Review Article

Serum diagnostic markers for malignant pleural mesothelioma: a narrative review

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Background and Objective: The prognosis of patients with malignant pleural mesothelioma (MPM) is poor, and early diagnosis is key to improving the prognosis. Pleural biopsy is the gold reference for diagnosing MPM, but it is an invasive method that can cause operation-related complications such as bleeding and infection. Serum biomarkers, with the advantages of mini-invasiveness, short turnaround time and objectiveness, represent a promising diagnostic tool for MPM.

Methods: We searched the PubMed database to identify clinical studies published between 1990 to July 2022 that investigated the diagnostic accuracy of serum biomarkers for MPM. The major findings of the verified studies were summarized.

Key Content and Findings: Currently, there are many available serum markers for MPM, including mesothelin, soluble mesothelin-related peptides, osteopontin, fibulin-3, high mobility group box 1, and microRNA. Systematic review and meta-analysis evidence indicates that the sensitivity and specificity of these serum markers are less than 0.90. In addition, a large portion of previous studies have limitations, especially the representativeness of the study cohort.

Conclusions: The diagnostic accuracy of currently available serum biomarkers is unsatisfactory, and further studies are needed to investigate novel serum biomarkers.

Keywords: Malignant pleural mesothelioma (MPM); diagnosis; serum biomarker; mesothelin; osteopontin; narrative review

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Introduction

Malignant pleural mesothelioma (MPM) is a malignancy that originates in the pleura. Although the overall incidence of MPM in the general population is only about 2.5/100,000 (1), the prognosis is extremely poor due to the lack of safe and effective treatment options and the fact that some patients are already in the advanced stages at the time of diagnosis. Most patients die within one year after MPM is confirmed (2-4). The overall survival of MPM is associated with histology, age, stage and treatment approach (4). Early diagnosis is key to improving the prognosis of MPM patients (2). Most MPM patients will develop pleural effusions during the course of the disease, and most patients present with chest pain and dyspnea, which are caused by pleural effusions (5). Therefore, pleural effusion cytology is the most straightforward way to confirm the presence of MPM. However, a recent systematic review showed that cytology only had a sensitivity of 28.9% for MPM (6).

Pleural tissue biopsy is the gold standard for MPM (7). However, the pleural biopsy is an invasive examination that can cause complications such as bleeding and infection (8). Moreover, cytology and pleural biopsy are subjective examinations, and their accuracies depend highly on the pathologist's experience (9). Therefore, finding minimally invasive or non-invasive, objective diagnostic approaches is essential. Serological markers are objective, minimally invasive, and easy to detect; therefore, they represent a promising diagnostic method for MPM. Here, we briefly review the history, characteristics and diagnostic accuracy of currently available serum diagnostic markers for MPM, especially the findings of systematic review and meta-analysis. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2873/rc).

Methods

We searched the PubMed database to identify clinical studies investigating the diagnostic accuracy of serum biomarkers for MPM. The latest search time was 1/7/2022. The search terms used were: "Pleural mesothelioma" and (biomarker* or marker*) and (diagnos*) and (sensitivity or specificity). We only considered research articles written in English. Two authors read the potential studies and wrote the draft. The search strategy is summarized in *Table 1*.

Highlight box

Key findings

- Mesothelin, soluble mesothelin-related peptides, osteopontin, and fibulin-3 are the most widely-studied serum marker for MPM.
- The diagnostic accuracy of these serum markers is moderate.
- The current evidence does not support using serum markers alone to confirm or rule out MPM.
- The quality of studies investigating the diagnostic accuracy of serum markers for MPM needs to be improved.

What is known and what is new?

- Serum marker has some advantages in diagnosing MPM, such as low cost, feasibility, objectivity and short turnaround time.
- We reviewed the history, characteristics, and diagnostic accuracy of serum markers for MPM, especially the findings of systematic review and meta-analysis.

What is the implication, and what should change now?

- The results of serum biomarkers should be interpreted in parallel with the clinical characteristics of patients.

Overview of findings

Mesothelin and soluble mesothelin-related peptides (SMRPs)

The 69-kDa mesothelin precursor protein can be cleaved by proteases into two molecules: a 31-kDa N-terminal soluble protein, commonly known as megakaryocyte potentiating factor (MPF), and the mesothelin, which is the remaining cell surface glycoprotein with a molecular weight of about 40 kDa. Mesothelin is mainly expressed in mesothelioma cells but can also be found in ovarian cancer, pancreatic cancer, and normal pleural mesothelium (10-12). Mesothelin has three isoforms that can be shed from the cell surface into the blood by enzyme digestion or frameshift mutations (13). In general, MPF and the cleaved form of mesothelin isoforms are collectively referred to as soluble mesothelin-related proteins (SMRP) (14). Serum mesothelin and SMRP are potential diagnostic markers for MPM.

In 2003, Robinson *et al.* reported the diagnostic value of serum mesothelin for MPM in *The Lancet* (15). They found that serum mesothelin had a sensitivity of 84% and a specificity of 95% for MPM (15). Subsequently, multiple studies have evaluated the diagnostic values of serum mesothelin and SMRP for MPM, but with inconsistent results. A systematic review and meta-analysis published in 2010 found that SMRP had an overall sensitivity of 64% and a specificity of 89% (16). This systematic review was updated several times in the years that followed (14,17,18), among which the individual patient data meta-analysis published in 2012 was the most important one (19). According to the meta-analysis, the components of a control group could affect the accuracy of SMRP. Since a history of asbestos exposure is a risk factor for MPM, and most MPM patients have a history of asbestos exposure-related benign conditions, patients with asbestos exposure may be the reasonable control population. When this population was used as a control group, SMRP had an area under the receiver operating characteristic (ROC) curve (AUC) of 0.80, indicating that serum SMRP had a moderate diagnostic value for MPM (19). Based on the latest meta-analysis (18), serum SMRP had an AUC of 0.81 for MPM, also suggesting a moderate diagnostic performance for MPM.

Currently, enzyme-linked immunosorbent assay (ELISA) is widely used for detecting SMRP, with the Mesomark kit (Fujirebio, Japan) being the most popular. The US FDA has approved it for the diagnosis of MPM (14,20). Notably, the Mesomark kit is the only ELISA kit approved by the US FDA for diagnosing MPM.

Table 1 The search strategy summary

Items	Specification
Date of search	1/7/2022
Databases and other sources searched	PubMed
Search terms used	"Pleural mesothelioma" and (biomarker* or marker*) and (diagnos*) and (sensitivity or specificity)
Timeframe	From 1/1/1990 to 1/7/2022
Inclusion and exclusion criteria	Diagnostic test accuracy DTA studies, systematic review and meta-analysis of DTA
Selection process	Two authors selected studies together

Osteopontin

In 2004, Pass *et al.* used a gene expression profiling approach to compare the expression profiles of mesothelioma and pleural tissue and found that osteopontin expression increased in mesothelioma tissue (21). In 2017, Pass *et al.* found that osteopontin was highly expressed in mesothelioma and could be released into the blood. They concluded that serum osteopontin was a potential diagnostic marker for MPM, with a sensitivity of 78% and a specificity of 86% (22). Several subsequent studies also validated the findings of Pass *et al.* and compared the diagnostic accuracy between osteopontin and SMRP (23,24). In general, although the diagnostic accuracy of osteopontin is inferior to that of SMRP, the combination of plasma osteopontin and SMRP can improve the diagnostic accuracy of MPM (23).

In 2013, a systematic review and meta-analysis found that osteopontin had a sensitivity of 65% and a specificity of 81% (25), indicating its diagnostic performance is unsatisfactory. After 2013, two original studies revealed that the AUC of blood osteopontin for the diagnosis of MPM was low (26,27); accordingly, a recently updated meta-analysis concluded that the AUC of serum osteopontin was only 0.66 (18), and the AUC of plasma osteopontin was only 0.69 (18).

Notably, the diagnostic accuracy of plasma osteopontin for MPM is higher than that of serum osteopontin, which has been indirectly supported by meta-analyses (18,25) but also directly supported by "head-to-head" studies. In three original studies (23,28,29), the diagnostic accuracy of plasma osteopontin was also higher than that of serum osteopontin. The reason may be that osteopontin can be easily degraded by thrombin in peripheral blood (30), resulting in a reduction in the difference in osteopontin concentration between MPM patients and the control group. Therefore, plasma concentration is preferred when osteopontin is used in the clinical diagnosis of MPM (31). Nevertheless, the diagnostic value of osteopontin (either serum or plasma level) for MPM is quite limited.

Fibulin-3

Like osteopontin, fibulin-3 is also a marker screened by Pass *et al.* using gene expression profiling techniques (21,22). In 2012, Pass *et al.* reported the diagnostic value of circulating fibulin-3 for MPM in the *New England Journal of Medicine* (32). The study included a total of 507 patients in three cohorts from Detroit, Toronto, and New York, all of which included patients with a history of asbestos exposure. It was found that the sensitivity and specificity of plasma fibulin-3 in the diagnosis of MPM were above 0.95, and the AUCs of fibulin-3 in the three cohorts were above 0.99, suggesting fibulin-3 was an excellent serologic marker for MPM (32). However, subsequent studies from other centers did not reproduce Pass's findings. For example, Tsim *et al.* found that the AUC of plasma fibulin-3 was only 0.61 (33). In this context, a systematic review is needed to explore the reasons for such inconsistency and to determine the overall accuracy of fibulin-3 (34).

In 2016, a systematic review found that blood fibulin-3 had a sensitivity of 87% and a specificity of 89% for the diagnosis of MPM (35). The overall diagnostic accuracy was similar between serum and plasma fibulin-3, suggesting that specimen type has less influence on the diagnostic efficacy of fibulin-3 (35). An updated systematic review published in 2021 also showed that blood fibulin-3 had high diagnostic accuracy for MPM and the AUC reached 0.91, even higher than those of plasma and serum mesothelin (18). Notably, in the meta-analysis, the populations used for evaluating the diagnostic values of mesothelin and fibulin-3 were not the same (indirect comparison). Therefore the result of the comparison was not reliable. In contrast, "head-to-head

comparison" studies on the same populations were more reliable (36). Several studies have compared the diagnostic value of fibulin-3 with the traditional MPM markers SMRP or mesothelin in a "head-to-head" manner, but their conclusions were inconsistent. For example, Napolitano *et al.* demonstrated that the accuracy of fibulin-3 and mesothelin in diagnosing MPM were comparable (26). In contrast, Creaney *et al.* argued that the accuracy of serum fibulin-3 was lower than that of mesothelin (37). Therefore, more "head-to-head" studies should be carried out to compare the diagnostic performance of fibulin-3 with those of SMRP and mesothelin.

High-mobility group box 1 (HMGB1)

HMGB1 is a non-histone chromosome-binding protein in cells and plays important biological roles in tissue damage, inflammatory response, DNA repair, and transcriptional regulation (38). In response to cellular injury or necrosis, HMGB1 is released from the nuclei and directly triggers the inflammatory response as a damage-associated molecular pattern (DAMP) (38). In 2012, using immunohistochemistry, Jube *et al.* found that the expression of HMGB1 in tumor tissue of MPM patients was significantly higher than that in normal pleural tissue, and the serum concentration of HMGB1 in MPM patients was also significantly higher than that in healthy controls (39). Therefore, it is hypothesized that tumor cells may release HMGB1 into the blood during the development of MPM. In 2013, Tabata *et al.* evaluated the diagnostic value of serum HMGB1 for MPM but found its diagnostic performance unsatisfactory, with an AUC of only 0.67 (40). Moreover, about half of the subjects in the control group were healthy individuals, a design that inherently overestimated the diagnostic value of the marker (36). Therefore, the actual AUC value of HMGB1 in diagnosing MPM might be even less than 0.67. In other words, serum HMGB1 has little diagnostic value for MPM. A subsequent study carried out in patients with malignant peritoneal mesothelioma also demonstrated the low diagnostic value of serum HMGB1 (41). A large-sample study (n=497) found that serum HMGB1 increased sequentially in healthy individuals, in patients with asbestos exposure for less than ten years, in patients with asbestos exposure for >10 years, in patients with pleural plaques, in patients with asbestosis, and in MPM patients (42). When patients with asbestosis were used as the control group, the AUC of serum HMGB1 for the diagnosis of MPM was only 0.56, showing a limited clinical value (42).

HMGB1 has two isoforms: one is unacetylated HMGB1, which is mainly present in the nucleus, and the other is highly acetylated HMGB1, which is mainly present in the cytoplasm and can be released extracellularly (43). Results from cell experiments showed that asbestos-stimulated human pleural epithelial cells released HMGB1, but mainly unacetylated HMGB1, while the HMGB1 released by pleural mesothelioma cells were predominantly highly-acetylated (26). The AUC in the diagnosis of MPM was only 0.83 for total serum HMGB1 but reached 1.00 for highly-acetylated HMGB1, which was higher than those of mesothelin, osteopontin, and fibulin-3 (26). Notably, the AUCs of serum mesothelin, osteopontin, and fibulin-3 were all larger than 0.90 in diagnosing MPM, which were much higher than the results of previous studies, indicating that this study might have potential selection bias and the diagnostic value of highly-acetylated HMGB1 might be overestimated. Therefore, more rigorously-designed studies are warranted to validate the above findings further. The diagnostic value of highly-acetylated HMGB1 for MPM remains controversial.

microRNAs

microRNAs (miRNAs) are a class of small single-stranded RNAs that are 21–25 nucleotides (NTs) in length and can finely regulate the expression of target genes at the post-transcriptional level. In addition to being an important regulator of gene expression, microRNAs can also enter the bloodstream and become markers for diagnosing diseases, known as circulating microRNAs (44). Comparisons of the peripheral blood microRNA expression profiles between healthy individuals and MPM patients by using microRNA array have revealed a series of differentially expressed microRNAs such as miR-197-3p (45), miR-625-3p (46), miR-29c (46), and miR-92 (46). However, the accuracies of these microRNAs are low in some small-sample studies. For example, the AUC of miR-197-3p and miR-625-3p was only 0.76 (45) and 0.80 (46), respectively. miR-548a-3p and miR-20a are two microRNAs with relatively high diagnostic values, with AUCs being 0.92 and 0.98, respectively (47). Overall, most of the currently available studies on the diagnostic value of these microRNAs had small sample sizes and design flaws (e.g., case-control design), and their findings should be interpreted with caution.

miRNA-126 is a well-studied circulating microRNA that can assist in the diagnosis of MPM (48,49). Unlike

traditional tumor markers, circulating miR-126 level in MPM patients is reduced rather than increased (50). A recently published meta-analysis reported that the overall sensitivity and specificity of circulating miR-126 for MPM were 0.71 and 0.69, respectively (51), showing a limited diagnostic performance.

The number of research on circulating microRNAs for MPM is rising, but the sample sizes of these studies were small, and the findings varied even for a given microRNA. The reasons for such differences can be multifaceted. In addition to the diverse characteristics of the study populations (such as the composition of the control group), the failure to standardize circulating microRNA detection methods may also cause the difference. There are still many problems to be solved in the standardized detection of circulating microRNAs, including extraction of microRNA, reverse transcription, primer design, and internal reference (52).

Other serological markers

In addition to the above proteins and nucleic acid markers, there are also some soluble serum markers [e.g., thioredoxin (53), integrin-linked kinase (54), and big glutamyltransferase (55)] that are still under investigation. In general, few studies have been conducted on these markers, and preliminary results suggest that their diagnostic accuracy is not promising.

Conclusions

Many recent studies have assessed the value of serological markers for MPM diagnosis, among which mesothelin, SMRP, osteopontin, and fibulin-3 are the most widely studied. However, these markers have only moderate or poor diagnostic accuracy and cannot meet clinical needs. According to the British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma (2018) (5), any of the currently available markers alone is not sufficient to be a diagnostic basis for MPM and is feasible only for patients who have suspicious cytology results but cannot undergo invasive examinations. In 2020, the ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma also indicated that the existing markers had limited diagnostic values for MPM, and more research should be done to investigate new markers (56). I believe that future studies should focus on the following aspect: (I) novel diagnostic marker verification with omics technologies; (II) high throughput technologies; (III) the combination of multiple markers; (IV) molecular diagnosis. Therefore, there is still a long way to go before new and efficient serological markers for MPM are identified and applied.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2873/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2873/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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