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The diagnostic value of survivin in malignant pleural effusion: A meta-analysis

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ABSTRACT

Background: Survivin in pleural effusion is a promising marker for the diagnosis of malignant pleural effusion.
Methods: Based on the principles and methods of Cochrane systematic reviews, PubMed, EMBASE, Web of Knowledge (ISI), the Cochrane Library, and China National Knowledge Infrastructure (CNKI) databases were searched to identify studies that assessed the diagnostic value of survivin in pleural effusion for malignant pleural effusion. Stata 12 and Meta-disc 1.4 software were used to test the heterogeneity and to perform the meta-analysis.
Results: Our search returned 167 articles, of which ten fulfilled the inclusion criteria. These studies included a total of 614 patients with malignant pleural effusion and 430 patients with benign pleural effusion as controls. The summary assessments revealed that the pooled sensitivity was 0.86 (95% CI: 0.82–0.88) and the pooled specificity was 0.92 (95% CI: 0.89–0.94). The positive likelihood ratio was 8.76 (95% CI: 5.41–14.20), the negative likelihood ratio was 0.16 (95% CI: 0.13–0. 20) and the diagnostic odds ratio (DOR) was 59.72 (95% CI: 39.60–90.05). The area under the curve (AUC) for the pleural effusion survivin tests was 0.9485, and the *Q index estimate for these tests was 0.8885.
Conclusions: Survivin in pleural effusion has potential diagnostic value with advanced sensitivity and specificity and it can be used as adjunct tool for non-invasive diagnosis of malignant pleural effusion.

1. Introduction

The etiological diagnosis of pleural effusion remains a common problem in clinical practice. Malignancy is one of the main causes of pleural effusion; studies have shown that 42–77% of exudative effusions are secondary to malignancy [1].

The initial diagnostic approach for pleural effusion includes thoracocentesis and cytological, histological and biochemical examinations [2]. However, the sensitivity of these noninvasive techniques is only 40–70% [3]. The sensitivity of conventional cytology for the detection of malignant cells in pleural effusion is insufficient [4].

The diagnosis of malignant pleural effusion (MPE) is often challenging because differentiating MPE from benign effusion can be difficult using the currently available tools derived from thoracentesis; only approximately 50–70% of patients with MPE can be diagnosed by cytological examination of the pleural fluids [1]. Therefore, various tumor markers found in pleural effusions, including carcinoembryonic antigen (CEA), Cyfra 21-1, CA125, CA19-9, neuron-specific enolase, and squamous cell carcinoma antigen, have been investigated for their ability to differentiate malignant from benign pleural effusions [5–7]. However, the sensitivity of these tests is relatively low, and false-positive results have been described in almost all series. Thus, it is necessary to identify and evaluate more sensitive biological markers for MPE diagnosis [8]. The ideal marker would be office-based, rapid, and inexpensive and would have high sensitivity and specificity in the target population; this might reduce the burden and expense of frequent biopsies of the pleura.

Survivin has recently received a great deal of attention due to its prominent expression in many different types of human tumors. Given the sharp differential expression of survivin in MPE vs benign pleural effusion (BPE), the detection of survivin appears to be a suitable tool for MPE diagnosis. It is a structurally unique inhibitor of apoptosis protein (IAP) that is characterized by a highly conserved baculovirus IAP repeat (BIR) domain, which inhibits apoptosis and promotes cell proliferation [9]. Survivin is a 12-amino acid protein (16.5 kDa) that is located at chromosomal region 17q25. Survivin is an inhibitor of programmed cell death and mediates the suppression of apoptosis by

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inhibiting caspases 3 and 7, the terminal effectors in apoptotic protease cascades [10]. The survivin promoter is highly active in human tumor cells, but not in normal cells, and is up-regulated by hypoxia in tumors [11]. It is undetectable in normal differentiated tissues but is notably expressed in patients with lung cancer, breast cancer, bladder cancer, multiple myeloma, and lymphoma [12–14].

In experimental and clinical studies, survivin has been investigated extensively, and it appears to be one of the most frequently investigated and most promising early biomarkers of MPE. Survivin is currently attracting considerable interest as a potential cancer biomarker [15]. However, with accumulating evidence, conflicting observations raise concern about using the level of survivin in pleural effusions as a biomarker.

2. Materials and methods

2.1. Search strategy

A comprehensive computer literature search for abstracts was performed to identify articles regarding the diagnostic performance of pleural effusion survivin for the detection of malignant pleural effusion. We did a systematic review of original articles published on July 30, 2014, that analyzed the diagnostic role of pleural effusion survivin in patients with malignant pleural effusion. For this meta-analysis, a literature search of PubMed, Cochrane Library, Web of Knowledge (ISI), Medline, EMBASE, CBM, CMCC, VIP, and CNKI databases was performed independently by two reviewers using the main search terms survivin, sensitivity, specificity, diagnosis, and cancer. The existing systematic reviews, meta-analyses and bibliographies of the reports were also checked for potentially relevant additional studies. We referred to the Bayes Library of Diagnostic Studies and Reviews to determine our search strategy in regard to combining keywords and using free words. All of the search strategies were determined by repeated presearch. We used Google Scholar and other search engines to find relevant literature on the Internet and traced the references of reports included in our study. No restrictions were placed on the publication language.

2.2. Selection criteria

Articles were selected in two steps. First, articles were excluded after inclusion and exclusion criteria were applied to the titles and abstracts of the articles that fulfilled the search criteria. Then, we determined the final studies included in the meta-analysis after applying the same inclusion and exclusion criteria to the remaining content of the articles. To be enrolled in the present study, the retrieved studies had to fulfill the following inclusion criteria: 1) sensitivity and specificity were reported to provide sufficient information to construct a 2×2 contingency table; 2) survivin was measured in pleural effusion; 3) the study included a per patient analysis; and 4) the appropriate gold standard method confirmed the case group and control group (such as malignant cells in cytology of the pleural fluid, and/or histopathologic examination of the pleural tissue obtained by VATS or pleural blind biopsy). The exclusion criteria were as follows: nonhuman study; review articles; letters; meta-analysis; conferences; editorial comments; case reports; and articles that did not include raw data. When data or subsets of data were presented in more than one article, only the largest series was included in the analysis. A cohort of patients was not included more than once in the same analysis. Included studies met the quality criteria for studies of diagnosis of the Oxford Centre for Evidence-Based Medicine. Briefly, the studies had clearly identified different groups of patients (with and without disease, and positive and negative tests). All included studies had a true-negative group that was free of the disease, according to the definition used in the present study.

2.3. Extraction of data

One reviewer screened the titles and abstracts identified by the search strategy, and 2 reviewers then independently assessed the full tests for inclusion. The database was designed to ensure the most relevant data in regard to first author, year of publication, demographics of the patients, tumor characteristics, geographic location, period of recruitment, study design, adoption of the blind, method, cut-off value, reference standard and data for a 2×2 table. If further information was needed, the corresponding authors were contacted. The data extracted from the articles were used to determine the number of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) cases, as confirmed by cytology of malignant cells in the pleural fluid and/or histopathologic examination of the pleural tissue by VATS or pleural blind biopsy. If not directly presented, the statistical parameters were calculated from the sensitivity and specificity or predictive values and the results of the reference test. Disagreements were resolved by consensus or arbitration by another reviewer.

2.4. Quality evaluation

Two reviewers independently evaluated the quality of the included studies using the version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, which has 14 items. Every included study was assessed as “yes”, “no”, or “unclear” from the variations (items 1 and 2), the bias (items 3–7, 10–12, and 14) and the report quality (items 8, 9, and 13), and the causes of bias and variations were identified.

2.5. Threshold effect analysis

Different thresholds to define positive test results may have been used in the included studies due to a lack of standardization. A differential threshold effect may be the reason for the detectable sensitivities and specificities of test accuracy studies. Summary ROC curves were constructed to observe the variation between studies and to quantitatively summarize the results. A threshold effect was suspected with the ROC space graph if the points aligned in a typical shoulder-like pattern. Computation of the Spearman correlation coefficient was also assessed for a threshold effect. A high correlation between sensitivity and specificity indicated such a threshold effect.

2.6. Homogeneity test

Heterogeneity was explored using the chi-square test and likelihood ratio (LR) I^2. LR I^2 measures the percentage of the total variation across studies that is due to heterogeneity rather than chance. LR I^2 is evaluated as follows: $I^2 = (Q - df)/Q \times 100\%$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom. An $I^2 > 50\%$ represents substantial heterogeneity. For the LR χ^2 test, we judged that heterogeneity was significant for $P < 0.05$. When there was evidence of heterogeneity, the data were analyzed using a random effects meta-analysis to obtain a summary estimate for the test sensitivity with 95% CIs. Studies in which positive results were confirmed were conducted using a pooled specificity with 95% CIs.

2.7. Subgroup analysis

Subgroup analysis was used to investigate the difference in the performance of pleural effusion survivin in diagnosing malignant pleural effusion in patients with lung cancers and all types of cancers. The diagnostic accuracy of malignant pleural effusion survivin generated by lung cancers and all types of cancers were compared based on the specificity and sensitivity of the subgroup.

To investigate the differences in the performance of a given method for different subgroups, we performed a subgroup analysis. The pooled