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Original Article

Diagnostic value of survivin for malignant pleural effusion: a clinical study and meta-analysis

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Abstract: Objective: To investigate the diagnostic accuracy of survivin for malignant pleural effusion (MPE). Methods: Pleural effusion samples were collected from 40 MPE patients and 45 non-MPE patients. Pleural levels of survivin were measured by ELISA. Literature search was performed in Pubmed and Embase to identify studies regarding the usefulness of survivin to diagnose MPE. Data were retrieved and the pooled sensitivity, specificity and other diagnostic indexes were calculated. The summary receiver operating characteristics (SROC) curve was used to determine the overall diagnostic accuracy. Results: The pleural levels of survivin were higher in MPE patients than non-MPE patients (844.17 ± 358.30 vs. 508.08 ± 169.58 pg/ml, $P < 0.05$), at a cut-off value of 683.2 pg/ml, the sensitivity and specificity were 57.50% and 88.89%, respectively. A total of six studies were included in present meta-analysis, the overall diagnostic estimates were: sensitivity 0.74 (95% CI: 0.59-0.85); specificity, 0.85 (95% CI: 0.79-0.89); positive likelihood ratio, 4.79 (95% CI: 3.48-6.61); negative likelihood ratio, 0.31 (95% CI: 0.19-0.50), and diagnostic odds ratio, 15.59 (95% CI: 7.69-31.61). The area under SROC curve was 0.86 (95% CI: 0.82-0.89). Conclusion: Our study confirms that the pleural survivin plays a role in the diagnosis of MPE. More studies at a large scale should be performed to validate our findings.

Keywords: Survivin, malignant pleural effusion, diagnosis, meta-analysis

Introduction

It is reported that approximately 1.5 million people develop a pleural effusion in the United States each year, and cancer-related malignant diseases is the leading cause of pleural effusion [1, 2]. Cancer-related pleural effusion, also defined as malignant pleural effusion (MPE), is a frequent problem faced by clinicians. To differentiate MPE from benign effusions is difficult, the sensitivity of conventional cytological test is just 60%, while only additional 7% of the cytology-negative MPE patients can be identified by closed pleural biopsy [3, 4]. Image-guided percutaneous pleural biopsy and thoracoscopic pleural biopsy can provide a relative high sensitivity, but they may not be widely used in facilities at all levels and well tolerated [4, 5]. Imaging techniques do not usually have enough sensitivity to differentiate MPE from benign pleural effusion. In addition, the current available biomarkers in pleural fluid do not currently provide an acceptable yield for MPE [5]. So it is imperative to find a novel diagnostic biomarker to facilitate the diagnostic accuracy [3-5].

Survivin is the well-known member of the inhibitor of apoptosis protein gene family and has been found to control mitotic progression and induce change in gene expression that is associated with tumor cell invasiveness [6]. Survivin is selectively up-regulated in many human tumors, where its overexpression correlates with poor clinical outcome [7]. Tissue expression of survivin has a critical role for diagnosis, prognosis and the prediction of response to therapy in patients with cancer [6, 7]. Although several primary studies have investigated the potential role of survivin in the diagnosis of MPE, there were limited data on diagnostic performance of survivin for MPE. Thus, we per-

Table 1. Clinical and demographic data of the study population

Age (years)	52±15
Sex (m/f)	58/27
Location	
Left	23
Right	38
Bilateral	24
Colour	
Yellow	59
Bloody	8
Yellow-Bloody	18
Diagnosis	
MPE	40
non-MPE	45
TPE	18
PPE	13
HF or Liver cirrhosis	10
Other	4

MPE, Malignant pleural effusion; TPE, Tuberculous pleural effusion; PPE, Parapneumonic pleural effusions; HF, Heart failure.

formed a clinical study to determine the discriminative power of survivin in proven cases of MPE and non-MPEs, in addition, we also carried out a meta-analysis to clarify the overall diagnostic performance of survivin for MPE based on current available studies.

Patients and methods

The study protocol was approved by our institutional review board for human studies of West China Hospital of Sichuan University (a 4300-bed comprehensive teaching hospital in Chengdu, China), and was conducted with the instruction of the guidelines of standards for reporting of diagnostic accuracy.

Study subjects

Between November 2012 and August 2013, a total of 85 patients with pleural effusions admitted for further investigation was included this prospective study. Written consents were obtained from all the patients. MPE was diagnosed if cancer cells were found on cytological examination or in a biopsy specimen [8]. In addition, 18 patients with tuberculous pleural effusion, 13 patients with parapneumonic pleural effusions, 10 patients with pleural effusion caused by heart failure or liver cirrhosis, and 4 other causes of transudative pleural effusion were also included as control group.

Measurement of survivin

All included subjects underwent a standard thoracocentesis procedure on the first 24 hours after admission. The pleural effusion samples were collected in 3.2% buffered sodium citrate and centrifuged at 2000 g for 15 minutes within 10 minutes of collection from each subject. Pleural effusion samples were snap frozen and stored at -80°C until analysis. Pleural levels of survivin were analyzed using an enzyme-linked immunosorbent assay (ELISA; Xitang Bio-Technology Co., Ltd., Shanghai, China). The clinical information of patients was blinded to the operators.

Statistical analysis

Patient demographics and disease characteristics were summarized using descriptive statistics. Data were expressed as the means ± SD. Difference between groups was analyzed by the Student's t-test, receiver operating curve (ROC) analysis was used to evaluate the threshold value of survivin in differentiating MPE from non-MPE. A cut-off point was determined as the value of the parameter that maximized the sum of specificity and sensitivity. Statistical analysis was carried out using SPSS 18.0 software (Chicago, IL, USA). A value of $P < 0.05$ was defined significant.

Meta-analysis

To find relevant studies, we performed a search of Pubmed, Embase, CNKI, Wanfang database, and Weipu database up to May, 2014, using the key words "pleural effusion", "malignant pleural effusions", "survivin", "sensitivity and specificity". A study was included in the present meta-analysis if it provided both sensitivity and specificity of the pleural survivin for the diagnosis of MPE. Two authors (PWT and YCS) independently screened the articles for inclusion. Disagreements between reviewers were resolved by consensus. Data were retrieved and the methodological quality of included articles were assessed independently by two authors and given a quality score by using the QUADAS (quality assessment for studies of diagnostic accuracy) [9]. The indexes of test

Table 2. Clinical and demographic data of the study population

	MPE (n = 40)	non-MPE (n = 45)	*P*
Glucose (mmol/l)	6.34 ± 2.77	5.91 ± 2.71	0.477
Protein (g/l)	36.64 ± 10.11	35.13 ± 12.49	0.546
LDH (U/l)	470.53 ± 643.31	312.38 ± 343.32	0.155
Survivin (pg/ml)	844.17 ± 358.30	508.08 ± 169.58	0.000

MPE, Malignant pleural effusion; LDH, Lactate dehydrogenase.

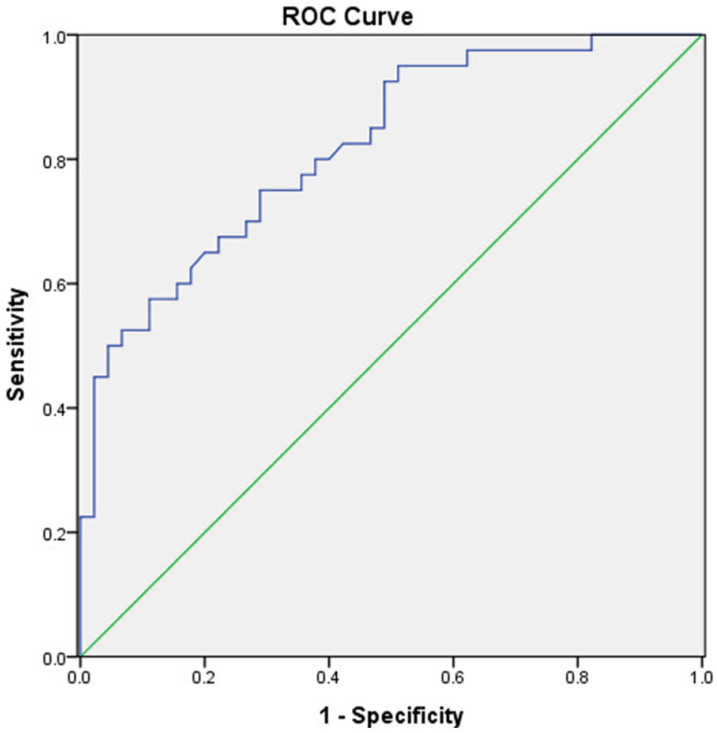

Figure 1. ROC analysis for survivin expression in pleural effusion. The plot was constructed by computing the sensitivity vs. (1-specificity) for the different possible cutoff points of the survivin ELISA assay.

accuracy, sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were pooled from each study using a bivariate model [10]. The diagnostic threshold identified for each study was used to plot a summary receiver operating characteristic (SROC) curve and the area under the curve (AUC) was calculated. Chi-square and Fisher's exact tests were used to detect statistically significant heterogeneity across studies. All analyses were performed using one statistical software program (Stata, version 11; Stata Corporation, College Station, TX, USA). All statistical tests were two-sided, and significance was set at $P < 0.05$.

Results

General characteristics of pleural effusions

A total of 85 patients were included for current study, the detailed demographic and clinical characteristics of the study subjects were summarized in **Table 1**, and biochemical characteristics in pleural effusion were illustrated in **Table 2**.

Diagnostic performance of survivin for MPE

The concentrations of pleural survivin in MPE were significantly higher than those in non-MPE (844.17 ± 358.30 *vs*. 508.08 ± 169.58 pg/ml, $P < 0.05$). To evaluate the diagnostic performance and find the best sensitivity and specificity of survivin levels for MPE, we calculated the ROC curve and AUC was calculated. The AUC was 0.820 (95% confidence internal: 0.733-907, $P < 0.05$) (**Figure 1**). With a cut-off value of 683.2 pg/ml, the sensitivity and specificity were 57.50% and 88.89%, respectively.

Meta-analysis

After systematically literature search and selection, we included 6 studies (including present study) examining the diagnostic accuracy of pleural survivin for patients with MPE [11-15]. There were 307 patients with MPE and 248 subjects with non-MPE. All included 6 studies had QUADAS scores ≥ 10, suggesting high quality of included studies. **Table 3** summarized the clinical characteristics of the patients in each study as well as the QUADAS scores for each publication.

The following pooled parameters were calculated over all 6 studies examining pleural survivin concentrations for diagnosing MPE: SEN, 0.74 (95% CI: 0.59-0.85); SPE, 0.85 (95% CI: 0.79-0.89) (**Figure 2**); PLR, 4.79 (95% CI: 3.48-6.61) (**Figure 2**); NLR, 0.31 (95% CI: 0.19-0.50); and DOR, 15.59 (95% CI: 7.69-31.61). The I^2 values for five performance indices were as fol-

Table 3. Clinical summary of included studies

Study	Year	Country	Sample size		Standard	Method	Cut-off value	TP	FP	FN	TN	QUADAS
			MPE	non-MPE								
Wu et al. [11]	2009	China	60	20	Histology/Cytology	ELISA	0.0062 ng/mg	51	5	9	15	11
Park et al. [12]	2012	Korea	67	68	Histology/Cytology	ELISA	0.0 pg/ml	31	10	36	58	10
Zhang et al. [13]	2012	China	60	60	Histology/Cytology	ELISA	60.24 ng/L	54	9	6	51	11
Görgün et al. [14]	2013	Turkey	51	27	Histology/Cytology	ELISA	7.5 pg/ml	37	6	14	21	10
Ma et al. [15]	2013	China	29	28	Histology/Cytology	ELISA	850 ng/L	23	3	6	25	10
Tian et al. [Current study]	2014	China	40	45	Histology/Cytology	ELISA	683.2 pg/ml	23	5	17	40	12

ELISA, Enzyme linked immunosorbent assay; TP, True positive; FP, False positive; FN, False negative; TN, True negative; QUADAS, Quality assessment for studies of diagnostic accuracy.

lows: SEN, 88.15%; SPE, 0.00%; PLR, 0.00%; NLR, 88.64%; and DOR, 99.86% (the *P* values of SEN, NLR, and DOR < 0.05), suggesting potential heterogeneity among the studies.

Figure 3 is the SROC curve, which shows a plot of the rate of true positives as a function of the rate of false positives for each study. Using the bivariate approach, which estimates not only the strength but also the shape of the correlation between SEN and SPE, we plotted the observed and predicted ellipses at a 95% CI. The AUC was 0.86 (95% CI: 0.82-0.89), indicating a medium discriminatory ability of pleural survivin. Deeks' funnel plot asymmetry test was used to evaluate likelihood of publication bias among included studies. The slope coefficient was associated with a *P* value of 0.71, suggesting symmetry in the data and low likelihood of such bias (**Figure 4**).

Discussion

The diagnosis of MPE remains a clinical challenge [16], growing studies suggest that survivin plays a role in diagnosing MPE, but with considerable varying results. Thus, we performed a validation study to assess the diagnostic performance of survivin for MPE. In addition, we also carried out a meta-analysis to summarize the overall diagnostic accuracy of survivin.

Our study found that the sensitivity and specificity of pleural survivin in the diagnosis of MPE were 57.50% and 88.89%, respectively. Our results revealed that the sensitivity of survivin is low, which limits the clinical utility of survivin as a screening biomarker for MPE. The specificity of survivin is 88.89%, it is relative high to confirm MPE. In addition to providing diagnostic information, measurement of pleural survivin can provide personalized information about patients with MPE. Görgün and colleagues found that pleural survivin levels can distinguish MPE patients who had poor prognosis from those who had good prognosis, elevated pleural levels of survivin were related to reduced overall survival in MPE patients, these findings were also supported by Wu's study [11, 14]. Park et al. also indicated a correlation between pleural survivin expression and a lack of response to chemotherapy in lung cancer patients, pleural survivin may provide additional information for the treatment of MPE patients [13]. So, survivin may be valuable not only for diagnosing MPE, but also for predicting chemosensitivity and prognosis, which will be helpful for improving the comprehensive management of patients with MPE.

Our meta-analysis suggests that survivin plays a role in the diagnosis of MPE with medium discriminative power. The SROC curve has been recommended to represent the performance of diagnostic tests, and it shows the trade-off between sensitivity and specificity [17]. Our SROC analysis showed an AUC of 0.86, suggesting a moderate overall accuracy. DOR, defined as the ratio of the odds of a true-positive to the odds of a false-positive, facilitates formal meta-analysis of studies on diagnostic test performance [18]. The value of a DOR ranges from 0 to infinity, with higher values indicating a better higher diagnostic accuracy. In our meta-analysis, the mean DOR was 15.59, indicating that survivin assay seemed to be helpful in the diagnosis of MPE. While in clinical practice, the SROC curve and the DOR are not easy to interpret, and the likelihood ratios are also considered clinically meaningful. Therefore, we also calculated the PLR and NLR of survivin assay to obtain a more comprehensive

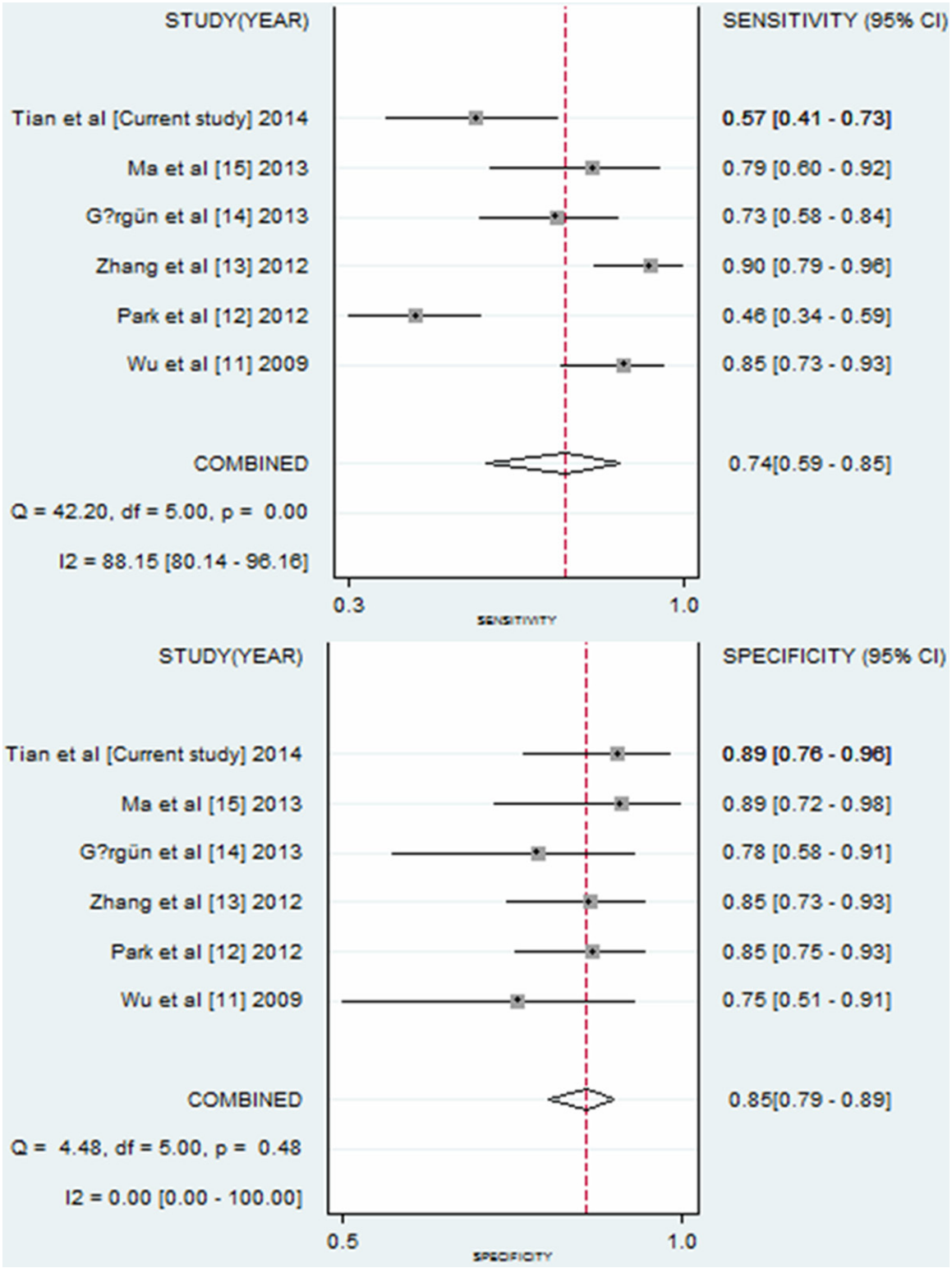

Figure 2. Forest plot of sensitivity and specificity of survivin for the diagnosis of MPE. The point estimates of sensitivity and specificity from each study are shown as solid squares. Error bars indicate 95% CIs.

picture of their diagnostic performance. The PLR value of 4.79 suggests that patients with MPE have an approximately five-fold higher chance of giving a positive survivin test result

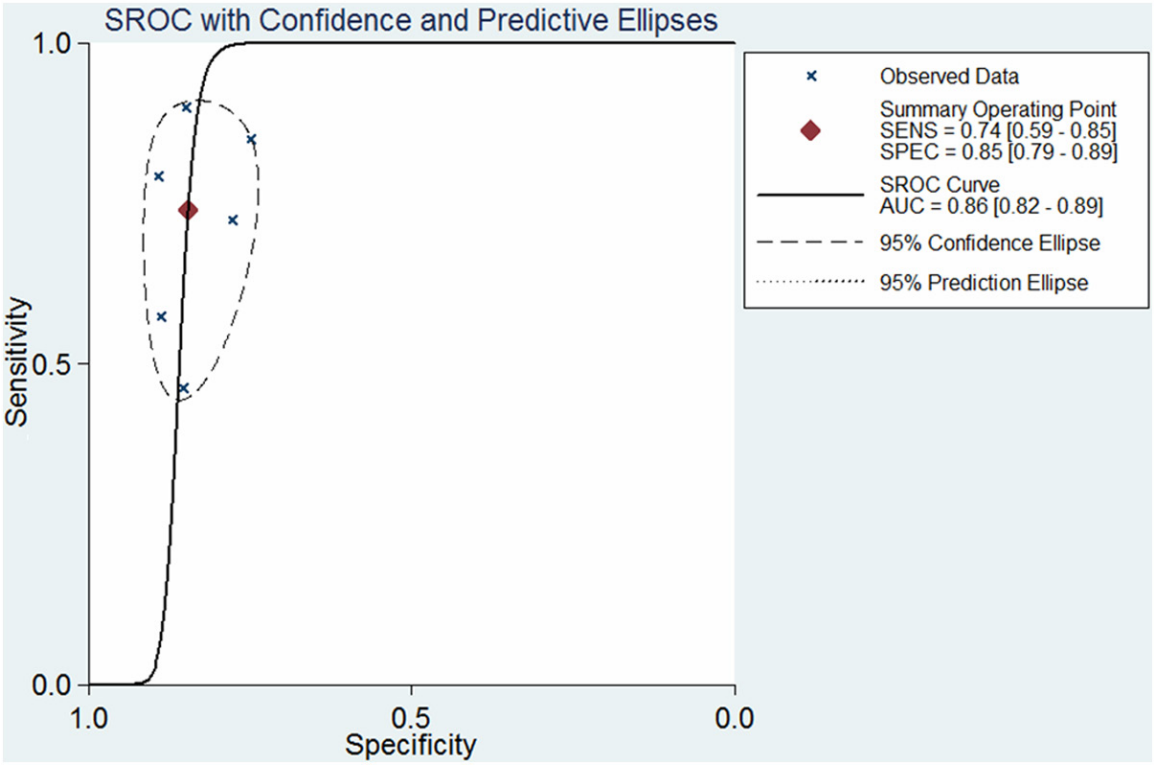

Figure 3. Summary receiver operating characteristic (SROC) curve of survivin for the diagnosis of MPE.

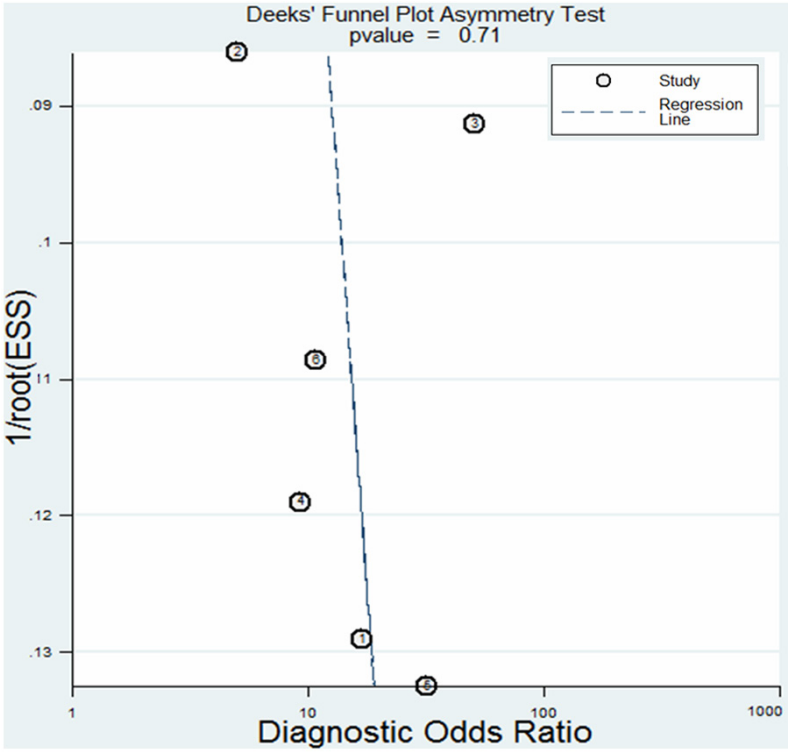

Figure 4. Linear regression test of funnel plot asymmetry. The statistically non-significant *P*-value of 0.71 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias.

than do patients without MPE, but it is still lower than 10, considered as the threshold for reliability. The pooled NLR was found to be 0.31, indicating that even a negative survivin test result is 31% likely to be a false-negative, which is not low enough to rule out MPE. Li et al. reported that survivin mRNA measurement achieves both high sensitivity (89.3%) and specificity (95.2%) in the diagnosis of MPE [19], which is better than survivin protein assay, further studies are needed to determine which one is a better matrix for MPE diagnosis. In addition, the combination of survivin and other classic tumor biomarker, such as Cyfra 21-1, will increase the diagnostic accuracy [13], we suggest

that the results of pleural survivin assays should be interpreted in parallel with the results of traditional biomarker tests and clinical information.

Our studies also have several limitations that should be addressed. First of all, only 85 patients were included in this study, and only six studies were met our inclusion criteria for meta-analysis, such sample size may be inadequate for drawing definitive conclusions about the ability of pleural survivin levels to discriminate between MPE and non-MPE. Secondly, we identified potential heterogeneity among included studies, due to the limited studies, we did not perform sub-group analysis to investigate possible covariates that may affect diagnostic accuracy. In addition, we only included studies published in English or Chinese, which may cause language bias. Anyway, more studies needed to investigate the diagnostic performance of pleural survivin for MPE and further identify its correlation with prognosis and treatment response.

In conclusion, our study and meta-analysis suggest that survivin plays a role in the diagnosis of MPE. More studies should be carried out to confirm our findings.

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Disclosure of conflict of interest

None.

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