Diagnostic accuracy of pleural effusion hyaluronic acid for malignant pleural mesothelioma: A systematic review and meta-analysis

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Abstract

Background

The diagnosis of malignant pleural mesothelioma (MPM) is generally difficult, and no single biomarker has been established. Hyaluronic acid (HA) is highly elevated in MPM and could thus be a diagnostic biomarker. However, to our best knowledge, no systematic review has evaluated the diagnostic accuracy of pleural HA. This systematic review aimed to evaluate the diagnostic accuracy of pleural effusion HA for MPM.

Methods

We searched MEDLINE via OVID, Embase via Embase.com, Central, and the International Clinical Trials Registry Platform databases for relevant articles. Prospective, retrospective, and case-control studies that assessed the sensitivity and specificity of pleural effusion HA for MPA diagnosis were included. The exclusion criteria were review articles, case reports, and animal studies. The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Forest plots were generated to summarize the sensitivity and specificity of HA in each included study. In addition, the pooled sensitivity and specificity of HA for MPA diagnosis was calculated using a bivariate random effects model.

Results

Overall, 6 studies involving 1,548 patients were included. There was a high risk of bias because 83% of the included studies had a case-control design. The pooled sensitivity and specificity were 50% (95% CI: 40–59%) and 97% (95% CI: 93–99%), respectively. We could not obtain a reliable estimate of the 95% confidence region or 95% prediction region because of the small sample sizes of the included studies.

Conclusions

Although HA in pleural effusion might have low sensitivity and high specificity for MPM diagnosis, we could not draw a valid conclusion because of the high risk of bias and small sample size. Further large-scale retrospective cohort studies are needed to more accurately estimate its sensitivity and specificity.

Background

Malignant pleural mesothelioma (MPM) is an aggressive malignancy and, thus, has poor prognosis, with a median survival of only approximately 10 months from diagnosis [1]. MPM diagnosis is challenging; cytology alone is insufficient, and international guidelines recommend surgical thoracoscopy [2]. However, surgical thoracoscopy is an invasive procedure; as such, alternative biopsy procedures are

considered for diagnosis [3]. However, all pleural biopsy procedures are associated with the risk of complications and discomfort. In addition, no single biomarker has been established for the diagnosis of MPM [4].

In 1939, researchers found that hyaluronic acid (HA), an important component of the extracellular matrix, was highly elevated in MPM, while it was moderately elevated in other diseases [5]. Thus, HA could be a specific biomarker for the diagnosis of MPM. However, only small-scale studies have been conducted, and international guidelines have not made a statement regarding pleural HA [6–11]. In addition, to our best knowledge, no systematic review has evaluated the diagnostic accuracy of pleural HA to date. As such, this systematic review aimed to evaluate the accuracy of HA in pleural effusion for the diagnosis MPM. We hypothesized that HA could be used to rule in and rule out MPM and avoid unnecessary pleural biopsy procedures.

Methods

In this systematic review and meta-analysis, MEDLINE via OVID, Embase via Embase.com, Central, and the International Clinical Trials Registry Platform databases were searched for relevant studies published until 29 November 2021. The search terms were based on the index test (HA) and target condition (MPM) (Supplementary Table S1). Prospective, retrospective, and case-control studies that assessed the sensitivity and specificity of HA in pleural effusion for the diagnosis of MPM were included. The inclusion criteria were sufficient information to create a two-by-two contingency table of true-positive, false-positive, false-negative, and true-negative. There were no restrictions on the publishing period or language. The exclusion criteria were review articles, case reports, and animal studies.

MPM was diagnosed based on history, physical examination, blood tests, and pleural biopsy. YM and OT independently screened the titles and abstracts. After screening, AS and OT reviewed the full text and selected the articles. AS and OT then searched for other potentially relevant studies by reviewing the references of the included publications and citation searches using Google Scholar. Data were extracted by OT and double checked by AS. These data included year, country, study setting, study participants, detailed information about the index test, and reference standards.

OT and AS evaluated the quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 tool [12]. This tool enabled us to evaluate the included articles from the perspectives of risk of bias and applicability in the four key domains: patient selection, index test, reference standard, and flow and timing. A forest plot was generated to summarise the sensitivity and specificity of HA in each included study. In addition, the pooled sensitivity and specificity of HA for MPM diagnosis was calculated using a bivariate random effects model. A hierarchical summary receiver operating characteristic (HSROC) curve was then created based on the parameters calculated using the model. Any disagreements that emerged during the review were resolved via discussion and consultation with AS.

All statistical analyses were performed using the STATA 15 software (STATA Corp. College Station, TX, USA) and RevMan v5.4.1 software (The Nordic Cochrane Centre, The Cochrane Collaboration,

Copenhagen Denmark). The systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary Table S2) [13].

Results

A total of 581 studies were initially identified after title and abstract screening. After a full-text review, 6 studies involving 1,548 patients (306 MPM patients) were finally included in the analysis (Figure 1) [6–11]. The study characteristics are summarised in Tables 1 and 2. The excluded studies are summarized in Supplementary Table S3. Overall, 6/7 (86%) included studies had a case-control design. The measurement method of pleural effusion HA varied among the included studies, and we could not obtain detailed information about the pathological diagnosis of MPM in all the studies, regardless of contact with the authors.

The quality of the included studies is summarised in Supplementary Figure 1 and 2. All the included studies had a high risk of bias in the domain of the index test and reference standard because there were no pre-specified cut-offs and reference standards, respectively. Clear information about blinding (i.e. whether researchers interpreted the HA results with knowledge of the clinical diagnoses) was also unavailable. The forest plot showed a large variability in the sensitivity of HA, while the specificity in all studies was quite high. The bivariate random-effects model showed a pooled sensitivity and specificity of 50% (95% CI: 40–59%) and 97% (95% CI: 93–99%), respectively. Figure 3 shows the HSROC curve of pleural PA with different cut-off values. Because of the small sample size of the included studies, we could not obtain a reliable estimate of the 95% confidence region or 95% prediction region.

Discussion

Our study revealed that the diagnostic accuracy of pleural effusion HA for MPM had a high risk of bias, and we could not draw a valid conclusion because of the small sample size. Researchers need to standardise the methods of measuring HA and the cut-off point. In addition, further large-scale retrospective cohort studies are needed to more precisely estimate sensitivity and specificity.

Although the included studies were of low quality, they all reported extremely high specificity of pleural HA, indicating the feasibility of MPM diagnosis without the need for invasive pleural biopsies. However, HA in pleural effusion cannot substitute pleural biopsies. The histological subtypes of epithelioid and sarcomatoid could provide important information about the indication for surgical treatment in MPM at the early stage. Pleural biopsy is also crucial for differential diagnosis in patients suspected of late-stage MPM. The high specificity may have a clinical implication in obtaining a provisional diagnosis of MPM in patients who have pleural effusion but are ineligible for pleural biopsies (e.g. those with multiple antiplatelet and anticoagulant therapy and with severe disease) or cancer treatment (e.g. those with low performance status). However, pleural HA had low sensitivity, indicating that it cannot be used to rule out MPM. A negative result for HA in pleural effusion cannot rule out MPM. HA may not be recommended as a screening tool in the first or second attempt at thoracentesis.

Our study has some limitations. First, the number of included studies was too small to estimate a 95% confidence region and 95% prediction region of the HSROC. In addition, four of six studies were conducted in Japan, and two studies had the same first author and institution. Thus, the findings may have limited generalisability. Second, the measurement of HA and the cut-off points were not pre-specified and not standardised among the included studies. Third, we could not obtain information about the reference standard. The diagnosis of MPM can be difficult even with pleural biopsy [14]. To address the ambiguity of diagnosis, clinicians should use immunohistochemistry.

Conclusions

Due to the low quality of the included studies, we could not reach a valid conclusion on the diagnostic accuracy of pleural HA for MPM diagnosis. HA may have high specificity and low sensitivity. Further retrospective cohort studies with standardised measurements and prespecified cut-off points are needed.

Abbreviations

HA hyaluronic acid

HSROC hierarchical summary receiver operating characteristic

MPM malignant pleural mesothelioma

Declarations

Ethics approval and consent to participate: This study was registered with the International Prospective Register of Systematic Reviews (CRD42021287973).

Consent for publication: Not applicable.

Availability of data and materials: Data is available on the request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: TO, AS, YS, KI, HS, KN, YM, and MT contributed substantially to the study conceptualization, methodology, data analysis, interpretation, and writing of the manuscript. All authors had full access to all data in the study and took responsibility for data curation. No funding was received for this study.

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Tables

Table 1: Study characteristics

Study	Country	Study design	Number of study participants	Inclusion and exclusion criteria
Fujimoto et al. [8]	Japan	Retrospective cohort study	334	Patients with pleural effusions and determined concentrations of HA in the pleural fluid. 334 patients (50 MPM, 48 benign asbestos pleurisy, 85 lung cancer, 18 other malignant diseases, 86 infectious pleuritis, 6 collagen disease, 41 other diseases)
Fujimoto et al. [9]	Japan	Case-control	860	Patients with pleural effusions and determined concentrations of HA in the pleural fluid. 860 patients (139 MPM, 76 benign asbestos pleurisy, 324 lung cancer, 74 other malignant diseases, 120 infectious pleuritis, 11 collagen disease, 116 other diseases)
Moriyama et al. [10]	Japan	Case-control	40	The pleural effusion of unknown origin or pleural thickening. 40 patients (26 MPM, 12 inflammatory change, 2 pleural dissemination of cancer.)
Dejmek et al. [7]	Sweden	Case-control	130	The pleural effusion from metastatic adenocarcinoma and MPA. 130 patients (57 MPM, 73 metastatic adenocarcinoma)
Atagi et al. [6]	Japan	Case-control	99	Patients with pleural effusion. 99 patients (19 MPM, 27 lung cancer, 1 breast cancer, 1 mediastinal tumor, 51 non-malignant diseases)

Pettersson et al. [11]	Finland	Case-control	85	Patients with pleural effusion.	Patients with empyema and patients with undetermined diagnosis.
				85 patients (15 MPM, 10 adenocarcinoma of lung, 7 small cell carcinoma of lung, 5 breast carcinoma, 1 renal carcinoma, 1 prostatic carcinoma, 1 carcinoma of the uterus, 1 ovarian carcinoma, 13 tuberculous pleurisy, 6 rheumatoid arthritis, 6 systemic lupus erythematosus, 6 pneumonia, 7 congestive heart failure.)	

Table 2: Measurement of hyaluronic acid in pleural effusions and reference standard

Study	Index test	Reference standard
Fujimoto et al.[8]	The latex agglutination turbidimetric immunoassay	Histological diagnosis
Fujimoto et al.[9]	The latex agglutination turbidimetric immunoassay	No mentioned
Moriyama et al.[10]	No mentioned	cytology of the pleural effusion, core-needle biopsy of the thickened pleura, thoracoscopic pleural biopsy
Dejmek et al.[7]	Quantitative HPLC-based method	Histological diagnosis
Atagi et al.[6]	An electro-phoretic method (Celaphore DP210 Cosmo)	Histological diagnosis
Pettersson et al.[11]	Radiometric assay	Cytologic and/or histologic

Figures

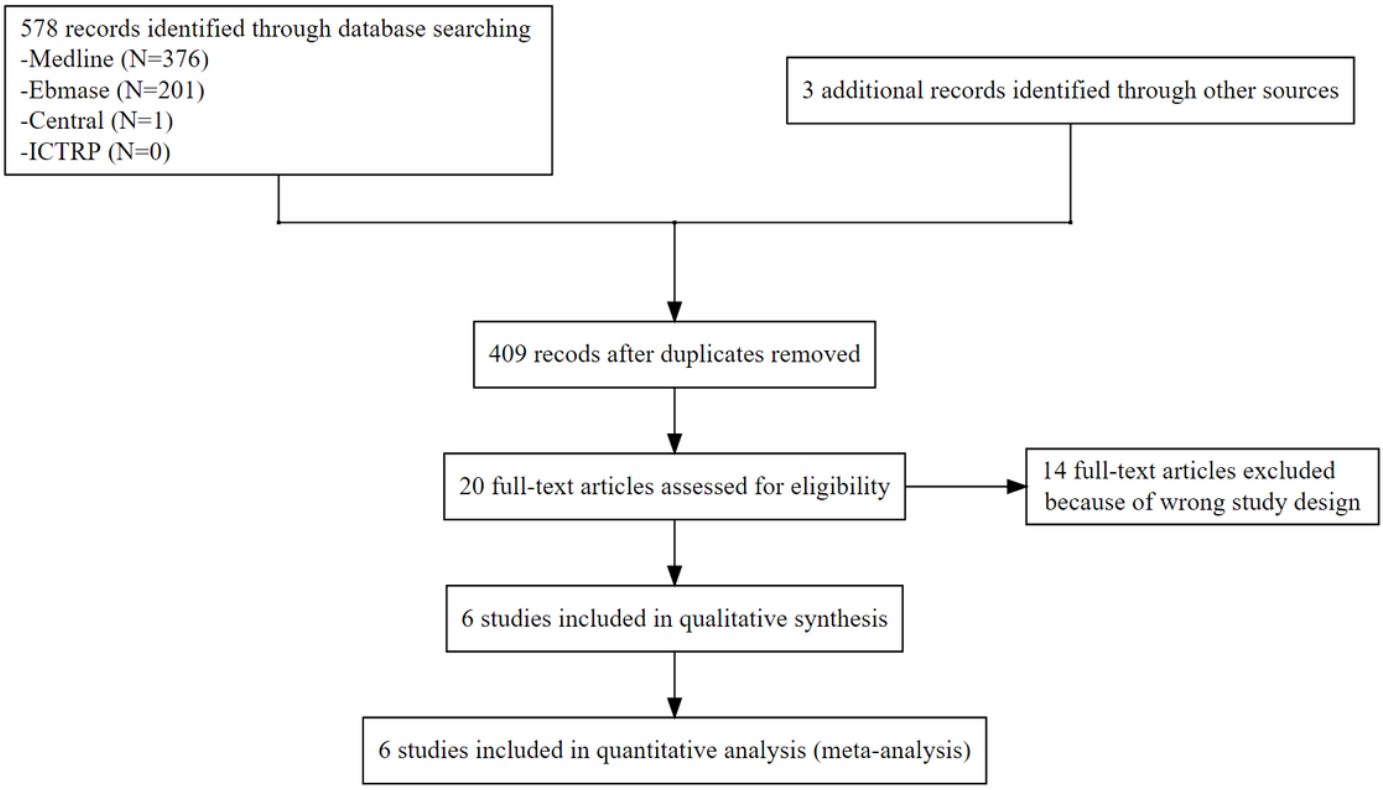

Figure 1

Study selection flow chart. The excluded studies after full-text review. Wrong study design: Yusa et al. [15], Brian et al. [16], Nurminen et al. [17], Roboz et al. [18], Thylen et al. [19], Fujimoto et al. [20], Fujimoto et al. [21], Grigoriu et al. [22], Creaney et al. [23], Martensson et al. [24], Mundt et al. [25], Tomasetti et al. [26], Welker et al. [27], Nurminen et al. [28].

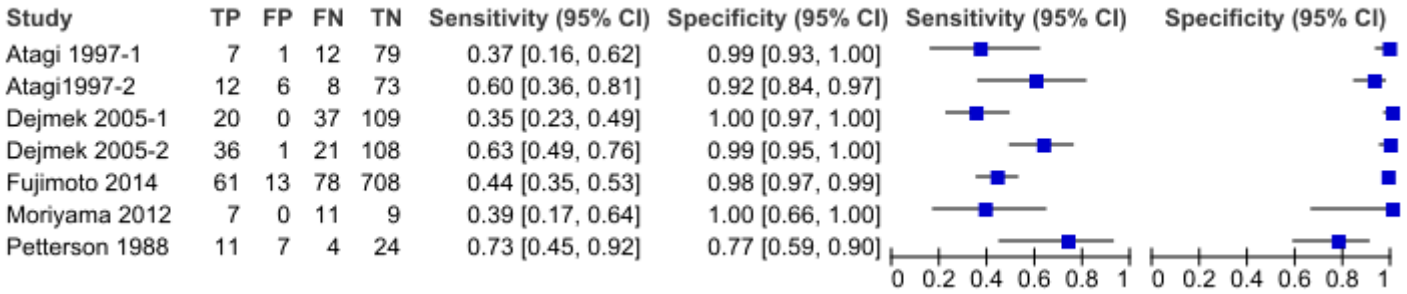

Figure 2

Forest plots of the sensitivity and specificity in the included study showed large variability of the sensitivity of HA while the specificity in all the studies was quite high. The bivariate random-effects model showed the pooled sensitivity and specificity of 50% (95% CI: 40–59%) and 97% (95% CI: 93–99%).

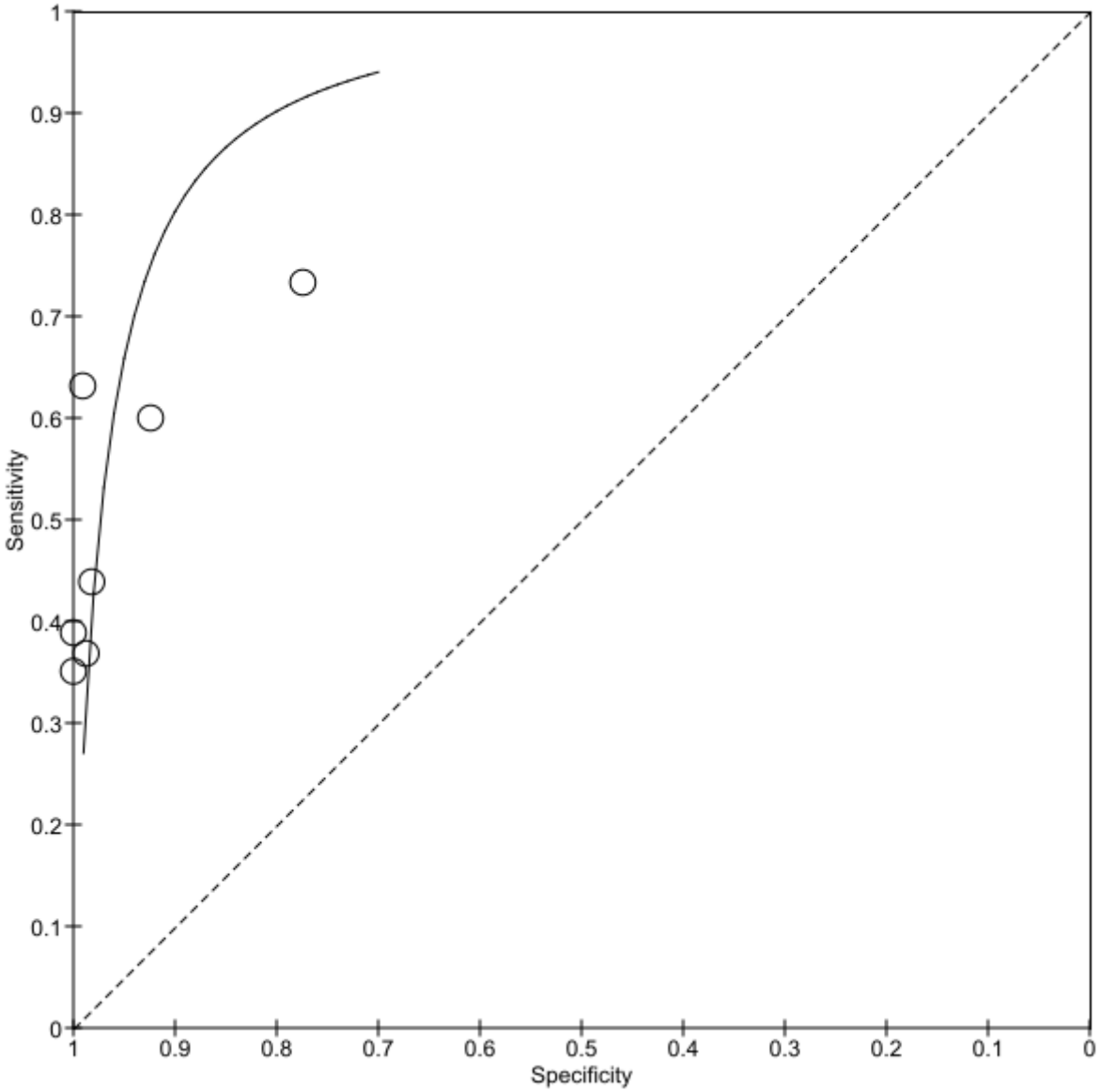

Figure 3

Hierarchical summary of the receiver operating characteristics curve of pleural HA with different cut-off values. Due to the small sample size of the included studies, we could not obtain reliable a estimate of 95% Confidence region or 95% prediction region.

Supplementary Files

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