ORIGINAL ARTICLE

Significance Level of Pleural Fluid Tissue Inhibitor Metalloproteinase-1 (TIMP-1) and Glucose Levels as Biomarkers of Malignant Pleural Effusion

Cleine Michaela[1*], Ngakan Putu Parsama Putra[1], Susanthy Djajalaksana[1], Nanik Setijowati[2], Aditya Sri Listyoko[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[3]Doctoral Student, Division of Respiratory Medicine and Rheumatology, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, Tottori, Japan.

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ABSTRACT

Introduction: Distinguishing between malignant and non-malignant pleural effusions is often challenging due to overlapping biochemical profiles. Conventional diagnostic methods, including cytology and biopsy, are limited by their invasive nature, high costs, and potential complications. Emerging biomarkers, such as tissue inhibitor of metalloproteinase-1 (TIMP-1) and pleural fluid glucose levels, show promise as alternative diagnostic tools, but their clinical utility requires further validation. This study investigated the diagnostic value of TIMP-1 and pleural fluid glucose levels in differentiating malignant from non-malignant pleural effusions and explored their correlation in malignant cases.

Methods: This cross-sectional analytical study included patients with exudative pleural effusion, categorized as malignant or non-malignant based on cytology and/or biopsy results. Biomarker levels of TIMP-1 and pleural fluid glucose were measured using enzyme-linked immunosorbent assay (ELISA) and biochemical analysis. Diagnostic thresholds for both biomarkers were determined using receiver operating characteristic (ROC) curve analysis.

Results: Among 88 patients studied (33 malignant, 55 non-malignant), pleural fluid glucose levels were significantly lower in malignant cases (55.97 vs. 93.71 mg/dL; p=0.001), while TIMP-1 levels were notably higher (13.88 vs. 13.34 pg/mL; p<0.001). Tissue inhibitor of metalloproteinase-1 demonstrated superior diagnostic accuracy (86.5%) compared to glucose (70.6%) and the combined biomarker model (76.5%), with the sensitivity and specificity of 84.8% and 83.6%, respectively.

Conclusion: Elevated TIMP-1 levels and reduced pleural fluid glucose levels are promising diagnostic biomarkers for malignant pleural effusion (MPE). Tissue inhibitor of metalloproteinase-1 exhibited the highest diagnostic accuracy, highlighting its potential as a non-invasive diagnostic tool in clinical practice.

INTRODUCTION

Pleural effusion is characterized by fluid accumulation in the pleural cavity and results from an imbalance between the production and absorption of pleural fluid. The estimated incidence is 3,000 cases per 1 million people annually.[1] Pleural effusion is associated with increased mortality, reaching 15% within one month and 32% within a year of diagnosis.[2] Common types of pleural effusions include malignant pleural effusions (MPE) caused by cancer and non-malignant effusions resulting from parapneumonic infections, heart failure, or tuberculosis. They often share similar biochemical profiles, thus accurate identification

*Corresponding author: cleinemichaela@student.ub.ac.id

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and diagnosis of pleural effusion types are crucial for determining appropriate therapeutic strategies. Conventional diagnostics, including thoracentesis, cytological analysis of pleural fluid, and histological examination, are considered gold standards. However, these are invasive, costly, and have potential complications.[3]

In recent years, pleural fluid biomarker analysis has emerged as a promising diagnostic approach for pleural effusion. It is less invasive, more cost-effective, and provides objective results. Proteolytic enzymes and matrix degradation processes play significant roles in the inflammatory response of pleural effusions, specifically matrix metalloproteinases (MMPs). Matrix metalloproteinases are counterbalanced by their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs). Among the four TIMP isoforms (TIMP-1, TIMP-2, TIMP-3, and TIMP-4), TIMP-1 has shown potential as a diagnostic biomarker for distinguishing between benign and MPE.[4] Pleural fluid glucose levels have also been widely investigated, as malignant effusions are hypothesized to exhibit low glucose levels due to tumor cell glycolysis. This study aimed to evaluate and compare the diagnostic value of pleural fluid TIMP-1 and glucose levels in these conditions. To date, this is the first article that has compared the performance of both markers (alone and in combination) in this context.

METHODS

This study employed an observational analytic design with a cross-sectional approach to evaluate the levels of TIMP-1 and glucose in the pleural fluid of patients with malignant and non-malignant pleural effusions. Additionally, comparisons of TIMP-1 and pleural fluid glucose levels were conducted between the two groups. The subjects were patients diagnosed with exudative pleural effusions, both malignant and non-malignant, who were hospitalized at Dr. Saiful Anwar General Hospital, Malang. A consecutive sampling method was used. The presence of exudative pleural effusion was confirmed using Light's criteria. Malignant and non-malignant pleural effusions were further confirmed through physical examination, medical history, cytological analysis, and/or pleural biopsy. Purposive sampling with a minimum sample size of 25 participants per group was calculated.

Inclusion criteria for this study were: 1) Patients diagnosed with exudative pleural effusion based on Light's criteria; 2) Aged above 18 years old; 3) Were willing to participate in the study and provided informed consent. Exclusion criteria included patients who had undergone chemotherapy for primary malignancy and patients with contraindications to pleural sampling procedures, such as: 1) circumferential pleural adhesions; 2) uncontrolled coughing; 3) significant hypercapnia (partial pressure of carbon dioxide/PCO_2 >60 mmHg); 4) pneumothorax; 5) myocardial infarction or stroke within the preceding six weeks; 6) coagulopathy (platelet <50,000, international normalized ratio/INR >2); (7) hypoxemia (partial pressure of oxygen/PO_2 <50 mmHg on room air).

The independent variables in this study were malignant and non-malignant exudative pleural effusions, while the dependent variables were the levels of TIMP-1 and glucose in pleural fluid. Data were processed and analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 26. Normality test was conducted using the Shapiro-Wilk test. Comparisons of TIMP-1 and pleural fluid glucose levels between malignant and non-malignant pleural effusions were analyzed using independent t-tests or Mann-Whitney U tests, depending on the data distribution. The cut-off values for TIMP-1 and pleural fluid glucose in differentiating malignant from non-malignant pleural effusions were determined using receiver operating characteristic (ROC) curves. Diagnostic tests were subsequently performed to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

RESULTS

Demographic Characteristics

This study analyzed data from 88 patients, with a mean age of 57.33 years old (range 23-87 years old). The distribution of gender was equal. Regarding smoking, 48.9% were smokers and 51.1% were non-smokers. The Brinkman Index showed 55.7% of participants as light smokers, 29.5% as moderate smokers, and 14.8% as heavy smokers. A significant proportion reported dyspnea, coughing, and chest pain. Weight loss was noted in 93.2% of patients. Among them, 37.5% were diagnosed with MPE, while 62.5% were categorized as non-malignant (Table 1).

Table 1. Baseline characteristics

Characteristic	Sample (n)	Percentage (%)	Mean±Standard Deviation/Median (Minimum-Maximum)
Age			57.33±13.02/23-87
<55 years old	40	45.5	
>55 years old	48	54.5	
Gender			
Male	44	50.0	
Female	44	50.0	
Smoking History			
No	45	51.1	
Yes	43	48.9	
Brinkman Index			
Light (0-199)	49	55.7	
Moderate (200-599)	26	29.5	
Heavy (≥600)	13	14.8	
Dyspnea			
No	2	2.3	
Yes	86	97.7	
Cough			
No	4	4.5	
Yes	84	95.5	
Chest Pain			
No	14	15.9	
Yes	74	84.1	
Weight Loss			
No	6	6.8	
Yes	82	93.2	
Group			
Malignant	33	37.5	
Non-Malignant	55	62.5	

The most common primary cancer was lung cancer, followed by breast cancer and ovarian cancer. Cytology findings indicated that 48.9% of patients were classified as class II, 19.3% as class III, 18.2% as class IV, and 13.6% as class V. The analysis of epidermal growth factor receptor (EGFR) mutation status revealed that 65.9% of patients did not have any mutations. A smaller proportion exhibited specific mutations, including 6.8% with wild-type mutations and 2.3% with mutations in exon 21. Adenocarcinoma was the most frequently identified cancer type. Notably, the cancer cell type remained unidentified in 19.3% of patients (Table 2).

Table 2. Primary cancer characteristics, pleural fluid cytology, epidermal growth factor receptor mutation, and cancer cell types

Characteristic	Frequency	Percentage (%)
Primary Cancer		
Unknown	16	18.2%
Lung cancer	49	55.7%
Breast cancer (Ca Mammae)	7	8.0%
Cervical cancer (Ca Cervix)	2	2.3%
Ovarian cancer (Ca Ovarium)	4	4.5%
Mediastinal tumor	2	2.3%
Non-Hodgkin lymphoma	3	3.4%
Hodgkin lymphoma	1	1.1%
Renal cancer (Ca Renal)	1	1.1%
Oropharyngeal cancer	1	1.1%
Nasal cancer	1	1.1%
Rectal cancer (Ca Recti)	1	1.1%

Differences in Tissue Inhibitor of Metalloproteinase-1 and Glucose Variables in Malignant and Non-Malignant Pleural Effusion

The distribution of glucose and TIMP-1 data was not normal (p-value<0.05). Therefore, the comparison between the MPE and non-malignant pleural effusion groups was analyzed using the Mann-Whitney U test. The average glucose level in the malignant group was 55.97 mg/dL, while the average glucose level in the non-malignant group was 93.71 mg/dL. A p-value of 0.001 indicated glucose levels in the malignant group were significantly lower than those in the non-malignant group.

Furthermore, the mean TIMP-1 value in the malignant group was 13.88 pg/mL vs 13.34 pg/mL in the non-malignant group. The Mann-Whitney test also

indicated a significant result (p-value of 0.000). This difference shows the TIMP-1 level in the malignant group to be higher compared to the non-malignant group.

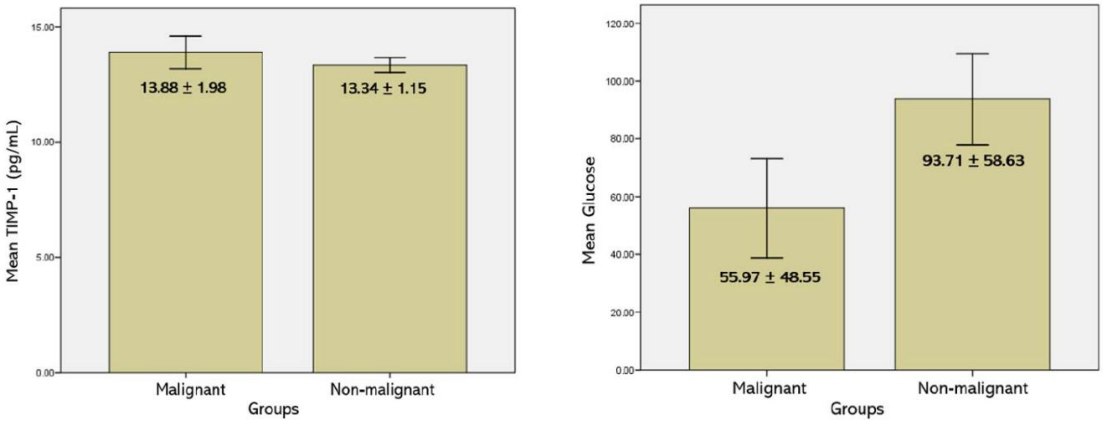

Figure 1. Comparison of mean levels of tissue inhibitor of metalloproteinase-1 (left) and pleural fluid glucose (right) between malignant and non-malignant groups

Glucose and TIMP-1 levels in the malignant and non-malignant groups differ significantly. This suggests a strong relationship between the malignant condition and changes in these biomarkers, where the malignant group exhibits distinct metabolic and biomolecular characteristics compared to the non-malignant group.

Cut-Off Point

Glucose, TIMP-1, and the combination of glucose and TIMP-1 exhibit good diagnostic capability. The area under the curve (AUC) values for glucose and the combination of glucose and TIMP-1 were 86.5% (p=0.000) for TIMP-1, 70.6% (p=0.001) for glucose, and 76.5% (p=0.000) for the combination of glucose and TIMP-1. All biomarkers had p<0.05, which indicated predictive ability.

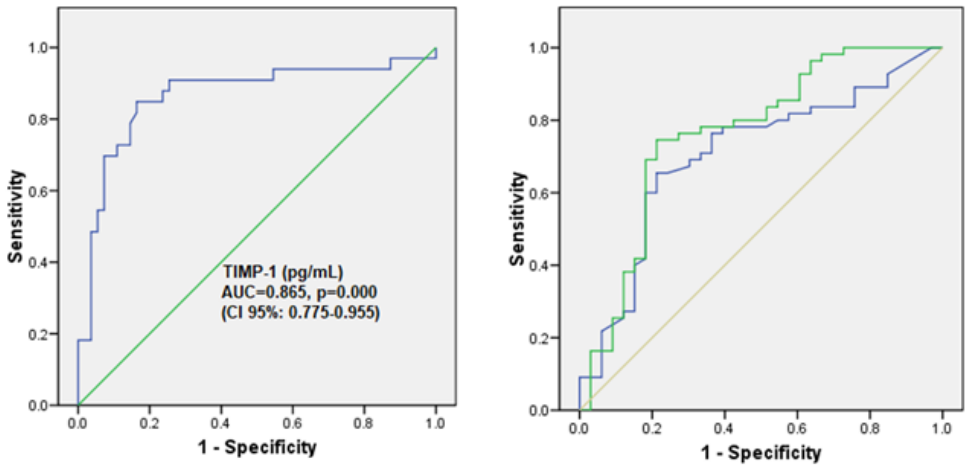

Figure 2. Receiver operating characteristic curve for tissue inhibitor of metalloproteinase-1 (TIMP-1) (left) and pleural fluid glucose and combination of TIMP-1 and pleural fluid glucose (right)

In this case, the three biomarkers were intended for diagnostic purposes. The threshold values set were 13.9025 pg/mL for TIMP-1, 78.5 mg/dL for glucose, and 0.613 for the combination of glucose and TIMP-1.

Analysis of Diagnostic Accuracy Values

Chi-square test showed a p-value of 0.000, indicating a significant relationship between TIMP-1 levels and the malignant and non-malignant patient groups. Patients with TIMP-1 levels >13.9025 pg/mL are 28.62 times more likely to be classified as malignant. For the relationship between glucose and the threshold value of 78.5 mg/dL, the p-value of 0.000 indicated a significant relationship between glucose levels and the malignant and non-malignant patient groups (odds ratio/OR 5.14 (95% confidence interval/CI: 2.01-13.12)). In the analysis of the combination of glucose and TIMP-1 with the threshold value of 0.613, the p-value of 0.000 indicated a significant relationship (OR 9.15 (95% CI: 3.36-24.9)).

Among these three biomarkers, TIMP-1 demonstrated the highest sensitivity (84.8%) and highest specificity (83.6%). The PPV for TIMP-1 was the highest (75.7%), while its NPV reached 90.2%. For the likelihood ratio (LR), TIMP-1 had the highest value at 5.19, meaning the test had a greater probability of detecting patients with malignant conditions. Overall, TIMP-1 showed the highest predictive accuracy at 84.1%, followed by the combination of glucose and TIMP-1 at 75.0%. The highest value of OR was obtained for TIMP-1, at 28.62, followed by the combination of glucose and TIMP-1 at 9.15, and glucose at 5.14. This suggests that TIMP-1 is the strongest predictor for distinguishing between malignant and non-malignant patients among the biomarkers tested (Table 3).

Table 3. Sensitivity and specificity of biomarkers

Biomarker	Sensitivity	Specificity	PPV	NPV	PLR	Accuracy	OR
TIMP-1 (cut off 13.9 pg/mL)	84.8%	83.6%	75.7%	90.2%	5.19	84.1%	28.62
Glucose (cut off 78.5 mg/dL)	69.7%	69.1%	57.5%	79.2%	2.25	69.3%	5.14
Glucose (78.5) and TIMP-1 (<13.9)	75.8%	74.5%	64.1%	83.7%	2.98	75.0%	9.15

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; OR: odds ratio; TIMP-1: tissue inhibitor of metalloproteinase-1

DISCUSSION

This study involved 88 patients, with 33 having MPE and 55 having non-malignant pleural effusion. The average age was 57.33 years old. There was no significant correlation between age and pleural effusion type (p=0.658). Both younger and older patients had similar chances of being in the malignant or non-malignant group. The OR of 1.22 (95% CI: 0.51-2.9) suggests a slight increase in the likelihood of older patients having MPE. Other studies have shown varying age distributions in pleural effusion cases. Sokkary, *et al*. (2022) reported an average age of 53.23±14.98 years old and more in males.[5] In contrast, James, *et al*. (2024) found an average age of 67.3 years old in hospitalized patients with MPE, primarily females.[6] These studies indicate that MPE is more common in older adults between 60 and 70 years old.[7]

A significant relationship was found between smoking history and pleural effusion group (p=0.024). The OR of 2.78 (95% CI: 1.13-6.85) suggests non-smokers had a 2.78 times higher chance of having MPE. However, no significant relationship was found between the degree of smoking (Brinkman index) and malignancy status (p=0.139). Though smoking history was not directly linked to pleural effusion onset, smoking is a significant risk factor for conditions like lung cancer, heart disease, and tuberculosis, which can cause pleural effusion. Passive smokers also face higher risks of lung cancer. Satolom, *et al*. (2012) found that passive smoking increased the risk of lung cancer by 24% in females and 37% in males.[8] Exosomal micro ribonucleid acid (miRNA) profiling has shown that specific miRNAs are involved in the development of MPE, indicating a molecular link between smoking-induced lung cancer and pleural effusion.[9]

The most common symptoms reported were shortness of breath (97.7%), cough (95.5%), chest pain (84.1%), and weight loss (93.2%). However, these symptoms are unable to predict whether the effusion is malignant or non-malignant.[10] A previous study also noted dry cough as a frequent symptom, with pleural effusion often being hemorrhagic.[7]

Among MPE patients, 55.7% had lung cancer as the primary malignancy, followed by breast cancer (8%) and ovarian cancer (4.5%). The relationship between pleural fluid cytology and pleural effusion group was highly significant (p=0.000), with class IV and V cytology being more common in the malignant group. Sensitivity for detecting malignancy varies between 51%-58%, and is higher for adenocarcinoma. A pleural effusion sample of 20-60 mL is recommended for cytological analysis.[11,12]

Lung, breast, cervical, and ovarian cancers were found to be more common in the malignant group. Adenocarcinoma patients were more likely to be in the malignant group, while those with unknown cell types were more likely to be in the non-malignant group (p=0.000). These findings show that cancer cell characteristics and primary cancer types greatly influence pleural effusion development, especially in adenocarcinoma patients who are prone to pleural metastasis. Most MPE cases were linked to lung adenocarcinoma.[13] Lung cancer is more common in males, but increasing cases in females may be related to passive smoking and hormonal factors affecting EGFR and gastrin-releasing peptide receptor (GRPR) mutations.[7,8]

Epidermal growth factor receptor mutation status was also significantly linked to pleural effusion group (p=0.000), with exon 21 mutations being more common in the malignant group. Epidermal growth factor

receptor mutations are crucial in non-small cell lung cancer (NSCLC) pathogenesis. Satolom, *et al*. (2012) found that EGFR receptor modifications are influenced by hormonal and genetic factors, especially in non-smoking females, emphasizing the importance of EGFR mutation testing for targeted therapy in NSCLC patients.[8]

Cancer cell type also affects TIMP-1 and glucose levels in pleural fluid. In adenocarcinoma and other aggressive cancers like small cell lung cancer (SCLC), metalloproteinase activity increases.[14] Tissue inhibitor of metalloproteinase-1 levels increase to compensate for the excess MMP-9 activity. The levels are higher in adenocarcinoma, adenosquamous carcinoma, and SCLC compared to squamous cell carcinoma (SCC).

Glucose levels in pleural fluid are influenced by cancer cell metabolism. In aggressive cancers like adenocarcinoma and SCLC, which require high energy, glucose levels are lower.[15] These further reduce glucose transport, whereas in SCC, glucose levels may not decrease significantly as pleural invasion is less common.

In addition, biomolecular markers like MMP, TIMP, vascular endothelial growth factor (VEGF), and carcinoembryonic antigen may enhance MPE diagnosis accuracy. These markers are related to inflammation, tumor growth, and vascular permeability, all of which contribute to pleural fluid accumulation in malignant conditions.[8,11]

Tissue inhibitor of metalloproteinase-1 level was found to be higher in the MPE group compared to the non-malignant group (13.88 pg/mL vs. 13.34 pg/mL, p=0.000). The elevated TIMP-1 levels in the malignant group suggest that this biomarker could be an effective diagnostic tool for distinguishing malignant from non-malignant pleural effusion. Similar results were reported by Rojiani, *et al*. (2015), who found that high TIMP-1 levels were associated with malignancy and might serve as a tumor indicator in pleural effusion.[16]

Receiver operating characteristic analysis showed that TIMP-1 had the highest AUC value (86.5%), followed by the combination of glucose and TIMP-1 (76.5%) and glucose (70.6%). This indicates that TIMP-1 has good diagnostic capability for predicting malignant conditions. Logistic regression analysis suggested that the combination of glucose and TIMP-1 was not significantly predictive of malignancy. Tissue inhibitor of metalloproteinase-1, with a threshold of 13.9025 pg/mL, demonstrated the highest sensitivity and specificity. Zhao, *et al*. (2021) also confirmed that TIMP-1 had high diagnostic value for distinguishing MPE from non-malignant pleural effusion.[17]

In the context of pleural effusion, TIMP-1 plays an essential role in regulating tissue remodeling during pleural fluid formation. Cancer cells often upregulate MMP activity to support invasion and metastasis, prompting the body to increase TIMP-1 production to balance MMP activity and prevent excessive tissue degradation.[16] An increase in TIMP-1 levels in pleural fluid can indicate the presence of a malignant tumor, causing pleural effusion. Tissue inhibitor of metalloproteinase-1 plays a critical role in maintaining the integrity of the extracellular matrix (ECM) by limiting excessive ECM degradation by MMP.[17] A previous study also suggested that TIMP-1 could promote cell proliferation and angiogenesis, supporting tumor growth and metastasis, including in the pleural cavity.[18]

In non-malignant pleural effusion, TIMP-1 levels are typically lower than MPE. Nevertheless, TIMP-1 remains essential in the inflammatory response by regulating the balance between degradation and ECM remodeling. In non-malignant conditions, TIMP-1 helps prevent excessive tissue damage during inflammation and plays a role in preventing pleural fibrosis in chronic pleural effusion by controlling MMP activity. Thus, TIMP-1 plays a key role in maintaining the balance of tissue remodeling processes and regulating responses to various pathophysiological processes in the pleural cavity.[19]

Glucose levels in the malignant group were lower than the non-malignant group (55.97 mg/dL vs. 93.71 mg/dL, p=0.001). This suggests that reduced glucose levels may serve as a significant indicator for MPE. Glucose (AUC 70.6%) demonstrated good diagnostic ability for predicting malignant conditions with a threshold of 78.5 mg/dL and showed the highest sensitivity and specificity.

Glucose in pleural fluid comes from plasma, and its decrease can result from various pathological mechanisms, such as increased metabolism by pleural cells or impaired glucose transport into pleural fluid.[20] In MPE, glucose levels in pleural fluid are often lower than in plasma. One of the leading causes is glucose consumption by tumor cells. Tumor cells in the pleura have high metabolic rates, requiring more glucose for energy, which leads to reduced glucose levels in pleural fluid. Additionally, tumor cells can damage pleural tissue, disrupting glucose transport from plasma to pleural fluid. This disruption is exacerbated by decreased glucose transporter activity due to tumor cell infiltration, further limiting glucose entry into pleural fluid.

Low glucose levels in pleural fluid in MPE often indicate the presence of a malignant tumor, although it is not entirely specific to malignancy. Very low glucose levels can also indicate extensive pleural involvement by the tumor or aggressive tumor behavior, which may

have implications for patient prognosis.[21] In non-malignant pleural effusion caused by infection or inflammation, glucose levels in pleural fluid may also decrease, but the mechanisms differ from those in MPE.[20,21]

In this study, the sensitivity, specificity, and accuracy of TIMP-1 and glucose levels in MPE were 75%, with a sensitivity of 75.8%, a specificity of 74.5%, and an OR of 9.15%. Tissue inhibitor of metalloproteinase-1 was higher in MPE. Receiver operating characteristic curve analysis revealed that TIMP-1 exhibited high sensitivity and specificity, with an accuracy of 84.1%, a sensitivity of 84.8%, and a specificity of 83.6%, indicating that TIMP-1 has superior diagnostic capabilities compared to glucose in identifying MPE.

This study also found that combining TIMP-1 and glucose levels reduced diagnostic accuracy to 75% compared to TIMP-1 at 84.1%. This phenomenon (on why TIMP-1 outperformed the combined model's performance) may be attributed to the fact that various factors like systemic conditions, metabolic drugs, and patient nutritional status may influence glucose levels, thus reducing its specificity in malignant pleural diseases.[22] In conclusion, TIMP-1 was found to offer an efficient and accurate, less-invasive diagnostic approach compared to conventional methods like pleural fluid cytology and/or pleural biopsy.

CONCLUSION

This study demonstrated that TIMP-1 levels were elevated in MPE in comparison to non-malignant pleural effusion, whereas glucose levels in pleural fluid were lower in patients with MPE. The levels of TIMP-1 and glucose were significantly different between malignant and non-malignant pleural effusions. Although the combination of TIMP-1 and glucose levels offers diagnostic accuracy, its accuracy is not as high as that of TIMP-1, indicating its potential as a biomarker for MPE.

LIMITATIONS OF THE STUDY

This study faced several limitations that need to be considered. The cross-sectional design was unable to account for changes over time. A longitudinal study would offer more insights into the changes in TIMP-1 and glucose levels and their relationship with disease progression and treatment response. Additionally, this study did not fully account for confounding factors such as complete medical history, nutritional status, or previous treatments, which could influence biomarkers of pleural fluid. A more comprehensive study controlling for these factors might yield more accurate and representative results regarding the relationship between biomarkers and pleural effusion type.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Study conception, initial manuscript, design: CM. Data collection, processing, review: CM, NPPP, SD, ASL. Statistical analysis: CM, NS. Literature review, final manuscript: CM, NPPP, SD.

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