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Original Article

Diagnostic accuracy of ascitic cholesterol concentration for malignant ascites: a meta-analysis

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Abstract: Many studies have investigated whether ascitic cholesterol can aid in diagnosis of malignant related ascites (MRA), and the results have varied considerably. To gain a more reliable answer to this question, we meta-analyzed the literature on using ascitic cholesterol as diagnostic tests to help identify MRA. Literature databases were systematically searched for studies examining accuracy of ascitic cholesterol for diagnosing MRA. Data on sensitivity, specificity, positive/negative likelihood ratio (PLR/NLR), and diagnostic odds ratio (DOR) were pooled using random effects models. Summary receiver operating characteristic (SROC) curves and area under the curve (AUC) were used to summarize overall test performance. At last, our meta-analysis included 8 studies involving 743 subjects. Summary estimates for ascitic cholesterol in the diagnosis of MRA were as follows: sensitivity, 0.82 (95% CI 0.78 to 0.86); specificity, 0.90 (95% CI 0.87 to 0.93); PLR, 9.24 (95% CI 4.58 to 18.66); NLR, 0.16 (95% CI 0.08 to 0.32); and DOR, 66.96 (95% CI 18.83 to 238.11). The AUC was 0.96. The ascitic cholesterol level is helpful for the diagnosis of MRA. Nevertheless, the results of ascitic cholesterol assays should be interpreted in parallel with the results of traditional tests and clinical information.

Keywords: Cholesterol, malignant ascites, diagnosis, meta-analysis

Introduction

Ascites is the pathological accumulation of fluid within abdominal cavity, which can present a challenging diagnostic problem [1]. Malignant ascites accounts for about 10% of all cases of ascites and is usually caused by ovarian, endometrial, lung, breast, colorectal, pancreatic, hepatobiliary, and primary peritoneal carcinomas [2, 3]. The differentiation between malignancy-related ascites (MRA) and nonmalignant ascites (NMA) is important for further diagnostic and therapeutic procedures [4, 5].

Cytodiagnostic investigation of ascitic fluid is characterized by a high specificity but a low sensitivity in detecting malignant disease because only a few neoplastic cells are present in the fluid [6, 7], or processing of specimens is suboptimal with lysis of tumour cells. To increase diagnostic sensitivity, cytologic evaluation has been coupled with the analysis in serum and ascitic fluid for total protein, various enzymes, fibronectin, tumor antigens, and lipids [2, 8, 9].

Recently papers about the detection of ascitic cholesterol have been published a lot and they have shown a relatively high diagnostic efficiency in differential diagnosis of MRA [2, 3]. However, conflicting results have been reported and the exact role of ascitic cholesterol concentration remains unclear. Therefore, we performed the present meta-analysis to establish the overall accuracy of ascitic cholesterol concentration for the diagnosis of MRA.

Materials and methods

Protocol and registration

Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) recommendations [10]. However, the systematic review and meta-analysis was not registered.

Search strategy and study selection

To find relevant studies, we performed searches of Pubmed and Embase databases up to June 10, 2015, using the key words 'ascites or peritoneal fluid or peritoneal effusion', cholesterol, and 'sensitivity or specificity or accuracy'. All searches were limited to English language publications concerning human studies. A manual search of the references of the retrieved articles was conducted subsequently. Inclusion criteria for this study were as follows: (1) they were original research articles published in English; (2) they examined the ability of ascitic cholesterol level for the diagnosis of MRA in humans; and (3) they reported sufficient data to allow calculation of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) rates. Reviews, letters to the editors, conference proceedings, studies published only as abstracts and articles published in a book or in languages other than English were excluded. We avoided duplication of data by examining the names of all authors and medical centers involved for each article. Authors that published multiple reports on the same sample were included once. To avoid selection bias, we also excluded studies involving fewer than 20 patients. Two authors (H. Zhu and Y-C Shen) independently screened the articles for inclusion. Disagreements were resolved by consulting a third author (K. Deng).

Data extraction and quality assessment

The final articles included were assessed independently by two reviewers (H. Zhu and Y-C Shen). Disagreements were resolved by consulting a third author (X. Liu). Data retrieved from the studies included author, publication year, country, test method, cut-off value, sensitivity, specificity and methodological quality. The quality of each study was scored independently by two reviewers (H. Zhu and Y-C Shen) with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool which features 14 questions and demonstrated to be an efficient tool for the quality assessment of diagnostic accuracy studies. Each question should be answered with "yes", "no", or "unclear". An answer of "yes" will get one score, while the "no" or "unclear" will gain a score of zero with a total score of 14 [11].

Statistical analyses

The standard methods recommended for the diagnostic accuracy of meta-analyses were used in the present study. First, we calculated pooled estimates of sensitivity and specificity as the main outcome measures, and we constructed summary receiver operating characteristic (SROC) curves. Based on the pooled estimates of sensitivity and specificity, we calculated positive likelihood ratios (PLR) and negative likelihood ratios (NLR). Sensitivity and specificity estimates were paired to generate diagnostic odds ratios (DOR), which we used as an overall index of diagnostic accuracy. DOR relates the odds of positive test results in those with the condition with the odds of positive test results in those without the condition. The diagnostic threshold identified for each study was used to plot a summary receiver operating characteristic (SROC) curve. The average sensitivity, specificity and other related indices of the studies were calculated using a random-effects model. Spearman's rank correlation was performed as a test for threshold effect. The χ^2 and Fisher's exact tests were used to detect statistically significant heterogeneity across the studies. If there were enough studies, subgroup analyses would be performed to explore potential between-study heterogeneity. All analyses were performed using two statistical software programs (Stata, version 12; Stata Corporation, College Station, TX, USA and Meta-DiSc 1.4 for Windows; XI Cochrane Colloquium, Barcelona, Spain). All statistical tests were two-sided and $P<0.05$ was considered to indicate a statistically significant result.

Results

Quality reports and study characteristics

After independent review, eight studies with 743 subjects on the use of ascitic cholesterol in patients with ascites were considered eligible for inclusion in the present meta-analysis [2, 3, 8, 9, 12-15]. The major reasons for excluding other studies were as follows: not published in English, not human subjects, reviews, without full text, conference abstract, letter, repeat data, not relevant to study question, not include sensitivity and specificity of the assay. The

Table 1. Clinical summary of included studies

Study	Year	Country	Sample size		Source	Stand	Method	Cut-off	TP	FP	FN	TN	QUADAS
			MRA	NMA									
Jüngst D	1986	Germany	51	41	ascites	histological and clinical criterion	enzymatically	48 mg/dl	46	2	5	39	10
Mortensen PB	1988	Denmark	32	20	ascites	histological and clinical criterion	enzymatic colorimetric method	1.2 mmol/L	28	4	4	16	9
Prieto M	1988	Spain	15	54	ascites	histological	SMA-C Technicon Autoanalyzer	46 mg/dl	15	2	0	52	9
Colli A	1989	Italy	26	40	ascites	histological and clinical criterion	NA	50 mg/dl	14	8	12	32	10
Gerbes AL	1991	Germany	34	37	ascites	histological and clinical criterion	enzymatically	45 mg/dl	31	2	3	35	9
Gulyás M	2001	Sweden	57	73	ascites	histological and clinical criterion	enzymatically	1.21 mmol/l	53	3	4	70	11
Rana SV	2005	India	25	25	ascites	histological and clinical criterion	NA	70 mg/dl	22	0	3	25	11
Zhang H	2011	China	96	117	ascites	histological and clinical criterion	CHOD-PAP	1.04 mmol/l	68	19	28	98	13

MRA, malignancy-related ascites; NMA, nonmalignant ascites; TP, true positive; FP, false positive; FN, false negative; TN, true negative; QUADAS, quality assessment for studies of diagnostic accuracy; NA, not applicabl.

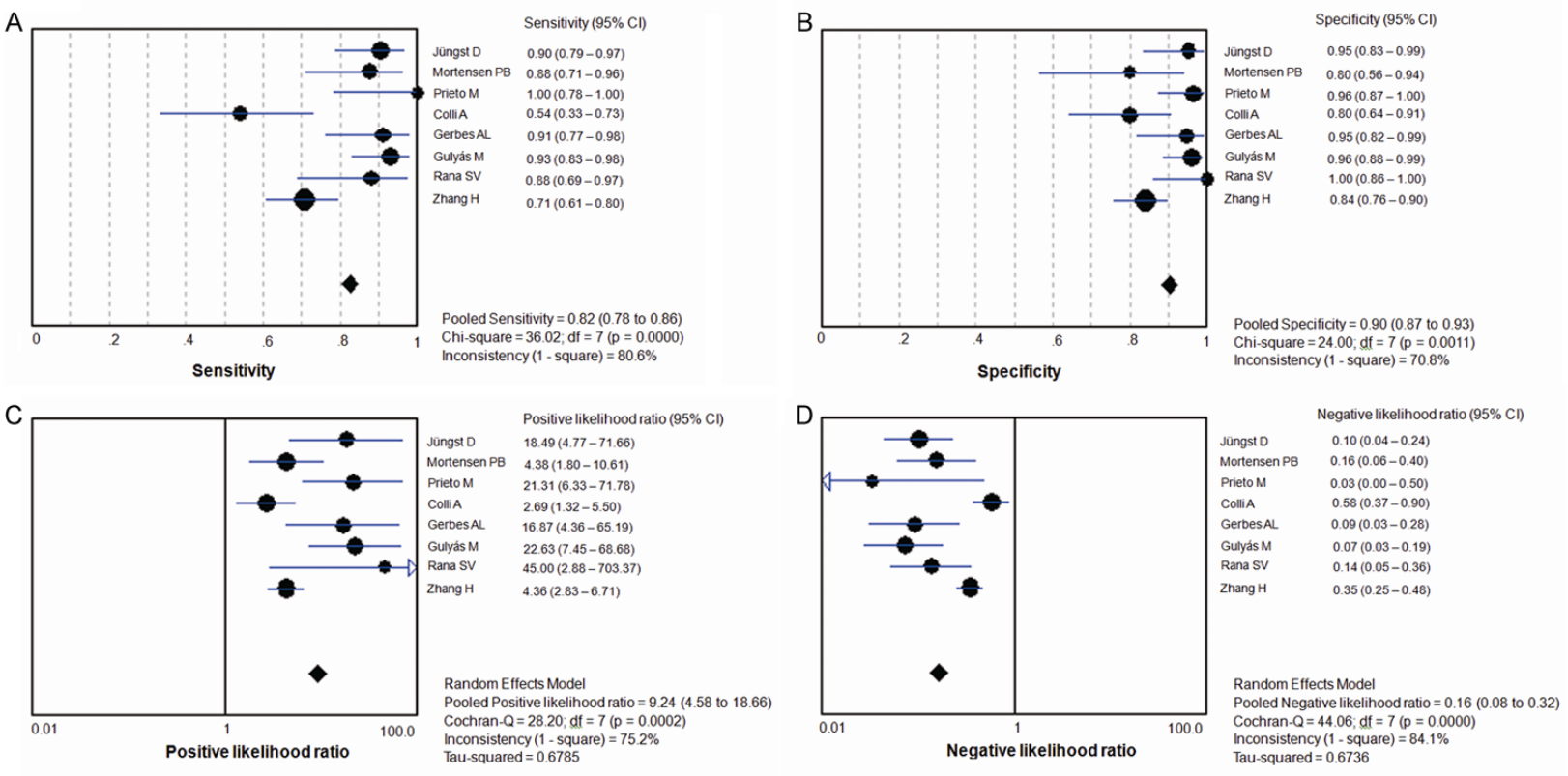

Figure 1. Forest plots of pooled sensitivity (A), specificity (B), positive likelihood ratio (C), negative likelihood ratio (D) of ascitic cholesterol for the diagnosis of MRA. The point estimates of sensitivity from each study are shown as solid circles. Error bars indicate 95% confidence intervals.

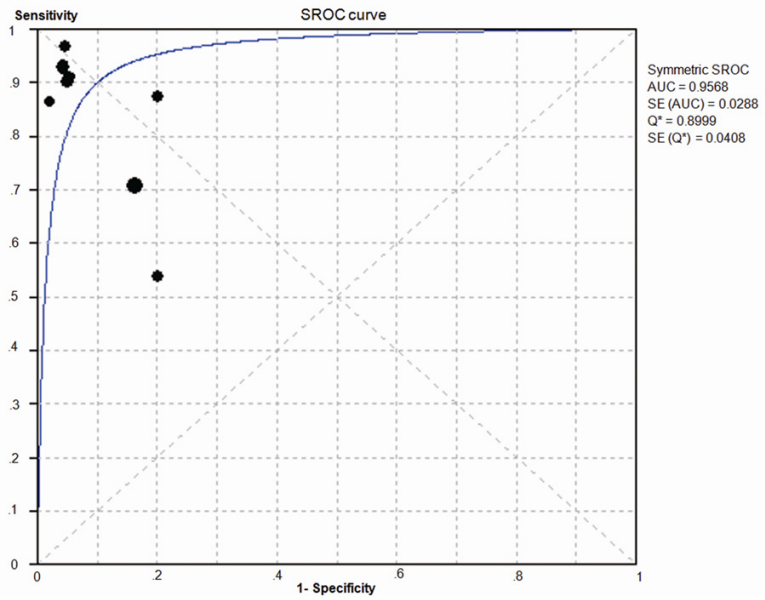

Figure 2. Summary receiver operating characteristic (SROC) curve of cholesterol for the diagnosis of MRA. The size of each solid circle represents the size of each study included in the present meta-analysis. The regression SROC curve indicates the overall diagnostic accuracy.

diagnostic characteristics of these studies and their QUADAS scores are outlined in **Table 1**.

Diagnostic accuracy

Forest plots of the sensitivity and specificity of these 8 studies concerning ascitic cholesterol assays in the diagnosis of MRA were shown in **Figure 1**. The average sample size of the studies included was 93 (range, 50-213). The sensitivity and specificity ranged from 0.54 to 1 [mean, 0.82; 95% confidence interval (CI), 0.78-0.86] and from 0.80 to 1.00 (mean, 0.90; 95% CI, 0.87-0.93), respectively. The PLR was 9.24 (95% CI, 4.58-18.66), the NLR was 0.16 (95% CI, 0.08-0.32) and the DOR was 66.96 (95% CI, 18.83-238.11). χ^2 values of sensitivity, specificity, PLR, NLR and DOR were 36.02, 24.00, 28.20, 44.06 and 40.58, respectively, with all *P*-values <0.01, suggesting a marked heterogeneity among the studies.

The SROC curve was shown in **Figure 2** plotting the true-positive against the false-positive rates of the individual studies. As a global measure of test efficacy we used the Q-value, which is 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 and corresponds to the highest common value of sensitivity and specificity for the test. This point does not indicate the only or even the best combination of sensitivity and specificity for a particular clinical setting, but represents an overall measure of the discriminatory power of a test. In the present meta-analysis, the maximum joint sensitivity and specificity of our study was 0.90 (the Q-value). The area under the curve (AUC) was 0.96, indicating that the level of overall accuracy was high.

Publication bias

Deeks' funnel plot asymmetry test was used to evaluate potential publication bias. The statistically non-significant value (P = 0.35) for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias (**Figure 3**).

Discussion

Our meta-analysis evaluates the diagnostic role of ascitic cholesterol in MRA and our data demonstrate that determining ascitic cholesterol results in a high sensitivity of 0.82 (95% CI, 0.78-0.86) and a specificity of 0.90 (95% CI, 0.87-0.93). These findings suggest that ascitic cholesterol may represent a new milestone in MRA diagnosis, though they probably cannot stand on their own and should be used in conjunction with more traditional tests.

The SROC curve presents a global summary of test performance and shows the trade-off between sensitivity and specificity [16]. The

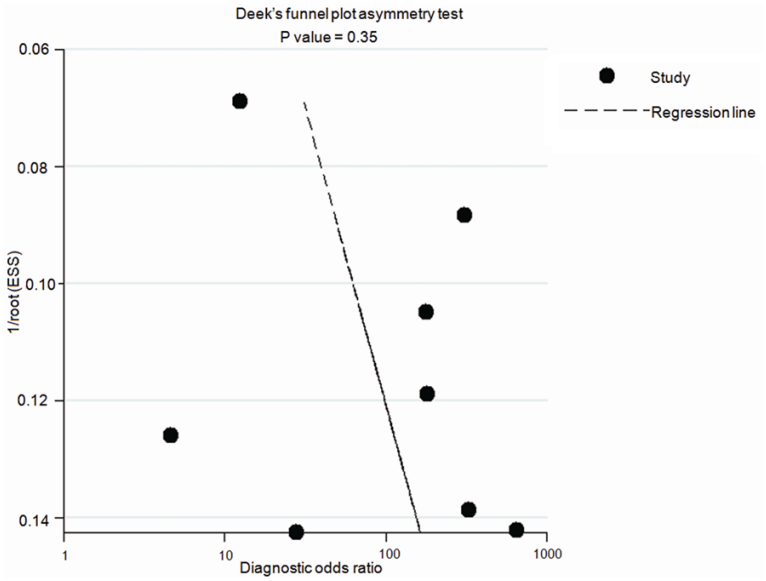

Figure 3. Linear regression test of funnel plot asymmetry. The statistically non-significant value (P = 0.35) for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias.

results of the analysis based on the SROC curve revealed that the maximum joint sensitivity and specificity was 0.90, while the AUC was 0.96, suggesting that the level of overall accuracy was high. DOR, the ratio of the odds of positive test results in patients with the disease relative to those in patients without the disease, is a single indicator of test accuracy that combines the data from sensitivity and specificity into a single number. The value of a DOR ranges from 0 to infinity, with higher values indicating a superior discriminatory test performance (higher accuracy). A DOR of 1.0 indicates that a test does not discriminate between patients with the disorder and those without it. In our meta-analysis, the mean DOR was 66.96, suggesting that ascitic cholesterol seemed to be useful in the diagnosis of MRA. Since the SROC curve and the DOR are not easy to interpret and use in clinical practice, while likelihood ratios are considered to be more clinically meaningful, we also presented PLR and NLR as measures of diagnostic accuracy. A PLR value of 9.24 suggests that patients with MRA have a more than 9-fold higher chance of being ascitic cholesterol assay-positive compared with patients without MRA. On the other hand, NLR was found to be 0.16 in the present meta-analysis. This means that, if the ascitic cholesterol assay result was negative, the probability that the patient has MRA is 16%, which is not low enough to rule out MRA.

Although the present study was performed with a comprehensive search strategy and data extraction, our meta-analysis has several limitations. First, we excluded conference abstracts and letters to the editor. This may lead to publication bias, which may also be introduced by inflation of diagnostic accuracy estimates, since studies that report positive findings are more likely to be accepted for publication. In addition, due to the limited numbers of the studies included, we were unable to explore whether study design, including blinded, cross-sectional, consecutive/random and prospective designs, affects the diagnostic accuracy. Our results may also be biased by our omission of unpublished studies, studies published in other languages and studies published in journals not indexed in the databases we searched.

The results of the present meta-analysis suggest that ascitic cholesterol may, to a certain extent, play a role in the diagnosis of MRA. Besides, our meta-analysis suggests an association between elevated ascitic cholesterol and the MRA, which implies that cholesterol contributes to MRA pathogenesis. It is not immediately clear how this happens, so future research should examine this question in order to provide a biological basis for the observed association. Our meta-analysis also points out the need for investigating the effect of cut-off value on the diagnostic accuracy of ascitic cholesterol levels. The values in our meta-analysis were remarkablely different. Further work should aim to identify the cut-off value that provides optimal diagnostic accuracy.

In summary, ascitic cholesterol determination plays a role in the diagnosis of MRA, while the results of cholesterol assays should be interpreted in parallel with clinical findings and the results of conventional tests.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

MRA, malignant related ascites; NMA, nonmalignant ascites; TP, true-positive; FP, false-positive; FN, false negative; TN, true negative; QUADAS, quality assessment of diagnostic accuracy studies; SEN, sensitivity; SPE, specificity; SROC, summary receiver operating characteristic; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve.

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