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Diagnostic Accuracy of Serum CA19-9 in Patients with Cholangiocarcinoma: A Systematic Review and Meta-Analysis

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Background: Cholangiocarcinoma (CCA) is a relatively rare cancer worldwide; however, its incidence is extremely high in Asia. Numerous studies reported that serum carbohydrate antigen 19-9 (CA19-9) plays a role in the diagnosis of CCA patients. However, published data are inconclusive. The aim of this meta-analysis was to provide a systematic review of the diagnostic performance of CA19-9 for CCA.





Material/Methods: We searched the public databases including PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI), and WANFANG databases for articles evaluating the diagnostic accuracy of serum CA19-9 to predict CCA. The diagnostic sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and summary receiver operating characteristic curve (SROC) were pooled by Meta-DiSc 1.4 software.

Results: A total of 31 articles met the inclusion criteria, including 1,264 patients and 2,039 controls. The pooled SEN, SPE, PLR, NLR, and DOR were 0.72 (95% CI: 0.70–0.75), 0.84 (95% CI: 0.82–0.85), 4.93 (95% CI, 3.67–6.64), 0.35 (95%CI, 0.30–0.41), and 15.10 (95% CI, 10.70–21.32), respectively. The area under SROC curve was 0.8300. The subgroup analyses based on different control type, geographical location, and sample size revealed that the diagnostic accuracy of CA19-9 tends to be same in different control type, but showed low sensitivity in European patients and small size group.

Conclusions: Serum CA19-9 is a useful non-invasive biomarker for CCA detection and may become a clinically useful tool to identify high-risk patients.

MeSH Keywords: CA-19-9 Antigen • Cholangiocarcinoma • Diagnosis • Review

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Background

Cholangiocarcinoma (CCA), tumor that arises from the epithelial cells of the bile duct, is a relatively rare cancer worldwide; however, its incidence is extremely high in Asia [1]. Over the past three decades, the incidence of CCA appears to be increasing, and accounts for approximately 3% of all gastrointestinal carcinomas in Western countries [2]. The percentage of patients who survive 5 years after diagnosis has not increased during this time period, remaining at 10% [3]. CCA is notoriously difficult to diagnose owing to its nonspecific symptoms, the low sensitivity and specificity of most diagnostic modalities, and the lack of absolute diagnostic criteria. Therefore, timely diagnosis of CCA is sometimes a challenging task for clinicians.

MRI and CT with endoscopic ultrasound and PET provide useful diagnostic information in certain patients. However, tumor biomarkers provide significant help in the diagnosis and are increasingly attractive because of their noninvasive features and relative inexpensiveness. To date, the most studied and the most used tumor markers in clinical practice are carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) [4]. Data suggests that the estimated sensitivity of CA 19-9 in predicting CCA in the context of primary sclerosing cholangitis is 38–89%, and a specificity is 50–98% [5]. CA19-9 level can be normal in patients with localized diseases, and high CA19-9 levels can also occur in benign bile duct diseases, including cholangitis, calculus of bile duct, and non-malignant jaundice [6,7]. Therefore, there is insufficient evidence to confirm the diagnostic accuracy of CA19-9 in CCA.

To address this issue, we conducted a meta-analysis of all eligible studies to evaluate the role of CA19-9 in CCA diagnostic accuracy, and to find if CA19-9 could be a potential marker for detecting CCA, anticipating providing an evidence base for medicine.

Material and Methods

Search strategy and inclusion criteria

Comprehensive databases have been used to identify the relevant studies published up to February, 2015. Databases include PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI), and WANFANG databases. The following search terms were employed: “cholangiocarcinoma”, “cholangiocellular”, “gastrointestinal carcinoma”; “carbohydrate antigen 19-9”, CA19-9; “blood”, “serum”, “circulating”; “diagnosis”; and “sensitivity and specificity” were used individually and in various pairwise combinations. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications.

All eligible studies satisfying the following criteria were firstly included in our analysis: (1) CA19-9 was assessed in CCA diagnostic studies; (2) Patients were referred to confirmed CCA; (3) sensitivity (SEN) and specificity (SPE) of CA19-9 were reported to provide sufficient information to construct two×two contingency tables, or sufficiently detailed data were presented to derive these numbers. Exclusion criteria were as follows: (1) incomplete data to construct 2×2 contingency tables; (2) duplicate studies; and (3) reviews, letters and comments.

Data extraction and Quality assessment

Two reviewers (Liang and Zhong) reviewed and extracted the data from each eligible study independently. The following data were collected for each eligible study: Author’s name, publication year, country, number of cases and controls, controls source, test method, sensitivity and specificity data, cut-off value. We assessed the methodological quality of the eligible studies for risk of bias and applicability using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria. Any disagreement was resolved by consensus.

Statistical analyses

Data were analyzed using STATA 12.0 software (Stata Corporation, College Station, TX) and Meta-Disc 1.4 software (XI Cochrane Colloquium, Barcelona, Spain). We extracted the numbers of all subjects with true positive (TP), true negative (TN), false positive (FP), and false negative (FN) from each included study, and the pooled SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curve (SROC) were analyzed using the bivariate meta-analysis model [8]. An examination of the potential sources of heterogeneity is indispensable for any meta-analysis before pooling the data from the included studies into summary assessments. We used a Spearman correlation analysis to quantify the heterogeneity due to the threshold effect among the included studies. Moreover, the Cochran-Q test and the inconsistency index (I^2) test were used to assess the non-threshold effect. When the result of the Q-test and I^2 statistics suggested heterogeneity ($P \leq 0.05$ and $I^2 > 50\%$), a random-effects model (DerSimonian-Laird method) was used; otherwise, a fixed-effects model (Mantel-Haenszel method) was adopted. The Deeks funnel plots was applied to assess the potential publication bias among studies [9], and $P < 0.05$ was considered to be representative of a significant statistical publication bias.

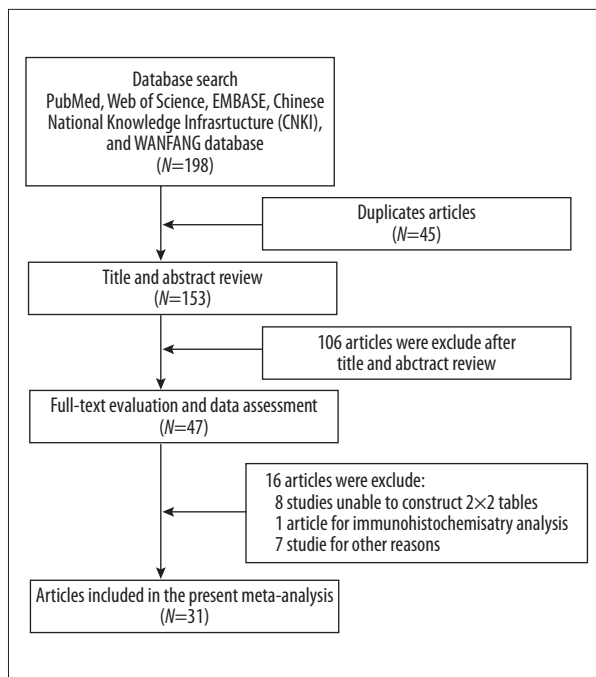


Figure 1. Flow chart of study selection process.

Results

Literature search

Flow chart for study selection was shown in Figure 1. In this study, we found 31 studies eligible for meta-analysis and the clinical characteristics were shown in Table 1 [10–40]. The 31 eligible studies included 1,264 patients of confirmed CCA and 2,039 controls. Of 31 studies, 19 studies were conducted in Asian countries [10,11,14–22,24–26,31–33,40], 7 studies in American countries [23,30,29,34–36,39], and 5 studies in European countries [12,13,27,37,38]. The characteristics of the control groups varied among the 31 articles. Eight studies used PSC patients as a control group [23,29,30,34,36–39], and the other studies used a mix of healthy volunteers and patients with other diseases [10–22,24–28,31–33,35,40]. Among the 31 studies, 20 studies were small-size sample (<100), and 11 studies were large-size sample (≥100). All studies were published from 1991 to 2015, and the sample sizes ranged from 22 to 320 subjects.

Quality assessment of the included studies

The risk of bias and applicability of the studies were evaluated based on QUADAS-2 summarized in Figures 2 and 3. A considerable proportion of studies (14/31, 45.2%) were considered to be at high risk of bias in the patient selection due to the case-control study design or inexplicit report. The index test domain in 13 studies (41.9%) was labeled as high risk of bias because the diagnostic threshold was not pre-specified. Concerning the flow and timing domain, four studies (12.9%) were considered

at high risk of bias because the authors did not disclose whether all of the participants received the same reference standard.

Quantitative data synthesis

Figure 4 showed the forest plot of diagnostic SEN and SPE of CA19-9 in all 31 included studies. The overall diagnostic SEN and SPE of CA19-9 were 0.72 (95% CI: 0.70–0.75) and 0.84 (95% CI: 0.82–0.85), respectively. SEN of individual studies ranged widely from 33% to 100%, while SPE of individual studies ranged from 31% to 100%. In addition, the pooled PLR, NLR, and DOR were 4.93 (95% CI, 3.67–6.64), 0.35 (95% CI, 0.30–0.41), and 15.10 (95% CI, 10.70–21.32), respectively. The SROC curve presents a global summary of test performance, and shows the tradeoff between SEN and SPE. In this meta-analysis, the area under the SROC curve was 0.8298, indicating a moderate and perfect level of overall accuracy, as shown in Figure 5.

Heterogeneity assessment and subgroup analysis

All five performances showed high I^2 values: SEN, 58.2%; SPE, 87.8%; PLR, 84.6%; NLR, 58.9%; and DOR, 61.8% (all $P < 0.01$). This suggests substantial heterogeneity among the included studies. When heterogeneity of these 31 studies was tested, the Spearman correlation coefficient was 0.216 ($P = 0.236$), which showed there must be factors other than threshold effect that results in the significant heterogeneity. Therefore, we performed subgroup analysis to investigate the possible sources of this heterogeneity according to geographical location, control group types, and sample size.

Subgroup analysis according to control group type showed that the type of control group (PSC group or Mixed group) had no noticeable effect on pooled SEN (0.73 [95% CI: 0.70–0.76] vs. 0.72 [95% CI: 0.70–0.75]), SPE (0.83 [95% CI: 0.81–0.85] vs. 0.83 [95% CI: 0.81–0.85]), PLR (4.69 [95% CI: 3.25–6.79] vs. 4.74 [95% CI: 3.33–6.76]), NLR (0.34 [95% CI: 0.29–0.40] vs. 0.35 [95% CI: 0.30–0.41]), DOR (14.21 [95% CI: 9.64–20.95] vs. 14.30 [95% CI: 9.90–20.66]), and AUC (0.8259 vs. 0.8271), as shown in Table 2. Subgroups analysis according to geographical location clearly showed a high degree of variability in SEN estimates, whereas SPE in all subgroups were similar. The SEN in European subgroup is lower (0.62, 95% CI: 0.54–0.69) than Asian subgroup (0.74, 95% CI: 0.71–0.77) and American group (0.71, 95% CI: 0.62–0.79). In addition, we conducted subgroup analyses stratified by the sample size. For sample size <100, the pooled SEN, SPE, PLR, NLR, DOR, and AUC were 0.69 (95% CI: 0.65–0.73), 0.79 (95% CI: 0.76–0.82), 4.33 (95% CI: 2.88–6.53), 0.40 (95% CI: 0.33–0.49), 12.34 (95% CI: 7.48–20.33), and 0.8207, respectively. The sample ≥100 improved the diagnostic power, with an increase in SEN of 0.75 (95% CI: 0.71–0.78), SPE of 0.84 (95% CI: 0.82–0.86), and DOR of 18.10 (95% CI: 11.00–29.78).

Table 1. The characteristics of 31 eligible studies.

Author	Year	Country	Case/controls	Control type	Test method	Cut-off values	SEN/SPE
Li Y	2015	China	30/30	HCC patients	CLIA	125.07 U/mL	76.67%/80.00
Wang S	2015	China	15/15	Normal controls	NA	28.915 ng/mL	66.7%/100%
Lumachi F	2014	Italy	24/25	Benign liver disease	CLIA	37 U/mL	74.1%/84.8%
Voigtländer T	2014	Germany	49/48	PSC, BDS	NA	130 U/mL	53%/82%
Kraiklang R	2014	Thailand	40/26	HCC, chronic biliary-liver disease	NA	100 U/mL	44.4%/100%
Ma H	2012	China	54/42	Healthy control	CLIA	27 U/mL	81.48%/31.35%
Leelawat K	2011	Thailand	50/50	Benign biliary tract disease	CLIA	100 U/mL	72%/86%
Jiang H	2011	China	68/115	BDS	CLIA	35 kU/L	73.53%/86.79%
Leelawat K	2010	Thailand	59/128	Benign biliary tract disease	CLIA	100 U/mL	68%/87%
Li Y	2009	China	115/205	Benign disease, blood donors	EIA	37 U/mL	68.4%/75.0%
Qin L	2009	China	35/50	Benign biliary tract disease	CLIA	39 U/mL	80%/860%
Liu L	2008	China	56/86	Benign hepatobiliary diseases, normal controls	EIA	NA	85.7%/100%
Chen J	2008	China	148/98	Benign polyp	CLIA	37 U/mL	82.43%/78.0%
Charatcharoenwitthaya P	2008	USA	23/207	PSC	CLIA	20 U/mL	78%/67%
Uenishi T	2007	Japan	71/90	Nonmalignant liver disease	CLIA	39 U/mL	62.0%/92.2%
Sun H	2007	China	35/31	Benign biliary tract disease	RIA	30 U/mL	80.00%/61.29%
Leelawat K	2006	Thailand	33/51	Benign biliary tract disease, volunteer	CLIA	100 U/mL	60.6%/80.49%
John AR	2006	UK	68/38	Benign liver tumors, benign bile duct disease	CLIA	35 kU/L	67.5%/86.8%
Qin X	2005	China	51/42	Benign bile disease		37 kU/L	86%/86%
Levy C	2005	USA	14/194	PSC	NA	129 U/mL	78.6%/98.5%
Furmanczyk PS	2005	USA	4/18	PSC	RIA	186 IU/mL	100%/94%
Tangkijvanich P	2004	Thailand	45/10	Benign biliary disease	EIA	100 U/mL	64.4%/100%
Qin X	2004	China	35/92	Benign biliary disease	RIA	37 kU/L	77.14%/84.78%
Wang Z	2003	China	34/21	Benign polyp	RIA	37 U/mL	80.15%/92%
Siqueira E	2002	USA	12/43	PSC	RIA	180 U/mL	75.0%/97.3%
Patel AH	2000	USA	36/41	Nonmalignant liver disease	RIA	100 U/mL	53%/76%
Chalasani N	2000	USA	13/41	PSC	NA	100 U/mL	75%/80%
Björnsson E	1999	Sweden	9/63	PSC	NA	200 ng/mL	38%/81%
Ramage JK	1995	England	15/59	PSC	RIA	200 U/mL	60.0%/86.3%
Nichols JC	1993	USA	9/28	PSC	RIA	100 U/mL	89%/86%
Pungpak S	1991	Thailand	14/52	Normal control	RIA	43.1 U/mL	64.3%/98.1%

PSC – primary sclerosing cholangitis; BDS – bile duct stone; HCC – hepatocellular carcinoma; CLIA – chemiluminescent immunoassay; EIA – sandwichenzyme-linked immunosorbent assay, RIA – radioimmunoassay; SEN – sensitivity; SPE – specificity.

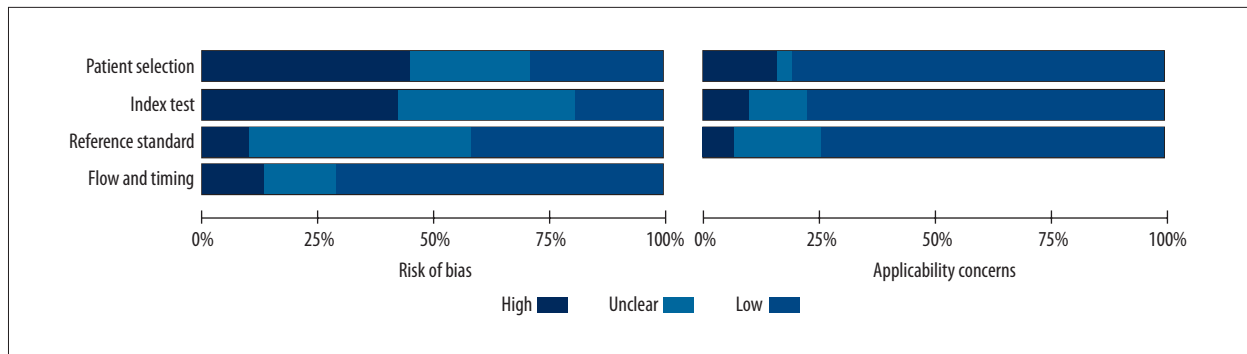


Figure 2. Quality assessment of all included studies according to QUADAS-2 criteria.

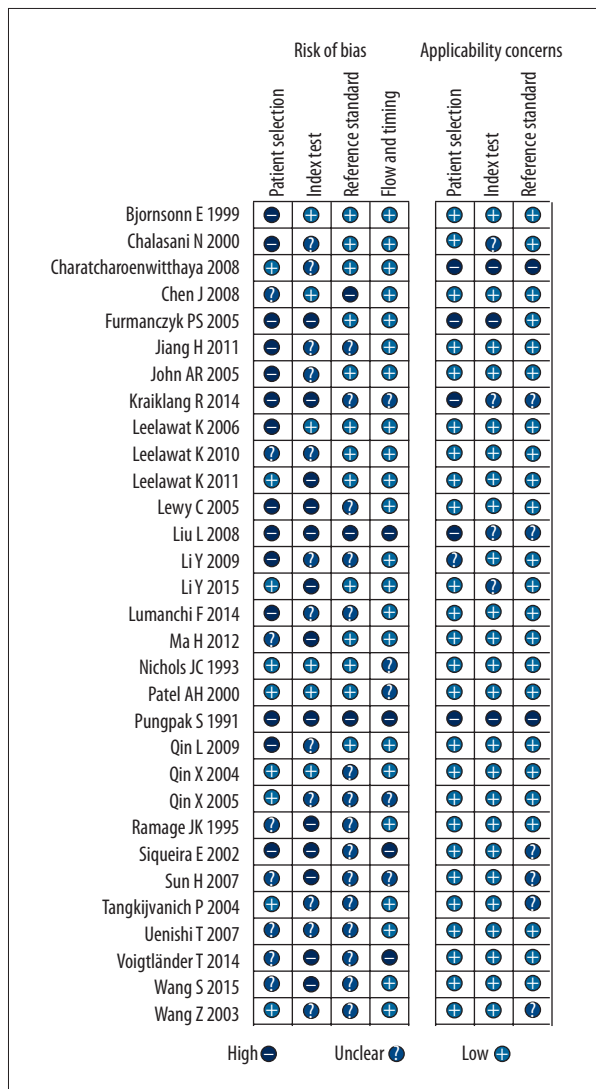


Figure 3. Risk of bias and applicability concerns summary.

Publication bias

We tested potential publication bias using Deeks funnel plots. The funnel plots did not reveal any evidence of obvious

asymmetry, which can be seen in Figure 6. The Deeks test also showed a statistically non-significant value ($P=0.380$), indicating that there was no potential publication bias.

Discussion

CCA is regularly diagnosed at advanced stages due to the lack of early symptoms or reliable tumor biomarkers. Despite significant advances in molecular biology and diagnostic techniques, it remains one of the most frustrating diseases for gastroenterologists and surgeons. Reliable marker for diagnosis of CCA is crucial for treatment and prognosis. CA19-9, a member of the Lewis antigen family, has been studied intensively. Many studies evaluated the diagnostic role of CA 19-9 levels in patients with CCA, but the results from those studies were inconsistent. To derive a more precise estimate of the diagnostic significance of serum CA 19-9 in patients with CCA, we performed a meta-analysis of published studies. To the best of our knowledge, the present study is the first meta-analysis on the diagnostic role of serum CA 19-9 in patients with CCA, and the findings can provide valuable information for clinicians.

Thirty-one studies with a total of 3,303 subjects were finally included into the meta-analysis. Our data yields moderate diagnostic performances of CA19-9, in which the overall pooled sensitivity was 0.72 (0.70–0.75) and specificity was 0.84 (0.82–0.85). Moreover, the DOR is a single indicator of test accuracy that combines the sensitivity and specificity data into a single number. A DOR of 1.0 indicates inability to discriminate CCA patients from controls without it [41]. In the present meta-analysis, we find that the DOR values for CA19-9 was 15.10 (95% CI, 10.70–21.32), indicating that CA19-9 could be helpful in the diagnosis of CCA. SROC is usually used to summarize overall test performance, and AUC is calculated to evaluate accuracy of the selected marker [42]. The AUROC value of 0.8300 indicates that CA19-9 could be a useful biomarker for CCA diagnosis. Overall, although the sensitivity is not as high as expected, CA19-9 has a good specificity in the diagnosis of CCA. Of note, 10% of individuals lack the Lewis antigen and

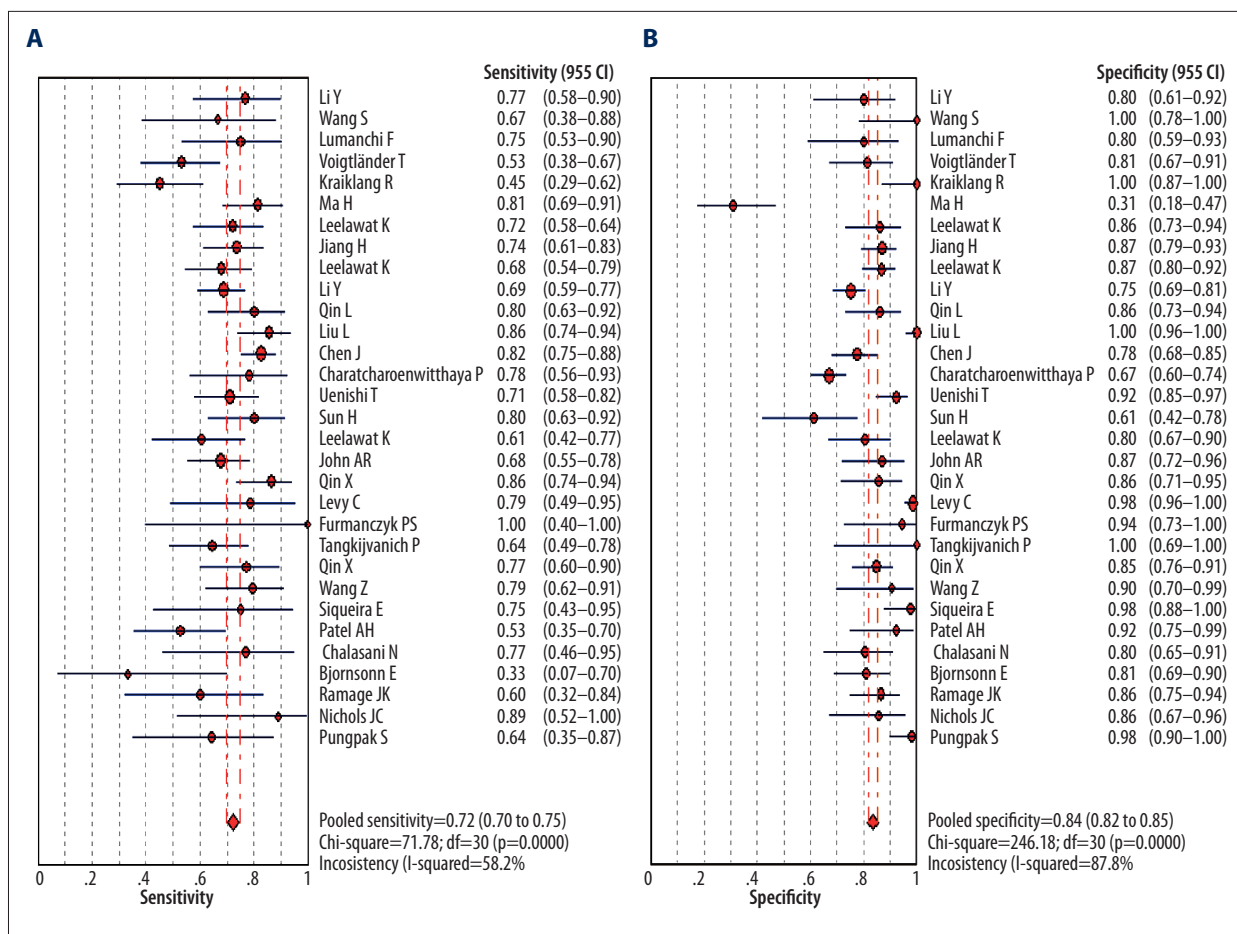


Figure 4. Sensitivity and specificity of CA19-9 in diagnosis of CCA assessed by Forest plots.

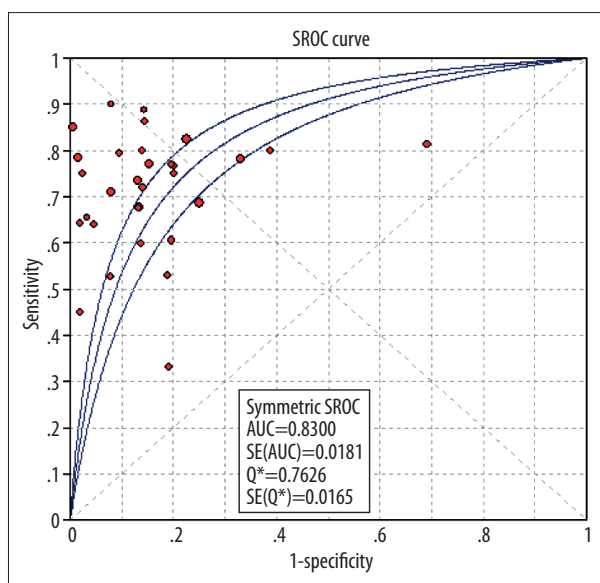


Figure 5. The summary receiver operating characteristic (SROC) curves of CA19-9 in diagnosis of CCA.

do not produce CA 19-9, and occasionally tumor cells lose the ability to express a tumor marker [43].

Most diagnostic evaluation show considerable heterogeneity between the included studies due to different factors. Therefore, we performed subgroup analyses according to geographical location, control type, and sample size for further description of the results. Our data suggested that CA199 had a relatively lower sensitivity of 62% in European group than in Asian group (74%) and American groups (71%), while the specificity was similar for three groups. This might be explained by different living backgrounds and different genetic factors between the three races. Another important reason may be that there is different range of cut-off values for CA199 levels and different assay methods in the included studies. Moreover, the small-size group (<100) achieved low sensitivity and specificity than large-size group (≥100). Thus, well-designed studies with a large sample size that examine multiple ethnicities are required. In addition, some epidemiological data suggested that many studies involving different controls tend to show different sensitivity and specificity, and differ with those recruiting patients with clinically suspected disease, consecutively

Table 2. Summary of subgroup analysis of the included studies by different study characteristics.

Variables	Number of studies	SEN (95%CI)	SPE (95%CI)	PLR (95%CI)	NLR (95%CI)	DOR (95%CI)	AUC
Overall	31	0.72 (0.70–0.75)	0.84 (0.82–0.85)	5.00 (3.68–6.78)	0.35 (0.30–0.41)	15.29 (10.72–21.80)	0.8300
Control type							
PSC	8	0.73 (0.70–0.76)	0.83 (0.81–0.85)	4.69 (3.25–6.79)	0.34 (0.29–0.40)	14.21 (9.64–20.95)	0.8259
Mixed	21	0.72 (0.70–0.75)	0.83 (0.81–0.85)	4.74 (3.33–6.76)	0.35 (0.30–0.41)	14.30 (9.90–20.66)	0.8271
Geographical location							
Asian	19	0.74 (0.71–0.77)	0.83 (0.81–0.85)	4.95 (3.28–7.46)	0.33 (0.28–0.39)	15.86 (10.34–24.32)	0.8346
American	7	0.71 (0.62–0.79)	0.84 (0.81–0.87)	8.47 (3.31–21.69)	0.31 (0.20–0.49)	32.74 (10.81–99.15)	0.8703
European	5	0.62 (0.54–0.69)	0.83 (0.78–0.88)	3.47 (2.43–4.94)	0.50 (0.36–0.69)	7.28 (3.95–13.44)	0.8947
Sample size							
≥100	11	0.75 (0.71–0.78)	0.84 (0.82–0.86)	5.43 (3.65–8.06)	0.31 (0.26–0.37)	18.10 (11.00–29.78)	0.8189
<100	20	0.69 (0.65–0.73)	0.79 (0.76–0.82)	4.33 (2.88–6.53)	0.40 (0.33–0.49)	12.34 (7.48–20.33)	0.8207

SEN – sensitivity; SPE – specificity; PLR – positive likelihood ratio; NLR – negative likelihood ratio; DOR – diagnostic odds ratio; AUC – area under curve; CI – confidence interval; PSC – primary sclerosing cholangitis.

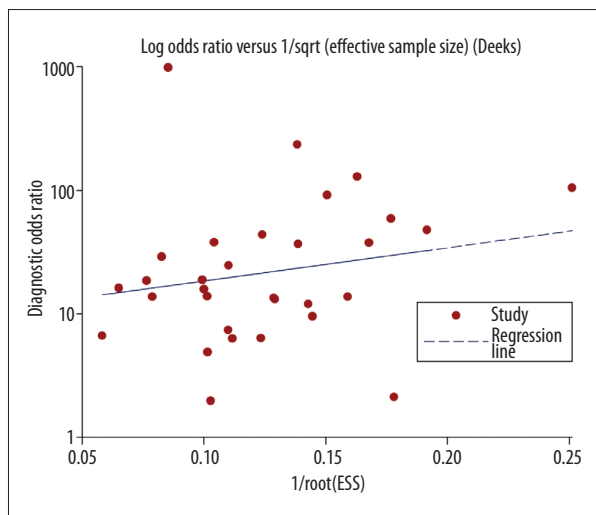


Figure 6. The funnel plot assessment of potential publication bias.

and prospectively in a representative clinical setting [44]. Therefore, the distinct type of negative control may also be a main source of heterogeneity. PSC is one of the strongest risk factors for CCA with a lifetime risk of 5–15%, and annual incidence of CCA in PSC is 0.5–1% [45,46]. We found that PSC control group displayed similar diagnostic performance with

mixed control group; however, the conclusion was still consistent in the overall comparisons. This possible explanation could be the limited number of PSC patients included and different grade PSC-associated CCA studied. In addition, the subgroup analyses results showed that the above-mentioned factors do not significantly affect heterogeneity, suggesting that the influencing factors are complex. Therefore, more multi-center samples and empirical validations are still needed for a consensus on robust and accurate conclusion.

There are some limitations that need to be taken into account when interpreting the results of this study. First, the number of studies included in our meta-analysis, particularly the subgroup analysis according to control type, was limited, potentially limiting the comprehensive evaluation of diagnostic performance of CA19-9 in CCA and influencing the statistical power of results. Second, our analysis was not adjusted for confounding variables such as age, gender, life style, etc, due to incomplete information. Third, the relatively high heterogeneity presented in the 31 included studies is also the limitation of this study. Finally, only the published studies were collected and evaluated, and the unpublished studies with negative results were not included.

Conclusions

The present meta-analysis suggested that serum CA19-9 is a reliable biomarker with a moderate sensitivity and high specificity for detecting CCA. Besides, our subgroup analysis showed diagnostic performance of CA19-9 was no significant difference in different control types, but showed low sensitivity in

European patients and small size group. Large-scale studies should be carried out to further validate the clinical application of CA19-9 as an effective tumor marker of CCA.

Conflicts of interest

The authors declare that they have no competing interests.

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