Journal of Izmir Chest Hospital 2023;37(1):34–40
DOI: 10.14744/IGH.2023.85520

RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

Diagnostic Value of Pleural Fluid Biochemical Parameters and Ratios for Differentiating Tuberculous Pleurisy from Parapneumonic Effusion and Malignant Effusion

Tüberküloz Plöreziyi Parapnömonik Efüzyon ve Malign Efüzyondan Ayırmak İçin Plevral Sıvı Biyokimyasal Parametreleri ve Oranlarının Tanısal Değeri

[1]Melike YÜKSEL YAVUZ
[2]Betül İkbal DOĞAN
[2]Ceyda ANAR
[3]Melih BÜYÜKŞİRİN
[3]Filiz GÜLDAVAL
[3]İbrahim Onur ALICI

[1]Department of Occupational and Occupational Diseases, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

[2]Department of Chest Disease, İzmir Katip Çelebi Training and Research Hospital, İzmir, Türkiye

[3]Department of Chest Disease, University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, İzmir, Türkiye

ORCID ID
MYY : 0000-0003-1674-2677
BİD : 0000-0001-9087-4921
CA : 0000-0002-3922-5800

ABSTRACT

Objective: The purpose of the present study was to examine the effectiveness of the rates of biochemical parameters used in our daily practice in patients with pleural effusion.

Material and Methods: The data of the patients with pleural effusion between January 2012 and October 2018 were analyzed retrospectively. Demographic data of all patients, concurrent serum glucose, albumin, protein, lactate dehydrogenase (LDH), pleural fluid (PF) pH, glucose, albumin, protein, adenosine deaminase (ADA), and LDH values were examined.

Results: Three hundred and eighty-one patients who had pleural effusion were enrolled in the study. Median PF-ADA levels in tuberculous pleural effusion (TPE), parapneumonic pleural effusion (PPE) and malignant pleural effusion (MPE) patients were 36, 15, and 9, respectively. The differences between groups were at significant levels (p=0.000). In receiver operating characteristics (ROC) curve analysis, the cutoff value was >3.0043, PF-ADA/serum C-reactive protein (CRP) ratio had 83% sensitivity, 55% specificity, positive predictive value (PPV) 48.7%, and negative predictive value (NPV) 86.8% for TPE identification. Serum LDH/PF-ADA ratio had 90.6% sensitivity, 69.6% specificity, PPV 58.4%, and NPV 93.9% for TB identification at ≤12.13 cutoff value. Another ratio was PF LDH/ADA, at a cutoff value of ≤28.6 PF LDH/ADA ratio had a sensitivity of 89.8%, specificity of 66.6%, PPV 60.7%, and NPV 91.9% for the identification of TPE. When we compare the ROC analysis for the identification of TPE, we found that PF-LDH/ADA and serum LDH/ADA gave significantly higher area under the curve values than PF-ADA/serum CRP.

Cite this article as: Yüksel Yavuz M, Doğan Bİ, Anar C, Büyükşirin M, Güldaval F, Alıcı İO. Diagnostic value of pleural fluid biochemical parameters and ratios for differentiating tuberculous pleurisy from parapneumonic effusion and malignant effusion. Journal of Izmir Chest Hospital 2023;37(1):34–40.

Received (Geliş): March 07, 2022 **Revised (Revize):** March 29, 2023 **Accepted (Kabul):** April 03, 2023 **Online (Çevrimiçi):** April 27, 2023
Correspondence author (Sorumlu yazar): Betül İkbal DOĞAN, MD. İzmir Katip Çelebi Atatürk Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Anabilim Dalı, İzmir, Türkiye.
Tel: +90 506 028 28 09 **e-mail:** betuldogan1993@hotmail.com

MB : 0000-0003-0700-2546
FG : 0000-0002-7712-5093
İOA : 0000-0002-9534-0897

Conclusion: This study provides parameters to distinguish TPE and PPE, MPE patients using existing routine laboratory tests. The combination of parameters reflecting different systemic and pleural features showed diagnostic performance only compared to biomarkers of systemic or pleural responses. Both serum LDH/ADA and pleural LDH/ADA ratio can be helpful in making an early differential diagnosis decision in a simple, fast, and objective way.

Keywords: Adenosine deaminase, C-reactive protein, lactate dehydrogenase, malignant effusion, parapneumonic effusion, tuberculous pleurisy.

ÖZ

Amaç: Bu çalışmanın amacı, plevral efüzyonlu hastalarda günlük pratiğimizde kullanılan biyokimyasal parametrelerin oranlarının etkinliğini incelemektir.

Gereç ve Yöntemler: Plevral efüzyonlu hastaların Ocak 2012 ile Ekim 2018 tarihleri arasındaki verileri geriye dönük olarak incelendi. Tüm hastaların demografik verileri, eş zamanlı serum glikozu, albümin, protein, laktat dehidrogenaz (LDH), plevral sıvı pH ve adenozin deaminaz (ADA) değerleri incelendi.

Bulgular: Çalışmaya plevral efüzyonu olan 381 hasta alındı. Tüberküloz plevral efüzyon (TPE), parapnömonik plevral efüzyon (PPE) ve malign plevral efüzyon (MPE) hastalarında ortanca plevral sıvı ADA düzeyleri sırasıyla 36, 15 ve 9 idi. Gruplar arasındaki farklar anlamlı düzeydeydi (p=0,000). ROC eğrisi analizinde cut-off değeri >3,0043, plevral sıvı ADA/S-C-reaktif protein oranı TPE tanımlaması için %83 duyarlılık, %55 özgüllük, pozitif prediktif değeri (PPV) %48,7 ve negatif prediktif değeri (NPV) %8,8 idi. Serum LDH/plevral sıvı ADA oranı, ≤12,13 cut-off değerinde tüberküloz tanımlaması için %90,6 duyarlılık, %69,6 özgüllük, %58,4 PPV ve %93,9 NPV'ye sahipti. Diğer bir oran ise plevral sıvı LDH/ADA, cut-off değeri ≤28,6 olan plevral sıvı LDH/ADA oranı %89,8 duyarlılık, %66,6 özgüllük, %60,7 PPV ve %91 NPV, TPE tanımlaması için %9. TPE tanımlaması için ROC analizini karşılaştırdığımızda, plevral sıvı LDH/ADA ve serum LDH/ADA'nın plevral sıvı ADA/S-C-reaktif proteinden anlamlı derecede daha yüksek AUC değerleri verdiği bulundu.

Sonuç: Bu çalışma, mevcut rutin laboratuvar testleri kullanılarak TPE ve PPE, MPE hastalarını ayırt etmek için parametreler sağlamaktadır. Farklı sistemik ve plevral özellikleri yansıtan parametrelerin kombinasyonu, yalnızca sistemik veya plevral yanıtların biyobelirteçleriyle karşılaştırıldığında daha iyi tanısal performans gösterdi. Hem serum LDH/ADA hem de plevral LDH/ADA oranı basit, hızlı ve objektif bir şekilde erken ayırıcı tanı kararının verilmesinde yardımcı olabilir.

Anahtar kelimeler: Adenozin deaminaz, C-reaktif protein, laktat dehidrogenaz, malign efüzyon, parapnömonik efüzyon, tüberküloz plörezi.

INTRODUCTION

Pleural effusion is one of the major causes of pulmonary mortality and morbidity, and its incidence is estimated as at least 1.5 million cases per year in the United States.[1] In our country, the common causes of exudative pleural effusions are malignant pleurisy 41%, parapneumonic pleurisy 16%, and tuberculous pleurisy (TPE) 15%.[2] A variety of biomarkers have been used to differentiate exudative pleural fluids (PF). Nevertheless, approximately 15–20% of pleural effusions cannot be diagnosed despite thoracentesis, cytology, and pleural biopsies.[3,4]

Pleural tuberculosis is the most common reason of extrapulmonary tuberculosis in adults in Türkiye.[5] Absolute diagnosis of TPE depends on detecting *Mycobacterium tuberculosis* in the sputum, PF, or pleural biopsy specimen.[6] For malignant effusion, cytological examination of the PF is used in diagnosing the pleural malignancy, but it was reported that there was approximately 40% false-negative rate.[7] In terms of parapneumonic effusions, there is no strong parameter that differentiates it from other exudative pleural effusions except for the appearance of pus in empyema. Therefore, the contribution of biochemical parameters in differential diagnosis is important to prevent further invasive procedures. In tuberculous pleurisy, the sensitivity and specificity of pleural adenosine deaminase (ADA) have been reported as 92% and 90%, respectively.[8] Furthermore, high ADA levels can sometimes be observed in PF from patients of parapneumonic effusion, empyema, and malignancy.[9] In addition, serum C-reactive protein (CRP) and serum-PF lactate dehydrogenase (LDH) levels were elevated in patients with tuberculous effusion, complicated parapneumonic effusion, empyema, and malignancy.[10–14]

The use of these parameters in the differential diagnosis may be satisfactory because of the lack of additional cost and intervention. We, as the same authors, have previously investigated the diagnostic value of PF LDH/ADA ratio to differentiate tuberculous pleurisy from parapneumonic pleural effusion (PPE).[15] If we use other biochemical rates (such as ADA/serum CRP [S-CRP], serum LDH/PF-ADA, etc.), we may increase the likelihood of diagnosis, or we may find it easier to reach the diagnosis when we use several rates based on biochemical parameters at the same time. In our previous study,[15] we found that the LDH/ADA ratio in the TBP group was significantly lower than the PPE group (p<0.001), and there was a statistically significant difference between the TBP group and all subgroups of PPE. The PF LDH/ADA ratio was found with 90% sensitivity, 59.85%

Table 1. Comparison of demographic and laboratory findings between tuberculous pleurisy and parapneumonic and malignant effusion patients

	Tuberculosis pleurisy (n=138) A	Parapneumonic (n=133) B	Malign effusion (n=110) C	p* A&B	p A&C	p B&C
Demographic data				0.000	0.000	0.000
Age, years	38	57	66.5			
Male/Female	43/95	53/80	26/84			
Blood						
S-CRP, mg/dL	5.21	5.14	4.66	0.740	0.766	0.610
Albumin, g/dL	3.50	3.70	3.56	0.053	0.805	0.051
S-protein	7	7	6.67	0.072	0.000	0.000
S-LDH, U/L	198	185	245.5	0.026	0.000	0.000
Pleural fluid						
Protein, g/dL	2.80	2.60	4.40	0.042	0.000	0.000
Glucose, mg/dL	99	98.5	105	0.417	0.464	0.780
PF-LDH, U/L	573	502	394	0.049	0.013	0.099
ADA, U/L	36	15	9	0.000	0.000	0.000
Ratio between two parameters*						
ADA/S-CRP	6.99	3.39	2	0.000	0.000	0.000
PF-LDH/S-LDH	2.27	2.58	1.52	0.000	0.680	0.000
PF-LDH/ADA	16.2	32.5	54.4	0.000	0.000	0.000
S-LDH/ADA	6.04	12.23	30.67	0.000	0.000	0.000

*: Mann-Whitney Test. S: Serum, CRP: C-reactive protein, LDH: Lactate dehydrogenase, PF-LDH: Pleural fluid lactate dehydrogenase, ADA: Adenosine deaminase.

specificity, 70.4% positive predictive value (PPV), and 84.9% negative predictive value (NPV), respectively when TBP was defined as ≤28. However, there was no malignant pleural effusion (MPE) group in that study. In this study, we included a MPE group and looked at the rates of other biochemical parameters to investigate whether we can increase the likelihood of diagnosis in differentiating tuberculous pleurisy from other common exudative pleural effusions. The purpose of the present study was to examine the effectiveness of the biochemical parameter rates used in our daily practice in patients with pleural effusion.

MATERIAL AND METHODS

Study Population

The present study was planned as a retrospective study and was conducted between January 1, 2014, and October 1, 2018, in İzmir University of Health Sciences Suat Seren Chest Diseases and Surgery Research Center. A total of 381 patients, 138 with TBP and 133 with PPE, and 110 with MPE were included in the study.

For the diagnosis of tuberculosis pleurisy, at least one of the following criteria was required:

- Tuberculosis bacilli isolation from PF or pleural tissue
- Detection of ARB positivity or caseous granuloma structure in pleural tissue
- Response to anti-tuberculosis treatment even though ARB is negative in pleural tissue
- Positive for tuberculosis bacillus in sputum culture and exclusion of other causes in a patient with PF
- The PF-ADA level being higher than 40 U/L, which cannot be explained by other pathology in the young patient population with no concomitant disease.

Criteria regarding PPE diagnosis: No malignant cell in PF, diagnosis of TBP, and lung TB excluded, the dominance of neutrophil, bacterial growth in non-specific culture, nonspecific inflammation detected in the pleural biopsy, and exudative fluid responsive to antibiotic therapy.

Criteria regarding MPE diagnosis: Detecting malignant cells in PF cytology or finding of malignancy by pleural biopsy and Video-associated thoracic surgery confirms the diagnosis of MPE.

Exclusion Criteria

The following criteria were excluded from the study:

- Patients below 15 years of age
- Patients with suspected pregnancy or pregnancy.

Table 2. Diagnostic yields of laboratory parameters to identify tuberculous pleural effusion

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	p
PF-ADA	≥20	91.3	75	67.7	93.7	0.85 (0.81–0.89)	<0.0001
PF-ADA/CRP	>3.0043	83.3	55.5	48.7	86.8	0.70 (0.64–0.75)	0.000
PF-LDH/S-LDH	>1.64	75.4	47.1	40	80	0.56 (0.50–0.63)	0.000
PF-LDH/ADA	≤28	89.8	66.6	60.7	91.9	0.84 (0.80–0.88)	0.000
S-LDH/ADA	≤12	90.5	69.4	58.4	93.9	0.83 (0.70–0.87)	0.000

*: Only ratio that yielded p value of p=0.000 among the three groups was included. PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval, PF-ADA: Pleural fluid adenosine deaminase, CRP: C-reactive protein, PF-LDH: Pleural fluid lactate dehydrogenase, S-LDH: Serum lactate dehydrogenase.

Academic board approval was obtained from the training planning board of İzmir University of Health Sciences Suat Seren Chest Diseases and Surgery Research Center. The names, protocol numbers, age, and gender of the patients included in the study were recorded. LDH, ADA, LDH/ADA ratio, glucose, albumin, protein, pH and serum albumin, CRP, protein, LDH, glucose, ADA levels, PF examination, culture, and cytology were recorded.

Statistical Analysis

The data were analyzed in IBM SPSS Statistics 25.0 statistical package program. Descriptive statistics were given as numbers (n), percentage (%), mean±standard deviation (x deviation±ss), and median (IQR) values. Pearson's Chi-square and Fisher's exact test were employed to assess categorical variables. Normal distribution of numerical variables was evaluated with Shapiro–Wilk, normality test, and Q-Q graphs. In the determination of the relationship between the two numerical values, Pearson was employed for variables with normal distribution and Spearman correlation analysis was used for the variables that did not show normal distribution. The comparison of the two groups of variables with normal distribution was made by the Independent sample t-test, and for the variables which did not fit the normal distribution, by Mann–Whitney U analysis. The comparison of three or more groups of variables with normal distribution was made with one-way variance analysis, and Kruskal–Wallis analysis was used for variables that did not show normal distribution. In the one-way analysis of variance, multiple comparisons were made by Tukey HSD test. The diagnostic value of ADA/CRP ratio to differentiate TBP from PPE and MPE was evaluated by receiver operating characteristics (ROC) test. Threshold values were determined using Youden index. Sensitivity and specificity values were calculated based on the threshold values obtained. P<0.05 was considered statistically significant.

RESULTS

Three hundred and eighty-one patients with pleural effusion were included in the study. There were TPE in 138 patients, PPE in 133 patients and MPE in 110 patients. Table 1 shows the groups' demographic and laboratory data. Serum LDH (S-LDH) levels were high at significant levels in the MPE group compared to TPE and PPE group (p=0.000), and S-CRP, albumin, and S-LDH levels were not different at significant levels among the groups.

The median PF-ADA levels in TPE, PPE, and MPE patients were 36, 15, and 9, respectively. The differences were at significant levels among the groups (p=0.000). In comparison of PF profiles, PF LDH was high at significant levels in TPE group compared to PPE and MPE group (p=0.049). PF protein and glucose concentrations were not different at significant levels among the groups.

The rate between two parameters was statistically significant (p=0.000) among the groups (Table 1). The ADA/S-CRP, PF-LDH/S LDH, PF-LDH/ADA, and serum-LDH/ADA ratios showed significant differences at the highest levels (p=0.000).

To identify TPE, the diagnostic performance of the ratios that had statistically significant differences (p=0.000) among the groups are given in Table 2. A cutoff value of >3.0043 for the PF-ADA/S-CRP ratio and had a sensitivity of 83%, specificity of 55%, PPV 48.7%, and NPV 86.8% in the ROC curve analysis for the TPE identification (Table 2 and Fig. 1). Furthermore, PF-ADA level had a sensitivity of 91.3%, specificity of 75%, NPV 93.7% for identification of TPE (Table 2). Serum LDH/PF-ADA ratio had a sensitivity of 90.6%, specificity of 69.6%, PPV 58.4%, and NPV 93.9% for TB identification at a cutoff value of ≤12.13 (Fig. 2). Another ratio is PF LDH/ADA, at a cutoff value of ≤28, 6, PF LDH/ADA ratio had a sensitivity of 89.8%, specificity of 66.6%, PPV 60.7%, and NPV 91.9% for TPE identification (Fig. 3). When we compared the ROC analysis for the identification of TPE, we found that PF LDH/ADA and serum LDH/ADA gave significantly higher area under the curve values than PF-ADA/S-CRP (Fig. 4).

Multivariate regression analysis indicated that PF-LDH/ADA ≤28 (p=0.000, OR: 9.1, CI: 3.9–20.8%) and having PF-ADA ≥20 (p=0.000, OR: 7.36, CI: 2.9–18.6%) were the parameters to detect tuberculous pleural effusion (Table 3).

DISCUSSION

This study shows the diagnostic performance of the ratio parameters for the identification of TPE between the TPE and PPE, MPE. In the ROC curve analysis, at >3.0043 cutoff value, the PF-ADA/S-CRP ratio had a sensitivity of 83%, specificity of 55%, PPV 48.7%, and NPV 86.8% to identify TPE. Serum LDH/PF-ADA ratio had a sensitivity of 90.6%, specificity of 69.6%, PPV 58.4%, and NPV 93.9% for TB identification at ≤12.13 cutoff value. PF-ADA/S-CRP ratio >5.62 provided 89% sensitivity, 88% specificity, positive likelihood ratio (LR) of 7.29, and negative LR of 0.13 for TPE identification in a recent study.[16] These ratios and biochemical parameters are simple, fast, and objective methods that are routinely evaluated in clinics. This informa-

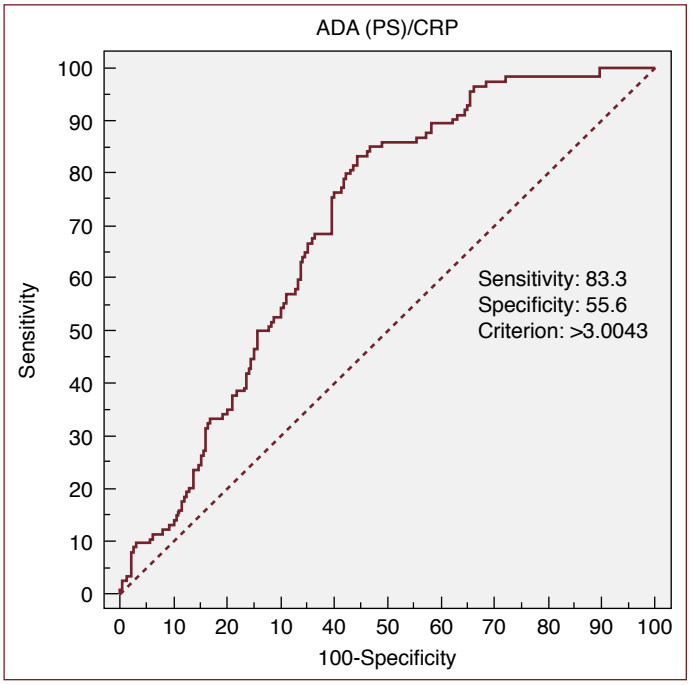

Figure 1: Pleural fluid adenosine deaminase/serum C-reactive protein ratio in receiver operating characteristics curve analysis for the TPE identification.

ADA: Adenosine deaminase, PS: Pleural fluid, TPE: Tuberculous pleural effusion.

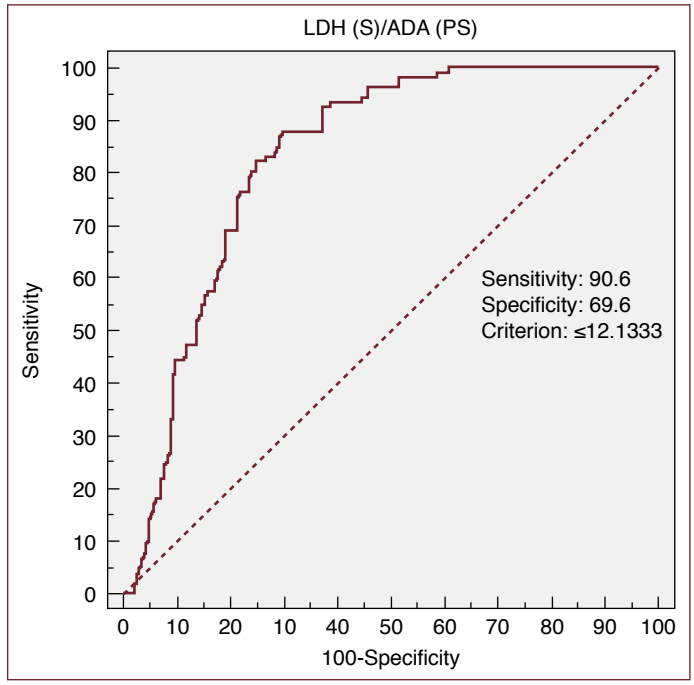

Figure 2: Serum lactate dehydrogenase/pleural fluid adenosine deaminase ratio in receiver operating characteristics curve analysis for the TPE identification.

S: Serum, PS: Pleural fluid, TPE: Tuberculous pleural effusion.

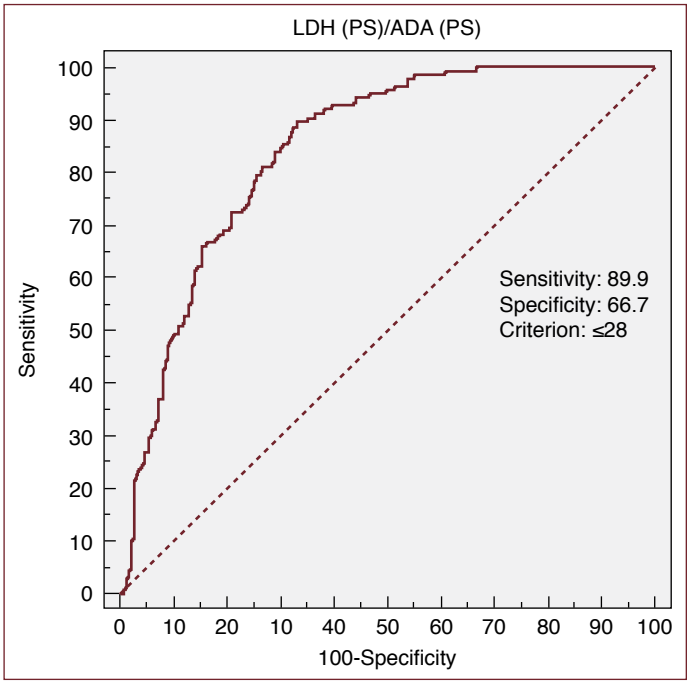

Figure 3: Pleural fluid lactate dehydrogenase/adenosine deaminase ratio in receiver operating characteristics curve analysis for the TPE identification.

PS: Pleural fluid, TPE: Tuberculous pleural effusion.

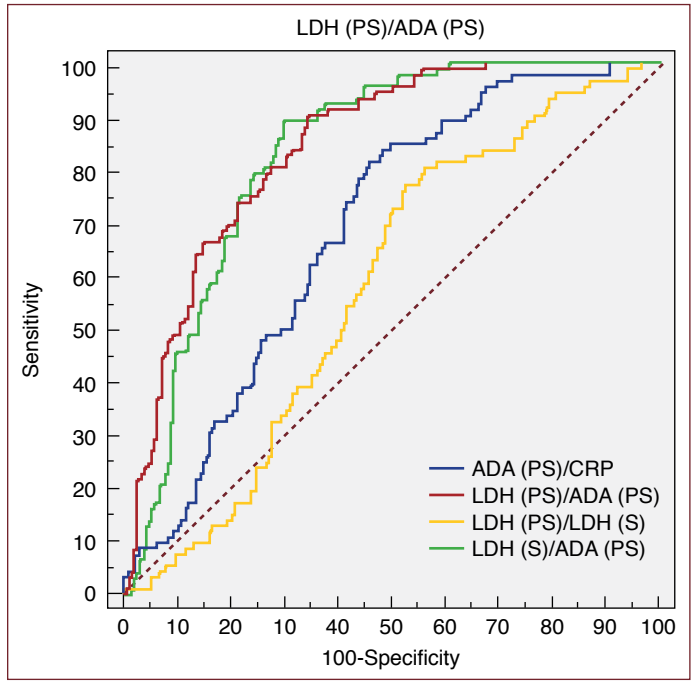

Figure 4: Compare the receiver operating characteristics analysis for the identification of TPE.

LDH: Lactate dehydrogenase, PS: Pleural fluid, ADA: Adenosine deaminase, S: Serum, TPE: Tuberculous pleural effusion.

tion might have greater significance in early clinical decision-making processes for proper management of such patients, which will result in better prognosis and prevention of potential negative outcomes.

High PF-ADA levels were attributed to high TPE probability and many PPE exhibited PF-ADA levels below 40 U/L.[17–20] It is an independent positive predictor for TPE in a previous study of

Table 3. Multivariate regression analysis of laboratory parameters to identify tuberculous pleural effusion

	Exp (B)	95% CI		p
		Lower	Upper	
PF-ADA ≥20	7.36	2.9	18.6	0.000
PF-LDH/ADA ≤28	9.1	3.9	20.8	0.000
S-LDH/ADA ≤12.1	3.2	1.2	8.6	0.019

CI: Confidence interval, PF-ADA: Pleural fluid adenosine deaminase, PF-LDH: Pleural fluid lactate dehydrogenase, S-LDH: Serum lactate dehydrogenase.

TPE and PPE patients with PF-ADA levels >58/L, neutrophilic dominance, and PF-ADA levels ≥40 U/L.[20] On the other hand, S-CRP levels have inverse properties between TPE and PPE.[19–21] Bacterial infections are present in 80–85% of patients with S-CRP concentrations higher than 10 mg/dL.[22] Furthermore, PF-CRP levels that might possibly show S-CRP levels are beneficial parameters to distinguish between different exudative pleural effusions.[23–25] Our findings regarding PF-ADA levels are compatible with the previous studies. However, contrary to the literature, serum CRP levels were not significant in distinguishing tuberculosis pleurisy, ADA/CRP ratio was statistically significant. In addition, PF-ADA/S-CRP ratio provided diagnostic accuracy in this study.

Another parameter known as cancer rate is serum LDH/PF-ADA. The ratio of serum LDH/PF-ADA, TPE is significantly lower in patients. Especially, serum LDH/PF-ADA ratio cutoff level for <12 highly predicts TPE in patients with exudative pleural effusion (whether lymphocytic or neutrophilic) with high sensitivity and specificity.

The present study had several limitations, one of which was the retrospective design. Second, the other causes of exudative effusions like connective tissue disease were not examined to validate the results in this patient group. Third, many patients that had malignant effusions also had lung cancer. Fourth, due to the retrospective nature of the study, the timing of sampling during thoracentesis could not be standardized. Therefore, most TBPs are likely to develop lymphocytic predominance within a week and an increase in ADA levels. In addition, we cannot completely exclude the potential effect of empiric antibiotics on patients with TBP and with PPE, and the implications of subsequent thoracentesis on PF analysis. Fifth limitation may be the absence of an evaluation of the increase in the level of ADA with recurrent thoracentesis and ADA isoenzymes. A future study with prospective design that will eliminate these limitations and will help to validate the findings of the present study.

CONCLUSION

As a conclusion, the present study provided parameters to distinguish between TPE and PPE, MPE patients using existing routine laboratory tests. The combination of parameters reflecting different systemic and pleural features showed diagnostic performance only compared to biomarkers of systemic or pleural responses. This convenient, fast and objective predictor can be useful in early clinical decisions and treatment of such patients.

Disclosures

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Y.Y.; Design – C.A.; Supervision – B.İ.D.; Fundings – M.B.; Materials – F.G., B.İ.D.; Data Collection and/or Processing – İ.O.A.; Analysis and/or Interpretation – M.Y.Y.; Literature Search – C.A.; Writing – İ.O.A.; Critical Reviews – M.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sahn SA. The value of pleural fluid analysis. Am J Med Sci 2008;335:7–15.
2. Selma M. Epidemiology of Pleural Diseases. Diagnosis and Treatment of Pleural Diseases for Chest Diseases Specialists. Ankara: TTD and TÜSAD Publication; 2016.
3. Light RW. Pleural Diseases. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.
4. Venekamp LN, Velkeniers B, Noppen M. Does 'idiopathic pleuritis' exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. Respiration 2005;72:74–8.
5. T.C. Sağlık Bakanlığı. Tüberküloz tanı ve tedavi rehberi. 2.baskı. Ankara; 2019.
6. Light RW. Pleural diseases. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
7. Porcel JM. Pearls and myths in pleural fluid analysis. Respirology 2011;16:44–52.
8. Liang QL, Shi HZ, Wang K, Qin SM, Qin XJ. Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: A meta-analysis. Respir Med 2008;102:744–54.
9. Hooper C, Lee YC, Maskell N; BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010;65(Suppl 2):ii4-17.
10. Chierakul N, Kanitsap A, Chaiprasert A, Viriyataveekul R. A simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirology 2004;9:66–9.
11. Mohamed SAA, Agmy GR, Wafy SM. Value of C-reactive protein in differentiation between tuberculous and malignant pleural effusion. Egypt J Bronchol 2017;11:49–55.
12. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 1972;77:507–13.
13. Wu KA, Wu CC, Liu YC, Hsueh PC, Chin CY, Wang CL, et al. Combined serum biomarkers in the noninvasive diagnosis of complicated parapneumonic effusions and empyema. BMC Pulm Med 2019;19:108.
14. Smith RP, Lipworth BJ. C-reactive protein in simple community-acquired pneumonia. Chest 1995;107:1028–31.
15. Anar C, Yüksel M, Alıcı İO, Güldaval F, Büyükşirin M. Diagnostic value of pleural fluid lactate dehydrogenase/adenosine deaminase ratio in differentiating parapneumonic effusion from tuberculous pleurisy. Egypt J Chest Dis Tuber 2021;70:547–53.
16. Lee J, Yoo SS, Lee SY, Cha SI, Park JY, Kim CH. Pleural fluid adenosine deaminase/serum C-reactive protein ratio for the differentiation of tuberculous and parapneumonic effusions with neutrophilic predominance and high adenosine deaminase levels. Infection 2017;45:59–65.

17. Porcel JM, Esquerda A, Bielsa S. Diagnostic performance of adenosine deaminase activity in pleural fluid: A single-center experience with over 2100 consecutive patients. Eur J Intern Med 2010;21:419–23.
18. Trajman A, da Silva Santos Kleiz de Oliveira EF, Bastos ML, Belo Neto E, Silva EM, da Silva Lourenço MC, et al. Accuracy of polimerase chain reaction for the diagnosis of pleural tuberculosis. Respir Med 2014;108:918–23.
19. Kiropoulos TS, Kostikas K, Oikonomidi S, Tsilioni I, Nikoulis D, Germenis A, et al. Acute phase markers for the differentiation of infectious and malignant pleural effusions Respir Med 2007;101:910–8.
20. Lee J, Lee SY, Lim JK, Yoo SS, Lee SY, Cha SI, et al. Radiologic and laboratory differences in patients with tuberculous and parapneumonic pleural effusions showing non-lymphocytic predominance and high adenosine deaminase levels. Infection 2015;43:65–71.
21. Lee J, Lim JK, Lee SY, Yoo SS, Lee SY, Cha SI, et al. Neutrophilic loculated tuberculous pleural effusion: Incidence, characteristics and differentiation from complicated parapneumonic effusion. Am J Med Sci 2016;351:153–9.
22. Morley JJ, Kushner I. Serum C-reactive protein levels in disease. Ann N Y Acad Sci 1982;389:406–18.
23. Daniil ZD, Zintzaras E, Kiropoulos T, Papaioannou AI, Koutsokera A, Kastanis A, et al. Discrimination of exudative pleural effusions based on multiple biological parameters. Eur Respir J 2007;30:957–64.
24. Porcel JM, Vives M, Cao G, Bielsa S, Ruiz-González A, Martínez-Iribarren A, et al. Biomarkers of infection for the differential diagnosis of pleural effusions. Eur Respir J 2009;34:1383–9.
25. Porcel JM. Pleural fluid tests to identify complicated parapneumonic effusions. Curr Opin Pulm Med 2010;16:357–61.