Original Article

Diagnostic accuracy of pleural fluid carbohydrate antigen 72-4 for malignant pleural effusion: a systematic review and meta-analysis

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Background: Several studies have evaluated the diagnostic accuracy of pleural fluid carbohydrate antigen 72-4 (CA72-4) for malignant pleural effusion (MPE), but the results were diverse. This systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of pleural fluid CA72-4 for MPE.

Methods: The PubMed and Web of Science databases were searched to verify potential studies investigating the diagnostic accuracy of pleural fluid CA72-4 for MPE. The last search date was August 2024. The quality of the eligible studies was assessed by this study using the revised diagnostic accuracy study quality assessment tool-2 to assess the quality of the eligible studies. This study used a summary receiver operating characteristic (sROC) curve and a bivariate model to pool the findings and their 95% confidence intervals (CIs) of available studies.

Results: Eight studies with 828 cases of MPEs and 963 cases of benign pleural effusion (BPE) were included in the present meta-analysis. The pooled sensitivity (95% CI) and specificity (95% CI) were 0.47 (0.39–0.55) and 0.98 (0.95–0.99). The area under sROC curves was 0.77 (95% CI: 0.73–0.80). The primary design weaknesses of the included studies were the representativeness of the participants and the data-driven threshold to define positive CA72-4. A significant publication bias was observed across the eligible studies.

Conclusions: Pleural fluid CA72-4 is an auxiliary diagnostic marker for MPE. However, its diagnostic accuracy may be overestimated by available studies.

Keywords: Carbohydrate antigen 72-4 (CA72-4); malignant pleural effusion (MPE); diagnostic; systematic review; meta-analysis

Submitted Sep 10, 2024. Accepted for publication Dec 17, 2024. Published online Feb 26, 2025.
doi: 10.21037/tcr-24-1664
View this article at: https://dx.doi.org/10.21037/tcr-24-1664

Introduction

Malignant pleural effusion (MPE) is a common sign in patients with advanced cancer. It has a poor prognosis, with a median survival of less than one year (1). Pleural effusion is not a specific sign of advanced cancer. It can also be caused by various diseases, including tuberculous pleurisy, heart failure, and pneumonia (2). Therefore, timely and accurate diagnosis of MPE in patients with undiagnosed pleural effusion is essential. The gold standards for MPE are cytology and pleural biopsy. Although the specificity of effusion cytological is 1.00, its sensitivity is only around 0.50 (3). For patients with negative effusion cytology,

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pleural biopsy is needed. However, pleural biopsy is invasive, hindering its implication in some patients, such as those with end-stage liver disease or coagulation disorders (4,5). In addition, the operation-related complications caused by biopsy are problematic (6). Tumor markers in the pleural fluid are alternative diagnostic tools for MPE due to their advantages of less invasiveness, low cost, rapidity and objectiveness (7-9). Numerous tumor markers found in pleural fluid can aid in diagnosing MPE. Notable markers include carcinoembryonic antigen (CEA) (10) and carbohydrate antigen 50 (CA50) (11). However, when used individually, these markers are insufficient for definitively confirming or ruling out MPE (8). Utilizing multiple tumor markers may enhance the diagnostic accuracy for MPE (8,12). Evaluating the diagnostic accuracy of a single tumor marker is essential for developing algorithms that incorporate multiple tumor markers for improved diagnosis.

Carbohydrate antigen 72-4 (CA72-4) is a tumor-associated epithelial mucin highly expressed in gastric, colon, and breast cancers (13). Many studies have investigated the value of serum CA72-4 in diagnosing cancers. Systematic reviews and meta-analyses revealed that it had moderate diagnostic accuracy for gastric cancer (14) and colon cancer (15). Several studies have evaluated its value in distinguishing MPE from benign pleural effusion (BPE) (16-19), but the results varied. The varied findings may be attributed to the participants enrolled, the CA72-4 assay, or the reference standard for MPE. No systematic review or meta-analysis has been performed to pool the findings of published studies.

This systematic review and meta-analysis aimed to evaluate the accuracy of pleural fluid CA72-4 for diagnosing MPE. We present this article in accordance with the PRISMA-DTA reporting checklist (20) (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1664/rc).

Highlight box

Key findings

- Our meta-analysis revealed the pooled sensitivity [95% confidence interval (CI)] and specificity (95% CI) of pleural fluid carbohydrate antigen 72-4 (CA72-4) for malignant pleural effusion (MPE) were 0.47 (0.39–0.55) and 0.98 (0.95–0.99), respectively.
- Available studies overestimated the diagnostic accuracy of pleural CA72-4.

What is known and what is new?

- Several studies have evaluated the diagnostic accuracy of pleural fluid CA72-4 for MPE. but the results were diverse.
- This is the first study investigating the diagnostic accuracy of pleural fluid CA72-4 using systematic review and meta-analysis. We pooled the findings of available studies and revealed the presence of publication bias. Patients with CA72-4 >21 U/mL had an extremely high risk of MPE.

What is the implication, and what should change now?

- Pleural CA72-4 is an auxiliary diagnostic marker for MPE.
- The probability of MPE is exceptionally high in patients with CA72-4 >21 U/mL.

Methods

Search strategy

The search algorithm in the PubMed database and Web of Science database was: ("CA 72-4" OR "CA 724" OR "CA-72-4" OR "CA-724" OR "CA72-4" OR "CA724" OR "carbohydrate antigen 724" OR "carbohydrate antigen 72-4" OR "carbohydrate antigen-72-4" OR "carbohydrate antigen-724" OR "cancer antigen 724" OR "cancer antigen 72-4" OR "cancer antigen-72-4" OR "cancer antigen-724" OR "CA-72-4 antigen"[nm]) AND (pleur* OR effusion*). The last search date was August 2024.

Study selection

The inclusion criteria of this systematic review and meta-analysis follow the PIDTA framework (21). P, patients with undiagnosed pleural effusion; I, the index test should be pleural fluid CA72-4; D, the study design can be prospective or retrospective; T, the target disease is MPE. Usually, the BPE should encompass tuberculous pleurisy, heart failure, or pneumonia; A, the study aimed to evaluate the diagnostic accuracy of pleural CA72-4. Studies meeting one of the following criteria were excluded: (I) animal studies; (II) non-English publications; (III) conference abstracts, literature reviews, commentaries, and case reports; (IV) a two-by-two table cannot be constructed due to the insufficient details reported. All retrieved literature was screened independently by two systematic reviewers. In the first round of literature screening, the reviewers read the title and abstract to exclude irrelevant studies. In the second round, the reviewers read the full text of the literature to determine the eligibility of the remaining studies.

Data extraction and risk of bias assessment

The data extracted from the eligible studies were the name

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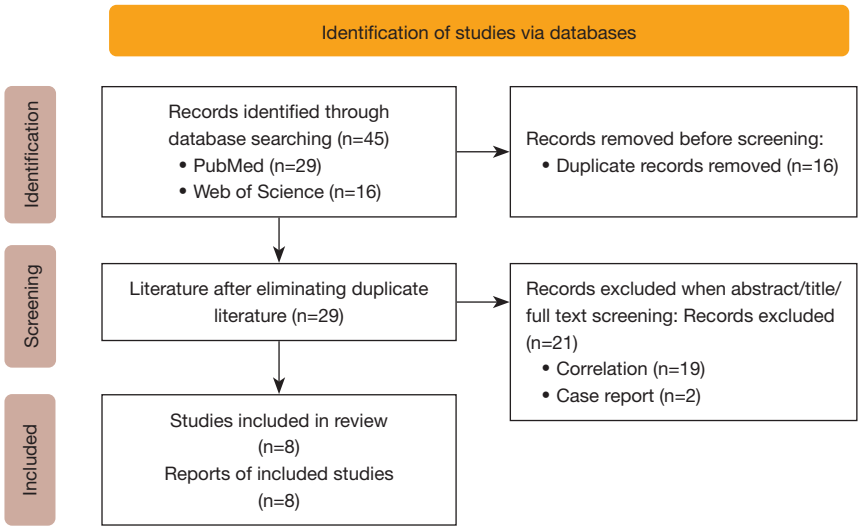

Figure 1 A flow chart of study selection.

of the first author, nationality of the participants, year of publication, the sample sizes of MPE and BPE, type of data collection (prospective or retrospective), CA72-4 assay, the reference standards for MPE and BPE, sensitivity, specificity, the area under the curve (AUC), and the threshold used to define positive CA72-4. According to the sample sizes of MPE and BPE, sensitivity, and specificity, a two-by-two table was constructed for each eligible study. The two-by-two table includes the numbers of patients with true positive (TP), false positive (FP), false negative (FN), and true negative (TN) CA72-4.

The revised diagnostic accuracy study quality assessment tool-2 (QUADAS-2) was to assess the quality of eligible studies (22). The data extraction and quality assessment were performed independently by two systematic reviewers. Any disagreement was resolved by consensus.

Statistical analysis

A bivariate model was utilized to combine the sensitivity and specificity along with their 95% confidence intervals (CIs) from the eligible studies (23). A summary receiver operating characteristic (sROC) curve was used to summarize eligible studies, and the AUC of sROC was used to measure the overall diagnostic performance of CA72-4 (24). The Deeks's test and a funnel plot were used to evaluate the degree of publication bias (25), and I^2 was used to determine the heterogeneity among studies (26). All data analyses were performed using Revman and Stata 16.0 (Stata Corp LP, College Station, TX, USA). A P value less than 0.05 was defined as statistically significant.

Results

Study selection process and characteristics of the eligible studies

Figure 1 is a flow chart depicting the study selection process. Eight studies with 828 MPEs and 963 BPEs were included in this meta-analysis. Five studies were prospective design, and one was retrospective (19). Participants in these studies were from China (n=1) (17), USA (n=1) (27), Brazil (n=1) (16), France (n=1) (19), Sweden (n=1) (28), and Spain (n=3) (18,29,30). CA72-4 levels in pleural fluid were measured by radioimmunoassay in two studies (27,29). One study used immunoradiometry to determine CA72-4 (30). Two studies used enzyme immunoassay to determine CA72-4 (19,28), and three used an electrochemiluminescence assay (16-18). The eligible studies are summarized in *Table 1*.

Quality assessment

Table 2 depicts the quality assessment results of the eligible studies. The patient selection domain in two studies was labeled high because patients were not consecutively enrolled or enrolled retrospectively (17,19). The index test domain in four studies was labeled high because the authors used a data-driven threshold to define positive CA72-4 (16,19,29,30). The flow and timing in two studies were high because not all

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Table 1 Characteristics of the eligible studies

First author	Country	Year	MPE/BPE	Design	CA72-4 assay	Consecutive	Reference standard
Ferroni (27)	USA	1990	78/68	Unclear	RIA	Unclear	Cytology, histology
Villena (30)	Spain	1996	65/142	Prospective	IRMA	Unclear	Cytology, histology
Miédougé (19)	France	1999	215/121	Retrospective	ELISA	Unclear	Cytology
Villena (29)	Spain	2003	101/151	Prospective	RIA	Yes	Cytology, histology
Ustün (28)	Sweden	2004	41/40	Prospective	ELISA	Unclear	Cytology, histology
Antonangelo (16)	Brazil	2015	114/42	Prospective	ECL	Unclear	Cytology, histology
Trapé (18)	Spain	2017	122/280	Unclear	ECL	Yes	Cytology, histology
Cao (17)	China	2024	92/119	Prospective	ECL	No	Cytology, histology, CRS

MPE, malignant pleural effusion; BPE, benign pleural effusion; CA72-4, carbohydrate antigen 72-4; RIA, radio immune assay; IRMA, immunoradiometric assay; ELISA, enzyme-linked immunosorbent assay; ECL, electrochemical luminescence; CRS, clinical reference standard.

Table 2 Quality assessment of the eligible studies

First author	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Antonangelo (16)	Low	High	Low	Unclear	Low	Low	Low
Ferroni (27)	Unclear	Low	Low	High	Low	Low	Low
Miédougé (19)	High	High	Unclear	Unclear	Low	Low	Low
Trapé (18)	Low	Low	Low	Unclear	Low	Low	Low
Ustün (28)	Unclear	Low	Low	Unclear	Low	Low	Low
Villena (30)	Unclear	High	Low	High	Low	Low	Low
Villena (29)	Low	High	Low	Low	Low	Low	Low
Cao (17)	High	Low	Low	Low	Low	Low	Low

patients were included in the data analysis (27,30).

Main findings of the eligible studies

The diagnostic accuracy of CA72-4 for MPE is summarized in *Table 3*. The threshold values of CA72-4 ranged between 3.4 and 21 U/mL, with sensitivities between 0.33 and 0.68 and specificity between 0.83 and 1.00. The AUCs reported in eligible studies ranged between 0.60 and 0.80.

Meta-analysis

Figure 2 is the forest plots of CA72-4 for diagnosing MPE. The pooled sensitivity was 0.47 (95% CI: 0.39–0.55), and the pooled specificity was 0.98 (95% CI: 0.95–0.99). The I^2 of sensitivity and specificity were 0.88 and 0.89. The positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 26.6 (95% CI: 10.0–70.1) and 0.54 (95% CI: 0.47–0.63).

Figure 3 is the sROC curve of CA72-4. The AUC was 0.77 (95% CI: 0.73–0.80). *Figure 4* is the funnel plot of CA72-4. Deeks's test showed a significant publication bias across all eligible studies (P=0.03). *Figure 5* shows a Fagan nomogram of CA72-4 for diagnosing MPE. Assuming the prevalence of MPE is 50% in a target population, the positive predictive value (PPV) of CA72-4 was 0.96, indicating that the possibility of MPE is 96% in patients with positive CA72-4. The negative predictive value (NPV) was about 35%, suggesting the possibility of BPE was 35% in patients with negative CA72-4.

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Table 3 Diagnostic accuracy for CA72-4 in the eligible studies

First author	TP	FP	FN	TN	AUC (95% CI)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
Ferroni (27)	40	1	38	67	NR	8.5 U/mL	0.51 (NR)	0.98 (NR)
Villena (30)	33	3	32	139	NR	8.9 U/mL	0.51 (0.38–0.63)	0.98 (0.94–1.00)
Villena (29)	35	3	66	148	0.73 (0.66–0.78)	10 IU/mL	0.35 (0.26–0.45)	0.98 (0.94–1.00)
Ustün (28)	19	2	22	38	NR	4 U/mL	0.46 (NR)	0.95 (NR)
Antonangelo (16)	56	7	58	35	0.60 (NR)	7.25 U/mL	0.49 (0.39–0.59)	0.83 (0.67–0.93)
Trapé (18)	40	0	82	280	NR	21 KU/L	0.33 (NR)	1.00 (NR)
Cao (17)	37	2	55	117	0.80 (0.74–0.86)	8 U/mL	0.40 (0.30–0.50)	0.98 (0.96–1.00)
Miédougé (19)	146	1	69	120	NR	3.4 U/mL	0.68 (NR)	0.99 (NR)

CA72-4, carbohydrate antigen 72-4; TP, true positive; FP, false positive; FN, false negative; TN, true negative; AUC, area under the curve; CI, confidence interval; NR, not reported.

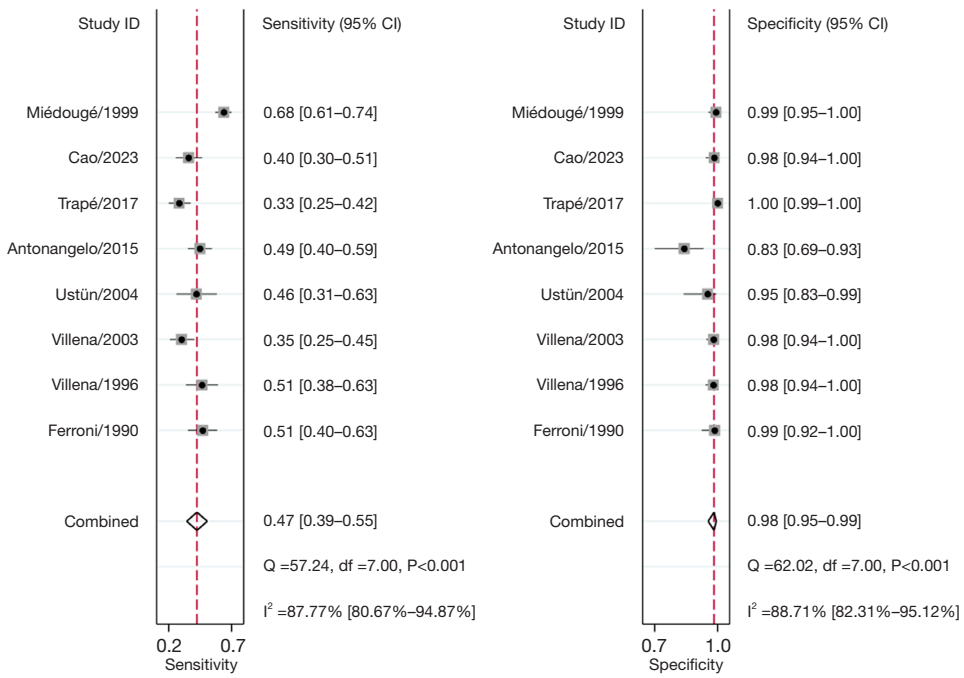

Figure 2 Forest map of CA72-4 in the pleural fluid to diagnose MPE. CI, confidence interval; CA72-4, carbohydrate antigen 72-4; MPE, malignant pleural effusion.

Discussion

This is the first systematic review and meta-analysis to investigate the diagnostic accuracy of pleural fluid CA72-4 for MPE. The present meta-analysis included eight studies with 828 MPEs and 963 BPEs. The pooled sensitivity and specificity of CA72-4 for MPE were 0.47 (95% CI: 0.39–0.55) and 0.98 (95% CI: 0.95–0.99), respectively. The AUC of sROC was 0.77 (95% CI: 0.73–0.80). The eligible studies have significant publication bias. These findings indicate pleural fluid CA72-4 is an auxiliary diagnostic marker for MPE.

The pooled sensitivity of CA72-4 was 0.47 (95% CI: 0.39–0.55), indicating that 53% of MPE would be missed if CA72-4 was used alone to confirm MPE. On the other hand, the pooled specificity of CA72-4 was 0.98 (95% CI: 0.95–0.99), indicating that only 2% of BPE would be misdiagnosed as

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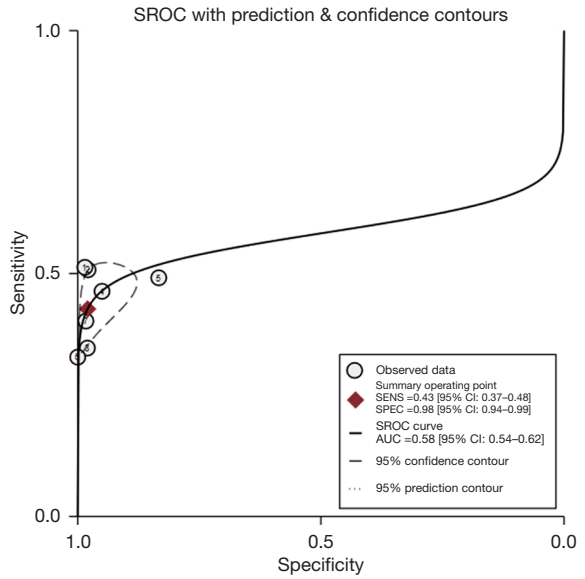

Figure 3 The sROC curve of pleural fluid CA72-4 for diagnosing MPE. sROC, summary receiver operating characteristic; SENS, sensitivity; SPEC, specificity; AUC, area under the curve; CI, confidence interval; CA72-4, carbohydrate antigen 72-4; MPE, malignant pleural effusion.

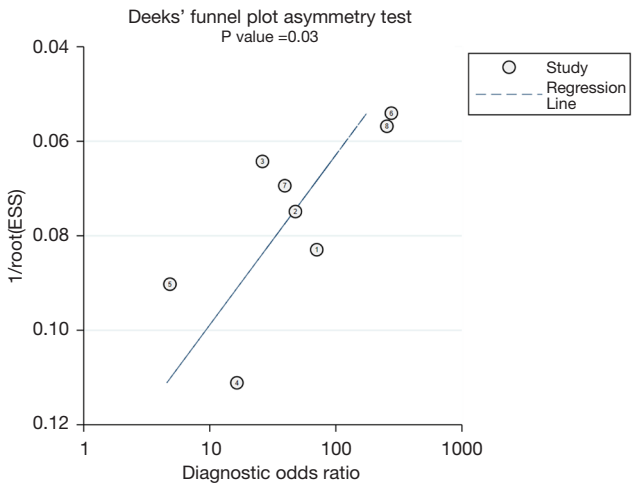

Figure 4 A funnel plot assessing publication bias of CA 72-4 for diagnosing MPE. ESS, effective sample size; CA72-4, carbohydrate antigen 72-4; MPE, malignant pleural effusion.

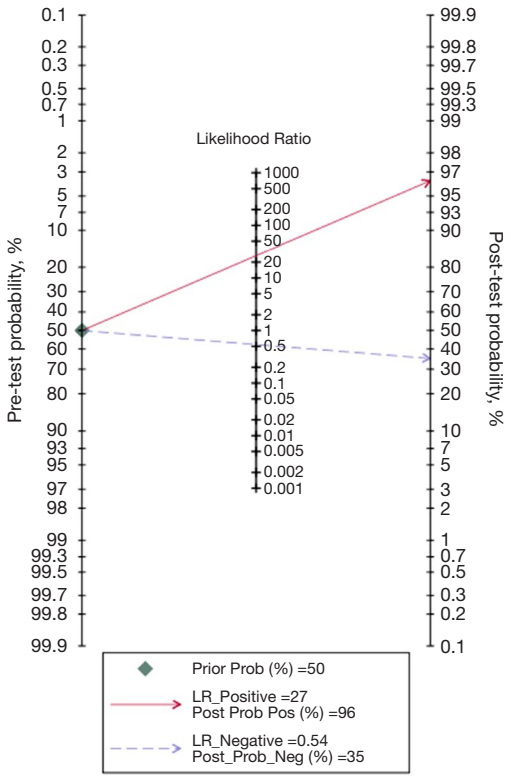

Figure 5 A Fagan plot depicting the predictive values of CA72-4 under different prevalences. LR, likelihood ratio; CA72-4, carbohydrate antigen 72-4.

MPE if CA72-4 was used alone to exclude MPE. Therefore, CA72-4 has moderate diagnostic accuracy for MPE. It may be used to confirm MPE rather than exclude.

Sensitivity and specificity are two basic diagnostic metrics of a diagnostic marker. A limitation of these two metrics is threshold-dependent. In other words, they only reflect the accuracy of a marker at a specified threshold. For example, most eligible studies set their thresholds between 3.4 and 21 U/mL, and the corresponding sensitivity and specificity were 0.40 and 1.00. These findings suggest that the sensitivity and specificity of CA72-4 were 0.40 and 1.00, with a threshold between 3.4 and 21 U/mL. What sensitivity and specificity will be obtained if a higher threshold is used remains unclear. Therefore, sensitivity and specificity are not suitable metrics to measure the global diagnostic accuracy of a marker (31). In contrast, the AUC of sROC is not affected by the threshold used and thus represents a global indicator of diagnostic accuracy (32). The AUC of the sROC curve is between 0.5 and 1.0, and a higher AUC indicates higher diagnostic accuracy (24). The AUC of CA72-4 was 0.77 (95% CI: 0.73–0.80), which also supports that CA72-4 is an auxiliary diagnostic marker for MPE.

NLR and PLR are two prevalence-independent metrics that exclude or confirm target disease. It is generally believed that PLR >10 strongly suggests the presence of

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disease, and NLR <0.1 strongly supports the exclusion of target disease (33). The PLR of CA72-4 was 26.6 (95% CI: 10.0–70.1), indicating that the risk of MPE was extremely high in patients with positive CA72-4. By contrast, the NLR of CA72-4 was 0.54 (95% CI: 0.47–0.63), which does not support the implication of CA72-4 in excluding MPE. Therefore, from a statistical perspective, patients with elevated CA72-4 can be used to confirm the presence of MPE.

The QUADAS-2 tool was used to assess the quality of the included studies. The available studies had some design weaknesses. Some studies did not enroll participants consecutively, which may impair the participants' representativeness of the available studies. The generalizability of these studies is thus problematic. The thresholds used in some studies were data-driven. This threshold selection method may overestimate the diagnostic accuracy of a biomarker (34). Further studies with rigorous designs are needed to validate the findings of available studies.

Many conventional tumor markers have been reported as useful diagnostic markers for MPE, such as CEA, neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), carbohydrate antigen 153 (CA153), carbohydrate antigen 199 (CA199), and cytokeratin-19-fragment (CYFRA21-1) (35). Two meta-analyses reported these tumor markers had a pooled sensitivity of 0.50 and a specificity of 0.90 for diagnosing MPE (36,37). The pooled sensitivity and specificity of CA72-4 were 0.47 (95% CI: 0.39–0.55) and 0.98 (95% CI: 0.95–0.99), respectively, indicating that the accuracy of CA72-4 in diagnosing MPE is comparable to that of conventional tumor markers. One study reported that CA72-4 had a specificity of 1 at the threshold of 21 U/mL (18). Therefore, CA72-4 >21 U/mL can be used to confirm MPE. This hypothesis is also supported by our previous study (17).

Publication bias is not uncommon in clinical research. Positive findings have a high probability of being published in academic journals. One aim of meta-analysis is to verify the presence of publication bias. The present study revealed a significant publication bias, suggesting that previous studies may have overestimated the diagnostic accuracy of CA72-4.

There are several limitations. First, the number of included studies, as well as the total sample size, is small. Therefore, the 95% CIs of sensitivity and specificity were wide. Further studies with large sample sizes are needed to improve the precision of sensitivity and specificity. Second, significant heterogeneity was observed across eligible studies. Still, due to the small number of included studies, subgroup analysis or meta-regression cannot be performed to explore the source of heterogeneity. Third, due to the limited resources, we did not search non-English databases; thus, the language bias cannot be excluded.

Conclusions

In summary, pleural fluid CA72-4 is an auxiliary diagnostic marker for MPE. With thresholds between 3.4 and 21 U/mL, CA72-4 helps confirm MPE, but its value is limited in ruling out MPE. Patients with CA72-4 >21 U/mL had an extremely high risk of MPE. Considering the small sample size, the design weaknesses of the eligible studies, and publication bias, further studies with large sample sizes and rigorous designs remain needed to evaluate the diagnostic accuracy of CA72-4 for MPE.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1664/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1664/prf

Funding: This study was supported by funding from the Program for Young Talents of Science and Technology in Universities of Inner Mongolia Autonomous Region (No. NJYT22018, to Z.D.H.).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1664/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.

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Cite this article as: Cao XS, Feng CM, Yan L, Zhang L, Jiao W, Wang MY, Zheng WQ, Hu ZD. Diagnostic accuracy of pleural fluid carbohydrate antigen 72-4 for malignant pleural effusion: a systematic review and meta-analysis. Transl Cancer Res 2025;14(2):1237-1245. doi: 10.21037/tcr-24-1664

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