Original Article

Association of Pleural Fluid Glucose, Pleural Fluid CYFRA 21-1, and Radiographic Pleural Effusion Size with Recurrent Malignant Pleural Effusion

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Abstract

Background: Recurrent malignant pleural effusion (MPE) remains a significant clinical problem that often necessitates repeated interventions and negatively affects patients' quality of life. This study evaluated the association of pleural fluid glucose, pleural fluid CYFRA 21-1, and radiographic pleural effusion size with recurrent malignant pleural effusion.

Methods: A single-center observational analytic study was conducted in 60 patients with malignant pleural effusion. Patients were classified into recurrent and non-recurrent groups based on pleural fluid reaccumulation requiring repeat thoracentesis within 30 days. Pleural glucose and CYFRA 21-1 levels were measured using enzyme-linked immunosorbent assay. One radiologist and one pulmonologist independently interpreted chest radiographs. Pleural effusion size was categorized according to the hilar level. Statistical analyses included the Chi-square test, Mann–Whitney U test, and receiver operating characteristic (ROC) curve analysis.

Results: Recurrent pleural effusion occurred in 55% of patients. Effusion extending above the hilar level was observed in all recurrent cases and was significantly associated with recurrence (P<0.001). Patients with recurrent pleural effusion had significantly lower pleural glucose levels (39.53 vs 107.46 mg/dL; P<0.001) and higher pleural CYFRA 21-1 levels (58.61 vs 27.26 ng/mL; P<0.001) than those in the non-recurrent group. ROC analysis demonstrated excellent discriminative performance for pleural glucose (AUC=0.905) and pleural CYFRA 21-1 (AUC=0.933), with optimal cut-off values of <85.85 mg/dL and ≥44.02 ng/mL, respectively. Chest pain was the only clinical symptom significantly associated with recurrent pleural effusion (P<0.001).

Conclusion: Lower pleural glucose levels, higher pleural CYFRA 21-1 levels, and radiographic pleural effusion extending above the hilar level were significantly associated with recurrent malignant pleural effusion. These parameters may serve as useful clinical markers to complement the evaluation of patients with recurrent MPE.

Keywords: CYFRA 21-1, malignant pleural effusion, pleural glucose, radiographic pleural effusion size, recurrence

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Submitted: February 16th, 2026
Accepted: July 26th, 2026
Published: July 31st, 2026

J Respirol Indones. 2026
Vol. 46 No. 3: 177-86
https://doi.org/10.36497/jri.v46i3.1181

INTRODUCTION

Pleural effusion is defined as the accumulation of fluid within the pleural cavity, the space between the parietal and visceral pleura. It may occur as an isolated condition or as a complication of underlying pulmonary or systemic diseases, including infection, malignancy, and inflammatory disorders. Pleural effusion contributes significantly to pulmonary morbidity and mortality.[1] Its prevalence is estimated at approximately 320 cases per 100,000 population in both industrialized and developing countries and accounts for around 0.5% of patients receiving home care services. Mortality associated with pleural effusion remains high, with reported rates of 22.6% within one month and up to 49.4% within one year, particularly in cases of bilateral or extensive effusions.[2,3]

Based on the modified Light's criteria, pleural effusion is classified into transudative and exudative types. The most common causes of exudative pleural effusion include malignancy, parapneumonic effusion, empyema, and tuberculosis, whereas transudative pleural effusion is mainly associated with heart failure, liver cirrhosis, and

hypoalbuminemia. A large study conducted in China identified parapneumonic effusion and empyema (25.1%), malignancy (23.7%), and tuberculosis (12.3%) as the three leading causes of pleural effusion.[4] Clinical manifestations vary depending on the volume of fluid and the underlying etiology. At the same time, some patients remain asymptomatic, others experience pleuritic chest pain, dyspnea, and non-productive cough, all of which significantly impair quality of life.[5]

Malignant pleural effusion (MPE) is particularly challenging due to its high recurrence rate, even after interventions such as pleurodesis or indwelling pleural catheter (IPC) placement. Post-mortem studies suggest that lymphatic obstruction caused by direct invasion of malignant cells contributes to impaired pleural fluid drainage, leading to recurrence.[6] Consequently, identifying factors that predict recurrent pleural effusion is essential for improving clinical management and patient outcomes.

Several biochemical and radiological parameters have been proposed as potential predictors, including pleural fluid glucose levels, pleural cytokeratin fragment 19 (CYFRA 21-1), and radiographic evidence of pleural effusion extending above the cardiac silhouette on chest radiography.[7,8] Pleural fluid glucose has been investigated as a diagnostic marker, as malignant pleural effusions are often associated with lower glucose levels due to increased glycolytic activity of tumor cells. However, evidence regarding its diagnostic and prognostic value remains inconclusive.[9]

CYFRA 21-1, a fragment of cytokeratin 19, has demonstrated utility as a sensitive biomarker for diagnosing malignant pleural effusion, determining prognosis, and monitoring therapy, particularly in non-small cell lung cancer (NSCLC). Elevated CYFRA 21-1 levels have been reported in various epithelial malignancies, including lung, ovarian, and breast cancers, as well as in mesothelioma and multiple myeloma. However, data from Asian populations remain limited.[10]

Radiological assessment, especially chest X-ray, plays a crucial role in evaluating pleural fluid volume and distribution and in monitoring disease progression. Persistent pleural effusion observed on post-drainage chest radiographs has been identified as an early indicator of recurrence.[8,11] Integrating biochemical markers such as pleural glucose and CYFRA 21-1 with radiological evaluation may enhance prediction of recurrent pleural effusion and optimize management strategies.

This study aimed to evaluate differences in pleural fluid glucose levels, pleural fluid CYFRA 21-1 levels, and effusion size between recurrent and non-recurrent pleural effusions in patients with malignant pleural effusion.

METHODS

An observational analytic study was conducted at Dr. Saiful Anwar General Hospital, Malang, and was approved by the Health Research Ethics Committee of Dr. Saiful Anwar Regional General Hospital (Approval No. 400/099/K.3/102.7/2025). The study population consisted of hospitalized patients with malignancy and pleural effusion. Exudative pleural effusion was confirmed through pleural fluid analysis based on one of Light's criteria, specifically by comparing pleural fluid LDH levels with ≥2/3 of the upper limit of normal serum LDH as defined by the Clinical Pathology Laboratory at Dr. Saiful Anwar General Hospital, Malang. Malignancy was confirmed through history taking, physical examination, and cytological and/or biopsy findings.

Patients were then classified into recurrent and non-recurrent groups based on pleural fluid reaccumulation requiring repeat thoracentesis within 30 days after the initial thoracentesis. One radiologist and one pulmonologist independently interpreted recurrence assessments. Chest radiographs and pleural effusion size were categorized as extending above or below the hilar level for analysis.

The sample size was calculated using the formula for comparing two independent proportions with a two-sided significance level (α) of 0.05 and a statistical power of 80%, based on the expected proportions of recurrent malignant pleural effusion

reported in a previous study.[11] The minimum required sample size was 27 patients per group, and 60 patients were enrolled in the study.

$$n = \left(\frac{Z\alpha\sqrt{2PQ} + Z\beta\sqrt{P_1Q_1 + P_2Q_2}}{P_1 - P_2} \right)^2$$

The inclusion criteria were patients aged ≥18 years with pathologically confirmed malignancy complicated by exudative pleural effusion and who agreed to participate in the study by providing written informed consent. The exclusion criteria included patients with contraindications to thoracentesis (such as circumferential pleural adhesions, uncontrollable cough, significant hypercapnia [PCO_2 >60 mmHg], pneumothorax, myocardial infarction or stroke within the previous six weeks, coagulopathy [platelet count <50,000 or INR >2], and severe hypoxemia [PO_2 <50 mmHg on room air]); patients with positive pleural fluid bacterial cultures; and patients with pleural effusion due to infection (parapneumonic effusion or pulmonary tuberculosis based on clinical criteria, Light's criteria, negative TCM results, and absence of fibroinfiltrative lesions on chest radiography) or heart failure.

Pleural fluid samples were obtained by thoracentesis in accordance with current clinical practice guidelines. The procedure included patient preparation and informed consent, positioning the patient in a seated posture with arms leaning forward, and determining the puncture site using thoracic ultrasound guidance or anatomical landmarks based on the Triangle of Safety. Local anesthesia was administered using 2% lidocaine, followed by gradual aspiration of pleural fluid. Fluid removal was limited to 1,000–1,500 mL and terminated earlier if the patient developed cough, dyspnea, chest pain, or signs of hemodynamic instability.

The obtained pleural fluid samples were sent for routine pleural fluid analysis, cytological examination, and bacterial culture. An aliquot of the pleural fluid was centrifuged, and the supernatant was stored for subsequent CYFRA 21-1 measurement by ELISA. Samples were centrifuged at 2,000–3,000 rpm for 20 minutes, and the supernatant was carefully collected for further analysis.

Routine pleural fluid biochemical analysis, including glucose measurement, was performed immediately after thoracentesis in the Clinical Pathology Laboratory of Dr. Saiful Anwar General Hospital as part of standard clinical care. Pleural fluid CYFRA 21-1 measurement was performed specifically for this study using a Human CYFRA 21-1 ELISA Kit (96T; Elabscience Biotechnology Inc., Houston, TX, USA) according to the manufacturer's instructions. The assay has a detection range of 0.31–20 ng/mL, an analytical sensitivity of 0.19 ng/mL, requires a sample volume of 100 µL, and has a total assay time of approximately 3 hours and 30 minutes.

Briefly, standards and samples were incubated in microplate wells, followed by sequential addition of a biotinylated detection antibody and horseradish peroxidase (HRP)-conjugated reagent. After substrate development and reaction termination, absorbance was measured at 450 nm using a microplate reader. All procedures were performed in accordance with the manufacturer's protocol and standard operating procedures to ensure assay reliability.

Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Shapiro–Wilk test. Continuous variables were presented as mean±standard deviation (SD) for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data. In contrast, categorical variables were presented as frequencies and percentages.

Comparisons between the recurrent and non-recurrent malignant pleural effusion groups were performed using the independent-samples t-test for normally distributed continuous variables or the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic

performance of pleural fluid glucose and CYFRA 21-1 levels in distinguishing recurrent from non-recurrent malignant pleural effusion. The optimal cut-off value for each biomarker was determined using the Youden Index (J = sensitivity + specificity − 1), which identifies the point providing the best balance between sensitivity and specificity. The area under the ROC curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Multivariable logistic regression analysis was not performed because the relatively small sample size limited the development of a reliable multivariable model after considering clinically relevant covariates. Therefore, the results are based on univariate analyses and should be interpreted as associations rather than independent predictors. A value of $P<0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the baseline demographic, clinical, laboratory, and radiographic characteristics of the study participants. A Total of 60 patients were included, comprising 33 patients (55.0%) with recurrent malignant pleural effusion and 27 patients (45.0%) with non-recurrent malignant pleural effusion. Dyspnea (98.33%), weight loss (98.33%), cough (96.67%), and chest pain (81.67%) were the most frequently reported presenting symptoms. Lung cancer was the predominant primary malignancy (55.00%), with lung adenocarcinoma representing the most common histopathological subtype (40.00%). Cytological examination most frequently demonstrated Class II findings (50.00%).

Table 2 presented that patients with recurrent malignant pleural effusion had significantly lower pleural fluid glucose levels than those without recurrence (39.53±38.66 vs. 107.46±30.59 mg/dL; $P<0.0001$). Conversely, pleural fluid CYFRA 21-1 levels were significantly higher in the recurrent group than in the non-recurrent group (58.61±6.44 vs. 27.26±17.90 ng/mL; $P<0.0001$). Radiographic pleural effusion extending above the hilar level was also significantly more common among patients with recurrent malignant pleural effusion ($P<0.0001$).

Table 1. Baseline Characteristics

Characteristics	n	%
Age, years		
19–44	11	18.33
45–64	27	45.00
65–84	22	36.67
Gender		
Male	27	45.00
Female	33	55.00
Smoking		
Yes	24	40.00
No	36	60.00
Dyspnea		
Yes	59	98.33
No	1	1.67
Cough		
Yes	58	96.67
No	2	3.33
Chest pain		
Yes	49	81.67
No	11	18.33
Weight loss		
Yes	59	98.33
No	1	1.67
Diagnosis		
Lung cancer	24	40.00
Non-lung cancer	36	60.00
Primary Cancer Type and Cancer cell type		
Adenocarcinoma lung cancer	24	40.00
Squamous cell lung cancer	6	10.00
Small cell lung cancer	3	5.00
Mediastinum tumor	2	3.33
Non-Hodgkin lymphoma	6	10.00
Hodgkin lymphoma	1	1.67
Thyroid Cancer	1	1.67
Breast cancer	3	5.00
Renal cell cancer	1	1.67
Ovarian cancer	6	10.00
Colon cancer	2	3.33
Uterine cervical cancer	1	1.67
Hepatocellular cancer	1	1.67
Leiomyosarcoma	1	1.67
Mesentery sarcoma	1	1.67
Malignant Melanoma	1	1.67
Pleura Cytology Class		
Class II	30	50.00
Class III	6	10.00
Class IV	13	21.67
Class V	11	18.33
Chest Radiograph		
Effusion above hilus	33	55.00
Effusion below hilus	27	45.00

These findings indicate that lower pleural fluid glucose levels, higher pleural fluid CYFRA 21-1 concentrations, and larger radiographic pleural effusion size were significantly associated with recurrent malignant pleural effusion.

The receiver operating characteristic (ROC) curve analyses for pleural fluid glucose and pleural fluid CYFRA 21-1 are presented in Figures 1 and 2, respectively. Both biomarkers demonstrated excellent ability to discriminate between recurrent and non-recurrent malignant pleural effusion.

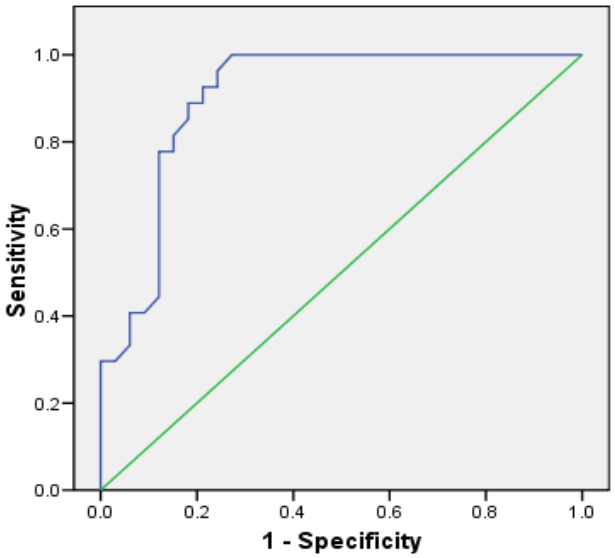

Figure 1. ROC of Pleural Glucose (cut-off value=85.85 mg/dL; AUC=0.905; *P*=0.0001; OR=24.64; 95% CI=0.827–0.983; Sensitivity=84.85%; Specificity=81.48%; PPV=86.49%; NPV=81.48%; LR+ = 4.58; Accuracy=83.33%)

For pleural fluid glucose, the area under the ROC curve (AUC) was 0.905 (95% CI=0.827–0.983; *P*<0.001), indicating excellent discriminative performance. The optimal cut-off value, determined using the Youden Index, was <85.85 mg/dL, which best balanced sensitivity and specificity. Pleural fluid glucose showed a sensitivity of 84.85%, specificity of 81.48%, positive predictive value (PPV) of 86.49%, negative predictive value (NPV) of 81.48%, and an overall diagnostic accuracy of 83.33%.

Similarly, pleural fluid CYFRA 21-1 demonstrated excellent discriminative performance, with an AUC of 0.933 (95% CI=0.859–1.000; *P*<0.001). The Youden Index identified an optimal cut-off of≥44.02 ng/mL, balancing sensitivity and specificity. Pleural fluid CYFRA 21-1 demonstrated a sensitivity of 96.97%, specificity of 81.48%, PPV of 86.49%, NPV of 95.65%, and an overall diagnostic accuracy of 90.00%.

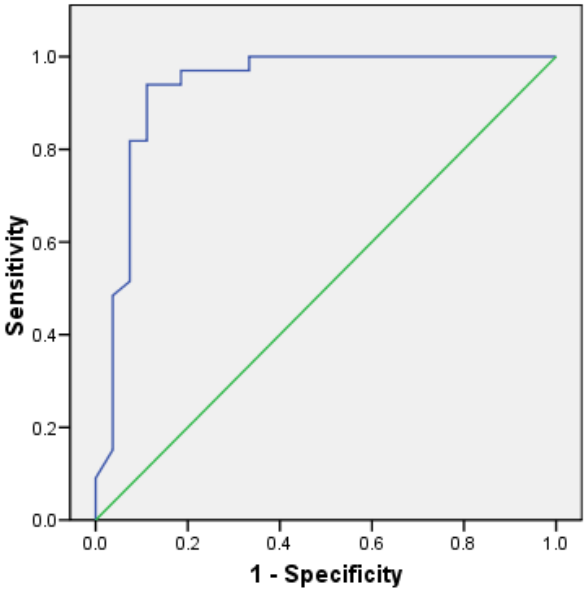

Figure 2. ROC of CYFRA 21-1 (cut-off value=44.02 ng/dL; AUC=0.933; *P*=0.0001; OR=140.8; 95% CI=0.859–1.000; Sensitivity=96.97%; Specificity=81.48%; PPV=86.49%; NPV=95.65%; LR+ = 5.24; Accuracy=90%)

Consistent with these findings, the positive likelihood ratio was higher for pleural fluid CYFRA 21-1 (LR+ = 5.24) than for pleural fluid glucose (LR+ = 4.58). In addition, patients with pleural fluid glucose levels below 85.85 mg/dL and those with pleural fluid CYFRA 21-1 levels ≥44.02 ng/mL were significantly associated with recurrent malignant pleural effusion.

Table 2. Cross-table Analysis

Characteristics	Recurrent Pleural Effusion (n=33)	No Recurrent Pleural Effusion (n=27)	*P*	OR (95% CI)
Chest Radiograph				
Effusion above hilus	33 (100.0%)	0 (0.0%)	0.0001*[a]	---
Effusion below hilus	0 (0.0%)	27 (100.0%)		
Pleural Glucose, mean±SD	39.53±38.66 mg/dL	107.46±30.59 mg/dL		
<60 mg/dL	25 (75.8%)	1 (3.7%)	0.0001*[b]	81.25 (9.46-697.61)
>60 mg/dL	8 (24.2%)	26 (96.3%)		
CYFRA 21-1, mean±SD	58.61±6.44 ng/mL	27.26±17.90 ng/mL		
>50 ng/mL	29 (87.9%)	3 (11.1%)	0.0001*[b]	58.00 (11.81-284.89)
<50 ng/mL	4 (12.1%)	24 (88.9%)		

Note: OR=odds ratio; CI=confidence interval; [a]chi-square; [b]Mann-Whitney U test; *significant with *P*<0.05;

Table 3. Cross-table Analysis Based on ROC cut-off

Variables	Recurrent Pleural Effusion (n=33)	No Recurrent Pleural Effusion (n=27)	*P*	OR (95% CI)
Pleural Glucose Levels				
<85.85	28 (84.8%)	5 (18.5%)	0.0001*	24.64 (6.33-95.96)
>85.85	5 (15.2%)	22 (81.5%)		
CYFRA 21-1				
>44.02	32 (97.0%)	5 (18.5%)	0.0001*	140.80 (15.38-1289.40)
<44.02	1 (3.0%)	22 (81.5%)		

Note: OR=odds ratio; CI=confidence interval; *significant with *P*<0.05

Table 3 presents the comparison of laboratory variables with the optimal cut-off value between patients with recurrent and non-recurrent malignant pleural effusion. Patients with pleural fluid glucose levels below the optimal cut-off value (<85.85 mg/dL) were significantly more likely to have recurrent malignant pleural effusion than those with higher glucose levels (OR=24.64; 95% CI=6.33–95.96; *P*<0.001). Likewise, pleural fluid CYFRA 21-1 levels ≥44.02 ng/mL were significantly associated with recurrent malignant pleural effusion (OR=140.80; 95% CI=15.38–1289.40; *P*<0.001).

DISCUSSION

This study demonstrated that lower pleural fluid glucose levels, higher pleural fluid CYFRA 21-1 concentrations, and larger radiographic pleural effusion size were significantly associated with recurrent malignant pleural effusion. These findings suggest that metabolic alterations, tumor burden, and the radiographic extent of pleural involvement provide complementary information for identifying patients who are more likely to experience recurrent pleural effusion.[12,13]

Pleural fluid glucose is an important biochemical parameter in evaluating pleural effusion because it reflects metabolic activity within the pleural space. Glucose enters the pleural cavity by diffusion from the circulation, and its concentration decreases when glucose consumption exceeds diffusion. In malignant pleural effusion, increased glucose utilization by metabolically active tumor cells together with chronic inflammatory cell infiltration contributes to lower pleural glucose concentrations.[11,13]

Furthermore, malignant infiltration of the pleural membrane may impair glucose transport by disrupting pleural integrity and reducing diffusion from plasma into the pleural space. Consequently, markedly reduced pleural glucose levels may indicate extensive pleural involvement and biologically aggressive disease, conditions that favor persistent pleural fluid accumulation and recurrence.[11,13]

Previous studies have similarly reported that low pleural glucose concentrations are associated with advanced pleural malignancy, poor therapeutic response, and recurrent malignant pleural effusion.[11,13] In the present study, recurrent malignant pleural effusion was defined as reaccumulation of pleural fluid requiring repeat thoracentesis within 30 days after the initial thoracentesis. This follow-up period is consistent with previous studies evaluating recurrent malignant pleural effusion.[14]

CYFRA 21-1 was selected in the present study as part of a sequential research program investigating pleural biomarkers associated with recurrent malignant pleural effusion. In a previous study, pleural fluid carcinoembryonic antigen (CEA) was significantly associated with recurrent malignant pleural effusion. Building upon these findings, the present study evaluated CYFRA 21-1 as another well-established epithelial tumor biomarker with a different biological basis.[6,15–18]

Unlike CEA, whose expression varies according to tumor histology and is predominantly elevated in adenocarcinoma, CYFRA 21-1 reflects cytokeratin-19 fragments released during apoptosis and necrosis of epithelial tumor cells. Consequently, CYFRA 21-1 provides a biological indicator of tumor burden, active tumor cell turnover, and pleural invasion, making it a relevant biomarker for malignant pleural effusion, particularly in non-small cell lung cancer.[6,15–18]

The association between elevated pleural fluid CYFRA 21-1 concentrations and recurrent malignant pleural effusion is biologically plausible. Increased

CYFRA 21-1 reflects accelerated tumor cell turnover and more extensive pleural infiltration, both of which indicate a greater tumor burden within the pleural cavity. Progressive pleural invasion disrupts lymphatic drainage and increases vascular permeability via the release of inflammatory cytokines and angiogenic mediators, particularly vascular endothelial growth factor (VEGF), leading to continuous pleural fluid formation and reaccumulation despite therapeutic drainage. Therefore, elevated pleural fluid CYFRA 21-1 is considered a marker of aggressive pleural disease and persistent malignant pleural involvement rather than a direct cause of recurrence. Previous studies have similarly demonstrated that elevated pleural CYFRA 21-1 concentrations are associated with poor pleurodesis outcomes, recurrent malignant pleural effusion, and reduced survival.[16,19–21]

The radiographic component of this study also deserves consideration because it provides information beyond simple confirmation of pleural effusion. Radiographic pleural effusion extending above the hilar level likely reflects a larger volume of pleural fluid, greater pleural surface involvement, and more extensive malignant infiltration. Progressive pleural invasion may obstruct pleural lymphatic drainage and increase microvascular permeability through tumor-related inflammatory and angiogenic mediators, particularly vascular endothelial growth factor (VEGF), resulting in persistent pleural fluid production despite therapeutic drainage. Consequently, radiographic effusion size may represent the severity of pleural disease rather than merely the volume of accumulated fluid.[7]

From a clinical perspective, chest radiography is inexpensive, widely available, and routinely performed during the evaluation and follow-up of patients with malignant pleural effusion. Therefore, assessment of radiographic pleural effusion size may complement pleural fluid glucose and CYFRA 21-1 measurements in identifying patients more likely to experience recurrent malignant pleural effusion. Patients presenting with extensive pleural effusion together with unfavorable pleural biomarker profiles may be considered for earlier definitive pleural interventions, such as pleurodesis or indwelling pleural catheter placement. However, these findings require validation in larger prospective multicenter studies.[7,15–18,21,22]

Previous studies have consistently demonstrated that elevated pleural fluid CYFRA 21-1 concentrations are associated with poor control of pleural effusion, unsuccessful pleurodesis, recurrent malignant pleural effusion, and reduced survival. These observations are biologically plausible because elevated CYFRA 21-1 levels reflect accelerated tumor cell turnover, apoptosis, and necrosis within the pleural cavity, indicating a greater tumor burden and more extensive pleural involvement. Progressive pleural infiltration disrupts lymphatic drainage and promotes persistent pleural fluid production through inflammatory cytokines and angiogenic mediators, thereby contributing to repeated pleural fluid accumulation despite therapeutic drainage. Consequently, elevated pleural fluid CYFRA 21-1 should be interpreted as a marker of aggressive pleural disease rather than a direct cause of recurrence.[16,19–21]

Receiver operating characteristic (ROC) analysis demonstrated that both pleural fluid glucose and CYFRA 21-1 showed excellent discriminative performance in distinguishing recurrent from non-recurrent malignant pleural effusion. The optimal cut-off values were determined using the Youden Index, which identifies the threshold providing the best balance between sensitivity and specificity. These cut-off values may facilitate the interpretation of pleural biomarkers in clinical practice. However, they should be considered exploratory and require external validation before routine application. The observed diagnostic performance is biologically plausible[12,21]

Reduced pleural fluid glucose reflects increased glucose consumption by metabolically active tumor cells, together with impaired glucose diffusion due to malignant pleural infiltration and chronic inflammation. Conversely, elevated pleural fluid CYFRA 21-1 reflects increased epithelial tumor cell turnover, apoptosis, and necrosis, indicating greater tumor burden and more extensive pleural

involvement. Therefore, pleural glucose and CYFRA 21-1 provide complementary information regarding the metabolic activity and biological behavior of malignant pleural disease rather than acting as direct causes of recurrent pleural effusion.[12,21]

From a clinical perspective, combining pleural fluid glucose, pleural fluid CYFRA 21-1, and radiographic pleural effusion size may improve the early identification of patients with malignant pleural effusion who are at higher risk of recurrence. This information may assist clinicians in selecting appropriate pleural management strategies, including earlier consideration of definitive pleural interventions, such as pleurodesis or indwelling pleural catheter placement, rather than repeated therapeutic thoracentesis alone.

Nevertheless, because this was a single-center study with a relatively small sample size and no multivariable analysis, these findings should be interpreted as significant associations rather than independent effects of the evaluated biomarkers. Furthermore, the relatively wide confidence intervals, particularly for the odds ratio of CYFRA 21-1, indicate limited precision of the estimated effect size, most likely reflecting the small sample size and the heterogeneity of malignancy types included in this study. Therefore, the magnitude of these associations should be interpreted cautiously and requires confirmation in larger multicenter prospective studies before routine clinical implementation.

LIMITATION

This study has several limitations that should be considered when interpreting the findings. First, this was a single-center, observational, analytic study with a cross-sectional design and a relatively small sample size, which may limit the generalizability of the findings to other populations and healthcare settings. Differences in patient characteristics, clinical practice, laboratory procedures, and radiographic interpretation across institutions may also influence the applicability of the identified biomarker cut-off values. Furthermore, because of the observational design, the present study demonstrates significant associations rather than causal relationships between pleural fluid glucose, pleural fluid CYFRA 21-1, radiographic pleural effusion size, and recurrent malignant pleural effusion.

Second, the study population included patients with various primary malignancies, histological subtypes, disease stages, and previous oncological treatments. This heterogeneity may have influenced biomarker expression and the occurrence of recurrent malignant pleural effusion. In addition, potentially important confounding factors, including age, cancer stage, performance status, pleural effusion volume, cytological findings, and previous systemic therapy, were not adjusted for because multivariable analysis was not performed. Considering the relatively small sample size and the limited number of recurrent events, multivariable logistic regression was not considered statistically robust. Therefore, the observed associations should not be interpreted as independent effects of the evaluated biomarkers.

Third, pleural fluid CYFRA 21-1 was measured only once for research purposes at the time of the second thoracentesis. In contrast, pleural fluid glucose levels were obtained from routine pleural fluid analysis performed as part of the same procedure. Consequently, serial changes in biomarker concentrations during disease progression or following treatment could not be evaluated. Moreover, the relatively wide confidence intervals observed, particularly for the odds ratio of pleural fluid CYFRA 21-1, indicate limited precision of the estimated effect sizes, most likely reflecting the relatively small sample size and the heterogeneous malignancy population included in this study.

CONCLUSION

The present study provides evidence that lower pleural fluid glucose levels, higher pleural fluid CYFRA 21-1 concentrations, and radiographic pleural effusion extending above the hilar level on chest radiography are significantly associated with recurrent malignant pleural effusion and clinically

accessible parameters. These biochemical and radiographic characteristics may provide complementary information for identifying patients with malignant pleural effusion who have features associated with recurrence. Although the identified cut-off values showed good diagnostic discrimination in this study, they should be considered exploratory and require external validation before routine clinical application. Required to further prospective studies with larger sample sizes and comprehensive multivariable analyses are warranted to validate these findings, determine whether these associations remain independent after adjustment for potential confounding factors, and establish more robust and generalizable models for clinical decision-making.

CONFLICT OF INTEREST

The authors declare that there are no potential conflicts of interest pertinent to the content of this study.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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