Original Article

Pleural carbohydrate antigen 50 and malignant pleural effusion: a prospective, double-blind diagnostic accuracy test

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Background: Serum carbohydrate antigen 50 (CA50) is an auxiliary diagnostic marker for various solid tumors, but it remains unclear whether CA50 in pleural fluid can assist in the diagnosis of malignant pleural effusion (MPE). This study aimed to evaluate the diagnostic accuracy of pleural fluid CA50 for MPE in pleural effusion patients with undetermined causes.

Methods: This study prospectively recruited pleural effusion patients with undetermined causes who visited the Affiliated Hospital of Inner Mongolia Medical University between September 2018 and July 2021. We measured pleural fluid CA50 level with an electrochemiluminescence assay. We analyzed the diagnostic accuracy of CA50 and carcinoembryonic antigen (CEA) for MPE with the receiver operating characteristic (ROC) curve. The net benefits of CA50 and CEA were analyzed using the decision curve analysis (DCA).

Results: We enrolled 66 MPEs and 87 benign pleural effusions (BPEs). MPE patients had significantly higher CA50 and CEA than BPE patients. The area under the ROC curve (AUC) of CA50 was 0.72 (95% CI: 0.63–0.80). CA50 had a sensitivity of 0.30 (95% CI: 0.19–0.41) and a specificity of 1.00 (95% CI: 1.00–1.00) at the threshold of 15 IU/mL. The decision curve of CA50 was above the reference line at the calculated risk probability of between 0.30 and 1.00. Venn diagram indicated that some patients with low CEA (<50 or <150 ng/mL) and/or negative cytology can be identified by positive CA50 (>15 IU/mL).

Conclusions: Pleural fluid CA50 has moderate accuracy and net benefit for detecting MPE. CA50 >15 IU/mL can be used to diagnose MPE. The combination of CA50 and CEA improves the diagnostic sensitivity for MPE.

Keywords: Diagnostic test accuracy; carbohydrate antigen 50 (CA50); malignant pleural effusion (MPE); sensitivity; specificity

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Introduction

Pleural effusion (PE) is a common clinical sign caused by fluid accumulation within the pleural cavity (1). It is common in various disorders such as pneumonia, malignancy, tuberculous pleurisy, and heart failure (HF) (2,3). Among these disorders, PE induced by primary or metastatic pleural tumors is categorized as malignant pleural effusion (MPE), while PE induced by other disorders is categorized as benign pleural effusion (BPE). The most frequent cancer that can cause MPE is lung cancer, followed by breast cancer, ovarian cancer, and lymphoma (2). The prognosis of MPE is extremely poor, with a median survival of less than one year (4,5). Differentiating between MPE and BPE is an important starting point for the treatment of MPE. The gold standards for MPE are pleural biopsy and cytology (6). Cytology has the advantages of low cost, rapidity, and high specificity, but its sensitivity is only around 60%, and its diagnostic accuracy depends on the pathologist's experience (7,8). Closed pleural biopsy with Abrahm's needle and medical thoracoscopic biopsy have high diagnostic accuracy for MPE (9), but they are invasive and operation-related complications (e.g., bleeding and infection) are problematic (10). Compared to cytology and pleural biopsy, pleural fluid tumor markers represent promising diagnostic tools for MPE because they are economical, easy to perform, objective and minimally invasive (11).

Serum carbohydrate antigen 50 (CA50) is a widely used diagnostic marker for various cancers, particularly pancreatic, lung, and colorectal cancers (12-14). Increased serum CA50 can also be observed in breast, uterine, gastric, and prostate cancers (12,15-18). A previous study revealed that MPE patients had higher pleural fluid CA50 than tuberculous pleural effusion (TPE) patients (19). However, the diagnostic accuracy (e.g., the area under curve, optimal threshold) of pleural fluid CA50 for MPE has never been assessed. In addition, the CA50 assay in the previous study was a radioimmunological assay, which is laborious and not widely used in current clinical practice. In this study, we used an electrochemiluminescence assay to measure the CA50 level in pleural fluid and evaluate its diagnostic accuracy for MPE in pleural effusion patients with unknown causes. We present this article in accordance with the STARD reporting checklist (20) (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-68/rc).

Highlight box

Key findings

- Pleural fluid carbohydrate antigen 50 (CA50) had moderate diagnostic accuracy for malignant pleural effusion (MPE). Patients with CA50 >15 IU/mL can be diagnosed as MPE. The combination of CA50 and carcinoembryonic antigen (CEA) had higher sensitivity for MPE

What is known and what is new?

- Serum CA50 is a useful diagnostic marker in various cancers, but the diagnostic accuracy of pleural fluid CA50 for MPE remains unknown.
- This study investigated the diagnostic accuracy and net benefit of pleural CA50 for MPE. We found that CA50 has moderate diagnostic accuracy for MPE and CA50 can improve the diagnostic accuracy of pleural CEA and effusion cytology.

What is the implication, and what should change now?

- Pleural fluid CA50 helps pulmonologist to estimate the probability of MPE.
- Patients with CA50 >15 IU/mL can be diagnosed as MPE.

Methods

Participants

The participants in this study were recruited from the SIMPLE, a prospective, pre-registered (Chinese Clinical Trial Registry: No ChiCTR1800017449) and double-blind diagnostic test accuracy study which aimed to investigate the diagnostic accuracy of soluble markers in pleural fluid and serum (21). The SIMPLE's inclusion/exclusion criteria, reference standards, and design details have been introduced in our previous studies (22,23). Briefly, we recruited patients with undiagnosed pleural effusions who attended the Affiliated Hospital of Inner Mongolia Medical University between September 2018 and July 2021. The exclusion criteria were: (I) patients whose diagnosis remained unknown at discharge; (II) pregnancy; (III) patients younger than 18 years; (IV) patients whose pleural effusion developed during hospitalization; and (V) operation- or trauma-induced pleural effusion. This study was approved by the Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University (No. 2018011). All participants have signed informed consent forms. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Diagnostic criteria

Pleural biopsy and effusion cytology were used to define MPE. In patients with a high probability of MPE but had negative cytology and were unwilling or unable to receive

Table 1 Clinical characteristics of the participants

Characteristics	MPE (n=66)	BPE (n=87)	P value
Age (years)	72 [65–78]	72 [64–80]	0.75
Sex, n (%)			0.48
Female	25 (38.0)	27 (31.0)	
Male	41 (62.0)	60 (69.0)	
WBC (10^6/mL)	942 [625–1,472]	737 [340–2,005]	0.21
LDH (U/L)	231 [176–447]	171 [94–385]	0.004
ADA (U/L)	8 [6–12]	10 [4–25]	0.38
Glucose (mmol/L)	5.6 [4.4–6.6]	5.7 [4.7–7.0]	0.47
Protein (g/L)	37 [31–43]	30 [17–41]	0.002
CEA (ng/mL)	41 [3–261]	1 [1–2]	<0.001
Causes	Lung cancer (n=55) Mesothelioma (n=5) Others (n=6)	PPE (n=32) TPE (n=20) HF (n=23) Others (n=12)	–

Data are presented as median [interquartile range] or absolute number (percentage). WBC, white blood cell; LDH, lactate dehydrogenase; ADA, adenosine deaminase; CEA, carcinoembryonic antigen; MPE, malignant pleural effusion; BPE, benign pleural effusion; PPE, parapneumonic pleural effusion; TPE, tuberculosis pleural effusion; HF, heart failure; Others, other types of pleural effusion.

pleural biopsy, MPE was diagnosed with the evidence of late-stage primary tumor, follow-up, the highly suggestive clinical picture of MPE, and the exclusion of BPE. The diagnostic criteria for TPE were pleural biopsy, *Mycobacterium tuberculosis* (Mtb) culture or Ziehl-Neelsen staining. In patients with a high probability of TPE but negative microbiological evidence and were unwilling to receive a pleural biopsy, TPE was diagnosed with clinical reference standard, including high pleural adenosine deaminase (ADA) activity, interferon-γ release assays (IGRAs), lymphocyte-predominant effusion, clinical signs and symptoms, particularly the response to anti-TB therapy and the exclusion of other disorders. Clinical reference standard were used to define pneumonic parapneumonic effusion (PPE), including the patient's imaging features, effusion bacterial cultures, physical examinations, medical history, and responses to antibiotic therapy. The diagnostic criteria for HF were clinical presentation, imaging features, serum natriuretic peptides, and responses to anti-heart failure therapies (24). Two senior clinicians (Z.D.H. and L.Y.) made the final diagnoses. Any disagreements were resolved by consensus.

Pleural fluid CA50 assay

We collected a pleural fluid specimen from each participant at the time of their admission. The baseline clinical characteristics of participants were recorded with a uniform case report form. The pleural fluid specimen was collected in an anticoagulant-free tube. After centrifugation, the supernatant was aliquoted and stored between −80 and −70 ℃. The CA50 concentration in pleural fluid was measured between December 2021 and April 2022. We used the MAGLUMI 2000 (Shenzhen New Industries Biomedical Engineering Company, China) to measure pleural CA50. The participants' clinical data were blinded to the laboratory technician who measured CA50.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs). Kolmogorov-Smirnov test was used to determine the normality of continuous variables. Independent Student's *t*-test or one-way ANOVA was used to compare normally distributed data. Mann-Whitney or Kruskal-Wallis test was used to compare skewed distributed data. We used the Chi-square or Fisher's exact probability test to compare categorical data. Receiver operating characteristic (ROC) curve was applied to evaluate the diagnostic accuracy of pleural fluid CA50 and carcinoembryonic antigen (CEA) for MPE. Decision curve analysis (DCA) was used to assess the net benefit of pleural fluid CA50 (25). All statistical analyses and graphs were performed with R (version 4.3.2). $P<0.05$ indicated the difference was statistically significant.

Results

Characteristics of the participants

We recruited 170 patients with undiagnosed pleural effusions. Seventeen of them were excluded, including eleven patients with unclear diagnoses after discharge, two who withdrew informed consent, and four patients who can be diagnosed by their medical history. Eventually, 153 patients were enrolled in this study, including 66 patients with MPE and 87 patients with BPE. The clinical characteristics of the participants are shown in *Table 1*. The patients with BPE included 32 cases of PPE, 20 cases of TPE, 23 cases of HF, and 12 other types

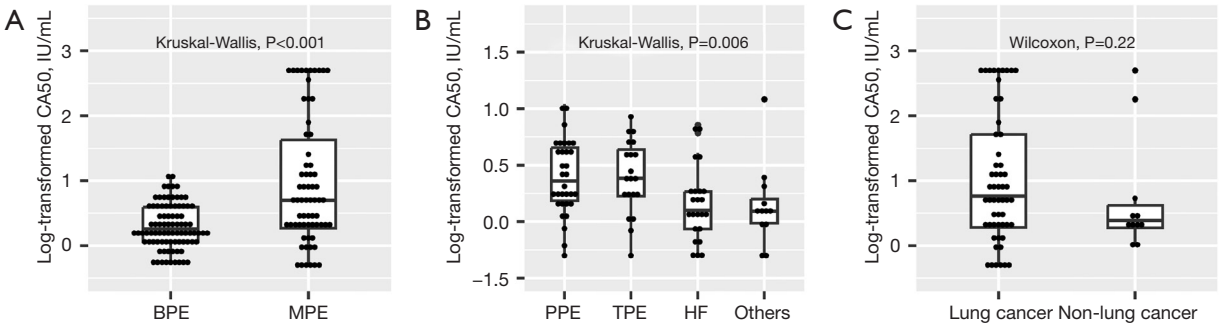

Figure 1 CA50 in pleural effusion patients. (A) Pleural CA50 in patients with BPE or MPE. CA50 level was log-transformed; (B) CA50 levels in BPEs; (C) CA50 in lung cancer- or other cancer-induced MPEs. CA50, carbohydrate antigen 50; CEA, carcinoembryonic antigen; BPE, benign pleural effusion; MPE, malignant pleural effusion; PPE, parapneumonic pleural effusion; TPE, tuberculous pleural effusion; HF, heart failure; Others, other types of pleural effusion.

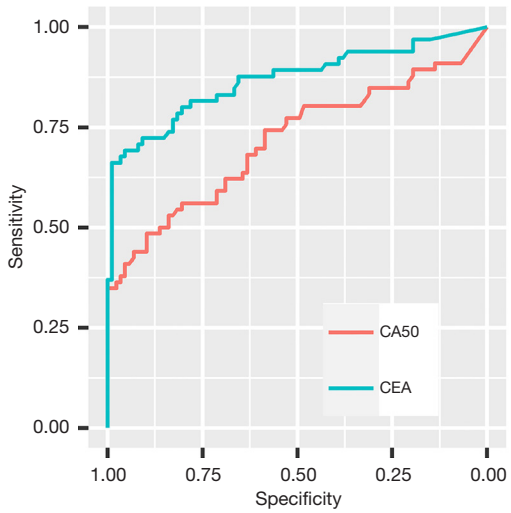

Figure 2 Receiver operating characteristic curves of CA50 and CEA. CA50 had an AUC of 0.72 (95% CI: 0.63–0.80), and CEA had an AUC of 0.87 (95% CI: 0.80–0.93). CA50, carbohydrate antigen 50; CEA, carcinoembryonic antigen; AUC, area under curve; CI, confidence interval.

of pleural effusion (1 hypoproteinemia, 2 interstitial lung disease, 1 pneumothorax, 1 liver cirrhosis, 2 mixed connective tissue disease, 4 pulmonary embolisms, 1 idiopathic pleural effusion). The MPE was composed of lung cancer (n=55), malignant pleural mesothelioma (n=5), breast cancer (n=1), gastric cancer (n=2), pulmonary synovial sarcoma (n=1), lymphoma (n=1) and unknown primary cancer (n=1). The lung cancer patients comprised 50 non-small cell lung cancers (NSCLCs) and 5 small cell lung cancers (SCLCs).

Pleural fluid CA50

The medians (interquartile ranges) pleural fluid CA50 were 5.0 (2.0–44.0) IU/mL in MPE patients and 2.0 (1.0–4.0) IU/mL in BPE patients (*Figure 1A*, P<0.001). There was a significant difference among all types of BPE (*Figure 1B*, P=0.006). In addition, no significant difference was found between MPE patients caused by lung and other cancers (*Figure 1C*, P=0.22).

Diagnostic accuracy of CA50 and CEA in pleural fluid

Figure 2 shows the ROC curves of CA50 and CEA. The area under the curve (AUC) was 0.72 (95% CI: 0.63–0.80) for CA50 and 0.87 (95% CI: 0.80–0.93) for CEA. The difference was statistically significant (P<0.001).

The diagnostic sensitivity and specificity of CA50 and CEA at different thresholds are shown in *Table 2*. When the threshold of CA50 was 5 IU/mL, the sensitivity was 0.50 (95% CI: 0.38–0.62), and the specificity was 0.86 (95% CI: 0.79–0.94). CEA's sensitivity and specificity were 0.66 (95% CI: 0.55–0.78) and 0.98 (95% CI: 0.95–1.00), respectively, at the threshold of 10 ng/mL. The specificity of 100% is particularly significant because the patient can be diagnosed as MPE at this threshold. When the CA50 was at the threshold of 15 IU/mL, the specificity was 1.00 (95% CI: 1.00–1.00), and the sensitivity was 0.30 (95% CI: 0.19–0.41). When the CEA threshold was set at 50 ng/mL, the sensitivity was 0.48 (95% CI: 0.36–0.60), and the specificity was 0.99 (95% CI: 0.97–1.00).

Previous studies revealed that CEA >50 ng/mL has a specificity of 1.00 for MPE in patients with non-purulent pleural fluid (26,27). In addition, CEA had a specificity

Table 2 Diagnostic accuracy of pleural fluid CA50 and CEA

Biomarkers	Thresholds	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)
CA50 [AUC: 0.72 (0.63–0.80)]	5 IU/mL	0.50 (0.38–0.62)	0.86 (0.79–0.94)	3.63 (2.03–6.46)	0.58 (0.45–0.75)
	15 IU/mL	0.30 (0.19–0.41)	1.00 (1.00–1.00)	–	0.70 (0.59–0.82)
CEA [AUC: 0.87 (0.80–0.93)]	10 ng/mL	0.66 (0.55–0.78)	0.98 (0.95–1.00)	28.77 (7.23–114.49)	0.35 (0.25–0.49)
	50 ng/mL	0.48 (0.36–0.60)	0.99 (0.97–1.00)	41.49 (5.81–296.12)	0.53 (0.42–0.67)

CA50, carbohydrate antigen 50; CEA, carcinoembryonic antigen; AUC, area under the curve; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

of 1.00 at the threshold of 150 ng/mL, irrespective of the pleural fluid's appearance. Therefore, we analyzed whether patients with CEA >50 ng/mL or CEA >150 ng/mL also had a CA50 >15 IU/mL. Venn diagram showed that not all patients with CA50 >15 IU/mL had CEA >50 ng/mL (*Figure 3A*) or CEA >150 ng/mL (*Figure 3B*).

Effusion cytology is preferred for diagnosing MPE because of its low cost. A pleural biopsy should be conducted in patients with negative effusion cytology (27). Therefore, we further analyzed how many cytology-negative MPE patients can be identified by CA50 (>15 IU/mL) and CEA (>50 or >150 ng/mL). *Figure 3C,3D* shows that both CEA and CA50 could identify MPE patients with negative cytology. Notably, an MPE patient with negative cytology and CEA (12.82 ng/mL) was identified by CA50 (CA50 >500 IU/mL). Altogether, these results suggest that CA50 >15 IU/mL can increase the diagnostic sensitivity for MPE without sacrificing specificity.

The net benefit of CA50

The decision curves of pleural fluid CA50 and CEA were above the reference lines (*Figure 4*). CA50 and CEA could provide a net benefit in patients who have an MPE probability of between 0.30 and 1.00.

Discussion

Our study revealed that MPEs had significantly higher pleural fluid CA50 than BPEs. CA50 had an AUC of 0.72 (95% CI: 0.63–0.80), suggesting its moderate diagnostic accuracy for MPE. DCA also showed that CA50 could provide a net benefit. CA50 >15 IU/mL had a sensitivity of 0.30 (95% CI: 0.19–0.41) and specificity of 1.00 (95% CI: 1.00–1.00), indicating that patients with CA50 >15 IU/mL could be definitely diagnosed as MPE. Furthermore, not all patients with CEA >50 ng/mL and/or negative cytology had CA50 >15 IU/mL, suggesting that the combination of CA50 can improve the diagnostic sensitivity of CEA and cytology for MPE without decreasing specificity.

To the best of our knowledge, this is the first study investigating the diagnostic accuracy of CA50 for MPE with ROC curve analysis. Compared with the previous study that only estimated the diagnostic sensitivity and specificity at a given threshold (19), our study has several advantages. First, our study is a prospective and double-blind diagnostic test accuracy study. The participants in this study are representative. Mainly, PPE, HF, and other types of BPE were considered in our study. Therefore, its conclusions are more reliable. Second, we simultaneously investigated the diagnostic accuracy of CA50, cytology, and CEA and found that the CA50 could increase the sensitivity of CEA and cytology without decreasing the specificity. Third, we evaluated the net benefit of CA50 using a DCA and found that CA50 could provide a net benefit.

A previous study revealed that the upper limit of the reference interval for serum CA50 was between 20 and 23 IU/mL (28). This study found that CA50 in the pleural fluid of BPE patients was <15 IU/mL, indicating that pleural CA50 is lower than serum CA50 in BPE patients. Therefore, we concluded that not all serum CA50 can passively diffuse into pleural fluid, and pleural fluid CA50 may also be derived from metastatic tumor cells in the pleura.

Several tumor markers (e.g., CEA, CA125, CA15-3, CA19-9) can be used to diagnose MPE (29). Evidence from the published systematic review and meta-analysis revealed that the sensitivities of these tumor markers were around 0.50, and the specificities were >0.90 (29). This study revealed the sensitivity of CA50 was 0.50 (95% CI: 0.38–0.62), and the specificity was 0.86 (95% CI: 0.79–0.94). Therefore, it seems that the diagnostic accuracy of pleural CA50 was slightly lower than that of traditional tumor markers. This study compared the diagnostic accuracy of CEA and CA50 in a head-to-head manner and found

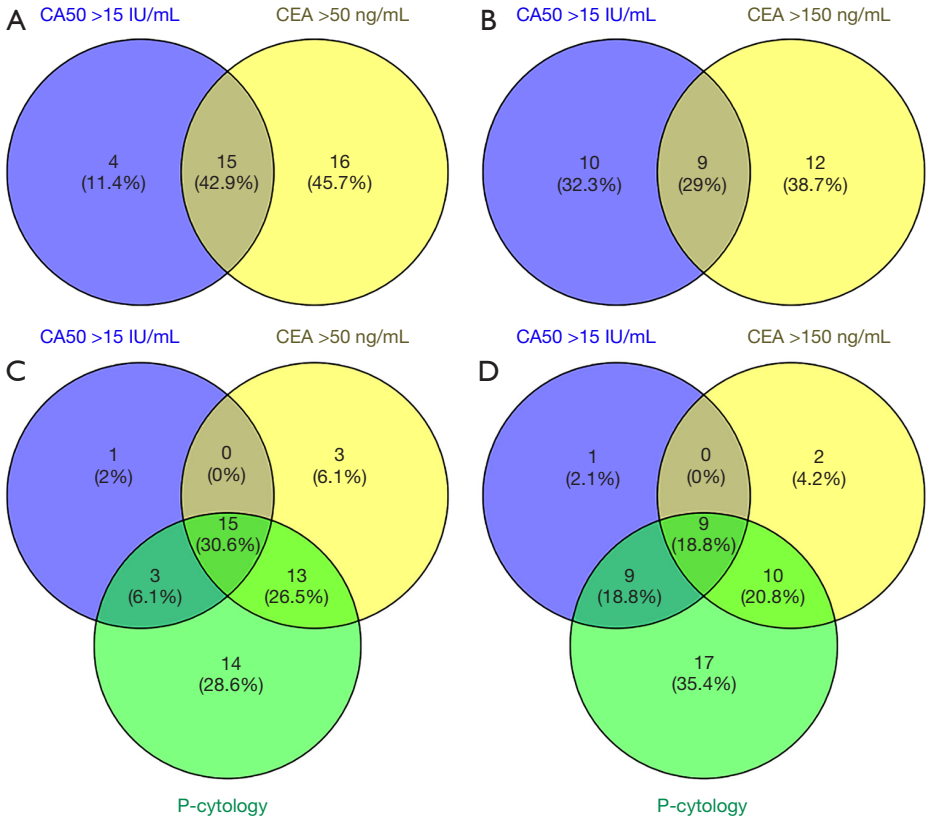

Figure 3 Venn diagram. Malignant pleural effusion patients with CA50 >15 IU/mL and CEA >50 ng/mL (A); CA50 >15 IU/mL and CEA >150 ng/mL (B); CA50 >15 IU/mL, positive cytology, and CEA >50 ng/mL (C); CA50 >15 IU/mL, positive cytology, and CEA >150 ng/mL (D). P-cytology, positive cytology. CA50, carbohydrate antigen 50; CEA, carcinoembryonic antigen.

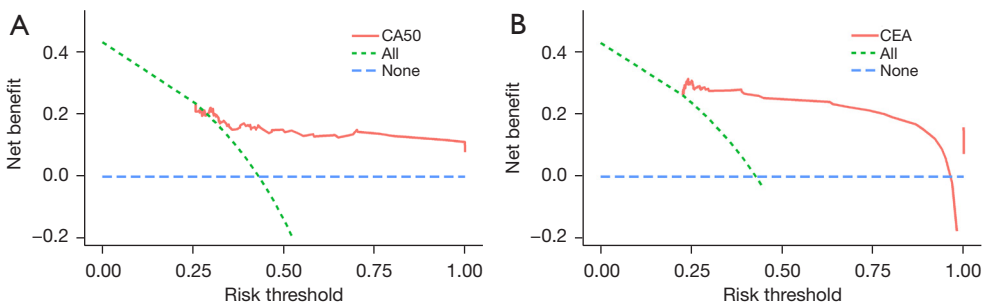

Figure 4 Decision curves of CA50 (A) and CEA (B). CA50, carbohydrate antigen 50; CEA, carcinoembryonic antigen.

that the AUC of CA50 was significantly lower than that of CEA, also supporting the hypothesis that the diagnostic accuracy of CA50 is inferior to that of the conventional tumor markers. However, we found that CA50 >15 IU/mL had a specificity of 1.00 and sensitivity of 0.30, indicating that about 30% of MPE patients can be detected by CA50 >15 IU/mL. In other words, about 30% of pleural biopsy in MPE patients can be avoided if CA50 was used to diagnose MPE. Furthermore, the combination of CEA and CA50 can further increase the diagnostic sensitivity of MPE, even in patients with negative cytology. Therefore, we concluded that tumor markers could be used to assess the probability of MPE and thus improve the diagnostic efficiency of MPE. Given that the mean age of this cohort is higher than that of

previous cohorts (27,30), the conclusions of this study need to be cautiously interpreted.

Although this is the first study to investigate the diagnostic value of CA50 for MPE with an ROC curve, it has some limitations. The first limitation is the small sample size and single-center design, which limits us to perform subgroup analyses. The second limitation is that we used the stored pleural fluid to determine CA50, and the long-term stability of CA50 in pleural fluid remains unknown. However, our previous study indicated that the long-term stability of CEA in frozen pleural fluid specimens was acceptable (23). The third limitation is that 83% of MPE patients have lung cancer, which may limit the generalization of the findings in clinical settings with a low prevalence of lung cancer among MPEs.

Conclusions

In conclusion, this study revealed that pleural fluid CA50 had moderate diagnostic value for MPE and could benefit patients. Moreover, the combination of CA50, cytology, and CEA can improve the diagnostic sensitivity of MPE. Patients with CA50 >15 IU/mL have a specificity of 1.00 and thus strongly suggest MPE. Given the small sample size and monocenter design of this study, as well as the devastating consequences of misdiagnosis, further studies are needed to validate our findings.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-68/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-68/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-68/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-68/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University (No. 2018011). All participants have signed informed consent forms. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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