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Original article

The role of serum lactate dehydrogenase / pleural fluid adenosine deaminase ratio and cancer ratio plus in the diagnosis of malignant pleural effusion: A retrospective study

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Abstract. *Background:* While serum LDH to pleural fluid ADA ratio (sLDH/pADA) and CRp, as calculated by dividing sLDH/pADA by the percentage of pleural fluid lymphocytes, show potential in identifying malignant pleural effusion (MPE), their diagnostic value in tuberculosis-endemic countries remains unclear. *Aims:* This study assessed their utility in distinguishing MPE among patients with exudative pleural effusion (PE). *Methods:* This retrospective study was conducted at Department of Pulmonary Medicine, Cho Ray Hospital (Vietnam) from January 2023 to June 2024, including patients with PE who met the inclusion criteria. All patients underwent blind pleural biopsy or pleural fluid cellblock analysis to confirm or exclude MPE. Clinical, laboratory, and pleural fluid data were collected. The optimal cut-off values, AUC, sensitivity, and specificity of sLDH/pADA and CRp were calculated to diagnose MPE. *Results:* 204 patients with exudative PE were classified into MPE (n=119, 58.3%) and non-MPE (n=85, 41.7%) groups. Compared to the non-MPE group, patients with MPE were older, had higher serum LDH, sLDH/pADA, and CRp (all p <0.05). They also had a lower pleural neutrophil ratio and ADA (all p <0.05). For sLDH/pADA, the optimal cut-off value was 20, yielding an AUC of 0.85 with 85% sensitivity and 79% specificity. For CRp, the optimal threshold was 18, corresponding to an AUC of 0.72, 73% sensitivity, and 58% specificity. *Conclusion:* sLDH/pADA showed high sensitivity and good diagnostic value for identifying MPE, while CRp did not enhance accuracy. The findings support sLDH/pADA as a useful tool for distinguishing MPE, especially in tuberculosis-endemic regions. (www.actabiomedica.it)

Key words: malignant pleural effusion, tuberculous pleural effusion, cancer ratio plus, cancer ratio, parapneumonic effusion, cellblock.

Introduction

Pleural effusion (PE) is a frequently encountered condition with diverse underlying etiologies. In addition to malignancy-related causes, PE may result from tuberculous pleural effusion (TPE), parapneumonic effusion (PPE), pancreatitis, trauma, systemic lupus erythematosus (SLE), cirrhosis, or renal failure (1).

Despite its prevalence, identifying the cause of PE is not always straightforward. The initial approach typically relies on clinical evaluation with imaging studies with blood and pleural fluid analyses. These investigations are advantageous due to their simplicity, affordability, and accessibility, making them feasible for performance even at primary healthcare levels. However, differentiating MPE from non-MPE cases remains challenging, and delays in diagnosing MPE can negatively impact outcomes (2). Invasive procedures such as pleural biopsy can improve diagnostic sensitivity but carry risks of complications (3). Moreover, pleural fluid cytological examinations, such as cellblock and liquid-based cytology, depend highly on laboratory procedures and the pathologist's ability to identify malignant cells (4). Consequently, these methods are challenging to implement at primary healthcare levels due to limitations in resources and specialized expertise. Therefore, there is a need for a simple, cost-effective, yet useful index to aid in the early detection of MPE. Several studies have evaluated the serum lactate dehydrogenase (LDH) to pleural fluid adenosine deaminase (ADA) ratio (sLDH/pADA) (5, 6) and cancer ratio plus (CRp) (7, 8), as calculated by dividing sLDH/pADA by the percentage of pleural fluid lymphocytes, as a potential diagnostic tool for identifying MPE. However, studies were conducted in developed countries with a low burden of tuberculosis. Vietnam is among the countries with the highest tuberculosis burden (9). Both MPE and TPE often share a common feature of lymphocyte-predominant pleural fluid, which may affect the diagnostic performance of sLDH/pADA and CRp (10). Therefore, the utility of these ratios in high-TPE-burden settings remains unclear. This is the first study in Vietnam to evaluate the role of sLDH/pADA and CRp in diagnosing MPE.

Materials and methodology

This retrospective study was conducted at the Department of Pulmonary Medicine, Cho Ray Hospital (Vietnam), from January 2023 to June 2024. Data were collected from medical records of patients diagnosed with PE at discharge who met the inclusion criteria.

Inclusion criteria

Patients aged 18 years or older were enrolled by identifying medical records with a discharge diagnosis coded as J90 (pleural effusion, not elsewhere classified) according to the International Classification of Diseases, Tenth Revision (ICD-10), during the study period. PE was diagnosed based on findings from chest computed tomography, pleural ultrasound, or thoracentesis showing a pleural fluid volume greater than 10 mL.

Exclusion criteria

We excluded medical records that met any of the following criteria: transudative PE, exudative PE of unknown etiology, empyema, hemothorax, medical records with incomplete data, stage 4–5 chronic kidney disease, severe cirrhosis with a Child-Pugh score ≥7, recent myocardial infarction within 7 days, idiopathic pulmonary hypertension, hematologic malignancy, or severe anemia (hemoglobin level <80 g/L). Patients currently undergoing anti-tuberculosis treatment were also excluded.

Sample size

We used the following formula to calculate the sample size based on the expected sensitivity and specificity (11):

$$N_{Sens} = \frac{Z^2_{1-\alpha/2}\, Sens(1-Sens)}{d^2(1-Prev)},$$

$$N_{Spec} = \frac{Z^2_{1-\alpha/2} Spec(1-Spec)}{d^2(1-Prev)}$$

N is the required sample size for estimating either sensitivity (N_{Sens}) or specificity (N_{Spec}). $Z_{1-\alpha/2}$ is the corresponding coefficient for a 95% confidence interval, where α = 5%. Sens is the sensitivity of sLDH/pADA with a cut-off value of 20 for diagnosing MPE is 98% (5). Spec is the specificity of sLDH/pADA, with the same cut-off for diagnosing MPE, is 94% (5). Prev is the prevalence of MPE among patients admitted with PE was 23.7% (12). d is the standard error, we chose d = 4%. Using this formula, the minimum

required sample size was calculated to be 199 patients for sensitivity and 178 patients for specificity. Our study included 204 patients.

Definition of variables

We defined transudative and exudative PE based on Light's criteria (13). MPE was diagnosed by identifying malignant cells on pleural tissue histology or immunohistochemistry of pleural fluid cellblock, with negative acid-fast bacilli (AFB) testing of pleural fluid (2). TPE was confirmed by positive pleural fluid AFB staining or biopsy findings consistent with tuberculosis (14). PPE was identified based on clinical and radiological signs of infection, characteristic pleural fluid (neutrophil predominance, low glucose, high LDH), positive cultures when available, and response to antibiotics (15). PE caused by SLE, chylothorax, and pancreatitis were diagnosed according to expert consensus and well-established diagnostic criteria (16-18). Pleural fluid cellblock and pleural tissue histopathology were performed using techniques previously reported at our institution (4, 19).

We collected the following data: age, sex, smoking history, hypertension, diabetes mellitus, history of tuberculosis, chronic obstructive pulmonary disease, dyspnea, chest pain, fever (body temperature >38°C), weight loss (>10% body weight within 6 months), hemoglobin, white blood cell count, serum glucose, protein, and LDH. The location of PE was determined by thoracic ultrasound (20), while the volume of PE was classified on chest X-ray as minimal, moderate, or massive (21). The following pleural fluid parameters were recorded: color, proportions of neutrophils and lymphocytes, LDH, ADA, glucose, and protein. Blood tests were performed simultaneously with thoracentesis. All patients underwent blind pleural biopsy or pleural fluid cellblock for the definitive diagnosis and exclusion of MPE.

Statistical analysis

Statistical analysis was conducted using STATA version 15.1 (StataCorp, College Station, TX). Continuous data was expressed as mean ± standard deviation or as median with interquartile range for variables not normally distributed. Categorical data were summarized as frequencies and percentages. Comparisons between the MPE and non-MPE groups were performed using the Chi-square test or Fisher's exact test for small sample sizes. The independent t-test was applied to compare means, while the Mann–Whitney U test was used for non-parametric comparisons. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. The diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis. An area under the curve (AUC) ≥0.9 was considered excellent, 0.8–0.9 as good, 0.7–0.8 as fair, 0.6–0.7 as poor, and 0.5–0.6 as failed (22). The optimal cut-off point was determined using the Youden index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were calculated. A p-value of <0.05 was considered statistically significant.

Medical ethics

The study was approved by the Ethical Review Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (Approval No. 805 IRB-VN01002/IORG0008603/FWA00023448). Informed consent was waived due to the retrospective nature of the study.

Results

Between January 2023 and June 2024, we reviewed 320 medical records of patients diagnosed with PE at the Department of Pulmonary Medicine, Cho Ray Hospital. Among these, 70 cases were identified as transudative PE, 44 exudative PE cases were excluded due to undetermined etiology resulting from inadequate data, along with 1 case of empyema and 1 case of hemothorax. Finally, 204 cases of exudative PE were recruited. Of these, 119 cases were MPE, 38 cases were TPE, 32 cases were PPE, and 15 were exudative PE due to other etiologies (6 cases of PE secondary to SLE, 4 cases of chylothorax, and 5 cases of PE associated with pancreatitis). The study population

was stratified into MPE group (n=119, 58.3%) and non-MPE group (n=85, 41.7%).

Patient characteristics

Table 1 presents the baseline characteristics of the study population. Compared to the non-MPE group, the MPE group was significantly older, had a lower proportion of fever, and a higher proportion of weight loss (all p <0.05). Serum LDH was significantly higher in the MPE group (p=0.03).

Pleural fluid characteristics

Table 2 outlines the pleural fluid characteristics of the study population. MPE cases showed significantly lower neutrophil ratio, ADA, LDH, and protein levels than the non-MPE group. Conversely, MPE patients had higher glucose, sLDH/pADA, and CRp (all p <0.05). We compared sLDH/pADA and CRp between MPE and TPE groups, finding significant differences for both parameters (p=0.001, Mann-Whitney U test). In comparisons between MPE and

Table 1. Baseline of the study population (N=204)

Variables	MPE (n=119)	Non-MPE (n=85)	TPE (n=38)	PPE (n=32)	p[a]
Age (median [IQR])	68 [61–76]	57 [41–71]	62 [45–75]	55 [42–69]	**0.001**[b]
Male (%)	65 (54.6%)	55 (64.7%)	27 (71.1%)	22 (68.8%)	0.194[b]
Smoker (%)	46 (38.7%)	44 (51.8%)	24 (63.2%)	16 (50.0%)	0.063[c]
Hypertension (%)	41 (34.5%)	36 (42.4%)	5 (13.2%)	16 (50.0%)	0.251[c]
Diabetes mellitus (%)	27 (22.7%)	20 (23.5%)	6 (15.8%)	9 (28.1%)	0.542[d]
History of tuberculosis (%)	17 (14.3%)	15 (17.6%)	8 (21.1%)	7 (21.9%)	0.561[d]
COPD (%)	15 (12.6%)	14 (16.5%)	4 (10.5%)	10 (31.3%)	0.542[d]
Dyspnea (%)	47 (39.5%)	33 (38.8%)	15 (39.5%)	11 (34.4%)	0.923[c]
Chest pain (%)	20 (16.8%)	12 (14.1%)	7 (18.4%)	5 (15.6%)	0.084[d]
Fever (>38°C) (%)	52 (43.7%)	72 (84.7%)	30 (78.9%)	32 (100.0%)	**0.001**[c]
Weight loss (%)	27 (22.7%)	9 (10.6%)	5 (13.2%)	4 (12.5%)	**0.027**[d]
Hemoglobin (g/dL) (mean ± SD)	107.7 ± 18.5	104.4 ± 17.0	104.1 ± 16.8	103.4 ± 15.7	0.194[e]
WBC (G/L) (median [IQR])	6.0 [3.0–12.0]	12.0 [8.0–23.0]	8.1 [4.0–12.2]	17.5 [12.0–25.0]	0.194[b]
Serum glucose (mg/dL) (median [IQR])	124 [87–199]	115 [67–197]	116 [87–217]	110 [65–230]	0.335[b]
Serum protein (g/L) (median [IQR])	5.8 [5.4–6.4]	6.1 [5.4–6.7]	6.0 [5.0–6.5]	5.8 [4.9–6.7]	0.084[b]
Serum LDH (U/L) (median [IQR])	299 [230–436]	265 [209–356]	270 [221–331]	296 [206–464]	**0.030**[b]
Location of pleural effusion Left (%) Right (%) Both sides (%)	 32 (26.9%) 35 (29.4%) 52 (43.7%)	 22 (25.9%) 38 (44.7%) 25 (29.4%)	 10 (26.3%) 17 (44.7%) 11 (28.9%)	 11 (34.4%) 11 (34.4%) 10 (31.3%)	0.051[c]
Volume of pleural effusion Minimal to moderate (%) Massive (%)	 68 (57.1%) 51 (42.9%)	 57 (67.1%) 28 (32.9%)	 34 (89.5%) 4 (10.5%)	 22 (68.8%) 10 (31.3%)	0.109[d]

Abbreviations: MPE: malignant pleural effusion; TPE: tuberculous pleural effusion; PPE: parapneumonic effusion; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; SD: standard deviation; WBC: white blood cells; LDH: lactate dehydrogenase. [a]Comparison between MPE and non-MPE groups. [b]Mann-Whitney U test. [c]Chi-square test. [d]Fisher's exact test, [e]Independent t-test. The p-value <0.05 is highlighted in bold.

Table 2. Pleural fluid characteristics of the study population (N=204)

Variables	MPE (n=119)	Non-MPE (n=85)	TPE (n=38)	PPE (n=32)	*p*[a]
Color Orange (%) Red (%) Pink (%) Yellow (%)	12 (10.1%) 36 (30.3%) 8 (6.7%) 63 (52.9%)	9 (10.6%) 15 (17.6%) 1 (1.2%) 60 (70.6%)	7 (18.4%) 6 (15.8%) 1 (2.6%) 24 (63.2%)	0 (0.0%) 6 (18.8%) 0 (0.0%) 26 (81.3%)	0.055[b]
Neutrophil ratio (%) (median [IQR])	19.4 [4.5–22.3]	39.6 [23.4–47.0]	5.5 [2.0–18.0]	81.0 [69.2–91.3]	**0.001**[c]
Lymphocyte ratio (%) (median [IQR])	51.1 [22.1–66.8]	48.6 [22.1–77.6]	81.0 [67.0–93.3]	7.0 [3.3–16.8]	0.573[c]
LDH (U/L) (median [IQR])	352 [192–577]	479 [267–1053]	323 [213–549]	1496 [708–3067]	**0.001**[c]
ADA (U/L) (median [IQR])	6.8 [2.3–10.9]	32.6 [16.6–45.7]	39.3 [17.1–49.7]	26.3 [13.4–58.0]	**<0.001**[c]
Glucose (mg/dL) (median [IQR])	116 [80–145]	89 [59–112]	93 [79–108]	65 [5–97]	**<0.001**[c]
Protein (g/L) (median [IQR])	3.6 [3.0–4.3]	4.1 [3.5–4.8]	4.1 [3.6–4.7]	4.0 [3.0–4.9]	**0.002**[c]
sLDH/pADA (median [IQR])	53.3 [25.0–143.0]	9.4 [5.9–17.3]	8.4 [5.4–17.9]	26.2 [13.4–58.0]	**<0.001**[c]
CRp (median [IQR])	1.3 [0.4–4.0]	0.3 [0.1–1.4]	0.1 [0.06–0.3]	1.8 [0.6–3.9]	**<0.001**[c]

Abbreviations: MPE: malignant pleural effusion; TPE: tuberculous pleural effusion; PPE: parapneumonic effusion; IQR: interquartile range; LDH: lactate dehydrogenase; ADA: adenosine deaminase; sLDH/pADA: serum lactate dehydrogenase to pleural fluid adenosine deaminase ratio; CRp: cancer ratio plus. [a]Comparison between MPE and non-MPE groups. [b]Fisher's exact test. [c]Mann-Whitney U test. The *p*-value <0.05 is highlighted in bold.

PPE groups, sLDH/pADA differed significantly (p <0.001, Mann-Whitney U test), while CRp did not (p=0.458, Mann-Whitney U test).

The value of diagnostic methods for malignant pleural effusion

Table 3 presents the diagnostic value of sLDH/pADA and CRp in identifying MPE based on different cut-off points. For sLDH/pADA, the best cut-off value is 20, which yields a sensitivity of 85%, specificity of 79%, PPV of 85%, and NPV of 79%. For CRp, the optimal cut-off is 18, with a sensitivity of 73%, specificity of 58%, PPV of 68%, and NPV of 42%.

Table 4 presents the diagnostic value of different methods for detecting MPE. Pleural fluid cellblock shows an AUC of 0.7 with low sensitivity (40.3%). Pleural tissue histopathology achieves the highest diagnostic accuracy, with an AUC of 0.9. sLDH/pADA (cut-off of 20) has an AUC of 0.85, sensitivity of 85%, and specificity of 79% (Figure 1). Meanwhile, CRp (cut-off of 18) yields an AUC of 0.72, with a lower specificity at 58.0% (Figure 1).

Discussion

Our study contributes to the literature by evaluating the diagnostic utility of sLDH/pADA and CRp in identifying MPE in a high tuberculosis burden setting. We found that sLDH/pADA effectively differentiated MPE from non-MPE, including TPE and PPE, with an optimal cut-off of 20 and an AUC of 0.85. Although CRp was expected to enhance diagnostic performance, it did not significantly differentiate MPE from PPE and showed lower performance (cut-off of 18 with 0.72 AUC) in both sensitivity and specificity in identifying MPE. MPE in patients with malignancy can originate through various mechanisms. Direct tumor effects, such as lymphatic obstruction or

Table 3. The value of sLDH/pADA and CRp based on the cut-off point

Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)	LR+	LR-
sLDH/pADA						
15	90	72	82	84	3.2	0.14
18	85	75	83	78	3.4	0.20
20	**85**	**79**	**85**	**79**	**4.0**	**0.19**
22	82	80	85	76	4.1	0.23
25	77	85	88	73	5.1	0.27
CRp						
16	65	85	97	15	4.4	0.4
17	70	67	83	33	2.1	0.5
18	**73**	**58**	**68**	**42**	**1.7**	**0.5**
19	65	85	97	15	4.4	0.4

Abbreviations: Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; sLDH/pADA: serum lactate dehydrogenase to pleural fluid adenosine deaminase ratio; CRp: cancer ratio plus. The best cut-off value is highlighted in bold.

Table 4. The value of diagnostic methods for malignant pleural effusion

Variables	AUC	Sens (%)	Spec (%)
Pleural fluid cellblock	0.70	40.3	100.0
Blind pleural biopsy	0.90	75.6	100.0
sLDH/pADA (cut-off of 20)	0.85	85.0	79.0
CRp (cut-off of 18)	0.72	73.0	58.0

Abbreviations: AUC: area under the curve; Sens: sensitivity; Spec: specificity; sLDH/pADA: serum lactate dehydrogenase to pleural fluid adenosine deaminase ratio; CRp: cancer ratio plus.

thoracic duct blockage, and systemic factors, including pulmonary embolism or hypoalbuminemia, are known contributors (23). Recent studies have highlighted the role of vascular endothelial growth factor secreted by tumor cells, which increases vascular permeability and promotes pleural fluid accumulation (24). Therefore, identifying malignant cells within the pleural cavity is crucial for determining appropriate treatment strategies. The gold standard for diagnosing MPE typically involves pleural fluid cytology or histopathological examination of pleural tissue (25). However, pleural fluid cytology has relatively low sensitivity, with an overall rate of 58.2% (26). Blind pleural biopsy has a lower sensitivity, around 43% (27). The diagnostic yield of these procedures can be influenced by the number of procedures performed, the histological type of malignancy, laboratory techniques, and the experience of the pathologist. Therefore, a reliable, accessible index is needed at the primary care level to identify high-risk MPE patients and ensure timely referral for specialized evaluation. LDH is a ubiquitously expressed enzyme, especially abundant in energy-demanding organs like muscles, liver, kidneys, lungs, heart, and blood cells (28). Elevated serum LDH can result from various conditions, including cardiopulmonary diseases, cancer, fractures, infections/inflammation, cirrhosis, hypothyroidism, uremia, idiopathic causes, idiopathic pulmonary hypertension, pulmonary hypertension secondary to hematologic malignancies etc, (28-30). ADA is a crucial enzyme involved in the differentiation of T-lymphocytes (31). ADA levels are typically elevated in chronic infectious diseases such as TPE (32). ADA comprises two isoenzymes, ADA1 and ADA2, in lymphocytes, monocytes, and macrophages. Therefore, elevated pleural fluid ADA levels may also be observed in PPE and connective tissue disease-related PE (31-33). An ADA cut-off value of 40 IU/L has been widely validated for its high sensitivity and specificity in diagnosing TPE, reflecting the robust activation of T-lymphocytes during the immune response (14, 31, 32). In contrast, although

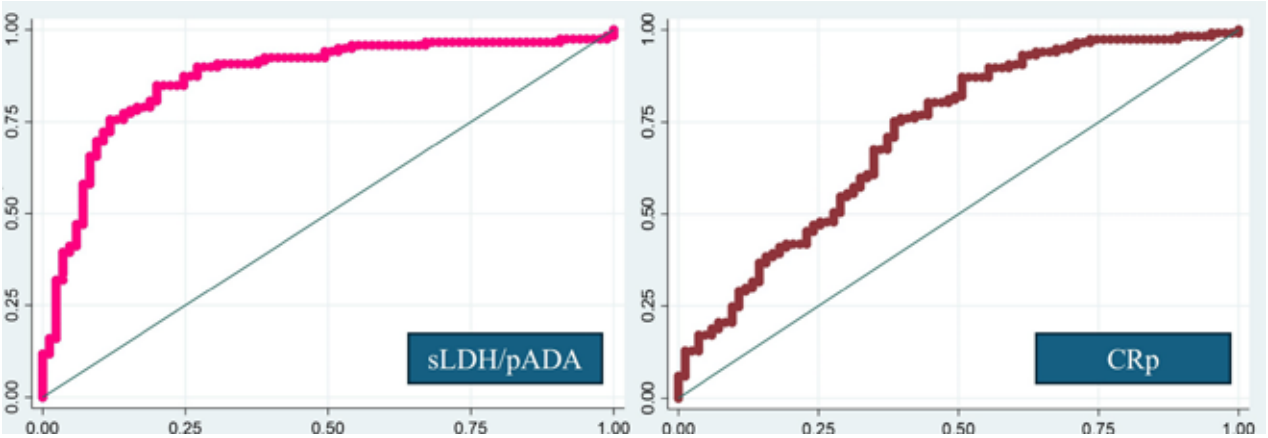

Figure 1. ROC curves of sLDH/pADA (cut-off of 20) and CRp (cut-off of 18) in the diagnosis of malignant pleural effusions. Abbreviations: sLDH/pADA: serum lactate dehydrogenase to pleural fluid adenosine deaminase ratio; CRp: cancer ratio plus; ROC: receiver-operating characteristic curve.

MPE may also present with lymphocyte-predominant pleural fluid, the functional activity of lymphocytes is often impaired by tumor progression, resulting in lower ADA levels (7, 34). However, serum LDH, pleural ADA, and lymphocyte ratio alone are unreliable for diagnosing MPE, although their differences between MPE and non-MPE groups were statistically significant in our study and others (Table 5). sLDH/pADA and CRp were developed based on the following observations: (1) serum LDH levels are generally higher in patients with MPE than in non-MPE cases, (2) pleural fluid ADA levels are typically lower in MPE, particularly compared to TPE and PPE, and (3) pleural lymphocyte ratios tend to be lower in MPE than in TPE (5-7, 33, 35). Therefore, both sLDH/pADA and CRp have been applied in several studies, demonstrating promising results (Table 5).

Table 5 shows that sLDH/pADA has a strong diagnostic value for MPE, with most studies reporting AUC ≥0.8, cut-off values from 10.6 to 20, sensitivity of 85–98%, and specificity of 68–94%, except for one study by Gayaf (2021) with a lower AUC. A possible explanation for the difference may arise from Gayaf's study including only MPE, TPE, and PPE cases, while ours had broader inclusion criteria for exudative PE and excluded conditions that elevate serum LDH (e.g., cirrhosis, renal failure, myocardial infarction). Additionally, Gayaf reported higher pleural ADA in MPE (11.5 ± 9.0 U/L vs. 6.8 U/L) but lower ADA in PPE (14.9 U/L vs. 26.3 U/L) compared to our findings. Several studies have reported markedly different median pleural fluid ADA levels in patients with MPE. For instance, Shimoda's study reported a median ADA level of 54.1 U/L (36), Lee's study found 23 U/L (37), and Terra's study reported 21.6 U/L (38). Moreover, elevated pleural ADA levels have been associated with poorer prognosis in patients with MPE (38). In cases of PPE, we also observed a wide variability in pleural fluid ADA levels across studies (8, 15, 33). This may be attributed to the biological nature of ADA as an enzyme present in lymphocytes and macrophages. Consequently, when pleural fluid contains a high cellular burden, such as abundant malignant cells or macrophages in empyema, ADA levels can vary significantly, potentially impacting the reliability of sLDH/pADA between studies. Therefore, the diagnostic value of sLDH/pADA may vary depending on population characteristics, anthropometric factors, cancer cell types, cancer stages, or, specifically in PPE cases, the timing of thoracentesis and prior antibiotic use. Hence, multicenter and multinational studies are essential to validate and promote the broader clinical application of sLDH/pADA. Regarding CRp, our study yielded rather disappointing results, as CRp did not improve the sensitivity or specificity compared to sLDH/pADA in diagnosing MPE. This outcome is

Table 5. The diagnostic value of sLDH/pADA and CRp in previous studies

Author (year)	AUC	Cut-off	Sens	Spec	PPV	LR+	LR-
sLDH/pADA							
Verma (2016) (5)	0.81	20.0	98.0	94.0	97.0	32.6	0.03
Verma (2016) (7)	0.81	20.0	95.0	85.0	94.0	16.0	0.13
Zhang (2017) (6)	0.84	10.6	94.0	72.6	N/A	N/A	N/A
Korczyński (2018) (35)	0.83	16.4	94.6	68.2	N/A	2.97	0.08
Gayaf (2021) (8)	0.73	14.3	84.2	52.7	61.6	1.78	0.30
Our study (2025)	0.85	20.0	85.0	79.0	85.0	4.0	0.19
CRp							
Verma (2016) (7)	0.86	30.0	97.6	94.1	97.0	41.0	0.06
Gayaf (2021) (8)	0.69	28.7	82.2	45.8	53.9	1.52	0.39
Our study (2025)	0.72	18.0	73.0	58.0	68.0	1.7	0.50

Abbreviations: AUC: area under the curve; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; LR: likelihood ratio; sLDH/pADA: serum lactate dehydrogenase to pleural fluid adenosine deaminase ratio; CRp: cancer ratio plus; N/A: not applicable.

understandable, given that the proportion of lymphocytes in pleural fluid did not significantly differ between the MPE and non-MPE groups in our study. Therefore, further research is needed to clarify the diagnostic role of CRp. Our study has several limitations. Firstly, the retrospective design introduces the possibility of data inaccuracy or missing information from medical records. Secondly, we included only patients with exudative PE, thus excluding approximately 10% of MPE cases that may present with transudative effusions (39, 40). Moreover, we did not have information on the primary origin of malignant cells in the MPE cases, so we could not analyze the influence of the histopathological type on sLDH/pADA and CRp. Thirdly, we did not analyze the diagnostic performance of sLDH/pADA and CRp across different age groups. Huang concluded that age may influence the diagnostic accuracy of sLDH/pADA in MPE, potentially limiting its value in elderly patients (41). Finally, the results of this study should be interpreted cautiously in countries with a low prevalence of TPE.

Conclusion

sLDH/pADA showed high sensitivity and good diagnostic value for identifying MPE, while CRp did not enhance accuracy. The findings support sLDH/pADA as a useful tool for distinguishing MPE, especially in tuberculosis-endemic regions. Multicenter and multinational studies are essential to validate and promote the broader clinical application of sLDH/pADA.

Ethic Approval: The study was approved by the Ethical Review Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (Approval No. 805 IRB-VN01002/IORG0008603/FWA00023448, 2024).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contributions: NVH, HNH, and NDM: conceptualization, methodology, investigation, resources, visualization, writing - original draft/review, and editing. KND, QKTL, NTN, and VLT: methodology, data curation, formal analysis, writing - review, and editing. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Musso V, Diotti C, Palleschi A, Tosi D, Aiolfi A, Mendogni P. Management of pleural effusion secondary to malignant mesothelioma. J Clin Med. 2021;10(18):4247. doi: 10.3390/jcm10184247.
2. Yang L, Wang Y. Malignant pleural effusion diagnosis and therapy. Open Life Sci. 2023;18(1):20220575. doi: 10.1515/biol-2022-0575.
3. Corcoran JP, Psallidas I, Wrightson JM, Hallifax RJ, Rahman NM. Pleural procedural complications: prevention and management. J Thorac Dis. 2015;7(6):1058-67. doi: 10.3978/j.issn.2072-1439.2015.04.42.
4. Nam VH, Thinh LPN, Khoa NĐ, et al. The diagnostic value of liquid-based cytology of pleural fluid in malignant pleural effusion: A prospective study. Biomed Res Ther. 12(2):7125-30. doi: 10.15419/bmrat.v12i2.957.
5. Verma A, Abisheganaden J, Light RW. Identifying Malignant Pleural Effusion by A Cancer Ratio (Serum LDH: Pleural Fluid ADA Ratio). Lung. 2016;194(1):147-53. doi: 10.1007/s00408-015-9831-6.
6. Zhang F, Hu L, Wang J, Chen J, Chen J, Wang Y. Clinical value of jointly detection serum lactate dehydrogenase/pleural fluid adenosine deaminase and pleural fluid carcinoembryonic antigen in the identification of malignant pleural effusion. J Clin Lab Anal. 2017;31(5)doi: 10.1002/jcla.22106.
7. Verma A, Dagaonkar RS, Marshall D, Abisheganaden J, Light RW. Differentiating Malignant from Tubercular Pleural Effusion by Cancer Ratio Plus (Cancer Ratio: Pleural Lymphocyte Count). Can Respir J. 2016;2016:7348239. doi: 10.1155/2016/7348239.
8. Gayaf M, Anar C, Canbaz M, Tatar D, Güldaval F. Value of Cancer Ratio plus and Cancer Ratio Formulation in Distinguishing Malignant Pleural Effusion from Tuberculosis and Parapneumonic Effusion. Tanaffos. 2021;20(3):221-231.
9. Nguyen QH, Nguyen TVA, Bañuls AL. Multi-drug resistance and compensatory mutations in Mycobacterium tuberculosis in Vietnam. Trop Med Int Health. 2025; doi: 10.1111/tmi.14104.
10. Chalamalasetty SP, Acharya P, Antony T, Ramakrishna A, Kotian H. The Use of "Cancer Ratio" in Differentiating Malignant and Tuberculous Pleural Effusions: Protocol for a Prospective Observational Study. JMIR Res Protoc. 2024;13:e56592. doi: 10.2196/56592.
11. Akoglu H. User's guide to sample size estimation in diagnostic accuracy studies. Turk J Emerg Med. 2022;22(4):177-185. doi: 10.4103/2452-2473.357348.
12. Tian P, Qju R, Wang M, et al. Prevalence, Causes, and Health Care Burden of Pleural Effusions Among Hospitalized Adults in China. JAMA Network Open. 2021;4(8):e2120306-e2120306. doi: 10.1001/jamanetworkopen.2021.20306.
13. Light RW. The Light criteria: the beginning and why they are useful 40 years later. Clin Chest Med. 2013;34(1):21-6. doi: 10.1016/j.ccm.2012.11.006.
14. Chan KKP, Lee YCG. Tuberculous pleuritis: clinical presentations and diagnostic challenges. Curr Opin Pulm Med. 2024;30(3):210-216. doi: 10.1097/mcp.0000000000001052.
15. Sahn SA. Diagnosis and management of parapneumonic effusions and empyema. Clin Infect Dis. 2007;45(11):1480-6. doi: 10.1086/522996.
16. Chen DY, Huang YH, Chen YM, et al. ANA positivity and complement level in pleural fluid are potential diagnostic markers in discriminating lupus pleuritis from pleural effusion of other aetiologies. Lupus Sci Med. 2021;8(1) doi: 10.1136/lupus-2021-000562.
17. Bhatnagar M, Fisher A, Ramsaroop S, Carter A, Pippard B. Chylothorax: pathophysiology, diagnosis, and management-a comprehensive review. J Thorac Dis. 2024;16(2):1645-1661. doi: 10.21037/jtd-23-1636.
18. Kumar P, Gupta P, Rana S. Thoracic complications of pancreatitis. JGH Open. 2019;3(1):71-79. doi: 10.1002/jgh3.12099.
19. Nguyen-Dang K, Bui-Thi HD, Duong-Minh N, et al. The Role and Associated Factors of Liquid-Based Cytology of Bronchoalveolar Lavage Fluid in Lung Cancer Diagnosis: A Prospective Study. Cureus. 2023;15(11):e48483. doi: 10.7759/cureus.48483.
20. Tran-Le QK, Thai TT, Tran-Ngoc N, et al. Lung ultrasound for the diagnosis and monitoring of pneumonia in a tuberculosis-endemic setting: a prospective study. BMJ Open. 2025;15(4):e094799. doi: 10.1136/bmjopen-2024-094799.
21. Blackmore CC, Black WC, Dallas RV, Crow HC. Pleural fluid volume estimation: a chest radiograph prediction rule. Acad Radiol. 1996;3(2):103-9. doi: 10.1016/s1076-6332(05)80373-3.
22. Nahm FS. Receiver operating characteristic curve: overview and practical use for clinicians. Korean J Anesthesiol. 2022;75(1):25-36. doi: 10.4097/kja.21209.
23. Gonnelli F, Hassan W, Bonifazi M, et al. Malignant pleural effusion: current understanding and therapeutic approach. Respir Res. 2024;25(1):47. doi: 10.1186/s12931-024-02684-7.
24. Ishimoto O, Saijo Y, Narumi K, et al. High level of vascular endothelial growth factor in hemorrhagic pleural effusion of cancer. Oncology. 2002;63(1):70-5. doi: 10.1159/000065723.
25. Poon IK, Chan RCK, Choi JSH, et al. A comparative study of diagnostic accuracy in 3026 pleural biopsies and matched pleural effusion cytology with clinical correlation. Cancer Med. 2023;12(2):1471-1481. doi: 10.1002/cam4.5038.
26. Kassirian S, Hinton SN, Cuninghame S, et al. Diagnostic sensitivity of pleural fluid cytology in malignant pleural effusions: systematic review and meta-analysis. Thorax. 2023;78(1):32-40. doi: 10.1136/thoraxjnl-2021-217959.

27. Kaul V, McCracken DJ, Rahman NM, Epelbaum O. Contemporary Approach to the Diagnosis of Malignant Pleural Effusion. Ann Am Thorac Soc. 2019;16(9):1099-1106. doi: 10.1513/AnnalsATS.201902-189CME.
28. Shipman AR, Bahrani S, Shipman KE. Investigative algorithms for disorders affecting plasma lactate dehydrogenase: a narrative review. J Lab Precis Med. 2024;9
29. Hu EC, He JG, Liu ZH, et al. High levels of serum lactate dehydrogenase correlate with the severity and mortality of idiopathic pulmonary arterial hypertension. Exp Ther Med. 2015;9(6):2109-2113. doi: 10.3892/etm.2015.2376.
30. Li M, Tang M, Zhao C, et al. Prognostic Potential of Pulmonary Hypertension in Patients with Hematologic Malignancy. Adv Ther. 2023;40(11):4792-4804. doi: 10.1007/s12325-023-02639-2.
31. Zeng T, Ling B, Hu X, et al. The Value of Adenosine Deaminase 2 in the Detection of Tuberculous Pleural Effusion: A Meta-Analysis and Systematic Review. Can Respir J. 2022; 2022:7078652. doi: 10.1155/2022/7078652.
32. Antonangelo L, Faria CS, Sales RK. Tuberculous pleural effusion: diagnosis & management. Expert Rev Respir Med. 2019;13(8):747-759.doi:10.1080/17476348.2019.1637737.
33. Wang J, Liu J, Xie X, Shen P, He J, Zeng Y. The pleural fluid lactate dehydrogenase/adenosine deaminase ratio differentiates between tuberculous and parapneumonic pleural effusions. BMC Pulm Med. 2017;17(1):168. doi: 10.1186/s12890-017-0526-z.
34. Kulandaisamy PC, Kulandaisamy S, Kramer D, McGrath C. Malignant Pleural Effusions-A Review of Current Guidelines and Practices. J Clin Med. 2021;10(23)doi: 10.3390/jcm10235535.
35. Korczyński P, Mierzejewski M, Krenke R, Safianowska A, Light RW. Cancer ratio and other new parameters for differentiation between malignant and nonmalignant pleural effusions. Pol Arch Intern Med. 2018;128(6):354-361. doi: 10.20452/pamw.4278.
36. Shimoda M, Hirata A, Tanaka Y, et al. Characteristics of pleural effusion with a high adenosine deaminase level: a case–control study. BMC Pulm Med. 2022;22(1):359. doi: 10.1186/s12890-022-02150-4.
37. Lee J, Park J, Lim JK, et al. Tuberculous and Malignant Pleural Effusions With Adenosine Deaminase Levels of 40–70 IU/L: Trends in New Cases Over Time and Differentiation Between Groups. J Korean Med Sci. 2025; 40(13)
38. Terra RM, Antonangelo L, Mariani AW, de Oliveira RL, Teixeira LR, Pego-Fernandes PM. Pleural Fluid Adenosine Deaminase (ADA) Predicts Survival in Patients with Malignant Pleural Effusion. Lung. 2016;194(4):681-6. doi: 10.1007/s00408-016-9891-2.
39. Ashchi M, Golish J, Eng P, O'Donovan P. Transudative malignant pleural effusions: prevalence and mechanisms. South Med J. 1998;91(1):23-6. doi: 10.1097/00007611-199801000-00004.
40. Assi Z, Caruso JL, Herndon J, Patz EF, Jr. Cytologically proved malignant pleural effusions: distribution of transudates and exudates. Chest. 1998;113(5):1302-4. doi: 10.1378/chest.113.5.1302.
41. Huang JH, Chen H, Zhang ZC, et al. Age affects the diagnostic accuracy of the cancer ratio for malignant pleural effusion. BMC Pulm Med. 2023;23(1):198. doi: 10.1186/s12890-023-02475-8.

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