

Utility of serum CA19-9 in diagnosis of cholangiocarcinoma: In comparison with CEA

Xing-Lei Qin, Zuo-Ren Wang, Jing-Sen Shi, Min Lu, Lin Wang, Quan-Ru He

Xing-Lei Qin, Zuo-Ren Wang, Jing-Sen Shi, Lin Wang,
Department of Hepatobiliary Surgery, First Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Min Lu, Quan-Ru He, Luoyang Central Hospital, Luoyang 471009, Henan Province, China

Correspondence to: Dr. Xing-Lei Qin, M.D., Department of Hepatobiliary Surgery, First Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China. qinxinglei@yahoo.com.cn
Telephone: +86-29-5274739 **Fax:** +86-29-5269313

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Abstract

AIM: The diagnosis of cholangiocarcinoma is often difficult, making management approaches problematic. A reliable serum marker for cholangiocarcinoma would be a useful diagnostic test. The aims of our study were to evaluate the usefulness of a serum CA19-9 determination in the diagnosis of cholangiocarcinoma.

METHODS: We prospectively measured serum CA19-9 and CEA concentrations in patients with cholangiocarcinoma ($n=35$), benign biliary diseases ($n=92$), and healthy individuals ($n=15$). Serum CA19-9 and CEA concentrations were measured by an immunoradiometric assay without knowledge of the clinical diagnosis.

RESULTS: The sensitivity of a CA19-9 value $>37 \text{ KU} \cdot \text{L}^{-1}$ and a CEA value $>22 \mu\text{g} \cdot \text{L}^{-1}$ in diagnosing cholangiocarcinoma were 77.14% and 68.57%, respectively. When compared with the benign biliary diseases group, the true negative rates of serum CA19-9 and CEA were 84.78% and 81.52%, respectively. The false positive rates of serum CA19-9 and CEA were 15.22% and 18.48%, whereas the accuracy of serum CA19-9 and CEA were 82.68% and 77.95%, respectively. Serum CA19-9 and CEA concentrations were significantly elevated ($P<0.001$ and $P<0.05$) in patients with cholangiocarcinoma ($290.31 \pm 5.34 \text{ KU} \cdot \text{L}^{-1}$ and $36.46 \pm 18.03 \mu\text{g} \cdot \text{L}^{-1}$) compared with patients with benign biliary diseases ($13.38 \pm 2.59 \text{ KU} \cdot \text{L}^{-1}$ and $13.84 \pm 3.85 \mu\text{g} \cdot \text{L}^{-1}$) and healthy individuals ($12.78 \pm 3.69 \text{ KU} \cdot \text{L}^{-1}$ and $11.48 \pm 3.37 \mu\text{g} \cdot \text{L}^{-1}$). In 15 patients undergoing curative resection of cholangiocarcinoma, the mean serum CA19-9 concentration was decreased from a preoperative level of $286.41 \pm 4.36 \text{ KU} \cdot \text{L}^{-1}$ to a postoperative level of $62.01 \pm 17.43 \text{ KU} \cdot \text{L}^{-1}$ ($P<0.001$), and the mean serum CEA concentration from $39.41 \pm 24.35 \mu\text{g} \cdot \text{L}^{-1}$ to $28.69 \pm 11.03 \mu\text{g} \cdot \text{L}^{-1}$ ($P<0.05$). In patients with cholangiocarcinoma, however, no correlation was found between serum CEA and CA19-9 concentrations ($r=0.036$).

CONCLUSION: These data suggest that the serum CA19-9 determination is a useful addition to the available tests for the differential diagnosis of cholangiocarcinoma. Serum CA19-9 is an effective tumor marker in diagnosing cholangiocarcinoma, deciding whether the tumor has been radically resected and monitoring effect of treatment.

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INTRODUCTION

Cholangiocarcinoma is a malignant tumor arising from bile duct epithelium. Unlike most human cancers, a pathological diagnosis of cholangiocarcinoma is often extremely difficult because of its location, size, and desmoplastic characteristics^[1-3]. Percutaneous fine needle aspiration is frequently not possible because many of these tumors are located in the liver hilum amid large vascular structures^[4,5]. Furthermore, tumor masses are often not even identifiable by CT, ultrasound, or magnetic resonance imaging^[6-8]. Endoscopic approaches are also of limited usefulness in tissue diagnosis because of the desmoplastic nature of these cancers. Indeed, bile cytology obtained at endoscopic retrograde cholangiography has a sensitivity of only 33-56%^[1,9-11], endobiliary brush cytology of 50-68%^[12-14], and endoscopic transpapillary biopsy of 53-86% for detecting cholangiocarcinoma^[15-18]. Because of the problems in obtaining diagnostic tissues, treatment and management decisions for patients with biliary disease that may be malignant are problematic.

Of the two possible tumor markers available for detecting cholangiocarcinomas, carcinoembryonic antigen (CEA) is a glycoprotein tumor marker with the immunodeterminant present on the protein moiety of the molecule. The other, carbohydrate antigen 19-9 (CA19-9), is a mucin-type glycoprotein in serum with the immunodeterminant present on the carbohydrate moiety of the molecule. Both tumor markers have been investigated for the diagnosis of malignancies in the stomach, colon and pancreas^[19-23] but have not been gained widespread use in bile duct. It has been reported that the sensitivity and specificity for CA19-9 value $>37 \text{ KU} \cdot \text{L}^{-1}$ for cholangiocarcinoma with primary sclerosing cholangitis (PSC) were 60% to 93% and 78% to 98%, respectively^[19,16,21,24-27]. The corresponding indexes of CEA value $>22 \mu\text{g} \cdot \text{L}^{-1}$ were 53% to 84% and 50% to 79%^[25-30]. Although widely used as a tumor marker, the clinical value of serum CA19-9 determination in the diagnosis of cholangiocarcinoma in the absence of PSC is unknown. Thus, the objective of this study was to determine the clinical usefulness of CA19-9 value for cholangiocarcinoma.

MATERIALS AND METHODS

Patients

From January 1995 to February 2003, we prospectively obtained serum samples from patients undergoing evaluation for benign and malignant biliary disease at the First Hospital of Xi'an Jiaotong University and Luoyang Central Hospital. Serum samples were also prospectively obtained from healthy individuals who served as the disease control group. Patients with the diagnosis of PSC were excluded from this study. Clinical information was obtained by a thorough review of

the medical histories. This study included 35 patients with cholangiocarcinoma, 92 patients with benign biliary diseases, and 15 healthy individuals. Of the 35 patients with cholangiocarcinoma, the diagnosis was established by surgical biopsy in 25 patients, endoscopic biopsy and brushing in six patients, and fine needle aspiration in four patients. In patients with cholangiocarcinoma, the stage and resectability of the tumors were ascertained using information obtained by imaging studies or at the time of surgery. Unresectability was defined by Bismuth stage 4 cancer arising from the right and left hepatic ducts and extending intrahepatically. Patients with intra- and extrahepatic metastasis were also deemed unresectable.

The benign biliary diseases group consisted of 92 patients and included 26 patients with benign bile duct stricture, 36 patients with cholecystolithiasis, 20 patients with cholecystic polyp, and 10 patients with chronic cholecystitis. The other control group consisted of 15 healthy individuals without any disease.

Methods

Blood samples obtained from patients were stored at -20°C until used. CA19-9 and CEA were assayed by means of an immunoradiometric method with a commercially available CA19-9 RIA diagnostic kit (ELISA-CA19-9, CIS Bio International, France) and CEA RIA diagnostic kit (CIS Bio Industries, Gif-Sur-Yvette, France). Cutoff values recommended for diagnostic purpose were $37\text{ KU}\cdot\text{L}^{-1}$ for CA19-9 and $22\text{ }\mu\text{g}\cdot\text{L}^{-1}$ for CEA. Values above the cutoff concentrations were considered positive in this study. Sensitivity in detecting each group was compared between CA19-9 and CEA.

Statistics

The results were expressed as mean values \pm standard deviation of the mean (mean \pm SD). Statistical analysis was performed using a statistical program (SPSS, 11.0 Inc, Chicago, IL). Statistical significance in mean values was evaluated by the Student's *t* test. The one-way analysis of variance (ANOVA) was used to compare the different groups, and the Mann-Whitney rank sum

test was used for intergroup comparisons. The relationships between CA19-9 and CEA, total bilirubin, alkaline phosphatase, or AST were determined by linear regression analysis.

RESULTS

Patients' characteristics

The Table 1 shows some of the characteristics of the different groups. Patients with cholangiocarcinoma were significantly older than either patients with benign biliary diseases or healthy individuals. However, the mean total serum bilirubin and serum alkaline phosphatase values were significantly higher in patients with cholangiocarcinoma, compared to the other two groups ($P<0.05$). Thus, the patients with cholangiocarcinoma had a more marked cholestatic profile than the other two groups of patients.

Serum CA19-9 and CEA values in cholangiocarcinoma, benign biliary diseases and healthy individuals

The mean CA19-9 and CEA concentrations were significantly greater in the cholangiocarcinoma group than those in the benign biliary diseases group or healthy individuals group (Figure 1). Table 1 shows the mean serum CA19-9 concentration in patients with cholangiocarcinoma was $290.31\pm5.34\text{ KU}\cdot\text{L}^{-1}$ in comparison with $13.38\pm2.59\text{ KU}\cdot\text{L}^{-1}$ in the benign biliary diseases group and $12.78\pm3.69\text{ KU}\cdot\text{L}^{-1}$ in the healthy individuals group ($P<0.001$). Their corresponding mean serum CEA concentrations were $36.46\pm18.03\text{ }\mu\text{g}\cdot\text{L}^{-1}$, $13.84\pm3.85\text{ }\mu\text{g}\cdot\text{L}^{-1}$ and $11.48\pm3.37\text{ }\mu\text{g}\cdot\text{L}^{-1}$, respectively ($P<0.05$).

Comparison of CA19-9 and CEA levels in serum in patients with cholangiocarcinoma and benign diseases

Table 2 shows the distribution of serum CA19-9 and CEA values in patients with cholangiocarcinoma and benign biliary diseases. Of the 35 patients with cholangiocarcinoma, 27(77.14%) had a concentration exceeding $37\text{ KU}\cdot\text{L}^{-1}$ in serum CA19-9. Using a CA19-9 concentration of $37\text{ KU}\cdot\text{L}^{-1}$, the true negative rate of a CA19-9 for cholangiocarcinoma was 84.78% when

Table 1 Patients' characteristics in three groups (mean \pm SD)

Characteristics	Cholangiocarcinoma	Benign biliary diseases	Healthy individuals
N	35	92	15
Age (yr)	60.37 \pm 11.2	49.78 \pm 10.6	27.6 \pm 4.7
Sex (M/F)	19/16	39/53	15/0
Total bilirubin ($\mu\text{mol/L}$)	47.4 \pm 2.1 ^a	8.3 \pm 0.7	8.6 \pm 0.9
AST (U/L)	79 \pm 21.2 ^a	26 \pm 3.5	21 \pm 4.6
ALP (U/L)	193 \pm 41.8 ^a	114 \pm 50.6	90 \pm 18.3
CA19-9 ($\text{KU}\cdot\text{L}^{-1}$)	290.31 \pm 5.34 ^{bc}	13.38 \pm 2.59	12.78 \pm 3.69
CEA ($\mu\text{g/L}$)	36.46 \pm 18.03 ^a	13.84 \pm 3.85	11.48 \pm 3.37

^a $P<0.05$, ^b $P<0.001$ vs benign biliary diseases or healthy individuals. ^c $P<0.05$ vs serum CEA. AST=aspartate aminotransferase, ALP=alkaline phosphatase, CA19-9=carbohydrate antigen 19-9, CEA=carcinoembryonic antigen.

Table 2 Comparison of serum CA19-9 and CEA levels in patients with cholangiocarcinoma and benign biliary diseases

	CA19-9 ^Δ	CA19-9	CEA	CA19-9 or CEA	CA19-9 and CEA
Sensitivity(true positive)*	65.71%(23/35)	77.14%(27/35) ^a	68.57%(24/35)	91.43%(32/35)	62.86%(22/35)
Specificity(true negative)**	88.04%(81/92)	84.78%(78/92)	81.52%(75/92)	76.09%(70/92)	86.96%(80/92)
Positive predictive value	67.65%(23/34)	65.85%(27/41)	58.54%(24/41)	59.26%(32/54)	64.71%(22/34)
Negative predictive value	87.10%(81/93)	90.70%(78/86)	87.21%(75/86)	95.89%(70/73)	88.89%(80/90)
Accuracy	81.89%(104/127)	82.68%(105/127)	77.95%(99/127)	80.31%(102/127)	80.31%(102/127)
False positive rate	11.98%(11/92)	15.22%(14/92)	18.48%(17/92)	23.91%(22/92)	13.04%(12/92)

*Number of positive tests/number of patients with cholangiocarcinoma. **Number of negative tests/number of patients with benign biliary diseases. ^a $P<0.05$ vs CEA. ^ΔWhen the cutoff value of serum CA19-9 was $100\text{ KU}\cdot\text{L}^{-1}$.

assessed as the benign biliary diseases. The sensitivity (true positive) and specificity (true negative) of CEA were 68.57% and 81.52%, respectively (Table 2). Among the 92 patients with benign biliary diseases, the false positive rates of serum CA19-9 >37 KU·L⁻¹ and CEA >22 µg·L⁻¹ were 15.22% (14/92) and 18.48% (17/92), respectively. The combination of CA19-9 and CEA showed the highest sensitivity and specificity, they were 91.43% and 76.09% when CA19-9 or CEA was positive, and they were 62.86% and 86.96% when both CA19-9 and CEA were positive, respectively. If the cutoff value was increased from 37 KU·L⁻¹ to 100 KU·L⁻¹, the sensitivity and specificity of CA19-9 were 65.71% (23/35) and 88.04% (81/92), respectively.

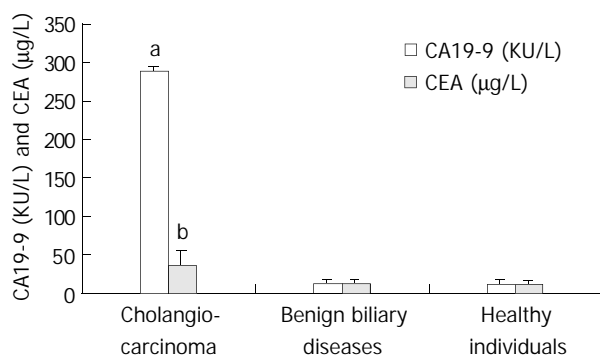


Figure 1 Mean serum CA19-9 and CEA concentrations. ^a $P<0.001$, ^b $P<0.05$ vs benign biliary diseases or healthy individuals. ^c $P<0.05$ vs serum CEA.

Correlation between serum CA19-9 and total bilirubin, ALP, AST or CEA in patients with cholangiocarcinoma

In patients with cholangiocarcinoma, no correlation was found between CEA and CA19-9 concentration ($r=0.036$). Likewise, no correlation was found among serum CA19-9, or ALP, AST, and total bilirubin ($r=0.015$, $r=0.037$ and $r=0.145$, respectively). Thus, elevated serum CA19-9 value could not be attributed to either cholestasis or hepatocellular injury.

Decrease of serum CA19-9 values in patients with cholangiocarcinoma after undergoing curative resection

Of the 35 patients with cholangiocarcinoma, 15 patients underwent curative resection and 20 had unresectable cancer. The mean preoperative and postoperative serum CA19-9 levels in the resectable group were 286.41 ± 4.36 KU·L⁻¹ and 62.01 ± 17.43 KU·L⁻¹, respectively. The corresponding indexes of serum CEA were 39.41 ± 24.35 µg·L⁻¹ and 28.69 ± 11.03 µg·L⁻¹, respectively (Figure 2 and Table 3). Thus, patients after curative resection had significantly lower mean serum CA19-9 and CEA concentrations than those before operation ($P<0.001$ and $P<0.05$). The mean serum CA19-9 concentration in the resectable group was 286.41 ± 4.36 KU·L⁻¹ as compared to 391.37 ± 5.76 KU·L⁻¹ in the unresectable group (Figure 2 and Table 3). Thus, patients with unresectable disease had a significantly higher mean serum CA19-9 concentration than those with resectable disease ($P<0.05$).

Table 3 Preoperative and postoperative change of serum CA19-9 and CEA concentrations in patients with cholangiocarcinoma undergoing curative resection (mean±SD)

Groups	CA19-9 (KU/L)	CEA(µg/L)
After the resectable (n=15)	62.01 ± 17.43^a	28.69 ± 11.03^c
Before the resectable (n=15)	286.41 ± 4.36	39.41 ± 24.35
The unresectable (n=20)	391.37 ± 5.76^b	43.28 ± 20.68

^a $P<0.001$, ^b $P<0.01$, ^c $P<0.05$ vs before the resectable group.

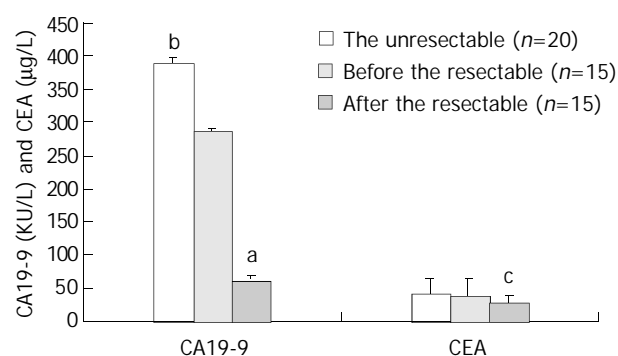


Figure 2 Mean postoperative serum CA19-9 and CEA levels of resectable group and mean serum CA19-9 and CEA levels of the unresectable group.

Relation between serum CA19-9 and CEA values and clinicopathologic features in 35 patients with cholangiocarcinoma

Perineural invasion by malignant cells was found in 23 of the 33 patients and more frequently encountered in cancer of the upper portion of extrahepatic bile ducts. Of the 35 tumors, lymph node metastasis was seen in 18 and venous invasion in 17. Histologically, 35 examples of cholangiocarcinoma were composed of 16 well-differentiated adenocarcinomas, 12 moderately-differentiated adenocarcinomas, 5 poorly-differentiated adenocarcinomas, 1 anaplastic carcinoma, and 1 adenosquamous carcinoma (Table 4). Table 4 shows statistically significant differences in serum CA19-9 and CEA between positive and negative lymph node metastases ($P<0.01$, $P<0.05$), perineural invasion ($P<0.01$, $P<0.05$), and venous invasion ($P<0.05$). However, there appears to be no relationship between the degrees of differentiation of carcinomas and the values of serum CEA and CA19-9.

Table 4 Relation between serum CA19-9 and CEA levels and clinicopathologic features of tumors in 35 patients with cholangiocarcinoma (mean±SD)

	No. of patients	CA19-9 (KU/L)	CEA (µg/L)
Well-differentiated adenocarcinoma	16	261.67 ± 6.31	34.37 ± 11.29
Moderately-differentiated adenocarcinoma	12	270.56 ± 4.57	38.42 ± 19.23
Poorly-differentiated adenocarcinoma	5	302.71 ± 5.81	48.23 ± 23.64
Anaplastic carcinoma	1	468	64
Adenosquamous carcinoma	1	293	27
Perineural infiltration			
Positive	23	310.12 ± 7.11^a	37.64 ± 10.35^b
Negative	10	195.16 ± 6.48	21.28 ± 13.15
Venous invasion			
Positive	17	318.49 ± 3.27^b	39.78 ± 18.41^b
Negative	18	253.08 ± 5.37	29.67 ± 20.13
Lymph node metastasis			
Positive	18	345.66 ± 4.23^a	46.37 ± 9.46^b
Negative	17	265.30 ± 4.58	31.89 ± 16.46

^a $P<0.01$, ^b $P<0.05$ vs negative groups.

DISCUSSION

Since koprowski *et al.*^[19] discovered CA19-9 from the human colon cancer cell line, which has been commonly used in the

diagnosis of pancreatic and biliary malignant diseases. Recently, its usefulness has been demonstrated in the staging, evaluation of resectability, and assessment of prognosis and recurrence, as well as in the initial diagnosis of malignant disorders, especially pancreatic cancer^[31-37].

Elevated concentration of serum CA19-9 ($>37 \text{ KU} \cdot \text{L}^{-1}$) in bile duct cancers has been frequently reported. Torzilli *et al.*^[38] described a positive rate of 97% in patients with cholangiocarcinoma, whereas Hultcrantz *et al.*^[39] described a rate of 76%, and Caturelli *et al.*^[40] described a 68% rate. We have also found an elevation of CA19-9 in 77.14% of cholangiocarcinomas, which was comparable to the rates reported in other studies. Furthermore, as shown in Table 2, the application of CA19-9 for differentiating cancer from benign biliary diseases was inspiring in our study because of its high sensitivity and specificity. The sensitivity and specificity in our study were 77.14% and 84.78%, respectively, which were similar to 78.2% and 81.4% reported by Kau *et al.*^[41]. However, the concentration of CA19-9 could raise in patients with benign inflammatory conditions as well as in malignant disease^[42-45]. Indeed, Ahrendt *et al.*^[46] reported a moderate increase in CA19-9 concentration in 13.8% of patients with benign biliary tract diseases. The positive serum rate was 28% in patients with acute cholangitis, as reported by Ker *et al.*^[47], and 35.6% in patients with bile duct stones, as reported by Shiozawa *et al.*^[48]. In our present study, an increased concentration of CA19-9 was found in 15.22% of patients with benign biliary diseases. According to Ker *et al.*^[47], CA19-9 was synthesized by normal biliary ductal cells and malignant cells. If bile flow is blocked by biliary obstruction in benign conditions, such as choledocholithiasis, epithelial cells will be markedly impaired by inflammation and will proliferate concurrently. As a result, more CA19-9 may be secreted and leaked out into the bloodstream. An elevated CA19-9 level often returns to normal with appropriate decompression of the common duct or relief of acute cholangitis. However, the increment of CA19-9 in benign diseases is usually not significant, and a concentration of CA19-9 exceeding $480 \text{ KU} \cdot \text{L}^{-1}$ is rare. In our study, only 2 (2.17%) patients with benign biliary diseases exhibited CA19-9 levels $>480 \text{ KU} \cdot \text{L}^{-1}$.

CEA is mainly secreted by digestive glandular cancers and their metastases. It has also been found in other types of cancer such as breast, lung, ovary, thyroid cancers. The sensitivity and specificity of serum CEA in our study were 68.57% and 81.52%, respectively, which were similar to 63.3% and 78.4% reported by Ramage *et al.*^[49]. The false positive rate of serum CEA was 18.48% (14/92). Serum CA19-9 was obviously superior to serum CEA in the diagnosis of cholangiocarcinoma and often considered the standard marker for pancreatic cancer and cholangiocarcinoma, with which other markers were compared^[50-53]. Our data also showed a much higher sensitivity with serum CA19-9 than with serum CEA in detecting cholangiocarcinomas, but the sensitivity and specificity could be raised by combining these two tumor markers. Furthermore, no correlation between the levels of serum CEA and CA19-9 was found ($r=0.036$).

Serum CA19-9 has been reported to be able to predict resectability of cholangiocarcinoma^[54-57]. In our study, marked elevation of serum CA19-9 tended to associate with advanced and unresectable biliary cancers. Both serum CA19-9 and CEA levels had a positive correlation with tumor stage. This positive correlation is theoretically helpful in assessing the therapeutic effect and monitoring tumor recurrence after treatment. CA19-9 and CEA have been claimed to have a prognostic value in cholangiocarcinomas^[7,21,24,30,58]. When applied to cholangiocarcinomas, both tumor markers could provide valuable prognostic information. In our study, serum CA19-9 and CEA concentrations were measured in 15 of 35 patients

with cholangiocarcinoma after undergoing curative resection. Within two weeks after operation, the average concentration of serum CA19-9 and CEA was $62.01 \pm 17.43 \text{ KU} \cdot \text{L}^{-1}$ and $28.69 \pm 11.03 \text{ } \mu\text{g} \cdot \text{L}^{-1}$, respectively, with an obvious decrease compared with those before operation ($P<0.001$ and $P<0.05$). Hence, serum CA19-9 could provide more important diagnostic and prognostic values than CEA in cholangiocarcinoma.

In summary, serum CA19-9 is an effective tumor marker in diagnosing cholangiocarcinoma, deciding whether the tumor has been radically resected and monitoring the effect of treatment. Serum CA19-9 determination is a useful adjunct in our diagnostic armamentarium for cholangiocarcinoma. However, serum CA19-9 has limitations in diagnosing cholangiocarcinoma. Indeed, our data clearly demonstrated that a negative test could not exclude cholangiocarcinoma. Moreover, for a patient suspected of having biliary cancer, consideration of the presence of acute cholangitis or cholestasis is suggested. If the patient has no evidence of acute cholangitis or cholestasis, a cutoff value of $37 \text{ KU} \cdot \text{L}^{-1}$ may be appropriate. However, if a patient shows symptoms and signs of acute cholangitis or cholestasis, application of CA19-9 should be delayed until after recovery from acute conditions or a cutoff value of $100 \text{ KU} \cdot \text{L}^{-1}$ should be used. Additional bile- or serum-based tests are needed in the diagnosis of cholangiocarcinoma. Ultimately, a profile of tests analogous to liver biochemistry measurement of serum or bile tumor markers and genetic analysis for cholangiocarcinoma-associated mutations will need to be developed to assist in the diagnosis of this disease.

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