusion resulted in lower pleural fluid glucose compare to non-complex pleural effusion.[27] Low pleural fluid glucose explained the chronic inflammation process of TB and estimated to be related with pleural thickening.

Exudate mononuclear dominant relations with TPE

This study found a significant relationship between exudate mononuclear dominant with TPE with p=0.001 and OR 13.090 (95% CI 2.680-63.932). [9]This result is in line with literature of Akhan that stated that tuberculin protein exposure accumulated and resulted exudate pleural effusion.[9] Other literature by Lei stated that due to cellular defense mechanism of body against TB infection, macrophage release cytokine such as IL-1, IL-6 and TNF- α. Then

the accumulation of lymphocyte and monocyte is formed and become dominant.[28] In literature Shaw stated that in high prebalence region, the increase of ADA and exudate mononuclear dominant has Positive Predictive Value (PPV) of 98%.[29]

Negative malignancy cytology relations with TPE

This research did not get a significant relationship between negative malignancy cytology and TPE. This result is not in line with Bays and Pierson that tuberculosis drugs can be initiated when exudate mononuclear dominant, complex thoracal ultrasound and low pleural fluid glucose is obtained.[30] Wande revealed that sensitivity of cytology examination is approximately 40%.[31] This insignificant result may be because malignancy as the most frequent comorbid in this research and limited sensitivity of cytology examination.

Complex thoracal ultrasound relations with TPE

This study found a significant relationship between complex thoracal ultrasound with TPE with p=0.001 and OR 9.040 (95% CI 2.325-35.151). This result is in line with study of Akhan that 90% of TPE consist of complex pleural effusion.[9] The formed of fibrin is advanced stage of pleuritis and can divide effusion into some cavity that divided by septae.[32] In other literature, Lee stated that combination of exudate mononuclear dominant and complex thoracal ultrasound got 47% sensitivity, 96% specificity, 94% PPV and 59% NPV.[27]

Blood NLR relations with TPE

This research did not get a significant relationship between blood NLR and TPE. This result is not in line with Kamelia that NLR is related to TB activity with cut-off value >2,9.[14] This result also not in line with Han that high NLR related with activity and prognosis of TB (aHR 1,08, IK 95% 1,03-1,13).[33] In other literature, Faria stated that acute condition and progressivity of malignancy can also increase NLR.[34] This insignificant result may be because malignancy as the most frequent comorbid in this research and mostly in acute condition.

Creation of scoring system

In the final model of multivariate analysis three predictor variables were exudate mononuclear dominant, complex thoracal ultrasound and pleural fluid glucose ≤70 mg/dL. Then these three variables were analyzed in order to create a scoring system. Each variables had one point with maximum score of 3 (three) and minimum score of 0 (null). The system score then tested in ROC curve in figure 1. In ROC curve resulted AUC 0.841 with p<0.001 (95% CI 0.762-0.926). It means prediction in diagnosis of TPE was 84.1%. This value was obtained at the best cut-off point ≥2 with sensitivity of 82.6% and sensitivity of 76.47%. Full results can be seen in table 4 and figure 1, 2. In this study there were 19 subjects which had score ≥2 with probability of 92,8%. This can be seen in table 5 and 6. This study used Hosmer–Lemeshow in terms of calibration and got p=0.662. After bootstrapping 1000 times this study resulted constant result of p=0.662. Value of p>0.005 suggest good calibration.

CONCLUSION

In this study, the predictor variables in final model were exudate mononuclear dominant, complex thoracal ultrasound and pleural fluid glucose ≤70 mg/dL. These variables had 1 point of each variables with maximum score of 3 (three) and minimum score of 0 (null), and optimal score to predict TPE was ≥2 with probability of 92.8%. In the future we suggest there will be research with more heterogenic population for instance in lower healthcare facilities especially second healthcare service and region with low prevalence of TB. We also suggest research with more variables such as Ca-125, IGRA and IP-10.

STATEMENTS

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Statement of Ethics

This study protocol has been reviewed and approved by the Ethical Committee of the Faculty of Medicine, Universitas Indonesia. With certificate of ethical approval number: KET-1129/UN2.F1/ETIK/PPM.00.02/2019.

Disclosure Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Table 1. Baseline Characteristics

Variable	N=91
Sex, n (%)	
Male	41 (45,1)
Female	50 (54,9)
Comorbid disease, n (%)	
DM	15 (16,7)
Renal impairment, n (%)	
eGFR >90	47 (51,6)
eGFR 60-89	26 (28,6)
eGFR 45-59	6 (6,6)
eGFR 30-44	7 (7,7)
eGFR 15-29	2 (2,2)
eGFR <15	3 (3,3)
Liver disease, n (%)	16 (17,6)
Cardiovascular disease, n (%)	20 (22)
Malignancy, n (%)	52 (57,1)
Infection, n (%)	21 (23,1)
HIV seropositive, n (%)	2 (2,2)
Stroke, n (%)	5 (5,5)
Age, n (%)	
<40 years	24 (26,4)
>40 years	67 (73,6)
Pleuritic chest pain, n (%)	
Exist	28 (30,8)
Not exist	63 (69,2)
Unilateral pleural effusion, n (%)	
Exist	58 (63,7)
Not Exist	33 (36,3)
Characteristic, n (%)	
Exudate MN dominant	49 (53,8)
Not Exudate MN dominant	42 (46,2)
Cytology, n (%)	
Negative malignancy	72 (79,1)
Positive Malignancy	19 (20,9)
Thoracal ultrasound, n (%)	
Complex septated	32 (35,2)
Complex not septated	9 (9,9)
Echogenic	22 (24,2)

Anechoic	28 (30,8)
Pleural fluid glucose	
≤ 70 mg/dL	20 (22,0)
> 70 mg/dL	71 (78,0)
Blood NLR, n (%)	
≥2,9	77 (84,6)
<2,9	14 (15,4)

Table 2. Bivariate Analysis

Variable	TPE		PR (CI 95%)	p
	Yes	No		
Age				
<40 years	8 (33,3)	16 (667)	1,489 (0,724-3,060)	0,432
>40 years	15 (22,4)	52 (77,6)		
Pleuritic chest pain				
Exist	10 (35,7)	18 (64,3)	1,731 (0,865-3,464)	0,205
Not exist	13 (20,6)	50 (79,4)		
Unilateral pleural effusion				
Exist	14 (24,1)	44 (75,9)	0,885 (0,431-1,819)	0,936
Not Exist	9 (27,3)	24 (72,7)		
Characteristic				
Exudate MN dominant	18 (36,7)	31 (63,3)	3,086 (1,253-7,597)	**0,013**
Not Exudate MN dominant	5 (11,9)	37 (88,1)		
Cytology				
Negative malignancy	19 (26,4)	53 (73,6)	1,253 (0,484-3,249)	0,772
Positive Malignancy	4 (21,1)	15 (78,9)		
Thoracal ultrasound				
Complex	17 (41,5)	24 (58,5)	3,455 (1,501-7,956)	**0,003**
Not complex	6 (12,0)	44 (88,0)		
Pleural fluid glucose				
≤ 70 mg/dL	11 (55,0)	9 (45,0)	3,254 (1,698-6,237)	**0,002**
> 70 mg/dL	12 (16,9)	59 (83,1)		
Blood NLR				
≥2,9	20 (26,0)	57 (74,0)	1,212 (0,415-3,539)	1,000
<2,9	3 (21,4)	11 (78,6)		

Table 3. Multivariate Analysis

Model	Variable	OR (CI 95%)	p
Model 1	Pleural fluid glucose	10,728 (2,572-44,757)	0,001
	Exudate MN dominant	12,390(2,543-60,373)	0,002
	Complex thoracal ultrasound	8,666 (2,219-33,839)	0,002
	Plauritic chest pain	1,485 (0,445-4,953)	0,520
Model 2	Pleural fluid glucose	11,168 (2,675-46,627)	0,001
	Exudate MN dominant	13,090 (2,680-63,932)	0,001
	Complex thoracal ultrasound	9,040 (2,325-35,151)	0,001

Table 4. Step to Create Scoring System of TPE

Variable	B	SE	B/SE	Score	Rounding off
Exudate MN Dominant	2,572	0,809	3,178	1,000	1
Complex thoracal ultrasound	2,202	0,693	3,178	1,000	1
Pleural fluid glucose ≤ 70 mg/dL	2,413	0,729	3,309	1,041	1
Constant	-7,227	1,947			

Table 5. TPE Scoring System

Variable	Kategori	skor
Exudate MN dominant	Exudate MN dominant	1
	Not exudate MN dominant	0
Complex thoracal ultrasound	Complex	1
	Not complex	0
Pleural fluid glucose ≤70 mg/dL	≤ 70 mg/dL	1
	> 70 mg/dL	0
Total Score		**3**

Figure 1. ROC Curve

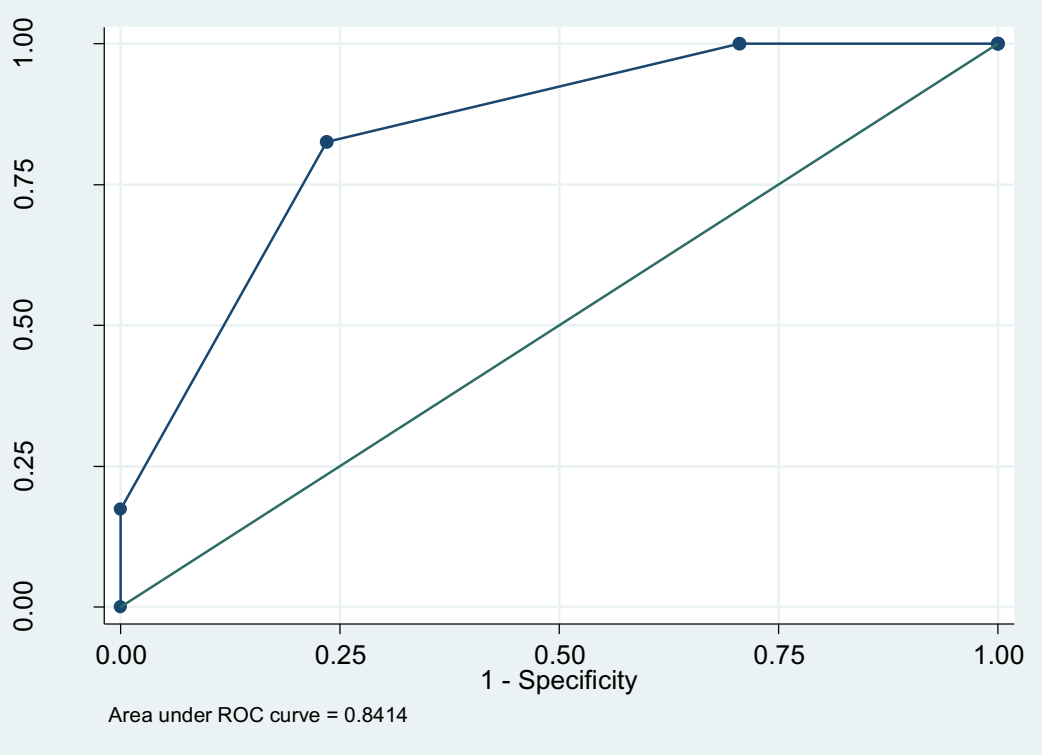

Table 6. Cut-off Value , Sensitivity and Specificity

Cut off point	Sensitivity (%)	Specificity(%)	LR+	LR-
0	100	0	1,000	
1	100	29,41	1,4167	0,0000
2	82,61	76,47	3,5109	0,2274
3	17,39	100		0,8261

Figure 2. Cut-off Curve of Sensitivity, Specificity and Total Score

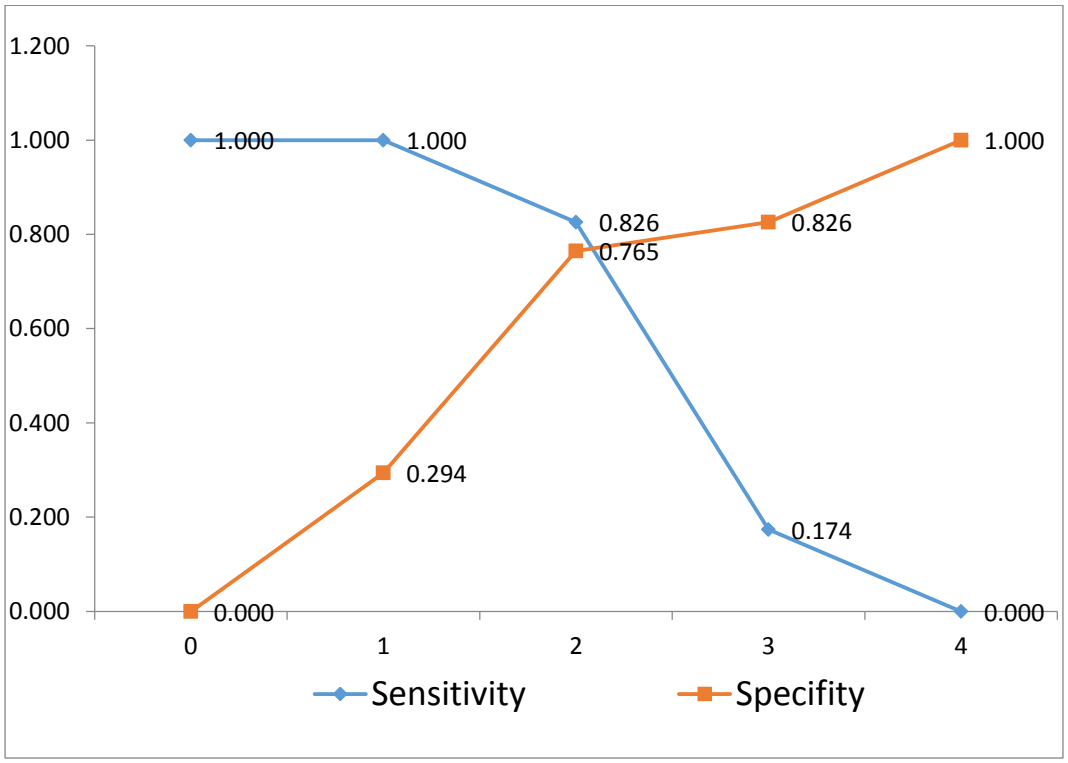

Table 7. Diagnosis Probability of each Score

Total Score	TPE	Not TPE	Probability
0	0	20	0,0
1	4	32	11,2
2	15	16	48,4
3	4	0	100,0

Table 8. Diagnosis Probability of TPE accoreding to final Scoring System

Total Score	TPE	Not TPE	Probability
<2	4	52	45,7%
≥2	19	16	92,8%