Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublisher.com

Clinical Pathology

Influence of Age and Sex on the Diagnostic Accuracy of Total Lactate Dehydrogenase as a Biomarker for Empyema and Complicated Parapneumonic Pleural Effusions

Paloma Ferreira Meirelles Vahia[1], Cyro Teixeira da Silva Junior[2*], Patricia Siqueira Silva[3], Joeber Bernardo Soares de Souza[1], Jorge Luiz Barillo[1], Elizabeth Giestal de Araujo[4], Analucia Rampazzo Xavier[5]

[1]MD, Physicians, Hospital Universitário Antônio Pedro, Fluminense Federal University, Niteroi, State of Rio de Janeiro, Brazil

[2]PhD, MD, Associate Professor, Department of Clinics, School of Medicine, Fluminense Federal University, Niteroi, State of Rio de Janeiro, Brazil

[3]Bsc, Biologist, Clinical Analysis Specialist, Fluminense Federal University, Niteroi, State of Rio de Janeiro Brazil

[4]PhD, MD, Full Professor, Department of Neurobiology, Fluminense Federal University, Niteroi, State of Rio de Janeiro, Brazil

[5]PhD, Associate Professor, Department of Clinical Pathology, School of Medicine, Fluminense Federal University, Niteroi, State of Rio de Janeiro, Brazil

Original Research Article

***Corresponding author**
Cyro Teixeira da Silva Junior

Article History
Received: 10.07.2018
Accepted: 18.07.2018
Published: 30.07.2018

DOI:
10.21276/sjams.2018.6.7.3

Abstract: Enzymes are biological molecules that can be used as biomarkers of diseases. An old enzyme found in pleural fluid and not attracting significant attention in recent years as biomarker of disease, is lactate dehydrogenase (LDH). Thus, our purpose in this study was to determine the influence of age and sex on the diagnostic accuracy of pleural fluid total lactate dehydrogenase (P-LDH) levels in the differential diagnosis of pleural effusions. LDH assays were performed to assess diagnostic accuracy. A total of 308 samples (serum [n=137], pleural fluid [n=171]) were tested. The median P-LDH levels from patients with complicated parapneumonic pleural effusions (CPPE) and empyemas were not differentiated using the Kruskal-Wallis test (P>0.05). There was negative and statistically significant correlation between P-LDH level and sex in patients with CPPE/pleural empyema (rho = -0.661, P=0.0376, r^2=0.4369). There was no significant correlation between P-LDH level and age dichotomized at 48 years (rho=0.170, P=0.5448, r^2=0.0289). For the diagnosis of CPPE/pleural empyema, the best P-LDH cut-off values according to receiver operating curve (ROC) analysis were > 1188.0 U/L for males (area under the curve [AUC] 0.957 [95% CI 0.902-0.986]; P<0.0001) and > 1372.0 U/L (AUC 0.985 [95% CI 0.912-1.00]; P<0.0001) for females. LDH was a useful diagnostic biomarker for pleural effusion syndrome. Sex had a significant influence on the cut-off value for P-LDH in the diagnosis of CPPE/pleural empyema, which should be treated as a single disease with chest tube drainage and other management.

Keywords: Lactate dehydrogenase; Reference values; Pleural effusion; Empyema; Complications.

INTRODUCTION

Pleural effusion syndrome (PES) is an excessive accumulation of fluid that occurs between the parietal and visceral pleura. It may be related to diseases of the lung or pleura, or to a systemic disorder with different pathophysiological mechanisms. Tuberculosis, cancer, congestive cardiac failure, pneumonia and pulmonary emboli, among others, are diseases or conditions that can complicate or be clinical signs in imaging examinations of PES [1]. Thoracentesis guided with extracardiac transthoracic ultrasonography (ETUS) is one of the most common medical procedures to diagnose PES, with adequate levels of several biomarkers present only in the pleural fluid [2]. Several biomarkers are useful to simplify the evaluation, and to reduce costs and increase the accuracy of diagnosis [3].

Enzymes are biological molecules that can be used as biomarkers of diseases. An old enzyme found in pleural fluid and not attracting significant attention in recent years as biomarker of disease, is lactate dehydrogenase (LDH). Nevertheless, in our daily clinics, LDH is a diagnostic test for different approaches in pleural diseases. First, the criteria proposed by Light for diagnosing transudates and

exudates in pleural diseases was defined as the ratio of pleural fluid LDH divided by serum LDH > 0.6, and/or pleural fluid LDH > 2/3 the upper limit of normal for serum LDH [4]. Second, a classification for exudates and transudates only in pleural fluids with an appropriate level of total proteins and LDH, with reference values at 3.4 mg/dL and/or 328.0 U/L, respectively, has demonstrated utility in recent years [5]. Third, a high LDH level (> 600 U/L) in malignant pleural effusion is associated with a poorer outcome in pleurodesis [6].

LDH (EC 1.1.1.27) is a key enzyme in lactic acid fermentation. It converts pyruvate to lactate and regenerates nicotinamide-adenine dinucleotide (NAD) for the continuation of glycolysis [7]. Although it has no metabolic function in extracellular localization, this cellular enzyme is present in the pleural space, where it is an important indicator suggestive of disturbances in tissue integrity induced by pathological conditions [8]. Thus, we hypothesized that LDH could be a novel biomarker for the diagnosis of PES.

OBJECTIVES

The primary objective of the present study, therefore, was to evaluate the value of pleural fluid total LDH (P-LDH) levels for the etiologic diagnosis of PES. The secondary objective was to determine the influence of age and sex on the diagnostic accuracy of P-LDH analysis in the differential diagnosis of pleural effusions selected according to our primary objective.

MATERIALS AND METHODS

To prevent or, at least, mitigate errors from occurring in this study, the methodological criteria recommended by the Clinical and Laboratory Standards Institute and the Standards for Reporting Diagnostic Accuracy were applied [9]. This original research was a prospective study of diagnostic accuracy conducted between March 2002 and June 2017, involving patients who underwent thoracentesis and pleural biopsy at the Center for Teaching and Research, a referral center in Pleurology at Universidade Federal Fluminense, located in the State of Rio de Janeiro, Brazil. The Ethics Committee approved this study in accordance with recommendations described in the Declaration of Helsinki under protocol number 80/02.

Approach to patients with PES

When the causal diagnosis of PES was not confirmed after thoracentesis using laboratory evaluations, other surgical procedures were performed. If PES persisted, or when it was not possible to differentiate malignancy from tuberculosis, the patient was forwarded for video-assisted thoracoscopic surgery [1, 10].

Inclusion criteria

The cause of PES was confirmed using standard examinations and appropriate surgical procedures [1, 3, 10]. The criteria described by Maranhão and Silva Junior were used to classify pleural effusions as transudate or exudate [5]. The diagnosis of tuberculous pleural effusion was confirmed after clinical presentation, and pleural biopsy specimens with granulomas in the pleura without evidence of other granulomatous diseases, or elevated levels of adenosine deaminase in the pleural fluid. Pleural effusion was diagnosed to be malignant when confirmed by positive cytology or conclusive pleural biopsy using samples obtained from the pleura. Uncomplicated parapneumonic effusion (UPPE) was diagnosed as pleural fluid that results from pneumonia, lung abscess or bronchiectasis, in patients who were cured using antibiotic therapy alone. A complicated PPE (CPPE) was defined as a non-purulent pleural fluid that required prompt drainage to avoid evolution to a pleural empyema. Empyema was defined as pus in the pleural space and/or a positive Gram stain or culture, or loculated pocket of pus, and pleural fluid analysis with low glucose levels. Pleural systemic lupus erythematosus (SLE) was diagnosed as clinical manifestations, positive serum biomarkers and pleural biopsy with immunofluorescence combined with light-microscopic examination. A diagnosis of pleural paracoccidioidomycosis was made in patients with compatible clinical manifestations, adequate epidemiological profile, imaging studies, and conclusive oral mucosa biopsy, with no other causes of PES investigated [1].

Exclusion criteria

Exclusion criteria were an absolute contraindication or noncompliance to thoracentesis or other invasive surgical procedure(s), use of immunosuppressive drugs, hemolysis in pleural fluids, renal failure, HIV infection, or PES without a known cause.

LDH assay

The LDH method was standardized according to the International Federation of Clinical Chemistry [11]. The LDH assay was performed using a commercial kit, in which the reaction velocity is determined by a decrease in absorbance at 340 nm resulting from the oxidation of NADH according to the reference procedures for measuring enzyme catalytic activities at 37°C [11]. The biological samples were obtained free of hemolysis and collected in tubes without anticoagulant. LDH and glucose in pleural fluids were quantified immediately. Other biomarkers were stored for seven days at between 2°C and 4°C, or for 20 days at -20°C.

Statistical approaches

In this study, we analyzed both descriptive and inferential statistics in all data using evaluations entered into Office Excel 2013 (Microsoft Corporation, Redmond, WA, USA) and exported to the database of NCSS version 11 (NCSS LLC, Kaysville, UT, USA), or

MedCalc version 16.4.3 (MedCalc Software, Ostend, Belgium) for Windows (Microsoft Corporation, Redmond, WA, USA). A two-tailed $P < 0.05$ was considered to be statistically significant, and to reject the null hypothesis and define a type I error. The Shapiro-Wilk test was used to assess the normality of the continuous variables. Quantitative variables with normal distribution were expressed as mean and standard deviation (SD), variables with non-normal distribution were expressed as median and interquartile range (IQR). Qualitative or categorical variables were expressed as proportions. The differences in the medians of serum LDH (S-LDH) and P-LDH were analyzed using the Mann-Whitney U test (Wilcoxon rank-sum test) for independent samples, which is ***a*** non-parametric alternative to the t-***test.*** The Kruskal-Wallis test and, where appropriate, followed by a post hoc Dunn test, were used to compare medians of the LDH results from sera and pleural fluids. This is a non-parametric test proposed by Kruskal and Wallis in 1952, and is used when the data do not satisfy the normality property and contain outliers. Spearman's rank correlation coefficient was used to identify the strength of the relationship between the P-LDH levels and specified variables (i.e., age and sex) for an entire sample of empyema and CPPE.

For medical decision limits, the best P-LDH cut-off value for the diagnosis of empyema and CPPE was selected using a receiver operating characteristic (ROC) curve [9]. The criterion for determining the optimal threshold point of P-LDH levels identified by the ROC curve was the highest value of area under ROC curve (AUC) [12]. The AUC (Z statistic) with 95% confidence interval (CI) was calculated using a non-parametric approach. The results obtained from empyema with CPPE and other diseases (control group) on the ROC curve for the P-LDH assay were sensitivity, specificity, predictive values, likelihood ratios, and diagnostic odds ratio [9]. A right-sided Grubb's test was performed to verify that only the largest values of P-LDH levels had a significant outlier to influence the cut-off point on the ROC curve.

RESULTS

A total of 174 patients were evaluated in this study, with 308 samples for total LDH in sera (n=137) and pleural fluids (n=171). The demographic characteristics and causes of PES in these 174 patients are summarized in Table 1. The greatest mean age was in patients with transudates. The greatest frequency of males was patients with pleural tuberculosis. A normal distribution for ages, determined by the Shapiro-Wilk test, was accepted for all groups of causes of PES ($P>0.05$).

The median, 25th and 75th percentiles, and ranges for comparisons between S-LDH and P-LDH are shown in Table 2. Patients with tuberculosis, UPPE, empyema, and CPPE exhibited higher P-LDH levels than in sera. The differences in median values according to Mann-Whitney U test were statistically significant ($P<0.0001$, $P=0.0184$, $P<0.0001$, and $P=0.0008$, respectively). Transudate, adenocarcinomas, and other diseases exhibited higher S-LDH levels than in pleural fluids, but only transudate was statistically significant ($P<0.0001$). The results revealed high levels of total LDH activity in the pleural fluid of patients with empyema (median, 4393.0 U/L) and CPPE (median, 1310.0 U/L), with values considered to be non-significant according to the Dunn test ($P>0.05$), as shown in Table 2.

The results from Table 2 were used for the statistical calculations in Figure 1, which lists the details of the results used in the P-LDH analysis, and Spearman's correlations with age and sex among 31 patients with CPPE and empyema. When P-LDH levels and age were dichotomized at a mean age of 48 years in this group, a non-significant positive correlation was observed (rho=0.170, $P=0.5448$). However, a significant and negative correlation for CPPE and empyema between sex and P-LDH levels was observed (rho=-0.661, $P=0.0376$) with a high coefficient of determination ($r^2=0.4369$). Cohen's standard was used to evaluate the correlation coefficient: correlation coefficients between 0.10 and 0.29 represent a small association; those between 0.30 and 0.49 represent a medium association; and those ≥ 0.50 represent a large association or relationship. Therefore, the ROC curves were plotted only for males and females with the purpose of diagnosing CPPE and empyemas to evaluate LDH as a biomarker in pleural fluids (Figure 2). A right-sided Grubb's test was performed to determine whether the largest extreme value of the P-LDH level had a significant outlier to influence the cut-off point on the ROC curve (Figure 2). A P-LDH value of 20,000 U/L was not removed because the Shapiro-Wilk test for normal distribution rejected the normality of data ($W=0.4360$, $P<0.0001$), and also because no analytical error was found. The diagnostic performance parameters obtained from the ROC curve for empyema and CPPE are shown in Figure 2. These parameters are important to establish clinical decision limits or potential utility of P-LDH as a biomarker at the cut-off points selected on the ROC curve. An interactive dot diagram is shown in Figure 3. The horizontal lines indicate the cut-off points with the best separation on ROC curves (minimal false-negative and false-positive results) between controls and cases (empyema and CPPE). The diagnostic performance of P-LDH (U/L) for empyema and CPPE (n=31), with optimum cut-off values for males (n=21) and females (n=10) among the 174 patients with PES, are shown in Table 3.

Table-1: Demographic and characteristics patients with pleural effusion syndrome (n=174)

Etiology	Patients, n	Age, years, mean ± SD	Male, n (%)	Female, n (%)
Tuberculosis	76	41.26±15.85 (13.0-80.0)	60 (79.0)	16 (21.0)
Transudate	22	61.64±12.02 (36.0-83.0)	14 (67.0)	8 (36.0)
Adenocarcinoma	19	59.05±8.83 (35.0-72.0)	9 (47.0)	10 (53.0)
Uncomplicated PPE	15	36.47±21.61 (12.0-80.0)	8 (53.0)	7 (47.0)
Empyema	20	46.30±18.40 (9.0-77.0)	13 (65.0)	7 (35.0)
Complicated PPE	11	52.18±25.2 (14.0-85.0)	8 (73.0)	3 (27.0)
Other	11	45.09±21.32 (18.0-80.0)	4 (36.0)	7 (64.0)

Abbreviations: SD, Standard deviation; PPE, Parapneumonic effusion. Shapiro-Wilk normality test (P>0.05 for allgroups). Other diseases: Lymphomas (n=3), squamous cell lung carcinomas (n=2), systemic lupus erythematosus (n=2), pulmonary embolism (n=2), paracoccidioidomycosis (n=1), and oat cell lung carcinoma (n=1).

Table-2: Table 2. Quantitative evaluation of total lactic dehydrogenase (LDH) analysis in sera (S-LDH) and pleural fluids (P-LDH) in patients with pleural effusion syndrome (n=174)

Diagnosis	S-LDH, U/L Sample (n) median (IQR)* (N =137)	P-LDH, U/L Sample (n) median (IQR)† (N=171)	P-value (Mann-Whitney U test)
Tuberculosis	63 329.0 (272.0-408.0)	74 492.0 (392.3-674.0)	U=1001 (P<0.0001)
Transudate	22 453.5 (244.3-572.5)	22 176.0 (118.8-262.3)	U=63.50 (P<0.0001)
Adenocarcinoma	16 435.5 (352.0-666.8)	18 379.5 (195.3-692.8)	U=115.0 (P=0.3254)
Uncomplicated PPE	10 320.0 (179.0-479.0)	15 470.0 (305.0-733.0)	U=32.0 (P=0.0184)
Empyema	8 409.0 (272.5-692.3)	20 4393.0 (2436.0-8038.0	U=3.000 (P<0.0001)
Complicated PPE	7 392.0 (318.0-494.0)	11 1310.0 (1050.0-1901.0)	U=1.000 (P=0.0008)
Other	11 395.0(240.0-531.0)	11 389.0 (236.0-713.0)	U=58.50 (P=0.9215)

Abbreviations: IQR, interquartile range; PPE, Parapneumonic effusion. *Shapiro-Wilk, W=0.9021 (P<0.0001), Kruskal-Wallis, H=11.56 (P=0.0725). † Shapiro-Wilk, W=0.4360 (P<0.0001), Kruskal-Wallis, W=0.4360 (P<0.0001), Dunn's test, P<0.05: Transudate vs. empyema, empyema vs. adenocarcinoma, empyema vs. UPPE, empyema vs. TB, empyema vs. other, CPPE vs. other. P>0.05: Empyema vs. CPPE.

Table-3: Diagnostic performance of pleural fluid lactate dehydrogenase levels (U/L) as a biomarker for empyema and complicated parapneumonic effusion (n=31) with an optimum cut-off values for males (n=21) and females (n=10) among 174 patients with pleural effusion syndrome

Diagnostic parameter	Male (95% CI)	Female (95% CI)
Best cut-off	>1188.0 (>1142->1994.0)	>1372.0 (>1932->3041.0)
Sensitivity (%)	76.19 (52.8–91.8)	90.00 (55.5–99.7)
Specificity (%)	97.89 (92.6–99.7)	95.83 (85.7–99.5)
Positive predictive value (%)	88.90 (66.5–97.0)	78.60 (61.66–97.35)
Negative predictive value (%)	77.00 (68.9-–84.8)	97.80 (79.56–119.43)
Positive likelihood ratio	36.19 (9.0–145.6)	21.60 (5.5–85.2)
Negative likelihood ratio	0.24 (0.10–0.50)	0.10 (0.020–0.70)
Accuracy (%)	95.70 (90.2–98.6)	98.5 (91.2–1.0)
Diagnostic odds ratio	150.79 (126.9–176.02)	216.0 (188.15–246.8)
Prevalence (%)	68.0	32.

Abbreviation: 95% CI, 95% confidential intervals

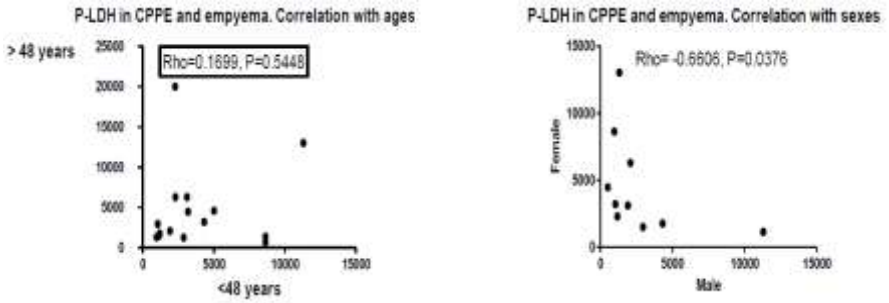

Fig-1: Spearman's correlation of pleural fluid lactate dehydrogenase (P-LDH) analysis with age and sex in 31 patients with pleural empyema (n=20) and complicated parapneumonic pleural effusion (CPPE [n=11]). P-LDH vs. sex: rho=-0.661 (95% CI -0.911-0.0530, P=0.0376, r^2=0.4369); P-LDH vs. age: rho=0.170 (95% CI -0.375-0.628, P=0.5448, r^2=0.0289). Abbreviations: Rho, Spearman's rank correlation coefficient, r^2, coefficient of determination

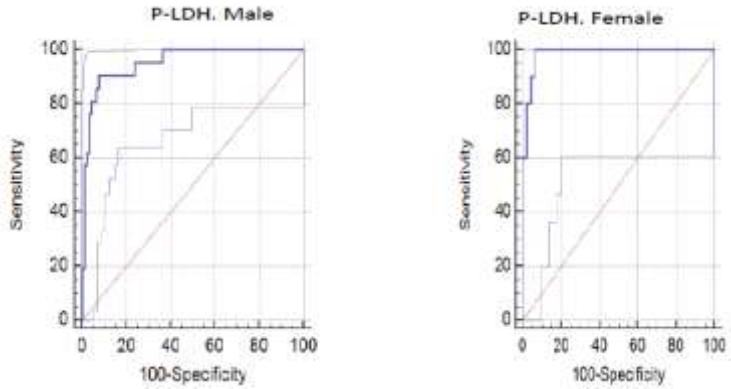

Fig-2: Receiver operating characteristic (ROC) curves of pleural fluid lactate dehydrogenase (P-LDH) in males, with optimal cut-off value >1188.0 U/L (area under the ROC curve [AUC]=0.957; standard error [SE], 0.0218; 95% CI 0.902-0.986; z statistic, 20.96; P<0.0001) and females with optimal cut off value > 1372.0 U/L (AUC=0.985, SE, 0.0117; 95% CI 0.91-1.00, z statistic, 41.43; P<0.0001)

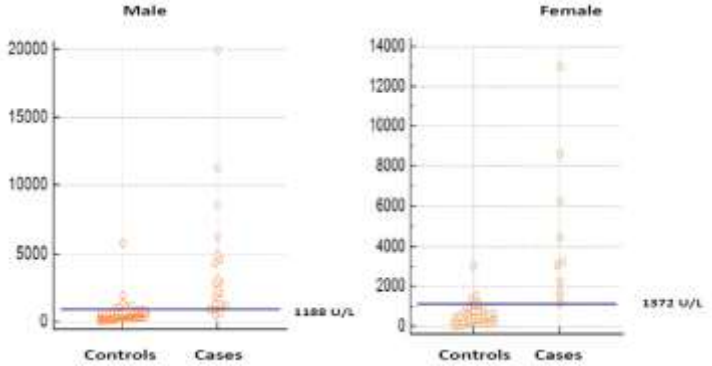

Fig-3: Interactive dot diagram. The horizontal lines indicate the cut-off points with the best separation on receiver operating characteristic curves (minimal false-negative and false-positive results) between controls and cases (empyema and complicated parapneumonic effusions).

DISCUSSION

Approximately 20% of patients with community-acquired pneumonia are complicated with PPEs, and in approximately 30% of these patients, the disease progresses to CPPE or empyema. P-LDH analysis may aid in decision-making for drainage of nonpurulent pleural fluids [13-16].

In a study from Brazil, pleural effusion was a complication in 44% of 85 children hospitalized with pneumonia. A significant relationship was found between complications and female sex, but age was not significant [17]. However, between 1991 and 2007, there was a significant reduction in mortality from pneumonia in children ≤ 4 years of age across Brazil [18]. The demographic characteristics of our patients

with PPE and other causes of pleural effusions are shown in Table 1.

A PPE can be classified as a UPPE, CPPE, or empyema based on pleural fluid analysis. An inadequate interpretation of pleural fluid analysis would result in a high rate of undiagnosed effusions [19]. UPPEs have a turbid appearance, with a pH > 7.30, a glucose level > 60 mg/dL, an LDH level < 700.0 IU/L, and negative microbiological test results. CPPE is associated with a pleural fluid pH < 7.20, a glucose level < 40.0 mg/dL, and an P-LDH > 1000.0 IU/L and, possibly, positive Gram stain and culture results. Pus in the pleural space is diagnostic of empyema. Although these criteria are widely used, there may be significant overlap among these groups [20].

A quantitative evaluation of LDH levels in sera (n=137) and pleural fluids (n=171) in the 174 patients with PES is shown in Table 2. The median P-LDH levels from CPPE and empyema were not differentiated using Dunn's test (P>0.05). Thus, we suggest that in the selection of patients for pleural drainage, PPE should be categorized as two groups: UPPE, and CPPE/pleural empyema.

The median activity of P-LDH was significantly increased in patients with tuberculosis, UPPE, CPPE, and empyema compared with S-LDH activity, as causes of PES (Table 2). The LDH concentration in pleural fluids reflects the degree of pleural inflammation, which is important in managing pleural effusion associated with pneumonia. The high content of total LDH in pleural fluids appears to be due to the release of this enzyme by polymorphonuclear and/or mononuclear cells involved in pleural inflammation [21].

In our significant model, only 43.69% of LDH levels for pleural CPPE and empyema were attributed to sex [22] (Figure 1). We performed a literature search for previous findings to compare with the results shown in Figure 1; however, no such results were found for comparison.

In disagreement with other diagnostic accuracy indices, ROC curves were plotted for the true-positive rate (sensitivity) against the false-positive rate (1 – specificity) for all possible cut off values. How does one select the best cut-off point for a biomarker? This question is highly significant because diagnostic accuracy will be depend on this decision. In general, higher AUC values indicate better biomarker performance [12]. It is recommended that each clinical laboratory establish its own cut-off point using a biomarker representative of its own population, taking into account sex, age, dietary habits, medications, and other population factors. In our study involving a Brazilian population, the best P-LDH cut-off values selected from the ROC curve were > 1188.0 U/L for males (AUC 0.957; SE, 0.0218 [95% CI 0.902-0.986]; z statistic, 20.96; P<0.0001) and > 1372.0 U/L (AUC 0.985 [95% CI 0.91-1.00]; SE, 0.0117; z statistic, 41.43; P<0.0001) for females for diagnosis of CPPE and pleural empyema (Figure 2 and Figure 3). Accurate diagnostic parameters for the biochemical analysis of P-LDH can contribute to a diagnosis of pleural empyema and CPPE (Table 3). The AUC with a 95% CI provides an estimate of the diagnostic efficiency of P-LDH. A higher AUC indicates higher specificity and sensitivity among all available cut-off values [12].

OBSERVATIONS

Finally, in this paper we attempted to show and discuss, what does this study add to this research field? This study adds a new reference value for P- LDH levels for the diagnosis of pleural empyema and CPPE.

What are the limitations? The use of a biomarker for diagnosis, however, is always limited by interpretations of previous analyses of clinical manifestations, imaging findings, epidemiological profiles of the evaluated patient, and a false-positive for other possible diseases [3].

What are the clinical practical implications? Our results indicate that CPPE and pleural empyema should be treated as a single disease, with chest tube drainage in CPPE and pleural empyema, together with infection control, good nutrition, and anti-thrombotic prophylaxis [16]. The routine use of a fibrinolytic agent is not indicated. Plasminogen activator and deoxyribonuclease can be recommended when indicated [23-26]. It is very important remember that performing early thoracoscopy or VATS by day 5 of hospitalization in children and adolescents presenting septations or loculations on ETUS was associated with shorter hospital stays, and duration of drainage and fever [27, 28].

What are the future perspectives? P-LDH can be used as an inflammatory biomarker for PPE because P-LDH had positive correlation with proinflammatory and antiinflammatory cytokine levels (IL-1β, IL-8, and vascular endothelial growth factor) in pleural fluids from CPPE [29]. Therefore, we do not agree with other authors regarding the clinical utility of LDH and its relegation to serve only as a cancer biomarker and to confirm hemolysis [30].

CONCLUSIONS

Within the limitations of the present study, we conclude that P-LDH levels may be considered a useful adjunctive biomarker in the integrated management of PES. CPPE and pleural empyema should be treated as a single disease, and only sex was correlated with P-LDH levels in this diseases.

REFERENCES

1. Hooper C, Lee YCG, Maskell N, BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax agosto de 2010;65 Suppl 2:ii4-17.
2. Sachdeva A, Shepherd RW, Lee HJ. Thoracentesis and thoracic ultrasound: state of the art in 2013. Clin Chest Med 2013;34(1):1–9.
3. Behrsin RF, Junior CT da S, Cardoso GP, Barillo JL, de Souza JBS, de Araújo EG. Combined evaluation of adenosine deaminase level and histopathological findings from pleural biopsy with Cope's needle for the diagnosis of tuberculous pleurisy. Int J Clin Exp Pathol 2015;8(6):7239–46.
4. Light RW, Macgregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77(4):507–13.
5. Maranhão BHF, Silva Junior CT da, Chibante AM da S, Cardoso GP. Determination of total proteins and lactate dehydrogenase for the diagnosis of pleural transudates and exudates: redefining the classical criterion with a new statistical approach. J Bras Pneumol 2010;36(4):468–74.
6. Martínez-Moragón E, Aparicio J, Sanchis J, Menéndez R, Cruz Rogado M, Sanchis F. Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. Respiration 1998; 65(2):108–13.
7. Gaspar P, Al-Bayati FAY, Andrew PW, Neves AR, Yesilkaya H. Lactate dehydrogenase is the key enzyme for pneumococcal pyruvate metabolism and pneumococcal survival in blood. Infect Immun 2014;82(12):5099–109.
8. Drent M, Cobben NA, Henderson RF, Wouters EF, van Dieijen-Visser M. Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. Eur Respir J 1996;9(8):1736–42.
9. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527.
10. McDonald CM, Pierre C, de Perrot M, Darling G, Cypel M, Pierre A. Efficacy and cost of awake thoracoscopy and video-assisted thoracoscopic surgery in the undiagnosed pleural effusion. Ann Thorac Surg 2018; S0003-4975(18)30377-1.
11. Schumann G, Bonora R, Ceriotti F, Clerc-Renaud P, Ferrero CA, Férard G. IFCC primary reference procedures for the measurement of catalytic activity concentrations of enzymes at 37 degrees C. Part 3. Reference procedure for the measurement of catalytic concentration of lactate dehydrogenase. Clin Chem Lab Med 2002;40(6):643–8.
12. Swets JA. The science of choosing the right decision threshold in high-stakes diagnostics. Am Psychol 1992;47(4):522–32.
13. Stankey CT, Spaulding AB, Doucette A, Hamre KES, Wheeler W, Pomputius WF. Blood culture and pleural fluid culture yields in pediatric empyema patients - A retrospective review, 1996-2016. Pediatr Infect Dis J 2018.
14. Ferreiro L, Porcel JM, Bielsa S, Toubes ME, Álvarez-Dobaño JM, Valdés L. Management of pleural infections. Expert Rev Respir Med 2018;12(6):521–35.
15. Porcel JM. Pleural fluid tests to identify complicated parapneumonic effusions. Curr Opin Pulm Med 2010;16(4):357–61.
16. Davies HE, Davies RJO, Davies CWH, BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2:ii41-53.
17. Riccetto AGL, Zambom MP, Pereira I s CMR, Morcillo AM. Influence of socioeconomic and nutritional factors on the evolution to complications in children hospitalized with pneumonia]. Rev Assoc Med Bras 2003;49(2):191–5.
18. Rodrigues FE, Tatto RB, Vauchinski L, Leães LM, Rodrigues MM, Rodrigues VB. Pneumonia mortality in Brazilian children aged 4 years and younger. J Pediatr (Rio J) 2011;87(2):111–4.
19. Ferreiro L, Toubes ME, Valdés L. Contribution of pleural fluid analysis to the diagnosis of pleural effusion. Med Clin (Barc) 2015;145(4):171–7.
20. Utine GE, Ozcelik U, Yalcin E, Dogru D, Kiper N, Aslan A. Childhood parapneumonic effusions: biochemical and inflammatory markers. Chest 2005;128(3):1436–41.
21. Saint-Rémy P, Buret J, Radermecker M. Significance of lactate dehydrogenases in pleural effusions. Rev Pneumol Clin 1986;42(2):74–81.
22. Boyd JC. Mathematical tools for demonstrating the clinical usefulness of biochemical markers. Scand J Clin Lab Invest Suppl 1997;227:46–63.
23. Yang W, Zhang B, Zhang Z-M. Infectious pleural effusion status and treatment progress. J Thorac Dis 2017;9(11):4690–9.
24. Porcel JM. Minimally invasive treatment of complicated parapneumonic effusions and empyemas in adults. Clin Respir J 2018;12(4):1361–6.
25. Porcel JM, Valencia H, Bielsa S. Factors influencing pleural drainage in parapneumonic effusions. Rev Clin Esp 2016;216(7):361–6.
26. Villena Garrido V, Cases Viedma E, Fernández Villar A, de Pablo Gafas A, Pérez Rodríguez E, Porcel Pérez JM. Recommendations of diagnosis and treatment of pleural effusion. Update. Arch Bronconeumol 2014;50(6):235–49.
27. Pereira RR, Alvim CG, Andrade CR de, Ibiapina C da C. Parapneumonic pleural effusion: early versus late thoracoscopy. J Bras Pneumol 2017;43(5):344–50.

28. Di Napoli G, Ronzini M, Paradies G. VATS: first step in the parapneumonic empyema. G Chir 2014;35(5–6):146–8.
29. Marchi E, Vargas FS, Acencio MM, Sigrist RMS, Biscaro MDA, Antonangelo L, Teixeira LR, Light RW. Proinflammatory and antiinflammatory cytokine levels in complicated and noncomplicated parapneumonic pleural effusions. Chest 2012;141(1):183–9.
30. Jialal I, Sokoll LJ. Clinical utility of lactate dehydrogenase: a historical perspective. Am J Clin Pathol 2015;143(2):158–9.