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Preoperative Alkaline Phosphatase-adjusted CA19-9 as a Superior Prognosticator for Extrahepatic Biliary Tract Cancer With Jaundice

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Abstract. *Background/Aim: The major limitation of carbohydrate antigen (CA)19-9 as a tumor marker is the high incidence of false-positive results during cholestasis. We evaluated preoperative CA19-9 and its adjusted values [ratios of CA19-9 to total-bilirubin (TB), direct-bilirubin (DB), and alkaline phosphatase (ALP)] to investigate the most suitable prognostic parameter in extrahepatic biliary tract cancer (eBTC) patients with or without jaundice. Patients and Methods: eBTC patients (n=140) who underwent resection were divided based on the absence (TB <2.0 mg/dl, n=90) or presence (TB ≥2.0 mg/dl, n=50) of preoperative jaundice. Within each group, the associations with overall survival (OS) were assessed for CA19-9, CA19-9/TB, CA19-9/DB and CA19-9/ALP ratios using Cox regression, receiver operating characteristic (ROC) analyses, and area under the curve (AUC) estimates. Results: In univariate analysis in the group without jaundice, both high CA19-9 and high CA19-9/TB ratio were associated with poor OS, whereas other parameters were not. ROC-AUC for OS prediction was greater in CA19-9 than in the CA19-9/TB ratio, and CA19-9 was identified as an independent prognosticator in multivariate analysis. In the group with jaundice, CA19-9 was not significant; however, CA19-9/TB, CA19-9/DB, and CA19-9/ALP ratios were all associated with poor OS. In ROC-AUC analysis, CA19-9/ALP ratio showed the highest predictive value; furthermore, it was an independent prognosticator in multivariate analysis. Conclusion: Adjustment of the CA19-9 value was less useful as a predictor in the absence of jaundice. On the other hand, the CA19-9/ALP ratio showed superior prognostic value in jaundiced patients with eBTC.*

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Biliary tract cancer (BTC) is a lethal malignancy that develops from the intra- or extrahepatic bile ducts. BTCs are relatively common in Asian populations and are the 6th leading cause of cancer death in Japan (1). Complete resection with negative margin represents the only curative option, but 5-year overall survival (OS) rate is still limited (approximately 20%-50%) (2).

Serum carbohydrate antigen (CA)19-9 is a widely used tumor marker in BTC patients for diagnosis, monitoring of treatment, and prognostic prediction (3, 4). Nevertheless, there are some limitations to CA19-9 in the clinical application, including false-negative results for Lewis negative phenotype, and false-positive results in various benign conditions such as cholestasis, pancreatitis, lung, and thyroid diseases (5-9). Serum CA19-9 value may not accurately reflect tumor burden in the presence of biliary obstruction caused by hepatobiliary or pancreatic malignancies (10-12). As most patients with extrahepatic BTC (eBTC) initially present with obstructive jaundice requiring bile duct exploration and drainage, repeated measurement of CA19-9 after successful treatment of jaundice should be recommended. However, not all operative candidates achieve sufficient reduction in serum bilirubin levels preoperatively; in addition, Japan's medical insurance system does not cover measurement of tumor markers more than once within the same month.

In order to reduce the potential bias caused by cholestasis-associated elevation of CA19-9, CA19-9 to total-bilirubin (TB) ratio was developed and investigated in pancreatic cancer and BTC patients (13-21). However, not only serum TB value, but also serum direct-bilirubin (DB) and alkaline phosphatase (ALP) values correlate with the degree of biliary obstruction; thus, they could all be candidates as variables for adjustment of CA19-9 value. The present study investigated four parameters: CA19-9, CA19-9/TB, CA19-9/DB and CA19-9/ALP ratios. The aim of this study was to determine which is the most suitable for use as a significant prognostic factor in eBTC patients.

Patients and Methods

Patients, data collection and ethics statement. A total of 156 consecutive patients with histologically proven eBTC who underwent surgical resection at Meiwa Hospital between January 2008 and December 2021 were retrospectively identified. Of these patients, patients with incomplete data (n=10), CA19-9 value of 0 U/mL (n=4), and those that had other active malignancies (n=2) were excluded; 140 patients were finally enrolled. There were 88 men and 52 women with a median age of 71 years (range=33-86 years). The cancer primary sites were hilar bile duct, distal bile duct, and ampulla of Vater in 44 (31.4%), 65 (46.4%), and 31 (22.1%) patients, respectively. One hundred and twenty-one (86.4%) patients who had biliary obstruction underwent biliary stenting as a bridge to surgery. Histopathological parameters included tumor node metastasis (TNM) stage according to the 7th edition UICC TNM system (22), tumor differentiation, perineural invasion, and status of resection margin. Resection margins were classified as follows: R0, no residual tumor; R1, microscopic residual tumor; and R2, macroscopic residual tumor. 10 of 140 patients (7.1%) were found to have limited metastatic disease during surgical exploration [para-aortic lymph nodes (n=4), liver (n=3), peritoneum (n=3)], but they underwent simultaneous resection of primary and metastatic lesions. Seven patients (5.0%) with ampullary cancer who underwent transduodenal ampullectomy without lymphadenectomy were categorized as N0 in this study. The OS was defined from the date of surgery to that of death from any cause or last contact with the patient.

The most recent preoperative laboratory data were reviewed for serum CA19-9 and for simultaneously measured serum TB, DB, and ALP values, all of which were post-procedure data in those who had received biliary stenting. CA19-9/TB, CA19-9/DB and CA19-9/ALP ratios were defined by dividing serum CA19-9 value by serum TB, DB, and ALP values, respectively. The cutoff of each variable was determined according to the upper normal limit for the institute's laboratory [CA19-9, 37 IU/ml; TB, 1.0 mg/dl; DB, 0.3 mg/dl; ALP for the Japan Society of Clinical Chemistry (JSCC), 340 U/l; ALP for the International Federation of Clinical Chemistry (IFCC), 115 U/l for men and 98 U/l for women (since April 2021)]. For example, CA19-9/DB ratio was classified as elevated based on the values of CA19-9 (37 IU/ml) and DB (0.3 mg/dl), giving a cutoff at ≥123 (IU/ml/mg/dl).

This study was approved by the Institutional Ethics Committee of Meiwa Hospital for a retrospective analysis of the collected data in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki.

Statistical analysis. Categorical variables were compared by Fisher's exact test. The median follow-up time was estimated using the reverse Kaplan-Meier method (23). Univariate and multivariate Cox regression models were used to identify prognostic variables affecting OS. Survival curves adjusted for confounders in Cox regression analysis were plotted by the Kaplan-Meier method and compared by the log-rank test. The time-dependent receiver-operating characteristic (ROC) curve for predicting median OS was generated and the area under the ROC curve (AUC) was used to estimate the predictive value of each variable. All statistical analyses were performed with R (Foundation for Statistical Computing, Vienna, Austria) and $p<0.05$ was considered significant.

Results

The subjects were stratified into two groups based on the presence or absence of preoperative jaundice. Jaundice was defined as serum TB ≥2.0 mg/dl. Ninety patients were assigned to the group without jaundice and the remaining 50 patients were assigned to the group with jaundice. As shown in Table I, preoperative biliary drainage (98.0% *vs*. 80.0%, $p=0.002$), lymph node metastases (66.0% *vs*. 42.2%, $p=0.008$), moderate or poor tumor differentiation (76.0% *vs*. 45.6%, $p<0.001$) and perineural invasion (76.0% *vs*. 57.8%, $p=0.04$) were more common in the group with jaundice. During the median follow-up of 69.1 months [95% confidence interval (CI)=47.9-76.6 months], the median OS was 45 months for all patients and 31.4 and 57.4 months for those with and without jaundice, respectively ($p=0.08$).

In the patients without jaundice, univariate analysis revealed that high CA19-9 and high CA19-9/TB ratio were significantly associated with poor OS, in addition to T stage, N stage, tumor differentiation, perineural invasion, and resection margin status (Table II). ROC-AUC analysis showed that CA19-9 (0.69) had higher predictive value than CA19-9/TB (0.61), CA19-9/DB (0.58), and CA19-9/ALP (0.59) ratios (Figure 1A). In multivariate analysis, high CA19-9 was an independent predictor of poor OS (hazard ratio, 3.98; 95% CI=1.71-9.24, $p=0.001$) (Table II). Kaplan-Meier curves, adjusted for confounding factors, showed that the median OS was 43.5 months for patients with high CA19-9 and not reached for patients with low CA19-9 ($p<0.001$) (Figure 2A).

In the group of patients with jaundice, resection margin status, high CA19-9/TB, high CA19-9/DB and high CA19-9/ALP ratios were significantly associated with poor OS in univariate analysis. In contrast to the group without jaundice, no significant association was found between CA19-9 and OS (Table III). ROC-AUCs were 0.56, 0.61, 0.63, and 0.71 for CA19-9, CA19-9/TB, CA19-9/DB and CA19-9/ALP ratios, respectively, showing that CA19-9/ALP ratio had the highest predictive value for OS (Figure 1B). In multivariate analysis, high CA19-9/ALP ratio remained an independent predictor of poor OS (hazard ratio=3.09; 95% CI=1.18-8.11, $p=0.02$) (Table III). Kaplan-Meier curves adjusted for resection margin status showed that the median OS for the patients with high *vs*. low CA19-9/ALP ratio was 24.5 months *vs*. not reached, respectively ($p=0.002$) (Figure 2B).

Discussion

In previous studies, the surgical outcomes of patients with eBTC were strongly linked to the presence of known prognostic factors, such as local tumor extension, presence of lymph node metastases, tumor differentiation, perineural invasion, and radicality of surgery (24-27), which were similar to the results of the present study. However, these

Table I. *Patient characteristics*.

	All patients (n=140)	Without jaundice (n=90)	With jaundice (n=50)	*p*-Value
Age, n (%)				
≥71 yr	76 (54.3)	49 (54.4)	27 (54.0)	1.00
<71 yr	64 (45.7)	41 (45.6)	23 (46.0)	
Sex, n (%)				
Men	88 (62.9)	56 (62.2)	32 (64.0)	0.86
Women	52 (37.1)	34 (37.8)	18 (36.0)	
Biliary drainage, n (%)				
No	19 (13.6)	18 (20.0)	1 (2.0)	0.002
Yes	121 (86.4)	72 (80.0)	49 (98.0)	
Tumor location, n (%)				
Proximal	44 (31.4)	31 (34.4)	13 (26.0)	0.41
Distal	65 (46.4)	38 (42.2)	27 (54.0)	
Ampulla	31 (22.1)	21 (23.3)	10 (20.0)	
Operation, n (%)				
Hepatectomy+BDR	42 (30.0)	30 (33.3)	12 (24.0)	0.09
BDR	7 (5.0)	4 (4.4)	3 (6.0)	
Pancreatoduodenectomy	84 (60.0)	49 (54.4)	35 (70.0)	
Ampullectomy	7 (5.0)	7 (7.8)	0 (0.0)	
T stage, n (%)				
T1/T2	68 (48.6)	46 (51.1)	22 (44.0)	0.48
T3/T4	72 (51.4)	44 (48.9)	28 (56.0)	
N stage, n (%)				
N0	69 (49.3)	52 (57.8)	17 (34.0)	0.008
N1	71 (50.7)	38 (42.2)	33 (66.0)	
M stage, n (%)				
M0	130 (92.9)	85 (94.4)	45 (90.0)	0.33
M1	10 (7.1)	5 (5.6)	5 (10.0)	
Tumor differentiation, n (%)				
Well	61 (43.6)	49 (54.4)	12 (24.0)	<0.001
Mod/por	79 (56.4)	41 (45.6)	38 (76.0)	
Perineural invasion, n (%)				
No	50 (35.7)	38 (42.2)	12 (24.0)	0.04
Yes	90 (64.3)	52 (57.8)	38 (76.0)	
Resection margin status, n (%)				
R0	112 (80.0)	72 (80.0)	40 (80.0)	1.00
R1/2	28 (20.0)	18 (20.0)	10 (20.0)	
Adjuvant chemotherapy, n (%)				
No	54 (38.6)	38 (42.2)	16 (32.0)	0.28
Yes	86 (61.4)	52 (57.8)	34 (68.0)	
CA19-9, n (%)				
Low	47 (33.6)	39 (43.3)	8 (16.0)	0.001
High	93 (66.4)	51 (56.7)	42 (84.0)	
CA19-9/TB ratio, n (%)				
Low	54 (38.6)	29 (32.2)	25 (50.0)	0.05
High	86 (61.4)	61 (67.8)	25 (50.0)	
CA19-9/DB ratio, n (%)				
Low	65 (46.4)	35 (38.9)	30 (60.0)	0.02
High	75 (53.6)	55 (61.1)	20 (40.0)	
CA19-9/ALP ratio, n (%)				
Low	65 (46.4)	46 (51.1)	19 (38.0)	0.16
High	75 (53.6)	44 (48.9)	31 (62.0)	

BDR, Bile duct resection; well, well-differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; CA19-9, carbohydrate antigen 19-9; TB, total-bilirubin; DB, direct-bilirubin; ALP, alkaline phosphatase.

prognosticators are only available postoperatively; thus, identification of preoperative biomarkers for the risk stratification is needed.

Several studies to date have shown the utility of TB-adjusted CA19-9, *i.e.*, the CA19-9/TB ratio in predicting resectability or postoperative prognosis for pancreatic cancer

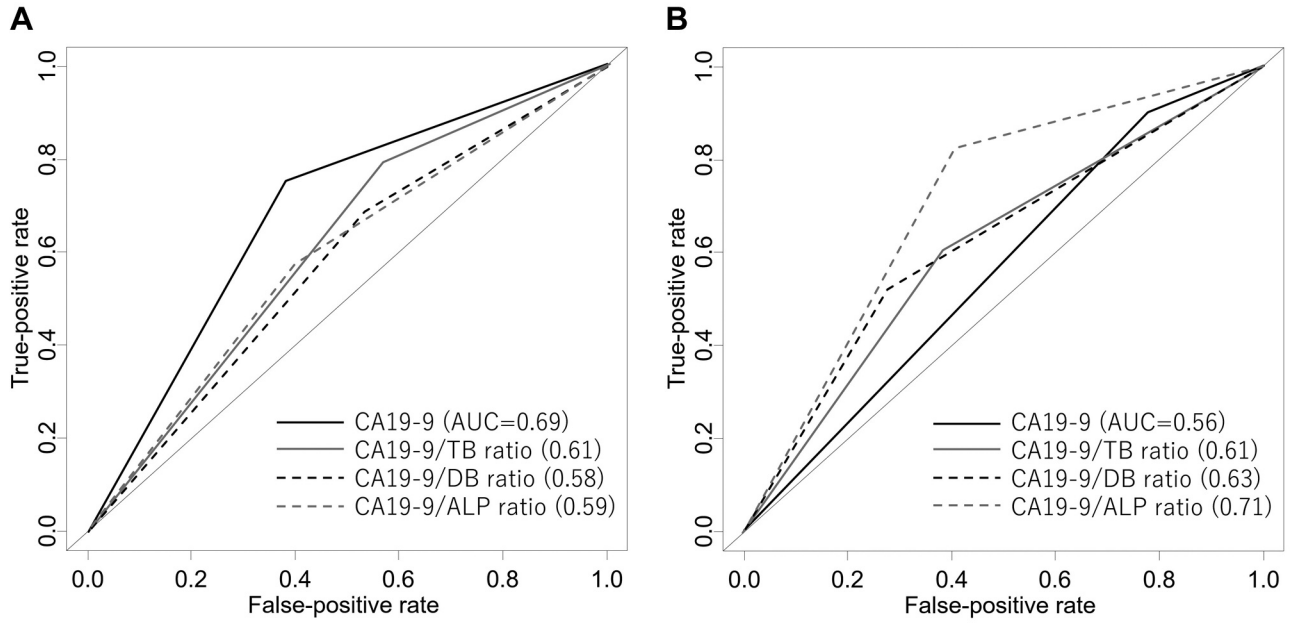

Figure 1. *Receiver-operating characteristics curves of CA19-9, and CA19-9 to total-bilirubin (TB), direct-bilirubin (DB), and alkaline phosphatase (ALP) ratios for median survival prediction. CA19-9 and CA19-9/ALP ratio showed the largest area under the curve (AUC) in the group without (A) and with (B) jaundice, respectively.*

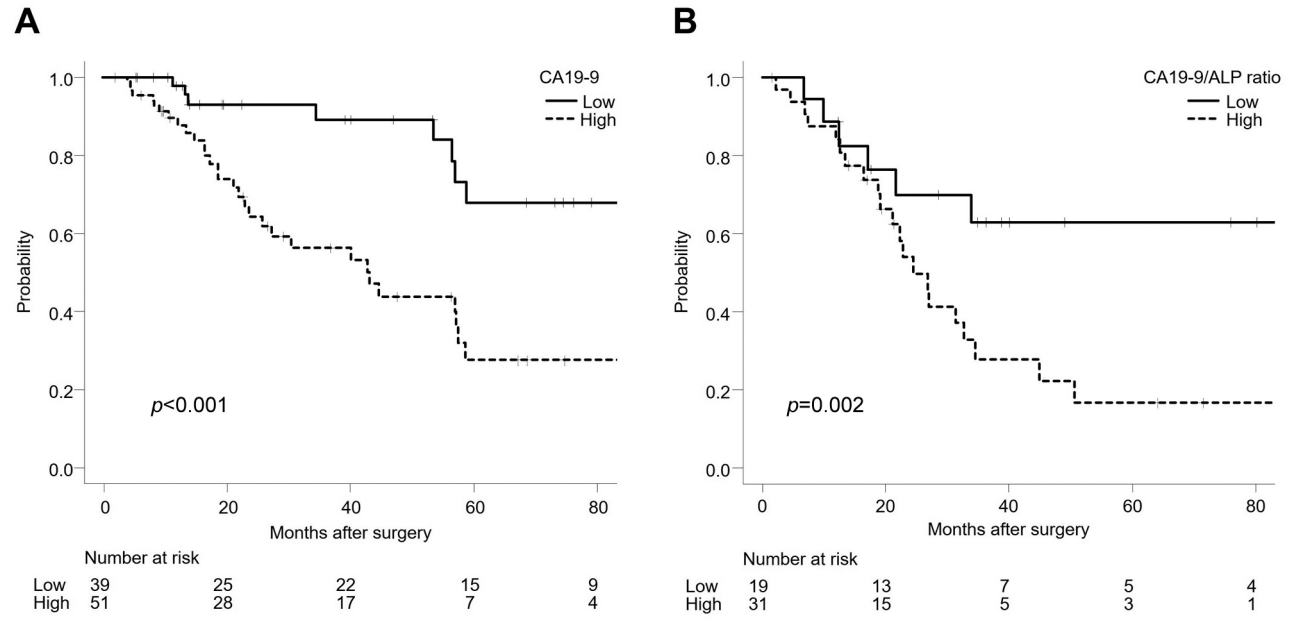

Figure 2. *Overall survival curves with regard to: (A) CA19-9, adjusted for T stage, N stage, tumor differentiation, perineural invasion, and resection margin status in the group without jaundice; (B) CA19-9/ALP ratio, adjusted for resection margin status in the group with jaundice.*

(13-17, 21). Kim *et al*. reported that TB-adjusted CA19-9 predicted the possibility of R1/2 resection or unresectability for pancreatic adenocarcinoma (16). Another study by Xu *et al*. showed that the CA19-9/TB ratio was an independent risk factor for tumor recurrence and long-term survival after curative resection of pancreatic head cancer (21). There are a few studies focusing on the CA19-9/TB ratio in BTC. In a multicenter analysis of 179 patients with distal BTC, Bolm

Table II. *Univariate and multivariate analysis of factors affecting overall survival in the group without jaundice.*

	Univariate	Multivariate	
	p-Value	HR (95% CI)	*p*-Value
CA19-9 (high *vs*. low)	<0.001	3.98 (1.71-9.24)	0.001
CA19-9/TB (high *vs*. low)	0.02		
CA19-9/DB (high *vs*. low)	0.08		
CA19-9/ALP (high *vs*. low)	0.06		
Age (≥71 *vs*. <71 yr)	0.56		
Tumor location (proximal *vs*. distal/ampulla)	0.43		
T stage (T3/4 *vs*. T1/2)	0.004	1.04 (1.00-1.07)	0.03
N stage (N1 *vs*. N0)	<0.001	1.48 (0.72-3.07)	0.29
M stage (M1 *vs*. M0)	0.05		
Tumor differentiation (mod/por *vs*. well)	0.003	0.95 (0.44-2.04)	0.89
Perineural invasion (yes *vs*. no)	<0.001	3.04 (1.25-7.38)	0.01
Resection margin status (R1/2 *vs*. R0)	0.004	2.53 (1.21-5.33)	0.01
Adjuvant chemotherapy (yes *vs*. no)	0.39		

CA19-9, Carbohydrate antigen 19-9; TB, total-bilirubin; DB, direct-bilirubin; ALP, alkaline phosphatase; well, well-differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; HR, hazard ratio; CI, confidence interval.

Table III. *Univariate and multivariate analysis of factors affecting overall survival in the group with jaundice.*

	Univariate	Multivariate	
	p-Value	HR (95% CI)	*p*-Value
CA19-9 (high *vs*. low)	0.14		
CA19-9/TB (high *vs*. low)	0.04		
CA19-9/DB (high *vs*. low)	0.02		
CA19-9/ALP (high *vs*. low)	0.005	3.09 (1.18-8.11)	0.02
Age (≥71 *vs*. <71 yr)	0.86		
Tumor location (proximal *vs*. distal/ampulla)	0.36		
T stage (T3/4 *vs*. T1/2)	0.97		
N stage (N1 *vs*. N0)	0.37		
M stage (M1 *vs*. M0)	0.47		
Tumor differentiation (mod/por *vs*. well)	0.22		
Perineural invasion (yes *vs*. no)	0.42		
Resection margin status (R1/2 *vs*. R0)	0.01	1.92 (0.79-4.67)	0.15
Adjuvant chemotherapy (yes *vs*. no)	0.30		

CA19-9, Carbohydrate antigen 19-9; TB, total-bilirubin; DB, direct-bilirubin; ALP, alkaline phosphatase; well, well-differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; HR, hazard ratio; CI, confidence interval.

et al. identified preoperative high CA19-9/TB ratio as a negative prognostic factor after resection (18). A similar result was reported by Li *et al*. who reported that preoperative CA19-9/TB ratio was a good prognosticator in eBTC patients (19). However, these studies only considered the CA19-9/TB ratio. This study was the first, to our knowledge, to investigate the prognostic value of the CA19-9/DB and CA19-9/ALP ratios as well as the CA19-9/TB ratio in eBTC patients. The results suggest that the CA19-9/ALP ratio was the most predictive for OS and was superior to CA19-9/TB and CA19-9/DB ratios in jaundiced patients.

DB is a water-soluble conjugated post-hepatic bilirubin, which includes conjugated bilirubin and bilirubin that is covalently bound to albumin (delta-bilirubin) (28). An abnormal increase in conjugated bilirubin typically suggests hepatocellular injury or cholestasis, while the elevation of unconjugated bilirubin indicates pre-hepatic or hepatic jaundice. Although elevations of both conjugated and unconjugated bilirubin are possible, a predominant elevation of conjugated bilirubin (DB fraction is >50% of TB) is most common in obstructive jaundice (29); thus, elevation of DB could more directly reflect eBTC-induced cholestasis than

that of TB. Meanwhile, ALP is a membrane-bound metalloenzyme mainly derived from the liver, bones, and in lesser amounts from small intestine, kidneys, and placenta (30). ALP is located in hepatic sinusoidal and biliary canalicular membranes, and its serum value usually has a greater sensitivity for cholestasis compared to the serum bilirubin value; for instance, low-grade or localized cholestasis may increase serum ALP value without any increase in serum bilirubin values (31, 32). Bilirubin rises due to a failure of bilirubin excretion whereas ALP rises because of the increased synthesis and membrane shedding of ALP from hepatocytes exposed to the increased biliary pressure of cholestasis (32). Similar to ALP, one possible source of non-specific CA19-9 elevation during biliary obstructive disorders may be irritated bile duct cells exposed to increased biliary pressure (12). We speculate these may partly explain why the role as a CA19-9 adjusting variable was greater in the order of ALP >DB >TB in patients with jaundice in this study.

This study also confirmed the usefulness of CA19-9 in cases of TB <2.0 mg/dl. Both high CA19-9 and CA19-9/TB ratios were associated with shorter OS in the present study; however, the predictive value of CA19-9 was higher compared to that of the CA19-9/TB ratio. Some previous studies calculated the CA19-9/TB ratio empirically only when the serum TB was ≥2.0 mg/dl (14-16); thus, our findings may support the rationale for their analysis method.

There were several limitations of this study. First, it was a retrospective, single-institution study with a small number of enrolled patients. Second, BTC patients may suffer from preoperative cholangitis, but cholangitis-related hepatobiliary enzyme abnormalities and CA19-9 elevation were not considered in the present study. Furthermore, neither liver-specific ALP nor gamma-glutamyl transpeptidase values were studied due to the lack of sufficient data from medical records. Third, this study did not include gallbladder cancer as it does not always interrupt bile flow from the hepatic duct through the common bile duct to the duodenum. Finally, dichotomous variables (high *vs*. low) were applied for ROC and AUC analysis because of the change in institutional cutoff of ALP value during the study period (from JSCC to IFCC), which made it difficult to use the CA19-9/ALP ratio as a continuous variable.

In summary, our findings suggest the need for an adjusted preoperative CA19-9 value that can better predict outcome of patients with eBTC. Moreover, interpreting the CA19-9 value adjusted to the serum hepatobiliary enzyme, especially to ALP value, is reasonable in evaluating prognosis of patients with jaundice. On the other hand, adjustment of the CA19-9 value was less useful as a predictor in the absence of jaundice. The CA19-9/ALP ratio is easily applicable and could be widely utilized as an alternative prognosticator for patients with eBTC. Further studies with a large number of patients will be required to confirm our findings.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

All the Authors have contributed significantly to the concept design of this manuscript and the work leading to the final manuscript. All Authors have reviewed the article and agreed with its content.

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