

ORIGINAL ARTICLE

폐쇄성 황달을 동반한 악성 및 양성 췌담도 질환에서 CA 19-9 상승의 임상적 해석

김민성, 전태주¹, 박지영¹, 최정민¹, 신원창¹, 박성은¹, 서지영¹, 김영문¹

서울대학교 의과대학 내과학교실 및 간연구소, 인제대학교 의과대학 상계백병원 소화기내과¹

Clinical Interpretation of Elevated CA 19-9 Levels in Obstructive Jaundice Following Benign and Malignant Pancreatobiliary Disease

Min Seong Kim, Tae Joo Jeon¹, Ji Young Park¹, Jeongmin Choi¹, Won Chang Shin¹, Seong Eun Park¹, Ji-Young Seo¹ and Young Moon Kim¹

Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Division of Gastroenterology, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine¹, Seoul, Korea

Background/Aims: Elevated carbohydrate antigen (CA) 19-9 level may be unable to differentiate between benign and malignant pancreatobiliary disease with obstructive jaundice. The study aims to determine the clinical interpretation and the diagnostic value of CA 19-9 level in pancreatobiliary diseases with coexistent obstructive jaundice.

Methods: We retrospectively reviewed the data of 981 patients who underwent biliary drainage due to obstructive jaundice following pancreatobiliary disease at Sanggye Paik Hospital for 5 years. 114 patients with serial follow-up data for CA 19-9 level were included in this study (80 patients with malignancy and 34 patients with benign diseases). We compared the levels of CA 19-9 levels and the biochemical value before and after biliary drainage.

Results: The rate of CA 19-9 elevation (>37 U/mL) was significantly different between the benign group and the malignant group (59% vs. 90%, $p=0.001$). Despite the decrease in serum bilirubin after biliary drainage, CA 19-9 levels remained elevated in 12% of patients in the benign group and in 63% of patients in the malignant group ($p<0.001$). Finally, 12% of patients in the benign group turned out to have malignant disease. A receiver operating characteristic analysis provided a cut-off value of 38 U/mL for differentiating benign disease from malignant disease after biliary drainage (area under curve, 0.787; 95% confidence interval, 0.703 to 0.871; sensitivity, 62%; specificity, 88%).

Conclusions: This study suggested that we should consider the possibility of malignant causes if the CA 19-9 levels remain high or are more than 38 U/mL after resolution of biliary obstruction. (*Korean J Gastroenterol* 2017;70:96-102)

Key Words: CA 19-9 antigen; Obstructive jaundice; Malignancy; Neoplasms, benign; Drainage

INTRODUCTION

Carbohydrate antigen (CA) 19-9 is one of the most commonly used tumor markers in gastrointestinal malignancies,

especially pancreatobiliary cancer. CA 19-9, a sialylated Lewis-a blood group antigen, was identified by a murine monoclonal antibody against a colorectal carcinoma epithelial cell.¹ This carbohydrate antigen is also expressed in benign

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교신저자: 전태주, 01757, 서울시 노원구 동일로 1342, 인제대학교 의과대학 상계백병원 소화기내과

Correspondence to: Tae Joo Jeon, Division of Gastroenterology, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine University, 1342 Dongil-ro, Nowon-gu, Seoul 01757, Korea. Tel: +82-2-950-1341, Fax: +82-2-950-1955, E-mail: drtj@paik.ac.kr

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diseases, as well as in pancreatic or biliary ductal epithelial cancers.¹⁻³ Previous studies have reported that the sensitivity and specificity of the CA 19-9 level in the diagnosis of pancreatic cancer were 70 to 80% and 80 to 90%, respectively.^{4,5} Elevated CA 19-9 serum level may be unable to differentiate between benign and malignant pancreatobiliary diseases in patients with obstructive jaundice. The cut-off value of CA 19-9 has been determined to distinguish between malignancy and benign disease by adjusting the serum bilirubin level.⁶⁻¹⁰ Because of this uncertain diagnostic accuracy, use of CA 19-9 is limited to the diagnosis of tumor recurrence and prognosis of pancreatic cancer.¹¹⁻¹³

The aims of this study were to determine the clinical interpretation and the diagnostic value of an elevated CA 19-9 serum level in pancreatobiliary diseases with coexistent obstructive jaundice. We investigated the diagnostic accuracy of CA 19-9 and the correlation between CA 19-9 and serum bilirubin levels before and after biliary drainage.

SUBJECTS AND METHODS

1. Patients and study design

We retrospectively reviewed the medical data of 981 consecutive patients who underwent biliary drainage due to cholestatic jaundice following pancreatobiliary disease at Inje University Sanggye Paik Hospital (Seoul, Korea) between January 2008 and February 2013. The patients were selected and confirmed based on the clinical manifestation and the initial radiologic evaluation, including ultrasonography, computed tomography, or magnetic resonance imaging for this study.

The selected patients underwent liver function test, which includes alkaline phosphatase, gamma-glutamyl transpeptidase, total and direct bilirubin, via routine blood sampling according to the hospital's protocol before biliary drainage. Serum CA 19-9 concentration was also obtained before the procedure. Blood samples of patients were sent to the Department of Laboratory Medicine at our institution for CA 19-9 assay before and after biliary drainage. Sample assays for CA 19-9 were measured by radioimmunoassay, Elecsys CalSet (Cobas e 602 analyzers, Roche, Basel, Switzerland). The normal level of CA 19-9 was defined as a level less than 37 U/mL. The detection range of the analyzer was a minimum of 0.6 U/mL and a maximum of 10,000 U/mL. Obstructive

jaundice was defined as an increase in the serum level of total bilirubin, a level more than 1.5 mg/dL. Pathologic specimens were obtained by endoscopic fine-needle biopsy and aspiration/brushing cytology. The diagnosis of malignancy was defined as pathological confirmation of carcinoma by the biopsy specimen or surgical resection, identification of malignant cells or highly suspicious malignant cells in cytology, and malignant findings on radiological evaluation (ultrasonography, computed tomography or magnetic resonance imaging). The other cases were defined as having benign disease.

2. Biliary drainage

Indications for biliary drainage were benign (ductal stenosis or choledocholithiasis) and malignant pancreatobiliary diseases causing obstructive jaundice. The methods for resolving cholestasis were endoscopic sphincterotomy (EST), biliary stenting through endoscopic retrograde cholangiopancreatography, and percutaneous transhepatic biliary drainage via radiological intervention. Follow-up serial CA 19-9 levels were obtained between 7 and 14 days after biliary drainage. The test was performed prior to administration of additional tumor-reducing therapies such as surgical resection, chemotherapy, or radiation therapy.

3. Statistical analysis

For comparison between malignancy and benign disease, we divided the patients into two subgroups. A large variation of CA 19-9 level was analyzed with distribution, median and interquartile range (IQR). We compared the levels of CA 19-9 and the biochemical value before and after biliary drainage. Wilcoxon two-sample test was used, and the chi-square test or Fisher's exact test was used wherever appropriate. Univariate correlation analysis was performed and the Pearson's coefficient (r) was obtained before and after biliary drainage to identify the correlation between CA 19-9 and bilirubin. The receiver operating characteristic (ROC) curve was compiled to determine pancreatobiliary malignancy before and after biliary drainage. The optimal cut-off value and the diagnostic accuracy with sensitivity and specificity were obtained by calculating the area under the curve (MedCalc version 16.8.4; MedCalc Software, Mariakerke, Belgium).

SPSS Statistics for Windows (version 19.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Null hypotheses of no difference were rejected if p -values were less than 5%.

RESULTS

1. Baseline characteristics before biliary drainage

Nine hundred and eighty-one patients underwent biliary drainage following confirmation of cholestasis, and 114 patients were enrolled in the present study. Of the 867 patients excluded from this study, 810 had no record of the follow-up CA 19-9 level between 7 and 14 days after biliary drainage and 57 were not followed up or examined during the study. Eighty out of the 114 patients had accompanying pancreatobiliary malignancy, while 34 patients (29.8%) had benign diseases (Fig. 1). The malignant group consisted of 51 men and 29 women, with a median age of 68 years, and the benign group consisted of 20 men and 14 women, with a median age 68 years. Malignant causes were pancreatic cancer, cholangiocarcinoma, gallbladder cancer, ampulla of Vater cancer and cancer invasion. Benign causes were cholangitis due to cholelithiasis, biliary pancreatitis, and benign stenosis.

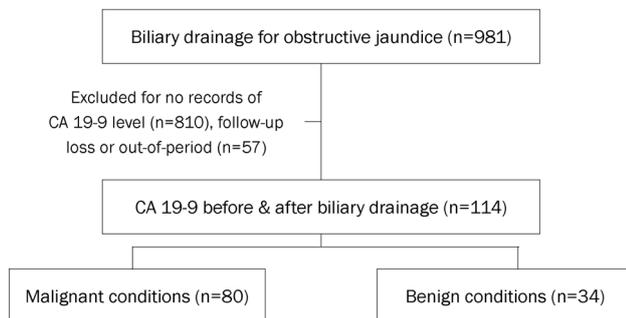


Fig. 1. Study flowchart and enrollment. CA, carbohydrate antigen.

The CA 19-9 level was significantly higher in patients with malignancies (median 442.4 U/mL, IQR 0.6-10,000 U/mL) compared to patients with benign diseases (median 67.4 U/mL, IQR 0.6-5,066 U/mL). After a level of positive CA 19-9 more than 37 U/mL was set as the cut-off level, there was also a significant difference in the rate of CA 19-9 elevation between 59% of patients in the benign group and 90% of patients in the malignant group at baseline ($p=0.001$). Another cholestasis marker, total bilirubin, and alkaline phosphatase and γ -glutamyl transferase levels in the malignant group were higher than those in the benign group (Table 1).

2. CA 19-9 level after biliary drainage

In the malignant group, the number of biliary drainage procedures was 57 stent insertions, 21 percutaneous catheter drainages and 2 ESTs. However, in the benign group, 29 ESTs, 3 stent insertions and 2 percutaneous catheter drainages were performed. There was a significant difference between the two groups with respect to the selection of procedure for biliary drainage. Bilirubin, alkaline phosphatase and γ -glutamyl transferase levels decreased after the procedure in all cases, but they did not return to normal level in several cases. After biliary drainage, the median and range of CA 19-9 level were 91.2 U/mL and 0.6-10,000 U/mL, respectively, in the malignant group, and the median and range of CA 19-9 level were 14.1 U/mL and 0.6-258.5 U/mL, respectively, in the benign group. CA 19-9 levels remained elevated in 4 patients (12%) of the benign group and in 50 patients (63%) of the malignant group, despite the decrease in serum bilirubin after biliary

Table 1. Baseline Characteristics before Biliary Drainage for Obstructive Jaundice Treatment in the Malignant and Benign Pancreatobiliary Disease Groups

Characteristics	Malignant (n=80)	Benign (n=34)	p-value
Gender			0.529
Male	51 (63.7)	20 (58.8)	
Female	29 (36.3)	14 (41.2)	
Age, years	68±10	68±11	0.840
Median CA 19-9 (range, U/mL)	442.4 (0.6-10,000)	67.4 (0.6-5,066)	
Positive CA 19-9 (>37 U/mL)	72 (90)	20 (59)	0.001
Total bilirubin (mg/dL)	10.4±6.6	6.8±6.8	0.010
Alkaline phosphatase (U/L)	549±496	263±196	<0.001
γ -Glutamyl transferase (U/L)	829±638	428±304	<0.001
Biliary drainage method			<0.001
EST : Stent : PCD	2 : 57 : 21	29 : 3 : 2	

Values are presented as mean± standard deviation, range or n (%).

CA, carbohydrate antigen; EST, endoscopic sphincterotomy; PCD, percutaneous catheter drainage.

drainage ($p < 0.001$) (Table 2).

With respect to the correlation between CA 19-9 and bilirubin, CA 19-9 levels were directly correlated with the degree of biliary obstruction, as indicated by the decrease in serum bilirubin. Unlike the benign group, CA 19-9 levels were elevated independently of the decrease in serum bilirubin after biliary drainage in the malignant group ($r = 0.021$, $p = 0.851$) (Fig. 2).

3. Diagnostic accuracy

The detection of malignancy was estimated by the ROC curve before and after biliary drainage. When the CA 19-9 cut-off value of 240 U/mL was determined before biliary drainage, sensitivity and specificity were 64% and 73%, respectively. The area under the curve was 0.752 (95% confidence interval, 0.625-0.880). ROC analysis provided a cut-off value of 38 U/mL for differentiating benign disease from malignant disease after biliary drainage. The area under the curve, sensitivity and specificity were 0.787 (95%

Table 2. CA 19-9 Level and Cholestasis Laboratory Findings after Successful Drainage

	Malignant (n=80)	Benign (n=34)	p-value
Median CA 19-9 (range, U/mL)	91.2 (0.6-10,000)	14.1 (0.6-258.5)	N/A
Positive CA 19-9 (>37 U/mL)	50 (63)	4 (12)	<0.001
Total bilirubin (mg/dL)	1.5±2.7	1.6±2.5	0.969
Alkaline phosphatase (U/L)	193±171	136±105	0.117
γ-Glutamyl transferase (U/L)	145±150	103±102	0.197

Values are presented as mean±standard deviation, range or n (%). CA, carbohydrate antigen; N/A, not applicable.

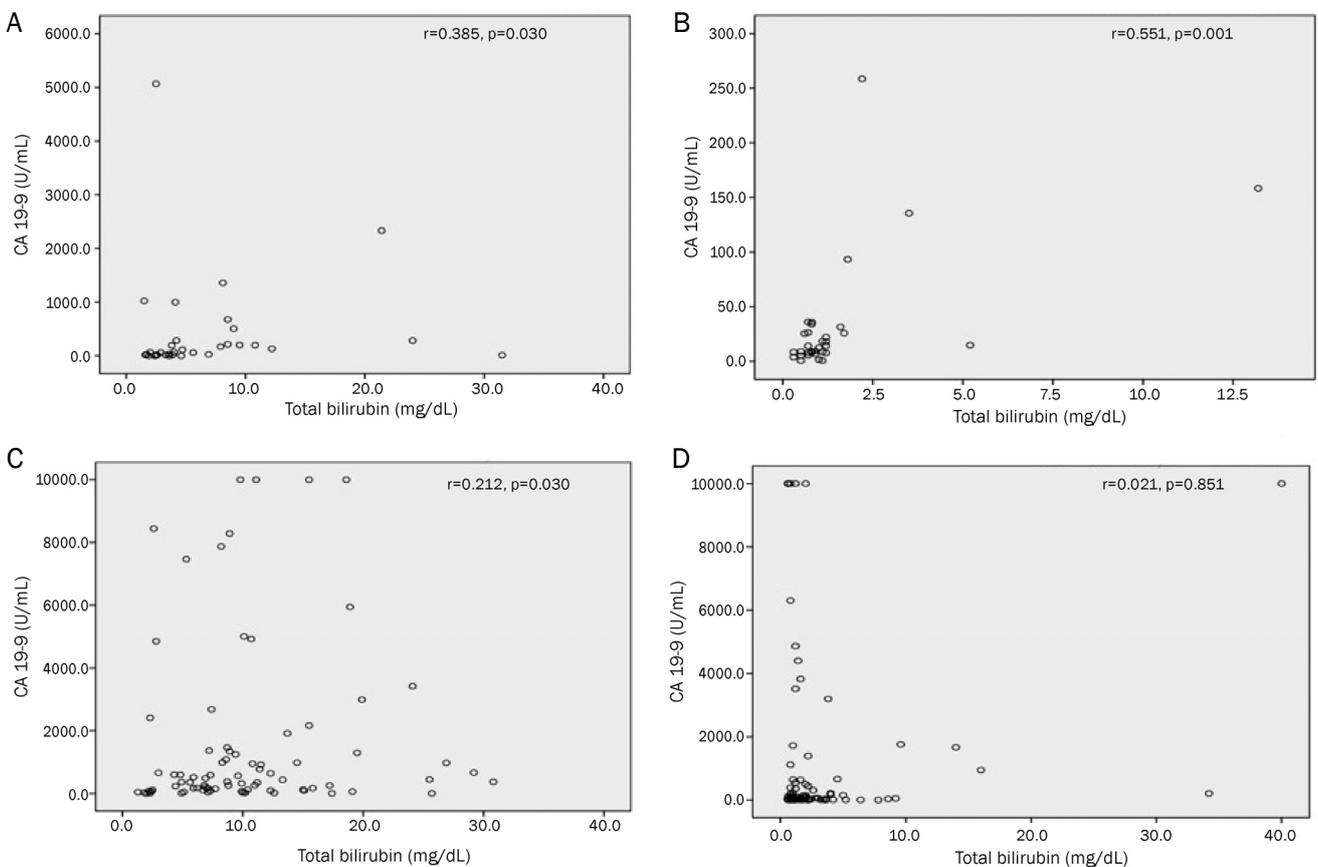


Fig. 2. The correlation between CA 19-9 and total bilirubin in benign diseases and malignant diseases. (A) Pre-drainage in benign diseases. (B) Post-drainage in benign diseases. (C) Pre-drainage in malignant diseases. (D) Post-drainage in malignant diseases. CA, carbohydrate antigen.

confidence interval, 0.703-0.871), 62% and 88%, respectively, and these values were relatively higher than those at baseline (Fig. 3).

Among the present cases, seven patients were proved to have been misdiagnosed. In 4 cases (12%) of the initially diagnosed benign diseases, the elevated CA 19-9 level persisted after biliary drainage. Subsequently, these cases turned out to have malignant disease on pathological and radiological evaluation. Conversely, 3 cases (4%) of malignant disease turned out to have benign disease (Table 3).

DISCUSSION

CA 19-9 as a diagnostic tumor marker has not been widely

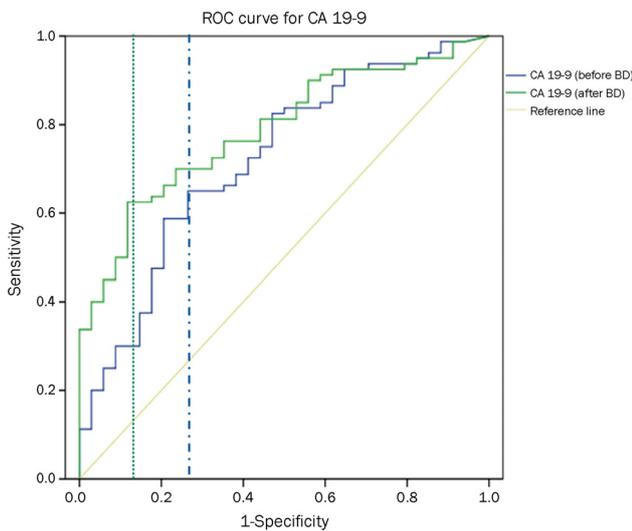


Fig. 3. The ROC and the cut-off level (pre-drainage: 240 U/mL, post-drainage: 38 U/mL) for CA 19-9 to distinguish between benign and malignant disease states. ROC, receiver operating characteristic; CA, carbohydrate antigen, BD, biliary drainage.

used in practice, while it is restrictively used in pancreatic cancer as the prognostic and predictive biomarker.¹² This narrow spectrum is caused by the low specificity of CA 19-9 for pancreatobiliary malignant diseases.¹³ An elevated level of serum CA 19-9 has been found in benign biliary tract disease, as well as in other gastrointestinal malignant diseases. Benign diseases, in which an elevated level of serum CA 19-9 has been found, include cholecystitis, cholangitis, choledocholithiasis, primary biliary cirrhosis, pancreatitis, viral hepatitis, and it has also been found in respiratory and infectious diseases, like tuberculosis.¹⁴⁻²³ A high CA 19-9 level has also been detected in other digestive system malignancies such as those of the esophagus, stomach and colorectal tract.²⁴⁻²⁷ Moreover, cholestatic jaundice is a potent reducing factor which plays the diagnostic role of CA 19-9.^{5,6} This condition causes an elevation of the CA 19-9 level and increases the false-positive value. Several studies have suggested an adjustment of cholestasis for the CA 19-9 level for the interpretation of a high CA 19-9 level in pancreatobiliary cancer.^{28,29} In the above studies, the appropriate normal range of CA 19-9 was determined to be less than 34 U/mL by using the ROC curve analysis. Patients whose CA 19-9 levels were within the normal range were included in the analysis as normal levels in the pancreatobiliary disease may be meaningful at levels lower than the reference level. In our study, more than half of the patients with obstructive jaundice in the benign group had positive CA 19-9. Even though 90% of patients in the malignant group had positive CA 19-9, resetting the cut-off value was needed for diagnostic discrimination.

Previous studies have used the ROC curve to determine the cut-off value of CA 19-9 level.⁴ One study determined a cut-off level of 70.5 U/mL, and both sensitivity and specificity were in the 80% range.⁹ These cut-off levels had a limitation due

Table 3. Cases of Change in the Initial Diagnosis

Case (Sex/Age)	Diagnosis		CA 19-9 (U/mL)		Total bilirubin (mg/dL)	
	Initial	Final	Initial	Final	Initial	Final
F/67	CCC	Benign stenosis	215.2	8.9	8.5	0.5
M/50	CCC	Benign stenosis	27.8	5.5	6.9	0.7
F/67	Cancer invasion	Benign stenosis	17.8	3.8	3.9	0.3
M/74	Calculous Dz	CCC	587.3	499.9	7.3	1.0
M/64	Calculous Dz	AOV cancer	198.3	644.8	6.9	0.5
M/64	Calculous Dz	Cancer invasion	2,681	4,401	7.4	0.7
M/87	Benign stenosis	CCC	5,946	3,196	18.9	1.9

CA, carbohydrate antigen; F, female; M, male; CCC, cholangiocarcinoma; Dz, disease; AOV, ampulla of vater.

to the inverse relationship between sensitivity and specificity. We analyzed by using the ROC curve and determined the cut-off value as 240 U/mL. Although a level of 240 U/mL is considerably high, the sensitivity and specificity were in the 60-70% range while setting this cut-off value. Setting a higher cut-off value results in higher specificity and lower sensitivity. Further larger studies are needed to set the cut-off level of CA 19-9 for diagnostic accuracy in cholestatic jaundice. We compared the CA 19-9 levels between patients with malignancy and benign disease to adjust the serum bilirubin level by biliary drainage, excluding surgical resection. Surgical resection could cause removal of epithelial cells of the tumor producing CA 19-9, as well as it can reduce the bilirubin concentration increased due to cholestasis.³⁰ CA 19-9 levels were found to decrease in both malignancy and benign groups, especially an obvious decrease was observed in the benign group. In all benign cases, the levels were decreased below those before biliary drainage, with 4 cases showing steady higher levels than the normal reference level. This study measured the CA 19-9 serum level after about 1-2 weeks, and the decrease was observed later than improvement of the bilirubin concentration. Biliary obstruction is not completely relieved, and the biliary drainage procedure can also be considered to cause epithelial irritation in the early phase. The CA 19-9 level in the malignant group remained high or was slightly decreased. Several studies have also suggested that the cut-off value was 90 U/mL, and specificity and sensitivity were 80-90% and 60-70%, respectively.^{10,29} We determined the cut-off value of CA 19-9 level as 38 U/mL after biliary drainage, and this cut-off value was almost equal to the normal reference level, 37 U/mL. Sensitivity and specificity were 62% and 88%, respectively, after biliary drainage. This finding is similar to the result of other studies for determining the appropriate CA 19-9 value.

The mechanism underlying the relationship of biliary cholestasis to CA 19-9 level has not been established completely. CA 19-9 is genetically influenced by the secretory status and Lewis genotype, including biliary mucous cells.³¹ Several hypotheses have been proposed which suggest that epithelial cells of the bile duct overproduce mucin and secretion contains the CA 19-9 epitope in the cholestatic situation. This can be explained by the dramatic reduction in the CA 19-9 level after biliary drainage in benign disease. Proliferating cells of the tumor itself play a major role in malignant disease and

CA 19-9 remains high due to overproduction of CA 19-9.³² However, a direct correlation between the CA 19-9 level and cholestasis was not observed in patients with malignancy and benign disease, but an obvious correlation (before $r=0.385$) was seen in patients with benign disease. Another confounding factor is C-reactive protein, one of the markers of inflammation, which could also affect the CA 19-9 level.¹⁰ In this regard, the present study excluded a confounding factor like inflammation due to surgical resection and infection.

Pathology and cytology are the confirmatory modalities for discriminating between malignancy and benign disease.³³ These modalities were not used in all cases, for the invasive and complementary step. Radiologic evaluations that correlated with the clinical manifestation were performed, and this will improve the diagnostic yield in pancreatobiliary disease.⁹

This study had a few limitations despite our efforts. Because of the retrospective nature of the study, cases were excluded if medical records were absent. Of the 981 patients who underwent biliary drainage due to obstructive jaundice, only 114 patients had records of CA 19-9 levels before biliary drainage and 1-2 weeks after biliary drainage. We analyzed that the proportion of patients in the malignant group was about 3 times more than that in the benign group. Tumor markers are frequently measured in patients with malignant disease. The results of the analysis are limited to the immediate application in clinical practice, and further studies are required. This study suggests that obstructive jaundice should be considered while interpreting CA 19-9 levels for differentiating between malignant and benign disease.

In conclusion, the present study suggested that we should consider the possibility of malignant causes of cholestasis if the CA 19-9 levels remain high or are more than 38 U/mL after resolution of cholestasis. Further larger studies will make it possible to determine the discriminatory diagnostic role of CA 19-9 in malignant and benign pancreatobiliary diseases and to define the cut-off value of CA 19-9 with accuracy in clinical practice.

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