

Received: 2020.04.10  
Accepted: 2020.06.22  
Available online: 2020.07.29  
Published: 2020.09.20

# The Clinical Role of Preoperative Serum CA19-9 and Carcinoembryonic Antigen (CEA) Levels in Evaluating the Resectability of Advanced Gallbladder Cancer

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**Background:** The present study was designed to study the ability of preoperative serum concentrations of the tumor-associated biomarkers carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and adjusted CA19-9 to assess the resectability of advanced gallbladder cancer (GBC).

**Material/Methods:** This retrospective study included patients with potentially resectable stage II–IV (AJCC 8<sup>th</sup>) GBC examined at our institution between January 2012 and December 2016. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value and optimal cut-off point of tumor-associated biomarkers for curative resection.

**Results:** Pathological examination of the 309 patients included in this study found that 169 (54.7%) underwent R0 (curative) resection, whereas 121 (39.2%) underwent R1/2 (non-curative) resection, and 19 (6.1%) were unresectable. The mean serum concentrations of CEA, CA19-9 and adjusted CA19-9 were significantly lower in patients who underwent R0 resection than in the other groups. ROC curve analysis showed that adjusted CA19-9 concentration was better able to predict resectability (area under the curve, 0.774; 95% confidence interval, 0.722–0.826;  $P < 0.001$ ) than total bilirubin, CEA, and CA19-9 concentrations. The optimal cut-off for adjusted CA19-9 concentration was 47.63 U/mL, which had a sensitivity of 69.82%, a specificity of 75%, a positive predictive value of 77.12% and a negative predictive value of 67.31%.

**Conclusions:** Adjusted CA19-9 concentration is an easily calculated parameter superior to CA19-9 and CEA concentrations in predicting the resectability of advanced gallbladder cancer.

**MeSH Keywords:** **Biological Markers • CA-19-9 Antigen • Carcinoembryonic Antigen • Gallbladder Neoplasms**

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/925017>

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## Background

Gallbladder cancer (GBC) is a relatively rare but highly lethal tumor of the biliary tract system, accounting for about 165000 cancer-related deaths per year worldwide [1,2]. The overall prognosis of patients with GBC is poor, with a 5-year mean survival rate of 5% to 10% [3]. Despite most patients being diagnosed at an advanced stage, because of the non-obvious symptoms and highly invasive nature of GBC, patients with advanced stage may benefit from aggressive radical resection, which may be the only potentially curative treatment [4,5]. Eligibility for radical resection is dependent on tumor stage and tumor biology [2,6], making preoperative assessment of the feasibility of curative resection for patients with advanced stage GBC essential. Moreover, accurate evaluation can avoid unnecessary surgery in patients ineligible for resection and reduce mortality rates.

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are cancer-associated antigens, measurements of which have been widely used to determine the diagnosis and prognosis of patients with tumors of the digestive system, including pancreatic [7], bile duct [8], colorectal [9], and gastric [10] cancer. Moreover, measurements of CEA and CA19-9 concentrations can be used to evaluate the resectability of various cancers [11,12], including GBCs [13]. Radical resection is possible in most patients with early stage GBC (stage 0–I, AJCC 8<sup>th</sup>), with a satisfactory prognosis [14,15]. However, the radical resection rate of advanced GBC (stages II–IV) is much lower and variable. The present study therefore evaluated the ability of serum concentrations of CEA, CA19-9 and CA19-9 relative to serum total bilirubin concentration (adjusted CA19-9) to determine the resectability of advanced (stages II–IV) GBC.

## Material and Methods

This retrospective, single-institution study analyzed patients who underwent surgery for potentially resectable stage II–IV GBC between January 2012 and December 2016 at the Third Affiliated Hospital of Second Military Medical University. The study protocol was approved by the Ethics Committee of our institution. The diagnosis of GBC was confirmed by pathological examination of a resected specimen or intraoperative biopsy. Tumor stage was intraoperatively classified based on the eighth edition of the American Joint Committee on Cancer (AJCC/TNM) staging system. All tumor resections were performed by senior surgeons. R0 resection was defined as resection with microscopically determined negative resection margins, R1 as microscopically positive resection margins and R2 as macroscopically minimal positive resection margins. Tumors were determined to be unresectable by intraoperative exploration. Patients with incomplete clinical data, those who received

preoperative radiotherapy or chemotherapy, and patients with other tumors were excluded.

Demographic characteristics, including age and sex, were recorded, as were concentrations of tumor-associated biomarkers and total bilirubin measured within one week before surgery. Because serum CA19-9 concentrations are affected by tumor-associated elevations in total bilirubin concentrations, CA19-9 may not reflect the actual tumor burden [16,17]. Therefore, CA19-9 concentrations were adjusted for total bilirubin concentrations. The upper limits of normal were 39 U/ml for CA19-9, 10 µg/L for CEA and 23 µmol/L for total bilirubin. If both CA19-9 and total bilirubin concentrations were above the upper limits of normal, adjusted CA19-9 concentration was calculated as the serum CA19-9 concentration divided by the fold elevation in total bilirubin concentration. If total bilirubin concentrations were within the normal range, the actual CA19-9 concentration was used.

## Statistical analysis

Continuous data were reported as the mean±standard deviation (SD) and compared by one-way ANOVA or the Kruskal-Wallis test. Categorical data were compared by Pearson's chi-squared test or Fisher's exact test. The optimal cut-offs for tumor-associated biomarkers were determined by receiver operating characteristic (ROC) curve analysis and determination of the area under the ROC curve (AUC). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for resectability were calculated for each cutoff value of each biomarker. Survival was analyzed by the Kaplan-Meier method and compared by log-rank tests. All statistical analyses were performed using SPSS 22.0 software, with  $P<0.05$  considered statistically significant.

## Results

During the study period from January 2012 to December 2016, 309 patients at our institution underwent surgery for potentially resectable of stage II–IV GBC. Of these 169 (54.7%) underwent R0 resection, as determined by postoperative pathological examination, 121 (39.2%) underwent R1/2 resection and 19 (6.1%) were unresectable. The demographic and clinical characteristics of these patients are summarized in Table 1. Patients were of mean age 60.0 years (range, 24 to 84 years), and 178 (57.6%) were women. Tumors were located in the body and fundus of the gallbladder in 169 (54.7%) patients, and in the neck and duct of the gallbladder in 140 (45.3%). Tumors in 238 (77.0%) patients were histologically classified as well and moderately differentiated, whereas tumors in 71 (23.0%) patients were poorly differentiated. Sex distribution, tumor site, and tumor differentiation did not differ significantly in the three

**Table 1.** Baseline characteristics of patients with gallbladder cancer.

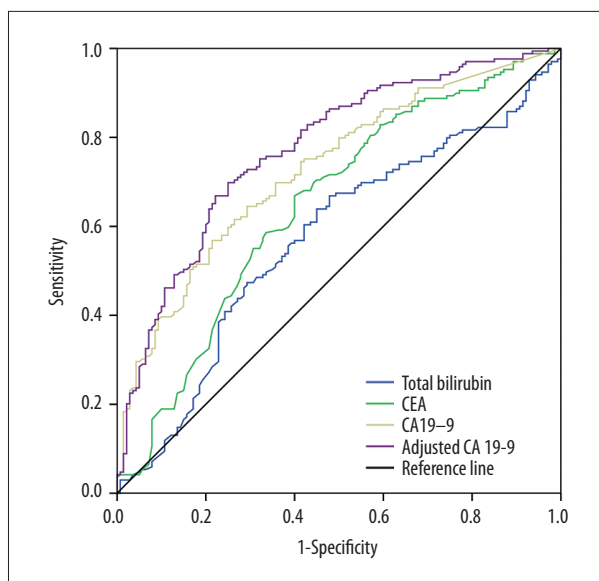
	Total	R0	R1/R2	Unresected	P value
No. patients	309	169	121	19	
Age. Yr, mean±SD	59.99±8.66	59.95±7.61	60.97±9.86	54.12±7.24	0.006
Gender (%)					0.855
Male	131 (42.4)	74 (43.8)	49 (40.5)	8 (42.1)	
Female	178 (57.6)	95 (56.2)	72 (59.5)	11 (57.9)	
Tumor location (%)					0.526
Body and fundus	169 (54.7)	88 (52.1)	69 (57.0)	12 (63.2)	
Neck and duct	140 (45.3)	81 (47.9)	52 (43.0)	7 (36.8)	
Tumor differentiation (%)					0.439
Well and moderate	238 (77.0)	133 (78.7)	89 (73.6)	16 (84.2)	
Poor	71 (23.0)	36 (21.3)	32 (26.4)	3 (15.8)	
AJCC staging, n					0.000
II	25	25	0	0	
IIIA	60	56	4	0	
IIIB	56	46	10	0	
IVA	70	42	28	0	
IVB	98	0	79	19	

AJCC – American Joint Committee on Cancer; SD – standard deviation.

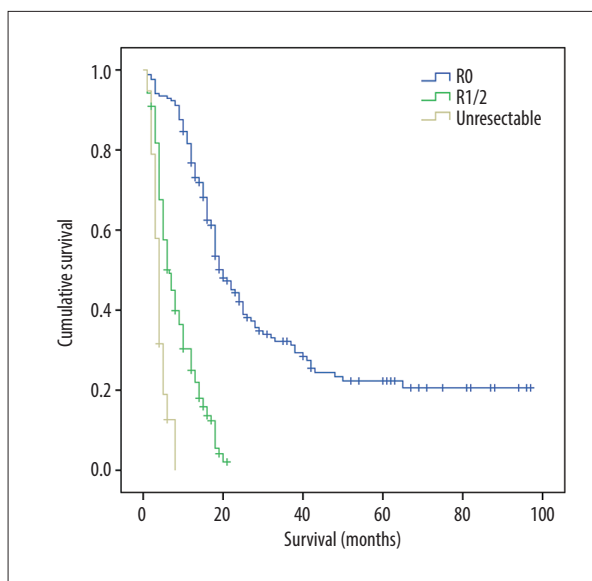
**Table 2.** Relationships of preoperative CEA, CA19-9, and adjusted CA19-9 concentrations with resectability, total bilirubin concentration and AJCC staging.

Variable	No.	CEA			CA19-9			Adjusted CA19-9		
		Median	Mean±SD	P value	Median	Mean±SD	P value	Median	Mean±SD	P value
Resectability										
R0	169	2.8	11.55±33.29	0.000	41	175.18±294.60	0.000	26.97	43.93±58.34	0.000
R1/R2	121	5.0	27.17±71.24		264.2	417.81±402.80		78.90	115.11±156.76	
Unresected	19	5.3	57.51±95.76		149	412.73±436.10		97.50	158.53±219.00	
Total bilirubin										
≤23 μmol/L	165	2.5	17.85±59.44	0.000	30	72.51±159.39	0.000	30	72.51±159.39	0.000
>23 μmol/L	144	5.1	23.52±54.41		403.1	528.04±390.75		68.16	86.12±69.41	
AJCC staging										
II	25	1.9	2.56±1.87	0.000	17	53.21±117.68	0.000	17	25.10±25.91	0.000
IIIA	60	2.75	8.17±24.49		46.3	195.10±321.34		27.40	42.72±42.55	
IIIB	56	4	13.63±29.87		71.5	264.86±361.82		41.68	57.38±80.93	
IVA	70	4.2	17.39±44.19		120.35	288.79±345.74		53.49	76.01±66.50	
IVB	98	5.1	38.75±88.92		159.50	407.32±415.73		77.26	128.98±194.19	

AJCC – American Joint Committee on Cancer; SD – standard deviation; CA19-9 – carbohydrate antigen 19-9; CEA – carcinoembryonic antigen.



**Figure 1.** ROC curves for preoperative serum CEA, total bilirubin, CA19-9, and adjusted CA19-9 levels in the determination of the resectability of gallbladder cancer.



**Figure 2.** Kaplan-Meier survival curves for patients who underwent R0 and R1/2 resection and those with unresectable tumors.

**Table 3.** The predictive accuracy of preoperative serum CEA, CA19-9, and adjusted CA19-9 concentrations for gallbladder cancer resectability.

	Resectability (R0 resection)		
	CEA <4.05 ng/mL	CA19-9 <78.5 U/mL	Adjusted CA19-9 <47.63 U/mL
No. patients	169	150	153
Sensitivity (%)	66.90	64.50	69.82
Specificity (%)	60.00	70.70	75.00
PPV (%)	66.90	72.67	77.12
NPV (%)	60.00	62.26	67.31

CA19-9 – carbohydrate antigen 19-9; CEA – carcinoembryonic antigen; PPV – positive predictive value; NPV – negative predictive value.

groups of patients with R0, R1/2, and unresectable tumors. In contrast, AJCC stage correlated significantly with tumor resectability ( $P < 0.001$ ). Patients with unresectable tumors were younger than those who underwent R0 and R1/2 resection.

The mean concentrations of CA19-9, CEA, and adjusted CA19-9 were significantly lower in patients who underwent R0 resection than in those who underwent R1/2 resection and those with unresectable tumors (Table 2). These three concentrations were higher in patients with elevated ( $>23 \mu\text{mol/L}$ ) than with lower ( $\leq 23 \mu\text{mol/L}$ ) serum total bilirubin concentrations and correlated significantly with AJCC stages. Taken together these findings indicate that the serum concentrations of these three parameters correlated with the severity of GBC.

ROC curves were constructed and AUC analysis performed to evaluate the predictive value of each parameter. Adjusted

CA19-9 had greater predictive value (AUC, 0.774; 95% confidence interval [CI], 0.722–0.826;  $P < 0.001$ ) than total bilirubin (AUC, 0.572; 95% CI, 0.507–0.636;  $P = 0.03$ ), CEA (AUC, 0.648; 95% CI, 0.586–0.71;  $P < 0.001$ ), and CA19-9 (AUC, 0.728; 95% CI, 0.672–0.784;  $P < 0.001$ ) concentrations (Figure 1). The optimal cut-off points to assess resectability were 4.05 ng/mL (sensitivity, 66.9%; specificity, 60.0%) for CEA, 78.5 U/mL (sensitivity, 64.5%; specificity, 70.7%) for CA19-9 and 47.63 U/mL (sensitivity, 69.82%; specificity, 75%) for adjusted CA19-9 (Table 3). At a threshold of 78.5 U/mL, serum CA19-9 had a 72.67% positive predictive value (PPV) and a 62.26% negative predictive value (NPV) for predicting resectability, whereas an adjusted CA19-9 concentration  $<47.63 \text{ U/mL}$  had a PPV of 77.12% and an NPV of 67.31%. These results indicated that adjusted CA19-9 was better than CA19-9 at predicting the resectability of GBC.

The 309 patients had a median survival time of 12 months and a 5-year survival rate of 5.83% (Figure 2). The 1-, 2-, and 5-year cumulative survival rates in patients who underwent R0 resection for GBC were 73.96%, 31.36%, and 9.47%, respectively, significantly better than for patients who underwent R1/2 resection. None of the patients with unresectable GBC survived for more than one year.

## Discussion

GBC is the most common cancer of the biliary tract and the sixth most common gastrointestinal cancer [18]. Due to their atypical symptoms, frequent local invasion, early and frequent metastases, most tumors are diagnosed at advanced stage, with only about 1 in 5 GBCs diagnosed in early stages [19]. Despite improvements in surgical methods, only 25% of patients are eligible for potentially curative surgery [20]. The radical resection rate in patients with advanced GBC, remains low and the proportion of fatal postoperative complications remains high. Moreover, unnecessary surgery for advanced GBC may delay appropriate systemic chemotherapy and increase health-care costs. An reliable and accurate preoperative assessment of GBC resectability is therefore of significant clinical importance.

Currently, the resectability of GBC is evaluated primarily by assessing clinical manifestations and performing radiological tests. Endoscopic ultrasonography (EUS) was regarded as the most sensitive diagnostic method for GB polypoid lesions, with a diagnostic sensitivity of 86% [21]. Multi-slice CT (MSCT) and MRI can provide more information about depth of tumor invasion, local extension and lymph node metastasis, but these methods frequently miss small occult hepatic and peritoneal metastases, resulting in unnecessary surgical exploration [22–24]. Although PET can be used for early detection of GBCs, as well as small (<1 cm) metastatic lymph nodes and lesions [25,26], its application is limited by the need for experienced radiologists and high costs. Staging laparoscopy has been recommended before laparotomy, as up to 37% of GBCs were determined to be unresectable by simple laparoscopy [27]. However, a study of 46 patients with potentially resectable GBC found that tumors were unresectable in 10 patients, two found by laparoscopy and eight at the time of laparotomy [28]. Simple and cost-effective measurements of tumor markers in serum may supplement radiological tests and staging laparoscopy to predict the resectability of GBCs.

CEA and CA19-9 are tumor-associated biomarkers in serum widely used to diagnose gastrointestinal cancers, including GBCs and to predict patient prognosis [29,30], indicating their

importance in evaluating GBC resectability. Serum CEA and CA19-9 concentrations may also predict the resectability of pancreatic cancers [31–33], whereas preoperative measurements of serum CEA, CA125, and CA19-9 concentrations can assist in evaluating the resectability of cholangiocarcinomas, a type of biliary tract cancer [12]. Moreover, a study of 292 patients with stage I–IV GBC reported that preoperative CA19-9 could predict tumor resectability [13], although that study did not consider the effect of tumor-associated elevation of total bilirubin concentration on serum levels of CEA and CA19-9. The radical resection rate of stage 0–I GBC is high, with these patients having a 5-year survival rate over 60% [15,19].

The present study assessed the ability of CEA, CA19-9 and adjusted CA19-9 concentrations to predict the resectability of advanced stage GBC. An AUC between 0.5 and 0.7 is regarded as having low diagnostic value, whereas an AUC between 0.7 and 0.9 has moderate diagnostic value. In assessing the ability of these potential biomarkers to predict the resectability of GBC, we found that the AUCs were 0.648 for CEA, 0.728 for CA19-9 and 0.774 for adjusted CA19-9, making the latter parameter more diagnostic of GBC resectability than CEA and CA19-9 concentrations.

Because of the high mortality rate and limited role of palliative resection in patients with advanced GBC, resectability in the present study was defined as R0 resection. Kaplan-Meier survival analysis showed that survival rates were significantly higher in patients who underwent R0 resection than in those who underwent R1/2 resection and patients with unresectable tumors [13].

In general, it is not accurate and reasonable to assess the resectability of GBC only by measuring serum biomarkers. These markers, however, could supplement the clinical features, imaging findings, and other correlated factors, with comprehensive analysis providing better guidelines for treatment.

## Conclusions

Adjusted CA19-9 concentration, which is easily calculated, is better than CA19-9 and CEA concentrations in predicting the resectability of advanced gallbladder cancer. Aberrantly high levels of adjusted CA19-9 and CA19-9 may indicate unresectable GBC. Prospective multicenter studies with larger patient cohorts are needed to assess this issue.

## Conflict of interest

None.

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