

Diagnostic accuracy of endostatin for malignant pleural effusion: a systematic review and meta-analysis

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Background: Diagnosing malignant pleural effusion (MPE) with pleural effusion (PE) biomarkers is of great value because it represents an mini-invasive, inexpensive, and objective diagnostic tool. Many studies have been performed to investigate the diagnostic value of PE endostatin for MPE, but the results were heterogeneous. This study aimed to systematically review the studies investigating the diagnostic accuracy of PE endostatin for MPE and pool their results.

Methods: We searched the PubMed and Web of Science databases to identify clinical studies investigating the diagnostic accuracy of PE endostatin for MPE. The last search date was June 1, 2020. The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess eligible studies' quality. A summary receiver operating characteristic (sROC) curve and bivariate model were used to pool the eligible studies' results.

Results: Finally, five studies with 491 patients (248 MPEs and 243 non-MPEs) were included in this metaanalysis. The sensitivity and specificity of endostatin were 0.631 and 0.773, respectively. Besides, the area under sROC curve was 0.71 (95% CI: 0.67–0.75). The major design weakness of eligible studies was patient selection bias.

Conclusions: The current evidence does not support PE endostatin as a useful diagnostic biomarker for MPE.

Keywords: Malignant pleural effusion (MPE); endostatin; diagnosis; meta-analysis; systematic review

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Introduction

Pleural effusion (PE) is a common sign in clinical practice with various etiologies. It was reported in previous studies that malignant PE (MPE) accounts for 20% to 50% of PE (1,2). Diagnosing MPE in PE patients with unknown etiology is a challenge for clinicians. The gold standard for diagnosing MPE is the closed pleural biopsy and medical thoracoscopy followed by pathological examination (3). However, both of those tools are invasive and observerdependent (4,5). Thus, it is of great value to develop noninvasive and objective diagnostic tools for MPE.

Tumor biomarkers in PE represent a diagnostic tool for MPE (6,7). To date, accumulated studies have been conducted to investigate the diagnostic accuracy of tumor biomarkers for MPE. The diagnostic accuracy of conventional tumor biomarkers, including carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 15-3, CA19-9, CA 125, cytokeratin fragment 19 (CYFRA 21-1), and neuron-specific enolase (NSE), has

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been widely studied. However, the evidence from metaanalyses indicates that these tumor biomarkers' diagnostic accuracy is unsatisfactory, with sensitivities around 0.50 and specificity around 0.90 (8-10). Therefore, it is essential to develop novel tumor biomarkers that can improve the diagnostic accuracy of conventional tumor biomarkers or replace them (7).

Previous studies reported that endostatin, an endogenous angiogenesis inhibitor, increased in MPE and represented a potential diagnostic biomarker for MPE (11). Several studies have investigated the diagnostic accuracy of PE endostatin for MPE, but the results were heterogeneous. Therefore, we conducted this systematic review to determine the accuracy of endostatin for MPE. We present the following article in accordance with the PRISMA-DTA reporting checklist (12) (available at http://dx.doi. org/10.21037/jlpm-20-91).

Methods

Literature retrieval

The study was not registered before performing. Two databases, the PubMed and Web of Science, were searched to identify eligible studies. The last search date was June 1, 2020. The search algorithm in PubMed is ("Endostatins"[nm] or endostatin or endostar) and (pleural or pleurisy or pleura or pleurae or pleuritis). A similar strategy was used in Web of Science. We also manually searched the references listed at the end of the review in this field and eligible studies.

Inclusion and exclusion criteria

We included the studies investigating PE endostatin for MPE. The exclusion criteria were: (I) animal studies; (II) review, case report, and editorial; (III) conference abstract; (IV) studies with insufficient detail to construct a two-by-two table for meta-analysis. In the first round of study selection, two reviewers independently screened the title and abstract of searched studies to identify obviously irrelevant studies. In the second round, a full-text review was performed to identify eligible studies.

Data extraction and quality assessment

Data extraction was performed by two reviewers independently. The data extracted were: name of the first author, country, year, component of control, sample sizes of MPE and non-MPE, study design (prospective or retrospective), consecutive enrollment, blinded test and interpretation, the reference standard for MPE diagnosis, endostatin assay, cutoff used for diagnosis, sensitivity, and specificity. We constructed a two-by-two table for each eligible study with the sensitivity, specificity, and sample sizes of MPE and non-MPE. The two-by-two table contains the numbers of true positive (TP), false negative (FN), true negative (TN), and false positive (FP).

The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the eligible studies' quality (13).

Statistical analysis

All statistical analyses were performed with the MetaDTA, an online tool for meta-analysis (14). A bivariate model was used to pool the sensitivities and specificities of included studies (15). A summary receiver operating characteristic (sROC) curve, which is threshold independent, was used to measure endostatin's overall diagnostic performance (16). I^{2} -was used to determine the heterogeneity across the eligible studies [13]. P<0.05 was considered statistically significant.

Results

Summary of the eligible studies

Figure 1 is a flowchart of study selection. Finally, five studies (11,17-20) with 248 MPEs and 243 non-MPEs were included. Characteristics of the eligible studies are summarized in Table 1. Four of the eligible studies were performed in China (17-20). The remaining one was performed in Japan (11). All eligible studies are prospective design and determine PE endostatin with ELISA. In four of the eligible studies, MPE was caused by lung cancer (11,18-20), while the remaining one study included patients with metastatic tumors (17). The disease profile of non-MPE was various, including tuberculous pleural effusion (TPE) (11,17-20), parapneumonic pleural effusion (PPE) (11,17-19), heart failure (HF) (17,18), liver cirrhosis (LC) (17), and pulmonary embolism (PE) (17). Patients in the two studies were consecutively enrolled (11,17), while the remaining three studies did not report whether patients were consecutively enrolled (18-20). Two studies did not report whether the PE endostatin results were masked to the clinicians who made



Figure 1 Flowchart of study selection.

Table 1 Characteristics of eligible studies

Author	Country	Year	MPE/ non-MPE	Non-MPE	MPE	Design	Consecutive	Blind	Assay	Reference standard
Zhou (20)	China	2009	62/64	TPE [64]	Lung cancer [62]	Prospective	Unclear	Yes	ELISA	Cytology
Zhang (19)	China	2012	52/50	TPE [39], PPE [7], empyema [4]	LA [38], LSCC [7], SCLC [7]	Prospective	Unclear	Unclear	ELISA	Cytology, histology
Tian (17)	China	2015	52/64	TPE [30], PPE [19], HF or LC [9], PE [3], others [3]	LA [18], LSCC [15], SCLC [8], metastatic tumor [11]	Prospective	Yes	Yes	ELISA	Cytology, histology
Zhu (18)	China	2017	44/36	TPE [29], PPE [2], HF [5]	Lung cancer [44]	Prospective	Unclear	Yes	ELISA	Cytology, histology
Sumi (11)	Japan	2003	38/29	PPE [16], TPE [13]	LA [29], LSCC [7], SCLC [1], LCC [1]	Prospective	Yes	Unclear	ELISA	Cytology, histology

The number in parenthesis indicates the absolute number of patients. MPE, malignant pleural effusion; TPE, tuberculous pleural effusion; PPE, parapneumonic pleural effusion; LA, lung adenocarcinoma; LSCC, lung squamous cell carcinomas; SCLC, small cell lung cancer; HF, heart failure; LC, liver cirrhosis; PE, pulmonary embolism; LCC, large cell carcinoma.

the final diagnosis (11, 19).

Diagnostic performance and quality assessment of eligible studies

The diagnostic accuracy of endostatin in eligible studies is listed in *Table 2*. Two of the eligible studies did not report the area under the receiver operating characteristic (ROC) curve (AUC). In the remaining three studies, the AUC of endostatin ranged from 0.69 to 0.75. Diagnostic thresholds adopted by the eligible studies ranged from 0.0112 to 163.57 ng/mL. The eligible studies' sensitivities ranged from 51.92% to 69.30%, and specificities ranged from 44.83% to 83.00%.

The quality assessment of the included studies is shown in *Table 3*. Four of the five eligible studies (11,18-20) have patient selection bias because their disease profile was not representative. One study only included TPE as control (20), and some studies were two-gate design (21). The three studies' index test domain was labeled as high because

Author	AUC	Threshold	Sensitivity (%)	Specificity (%)	TP	FP	TN	FN
Zhou (20)	0.69	4 ng/mL	69.00	83.00	43	11	53	19
Zhang (19)	NR	163.57 ng/mL	69.30	71.50	36	14	36	16
Tian (17)	0.75	79.7 ng/mL	51.92	85.94	27	9	55	25
Zhu (18)	0.73	79.32 ng/mL	52.27	86.11	23	5	31	21
Sumi (11)	NR	11.2 pg/mL	68.42	44.83	26	16	13	12

 Table 2 Diagnostic accuracy of endostatin in eligible studies

AUC, an area under the curve; NR, not reported; TP, true positive; FP, false positive; TN, true negative; FN, false negative.

Table 3 Quality assessment of the eligible studies

Author		Risk c	of bias	Applicability concerns			
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Zhou (20)	High	Unknown	Low	High	High	Low	Low
Zhang (19)	High	High	Low	Unknown	High	Low	Low
Tian (17)	Low	High	Low	High	Low	Low	Low
Zhu (18)	High	High	Low	Unknown	High	Low	Low
Sumi (11)	High	Low	Low	Unknown	High	Low	Low

the diagnostic threshold was not prespecified (17-19). A previous study has revealed that a data-driven threshold may overestimate an index test's diagnostic accuracy, especially in studies with small sample size (22). Two of the eligible studies were marked as high regarding the flow and timing domain because of partial verification bias (17,20). In partial verification design, not all subjects receive reference standard (23). This type of design may introduce bias because some patients with target disease may be missed. The remaining three studies were labeled as unknown because partial verification bias was not indicated in the report.

Meta-analysis

Figure 2 is a forest plot of endostatin. Pooled sensitivity and specificity of endostatin were 0.63 (95% CI: 0.55–0.71) and 0.77 (95% CI: 0.63–0.87), respectively. Positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were was 2.78 (95% CI: 1.49–5.43) and 0.48 (95% CI: 0.34–0.72), respectively. The diagnostic odds ratio (DOR) was 0.50 (95% CI: 2.08–16.07). The sROC curve of endostatin is shown in *Figure 3*. Heterogeneity across the eligible studies

measured by I^2 was 82% (95% CI: 60–100%). AUC of the sROC was 0.71 (95% CI: 0.67–0.75).

Discussion

In this study, we performed a systematic review and metaanalysis to ascertain the diagnostic accuracy of endostatin for MPE. With five included studies, we found that the pooled sensitivity and specificity of endostatin for diagnosing MPE were 0.63 and 0.77, respectively. The area under the sROC curve was 0.71. These results do not support PE endostatin as a useful diagnostic biomarker for MPE.

Compared with a previous meta-analysis published in 2015 (17), our study has some advantages. The first advantage is we searched the Web of Science database and included the studies published after 2015. The second advantage is that our study's quality assessment tool is QUADAS-2, which is more comprehensive than the first version of QUADAS (13).

Sensitivity and specificity are two main indicators to measure an index test's diagnostic accuracy, and both of them are greatly affected by the adopted threshold of the







Figure 3 Summary receiver operating characteristic curve of endostatin. HSROC, hierarchical summary receiver operating characteristic.

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index test (24). By contrast, the AUC of an index test is threshold independent, and it is a better metric to estimate the diagnostic accuracy of an index test. This study found that the AUC of endostatin was only 0.71, indicating that endostatin's diagnostic accuracy is low. NLR and PLR are two indicators used for ruling in or ruling out of target disease. It is widely accepted that PLR >10 or NLR<0.1 is strong evidence to rule in or rule out target diagnosis, respectively (25). In this study, the PLR and NLR were 2.78 and 0.48, respectively, indicating that endostatin, when used alone, is insufficient to rule in or rule out MPE. Taken together, the current evidence does not support using PE endostatin for diagnosing MPE.

Currently, some studies have been performed to investigate the diagnostic accuracy of PE biomarkers for MPE. According to the published meta-analyses, these markers' diagnostic sensitivities were around 50%, and the specificities were about 90% (8,9,26,27). Their AUCs were around 0.80. By contrast, this study found that endostatin has a sensitivity of 63%, a specificity of 77%, and an AUC of 0.71, suggesting that endostatin's diagnostic accuracy is inferior to the conventional biomarkers.

This meta-analysis has some limitations. First, the small sample size is the major weakness of this systematic review and meta-analysis. Therefore, the results of this metaanalysis were not sufficiently robust. Second, we could not perform meta-regression to explore the heterogeneity sources. Third, we did not perform publication bias analysis because of the small sample size.

In conclusion, our results do not support PE endostatin as a useful diagnostic marker for MPE. Given the small sample size of this meta-analysis, further studies with a large sample size are needed to validate this study's findings.

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Footnote

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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. The study does not require any ethical approval and individual consent because this is a systematic review and meta-analysis.

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