

Original Article

Performance of osteopontin in the diagnosis of malignant pleural mesothelioma: a meta-analysis

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Abstract: It is reported that osteopontin has shown promising diagnostic value for malignant pleural mesothelioma (MPM), this meta-analysis aimed to establish the overall diagnostic accuracy of the osteopontin measurement for diagnosing MPM. Based on a systematic review of English language studies, the sensitivity, specificity and other measures of accuracy of osteopontin in the diagnosis of MPM were pooled using random-effects model. Summary receiver operating characteristic curves were used to summarize overall test performance. Seven publications met our inclusion criteria, the pooled sensitivity was 0.57 (95%CI: 0.52-0.61), specificity was 0.81, 95%CI: 0.79-0.84). The PLR was 3.78 (95%CI: 2.23-6.41), the NLR was 0.51 (95%CI: 0.38-0.67) and the DOR was 9.04 (95%CI: 5.28-15.48), the area under the summary receiver operating characteristic curve was 0.80. Our data suggest that osteopontin is likely to be a useful diagnostic marker for MPM, considering for the limited studies and patients included, larger studies are needed to confirm these findings.

Keywords: Osteopontin, malignant pleural mesothelioma, meta-analysis

Introduction

Malignant mesothelioma (MPM) is an aggressive tumor with a poor prognosis and short survival, it is reported that the incidence of MPM is increasing and is expected to rise sharply worldwide in the next 20 years [1, 2]. Since the clinical signs and symptoms of MPM patients are not specific, to make an early and accurate diagnosis of MPM is still a challenge.

The diagnosis of MPM is difficult. Due to the variety of histopathologic patterns, immunohistochemistry examination can only provide additional support for the diagnosis of MPM, the sensitivity of cytologic examination is not enough to screen for MPM patients and there is limited role of cytology in the primary diagnosis of MM [3, 4]. To find a reliable diagnostic marker for MPM is still a challenging endeavor. One recently published meta-analysis investigated the diagnostic accuracy of soluble mesothelin-related peptides for MPM with pooled sensitiv-

ity only 0.64 [5], no unique marker has been shown with both high sensitivity and specificity. So it is imperative to find a novel diagnostic marker to facilitate the diagnostic accuracy.

Osteopontin (OPN) is a glycoprotein which over-expressed in several human neoplasms such as lung, breast, prostate, and colon cancer [6]. Recent studies reported that serum or plasma OPN levels in patients with MPM are higher than in healthy subjects, osteopontin may be function as a useful diagnostic marker for MM patients [7, 8]. In fact, the diagnostic accuracy of OPN for MPM has been investigated in several studies, but the exact role of OPN needs to be elucidated. The purpose of the present meta-analysis was to establish the overall diagnostic accuracy of OPN for MPM.

Materials and methods

The present meta-analysis was performed according to the guidelines of the preferred

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Table 1. Basic information of included studies

Studies	Year	Country	Patient Characteristics		Reference Standard	Method
			MM	non-MM		
Pass et al	2005	USA	76	Subjects with asbestos-related benign lung disease (n=69)	Histology	ELISA
Grigoriu et al	2007	France	96	Asbestos exposed healthy subjects (n=112)	Histology	ELISA
Creaney et al	2008	Australia	66	Healthy controls (n=20) Subjects with asbestos-related lung or pleural disease (n=21)	Histology/Cytology	ELISA
Paleari et al (a)	2009	Italy	24	Non-malignant lung disease (n=31)	Histology/Cytology	ELISA
Paleari et al (b)	2009	Italy	24	Healthy controls (n=37)	Histology/Cytology	ELISA
Cristaudo et al (a)	2010	Italy	32	Healthy controls (n=94)	Histology	ELISA
Cristaudo et al (b)	2010	Italy	24	Subjects with benign lung disease (n=113)	Histology	ELISA
Creaney et al (a)	2011	Australia	66	Healthy controls (n=80) Subjects with benign lung disease (n=92)	Histology	ELISA
Creaney et al (b)	2011	Australia	66	Subjects with benign asbestos-related lung or pleural disease (n=47) Subjects with benign lung or pleural disease (n=42)	Histology/Cytology	ELISA
Mundt et al	2013	Sweden	46	Subjects with benign asbestos-related lung or pleural disease (n=47) Subjects with benign lung or pleural disease (n=42)	Histology/Cytology	ELISA
				Malignant disease (n=49), Subjects with benign lung disease (n=95)	Histology	ELISA

ELISA: enzyme linked immunosorbent assay. a, b means single studies in one publication.

reporting items for systematic reviews and meta-analysis (PRISMA) statement and with methods recommended by the Cochrane Diagnostic Test Accuracy Working Group [9, 10].

Literature search strategies

We conducted a comprehensive literature search in Pubmed, Embase and Cochrane database until Dec 15, 2013. The search keywords were “mesothelioma” and “osteopontin”. We also reviewed the reference lists of selected research papers to identify additional relevant studies. For articles which may have been based on the same study or data, only the best quality one was included. Conference abstracts or letters to the editor were excluded because of limited information present in them. Only English articles were used for the full-text review and final analysis.

Data extraction and quality assessment

The studies provided both sensitivity and specificity of OPN assay were included for the present meta-analysis. The final set of articles was assessed independently by two reviewers, the reviewers were blinded to the article details, and the differences between them were solved by consensus. The following data from each publication were retrieved: author, publication year, reference standard, test specimen, test method, sensitivity and specificity data; methodological quality. In studies containing two

groups that used different specimens, each group was treated as a single study in the meta-analysis. If no data on the above information presented in the primary studies, we marked it with “NA”.

To assess trial methodology, articles were reviewed independently by two authors and given a quality score by using the QUADAS (quality assessment for studies of diagnostic accuracy, an evidence based quality assessment tool to be used in systematic reviews of diagnostic accuracy studies, maximum score 14) tools [11].

Statistical analyses

The standard methods recommended for diagnostic accuracy meta-analyses were used in the present study [12]. The following indexes of test accuracy were computed for each study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). The analysis was based on a summary receiver operating characteristic (SROC) curve [13], the area under the curve (AUC) represents an analytical summary of test performance and display the trade-off between sensitivity and specificity. The average sensitivity, specificity and other related indexes across studies were calculated using a random-effects model [14]. Spearman rank correlation was performed as a test for threshold effect. Chi-square and Fisher’s exact tests were used to detect statistically significant heterogeneity

Table 2. Clinical summary of included studies

Studies		Cut-off	TP	FP	FN	TN	QUADAS
Pass et al	Serum	48.3 ng/ml	59	10	17	59	12
Grigoriu et al	Serum	NA	67	30	29	82	10
Creaney et al	Serum	NA	31	2	35	39	11
Paleari et al (a)	Plasma	12.2 ng/ml	23	23	1	8	9
Paleari et al (b)	Plasma	60.8 ng/ml	10	0	14	37	9
Cristaudo et al (a)	Plasma	878.65 ng/ml	22	32	10	175	10
Cristaudo et al (b)	Serum	16.06 ng/ml	15	22	9	150	10
Creaney et al (a)	Plasma	NA	26	4	40	85	10
Creaney et al (b)	Serum	NA	13	4	53	85	10
Mundt et al	Pleural effusion	NA	28	59	18	85	11

TP: True Positive; FP: False Positive; FN: False Negative; TN: True Negative; NA: Not available.

across studies. Since publication bias is a concern in meta-analyses of diagnostic studies, we tested for it using Deeks' funnel plots. All analyses were performed using statistical software programs: Meta-DiSc for Windows (XI, Cochrane Colloquium, Barcelona, Spain) and Stata (version 12, Stata Corporation, College Station, TX, USA), and all statistical tests were two-sided, and significance was set at $p < 0.05$.

Results

After independent literature search and systematic review, seven publications with eight studies using OPN assay for the diagnosis of MPM were included in the present meta-analysis [15-21].

Quality of reporting and study characteristics

Seven publications with ten studies investigated the value of OPN in the diagnosis of MM were available for the meta-analysis. Diagnosis of MM patients were made based on histopathological or/and cytological findings, which are reliable for the diagnosis of MM. The specimens of OPN assay included serum (n=4), plasma (n=4), pleural effusion (n=1). The information of author, publish year, research country, reference standard, OPN assay method, patient characteristics of each study were summarized in **Table 1**.

Of the seven publications of OPN in the diagnosis of MM, six had QUADAS scores ≥ 10 . The detailed patient information of included studies and QUADAS scores were summarized in **Table 2**.

Diagnostic accuracy

The forest plots of sensitivity and specificity of OPN assays for the diagnosis of MM were shown in **Figures 1** and **2**. The pooled sensitivity was 0.57 (95%CI: 0.52-0.61), specificity was 0.81, 95%CI: 0.79-0.84). The PLR was 3.78 (95%CI: 2.23-6.41), the NLR was 0.51 (95%CI: 0.38-0.67) and the DOR was 9.04 (95%CI: 5.28-15.48).

The X^2 values of sensitivity, specificity, PLR, NLR, and DOR were 94.29 ($p=0.00$), 148.37 ($p=0.00$), 101.96 ($p=0.00$), 72.51 ($p=0.00$), and 24.18 ($p=0.00$), respectively, suggesting significant heterogeneity among studies.

The **Figure 3** showed the SROC curve plotting the true-positive against the false-positive rates of individual studies. As a global measure of test efficacy we used the Q-value, the intersection point of the SROC curve with a diagonal line from the left upper corner to the right lower corner of the ROC space, which corresponds to the highest common value of sensitivity and specificity for the test. It represents an overall measure of the discriminatory power of a diagnostic test. In the present meta-analysis, the maximum joint sensitivity and specificity was 0.74 (the Q value), the AUC was 0.85, indicating a relative high level of overall accuracy.

Of the ten studies, five tested OPN in serum, while 4 tested OPN in plasma. We conducted subgroup analysis to identify whether one type of assay gave better diagnostic accuracy than the other. The pooled sensitivity, specificity, PLR, NLR, and DOR for serum specimens were 0.56 (95%CI: 0.51-0.62), 0.86 (95%CI: 0.82-0.89), 4.25 (95%CI: 2.76-6.55), 0.47 (95%CI: 0.28-0.79), 10.00 (95%CI: 5.82-17.17). The corresponding values for plasma specimens were: 0.55 (95%CI: 0.47-0.64), 0.84 (95%CI: 0.80-0.87), 4.79 (95%CI: 1.20-19.15), 0.53 (95%CI: 0.38-0.73), 13.02 (95%CI: 6.97-24.32). For serum specimens, the maximum joint sensitivity and specificity were 0.77, and AUC was 0.84; for plasma specimens, the corresponding values were 0.77 and 0.84.

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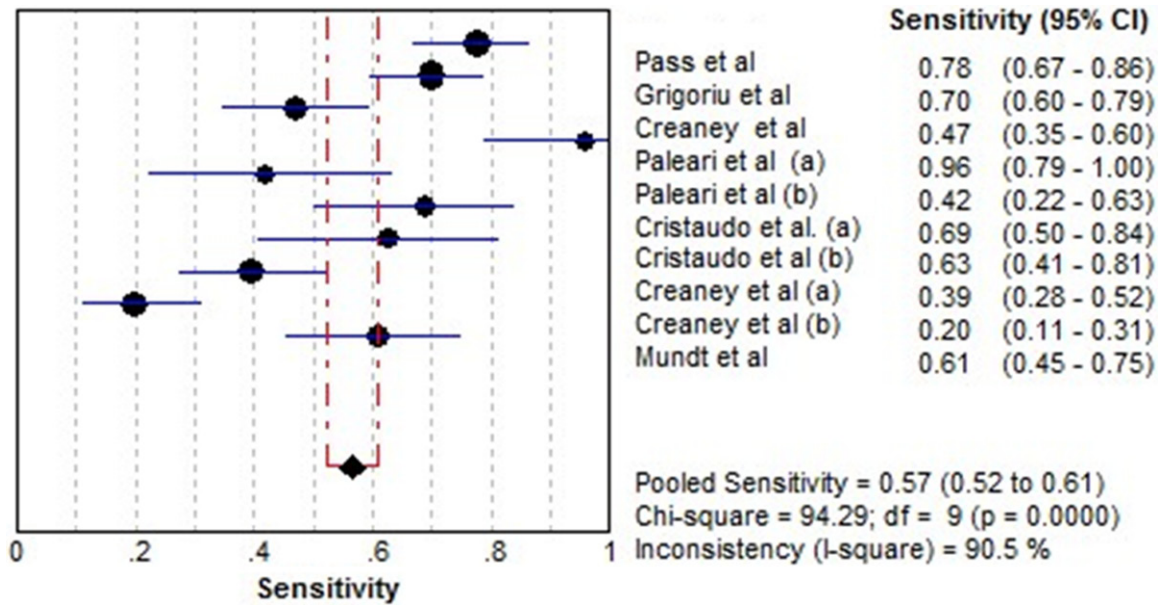


Figure 1. Forest plots of sensitivity for OPN assay for the diagnosis of MPM. The point estimates of sensitivity from each study are shown as solid circles. Error bars indicate 95% confidence intervals.

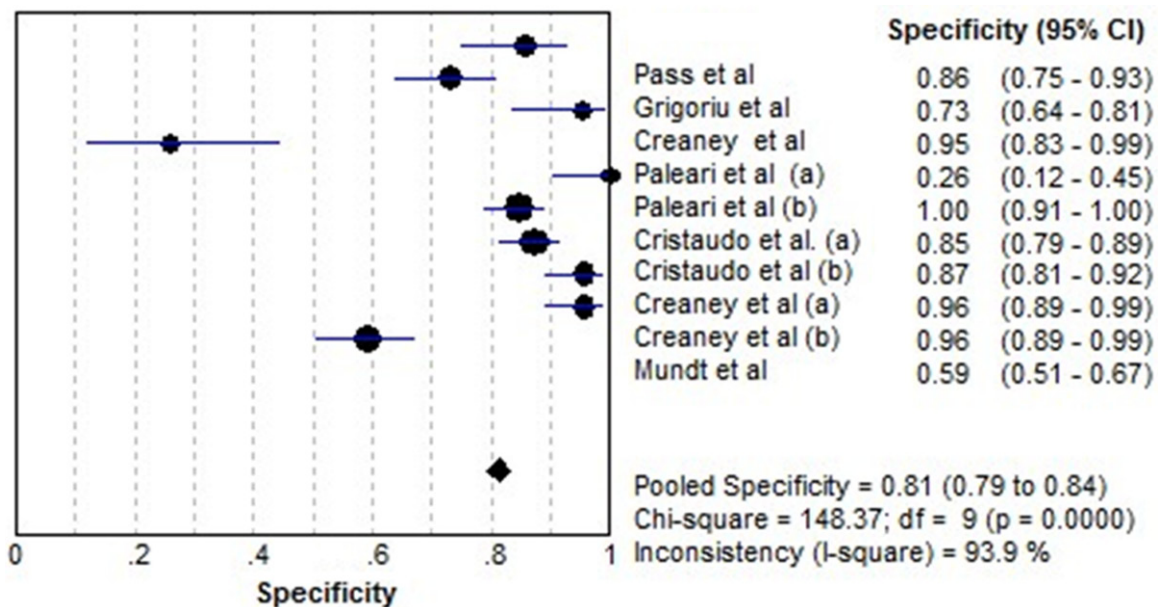


Figure 2. Forest plots of specificity for OPN assay for the diagnosis of MPM. The point estimates of specificity from each study are shown as solid circles. Error bars indicate 95% confidence intervals.

Publication bias

Deeks' funnel plot asymmetry test was used to evaluate the final set of studies for potential publication bias. The slope coefficient was associated with a *p* value of 0.22, suggesting symmetry in the data and a low likelihood of publication bias (**Figure 4**).

Discussion

The diagnosis of MPM is an important clinical challenge because the incidence of this high aggressive tumor is increasing, however, the limited biopsy material that lack definitive evidence of invasion and the lack of classic morphologic signs of malignancy with only subtle

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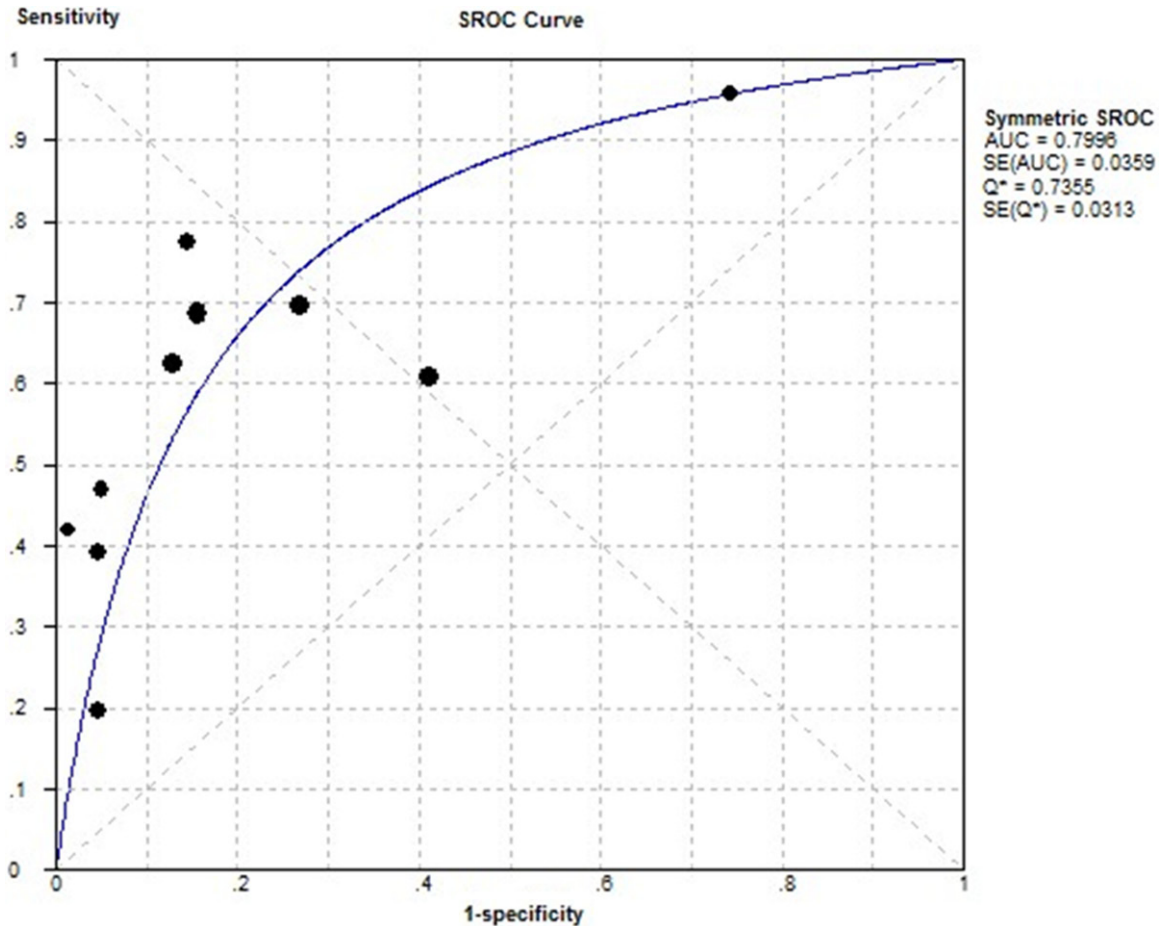


Figure 3. Summary receiver operating characteristic (SROC) curve of OPN assay for the diagnosis of MPM. The size of each solid circle represents the size of each study included in the present meta-analysis. The regression SROC curve indicates the overall diagnostic accuracy.

cytologic abnormalities make the definitive diagnosis of MPM difficult. To find a new and effective diagnostic marker for MPM will be of great importance for its treatment and prognosis [22]. The present meta-analysis investigated the overall diagnostic role of OPN assay in the diagnosis of MPM with a relative high specificity 0.81, 95%CI: 0.79-0.84), while the sensitivity was only 0.57 (95%CI: 0.52-0.61). Our data indicated that OPN assay might be somehow helpful in the confirmation of MPM, rather than to screen for MPM patients, but these assays maximize the specificity at the cost of sensitivity and have significant influence on clinical implications.

The SROC curve presents a global summary of test performance and indicates the trade-off between sensitivity and specificity [13, 23]. Our meta-analysis based on SROC curve showed the maximum joint sensitivity and specificity was 0.74, and the AUC was 0.85, indicating a

relative high level of overall accuracy. DOR, the ratio of the odds of OPN assay-positive test between patients with disorder and those without it, is another indicator of test accuracy which combines the data from sensitivity and specificity into a single number [24]. The value of a DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. In the present study, the DOR was 9.04 (95%CI: 5.28-15.48), indicating that OPN assay seemed to be useful in the diagnosis of MPM. Because the SROC curve and DOR are not easy to interpret and use in clinical practice, while likelihood ratios are considered more clinically meaningful, we also presented both PLR and NLR as our measures of diagnostic accuracy. A PLR value of 3.78 suggests that patients with MPM have about 4-fold higher risk of being OPN assay-positive compared with patients without MPM, it is helpful for the clinical practice. The NLR was found to be 0.53 in

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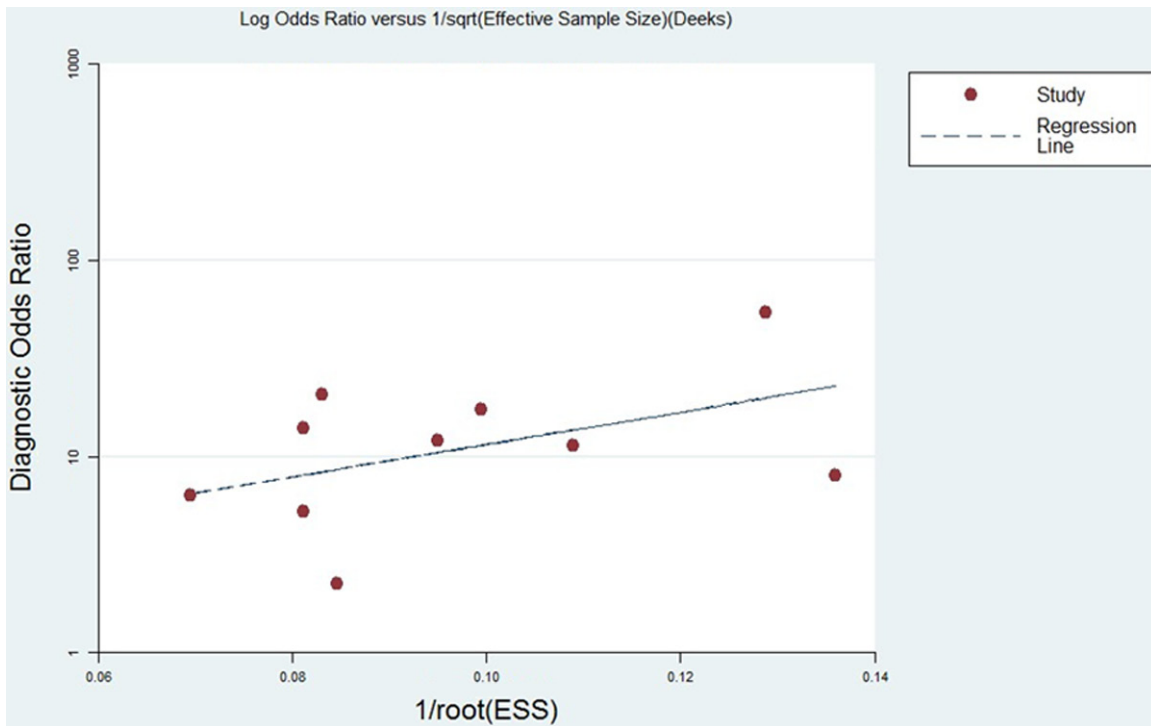


Figure 4. Linear regression test of funnel plot asymmetry. The statistically non-significant p value of 0.22 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias.

the present meta-analysis. It means if the OPN assay result was negative, the probability that this patient has MPM is 53%, which is not low enough to rule out MPM. In addition, our study also compared the diagnostic performance of different specimens, in this study, we can't make a conclusion that the serum, or plasma is a better matrix.

To combine OPN with other markers will be helpful to improve the diagnostic accuracy for MPM, for instance, the combination of OPN and soluble mesothelin-related peptides had a better performance in MM diagnosis compared with each single marker with both increased sensitivity and specificity [8], these findings were also supported by Creaney's study [17]. OPN also plays a prognostic role in MPM, patients with a high serum osteopontin (>350 ng/mL) had a significantly shorter survival (median, 5 months; 95%CI, 2-8 months) than patients with low serum osteopontin level (median, 15 months; 95%CI, 11-19 months) [16]. To perform OPN assay, MPM patients will benefit from both diagnostic and prognostic aspects. In addition, thoracoscopy is one of the diagnostic tools for MPM [25], while the invasive thoracoscopy may not be available in any

hospital of different medical level, so the meaning of OPN test is not only represents a helpful adjunct to conventional diagnostic markers in diagnosing MPM, but also guides the inclusion of patients who might benefit from further invasive procedures.

The present study suggests that OPN assay may be useful for diagnosing MPM, however, there are still several challenges exist. Firstly, although we made comprehensive search strategy, the screening, study selection, data extraction and quality assessment were done independently and reproducibly by two reviewers, there were only five publications included, the limited patients numbers may have influence on the outcomes. The second, the OPN test specimen is a problem, in the present meta-analysis, four studies used plasma, the rests used serum, which one is the best specimen for diagnosing MPM is unclear due to the limited studies. Further studies at a large scale and good study design may be needed to confirm the diagnostic role of OPN assay in MPM, and it should pay attention to the test specimen. Owing to the limited publications included, we did not use QUADAS scores to perform the meta-regression analysis to assess the effect

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of study quality on relative DOR of OPN assay in the diagnosis of MPM. And for the same reason, we could not explore whether or not study design such as blinded, cross-sectional, consecutive/random and prospective design affect the diagnostic accuracy, either.

To summarize, OPN plays a role in the diagnosis of MPM. Limited to the number of current available studies, during clinic practice, the results of OPN assay should be interpreted in parallel with clinical findings and the results of conventional tests.

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Disclosure of conflict of interest

None.

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