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MASAKI HORIIKE, YOSHIKI MOROTOMI, SHIGEKAZU TAKEMURA et al. Identification of Factors Predicting the Onset of Gallbladder Cancer Complicated with Pancreaticobiliary Maljunction. *Osaka City Medical Journal.* 2020, 66, 49-57.

Osaka City Med. J. Vol. 66, 49-57, 2020

Identification of Factors Predicting the Onset of Gallbladder Cancer Complicated with Pancreaticobiliary Maljunction

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Abstract

Background

Pancreaticobiliary maljunction (PBM) is a congenital anomaly in which bile and pancreatic juice flow into each other and is well known to promote carcinogenesis. Further, carcinogenesis has a wide age range, from early childhood to old age. It is believed that differences in the confluence form, such as the junction angle θ between the bile duct and pancreatic duct, and the cross-sectional area of each lumen is strongly affected. We aimed to identify predictive factors of carcinogenesis.

Methods

We measured several confluence form parameters and examined differences between patients with and without gallbladder (GB) cancer who underwent surgery at our hospital.

Results

The cosine of θ (cosθ), junctional bile duct cross sectional area (Cb), and shape of the common bile duct {ratio of the maximum diameter of the congenital biliary dilatation to the diameter of the bile duct [MCBD/Db]} significantly differed between the groups.

Conclusions

We defined several cut-offs predicting the carcinogenesis of GB cancer as follows:

(1) $\cos\theta \geqq 0.84$, (2) $Cb \geqq 8.0$, and (3) $MCBD/Db \leqq 4.3$.

While it is impossible to measure the degree of reciprocal flow of bile and pancreatic juice in vivo, these cutoff values can be important indicator of the risk of GB carcinogenesis in PBM cases.

Key Words: Biliary tract neoplasms; Carcinogenesis; Pancreatic juice; Common bile duct; Pancreatic ducts

Introduction

Pancreaticobiliary maljunction (PBM) is a congenital anomaly in which the pancreatic and bile

Received October 29, 2019; accepted June 9, 2020.
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ducts merge outside the duodenal wall, and bile and pancreatic juice flow into each other because the sphincter of Oddi does not control the junction[1]. The reflux of pancreatic juice into the biliary tract provokes higher rates of biliary tract cancer[2-5] and is its most important prognostic factor. According to the results of a nationwide survey[6], bile duct and gallbladder cancers were found in 6.9% and 13.4% of adult patient with PBM, respectively. Biliary tract cancers develop about 15-20 years earlier in patients with PBM than in individuals without PBM. The carcinogenesis of biliary tract cancer accompanying PBM is considered to involve a hyperplasia-dysplasia-carcinoma sequence induced by chronic inflammation caused by bile and pancreatic juice flow into each other, which is different from the adenoma-carcinoma sequence or the de novo carcinogenesis associated with biliary tract cancers in patients without PBM. It is well known that the time of carcinogenesis varies widely from early childhood to old age[7-9]. This suggests that there are important factors controlling the appearance of carcinogenesis. Since PBM is a confluence phenomenon of the biliary tract and pancreatic duct, it is appropriate to quantify it with hydrodynamic considerations. However, to our knowledge no previous study has used a fluid dynamics approach to understand PBM.

Furthermore, biliary tract cancer has poor prognosis, and it is very useful to predict carcinogenesis in cases of PBM and to start treatment before carcinogenesis. We therefore studied PBM using a confluence model that considers two viscous fluids, bile and pancreatic juice, as a new hydrodynamics approach[10,11], and we aimed to identify predictive factors of carcinogenesis.

Methods

Patients

Among 91 patients with PBM who underwent hepaticojejunostomy between September 1990 and September 2017 at our hospital, we studied 37 patients for whom clear medical image findings and test results were available. We focused on the carcinogenesis of gallbladder (GB) cancer, and patients were grouped by whether they had GB cancer or not.

The clinical records, laboratory test results, and clear medical image findings of magnetic resonance cholangiopancreatography and abdominal computed tomography, which are pressure-free images of the biliary tract, were reviewed.

The local ethics committee approved this study (authorization number, 4013).

Parameter calculations

To consider PBM as a confluence of two viscous fluids, the key points to explain the phenomenon precisely are the flow quantity (including the lumen cross-section), junction angle, and lumen form. We set the following parameters to examine the confluence of PBM: diameters of the bile duct and pancreatic duct at the junction site, length of the common channel, maximum diameter of the congenital biliary dilatation (MCBD), and the ratio of MCBD to bile duct diameter at the junction site (MCBD/Db). Figure 1 visually illustrates these parameters. Additional parameters included in the model were the angle (θ) formed from the lines extending from the pancreatic and bile ducts, cross sections of the pancreatic and bile ducts at the junction site, and amylase in the gallbladder (AMY).

The bile duct cross-sectional area (Cb) and pancreatic duct cross-sectional area (Cp) were calculated as follows:

$Cb = \pi (Db / 2)^2$, $Cp = \pi (Dp / 2)^2$,

Where Db and Dp are the diameters of the bile and pancreatic ducts at the junction site, respectively.

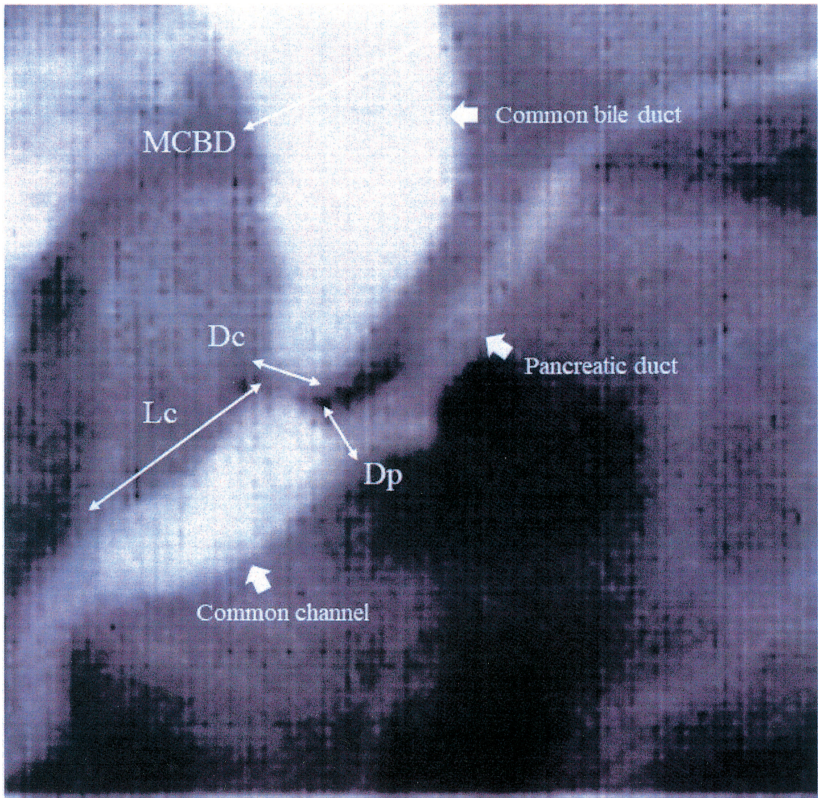

Figure 1. Parameters chosen to examine the confluence of pancreaticobiliary maljunction. MCBD, maximum diameter of the congenital biliary dilatation; Db, diameter of the biliary duct; Dp, diameter of the pancreatic duct; and Lc, length of the common channel.

The trigonometric function cosθ was calculated as follows:

(1) We draw a line crossing both extension lines from the bile duct and pancreatic duct, and make a triangle.

(2) We define the lengths of the triangle forming θ as a and c, and the length of the intersection is defined as b.

(3) We measure each length five times and calculate the average.

(4) Using the average values from step (3), we calculated cosθ as follows:

$$\cos\theta = (a^2 + c^2 - b^2) / 2ac \quad (-1 \leqq \cos\theta \leqq 1)$$

Figure 2 visually illustrates θ and cosθ to make them easier to understand, and the parameters mentioned above for the confluence of two viscous fluids are summarized in Table 1.

It is believed that free reflux of pancreatic juice into the biliary tract and gallbladder can induce chronic damage to them, and eventually cause biliary carcinogenesis. Because AMY is representative of the refluxing pancreatic enzymes, we were interested in the relationship between AMY and other parameters at the confluence of PBM. Therefore, we performed a correlation analysis between them.

Statistical analysis

Normally distributed continuous data were expressed as the mean±standard deviation (SD). Continuous variables were examined using the Mann-Whitney U test. Differences were considered significant at the level of $p<0.05$.

Spearman's rank correlation coefficient test was used to examine correlations between parameters, while the GB carcinogenic rate for each type was analyzed using the Chi-square test for independence.

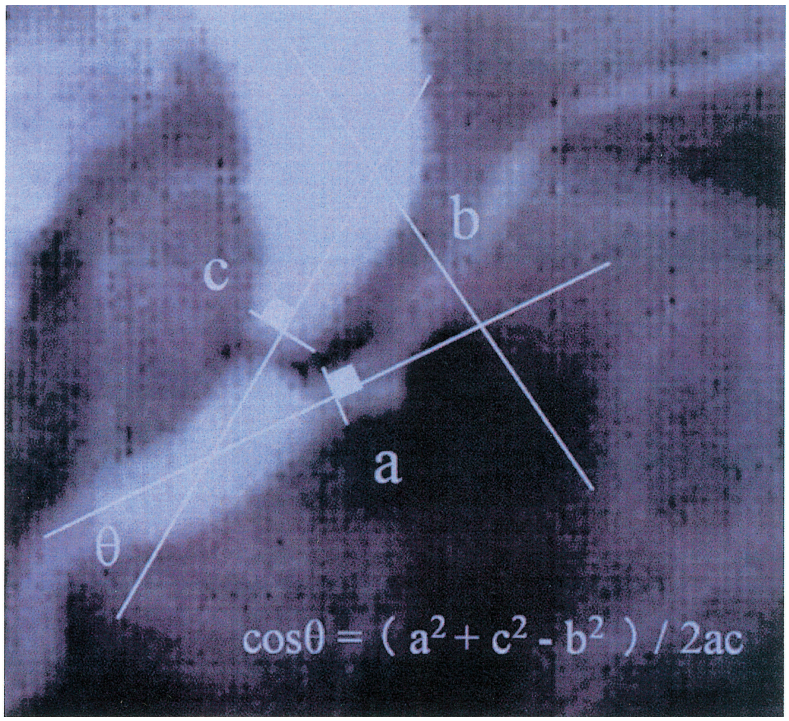

Figure 2. Visual illustration of θ, cosθ and three side lengths of the triangle a, b, and c.

Table 1. Parameters characterizing the fluid junction

Parameter	Abbreviation
Bile duct diameter	Db
Pancreatic duct diameter at juntion	Dp
Angle formed from the two extension lines	θ
Trigonometric function for θ	cosθ
Length of common channel	Lc
Bile duct cross section	Cb [= π (Dc /2)^2]
Pancreatic duct cross section	Cp [= π (Dp /2)^2]
Widest diameter of the choledochal cyst	MCBD
Proportion of the choledochal cyst	MCBD/Db
Amylase in the gall bladder	AMY

Data were analyzed using JMP, version 13 (SAS Institute Inc. Cary, NC, USA).

Results

Of 37 cases, there were 10 cases with GB cancer and 27 without. Table 2 presents the clinical characteristics between the groups. There was no significant difference except surgical age. Eleven cases were type Ⅰa, 15 were type Ⅰc, and 11 were Ⅳ-A, according to the Todani classification[1]. Figure 3 shows the age distribution of each type. The surgical age range was wide, and all types were observed in patients with GB cancer. Figure 4 shows the average surgical age for patients without GB cancer. There was no significant difference between types.

Figure 5 shows that the carcinogenic rate clearly differs between each type ($p=0.012$). Table 3 presents the comparisons of these parameters between patients with and without GB cancer. For

Table 2. Comparison of patients' characteristics

Variable	GB cancer Yes (n=10)	GB cancer No (n=27)	p value
Surgical age	56±10	17±18	<0.001
Male:female	2:08	9:18	0.47
Biliary calculus	2/10 (20%)	11/27 (40.7%)	0.34
AST U/L	95±182	101±167	0.79
ALT U/L	109±232	74±107	0.53
γGTP U/L	206±367	142±240	0.36
ALP U/L	541±860	719±151	0.34
T-Bil mg/dL	1.35±1.07	1.63±3.09	0.37
D-Bil mg/dL	0.65±0.89	0.51±0.92	0.5
LDH U/L	287±124	396±282	0.5
WBC /μL	6475±1817	8071±4239	0.37

GB, gallbladder; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, gamma-glutamyl transferase; ALP, alkaline phosphatase; T-Bil, total bilirubin; D-Bil, direct bilirubin; LDH, lactate dehydrogenase; and WBC, white blood cells.

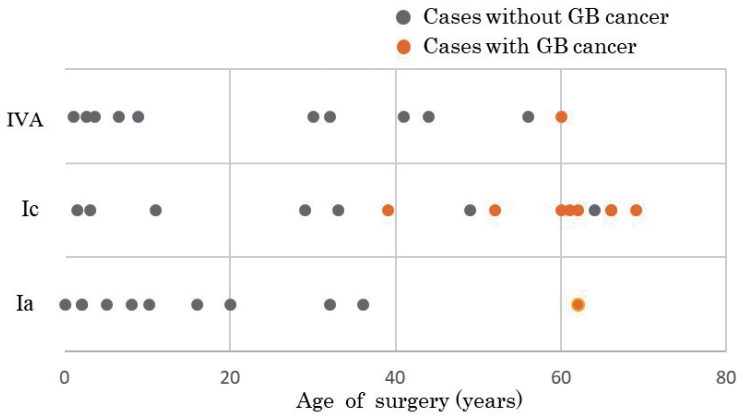

Figure 3. Age distribution of each type in the Todani classification. GB, gallbladder.

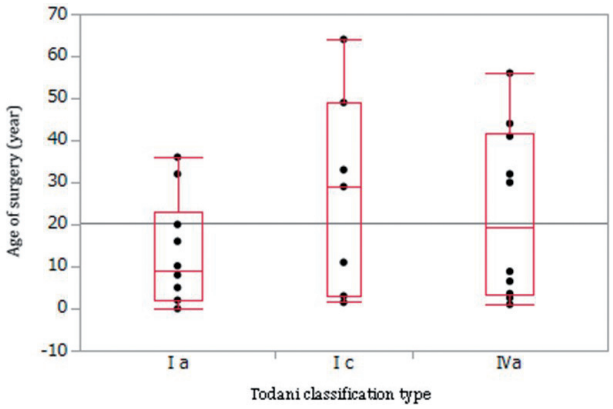

Figure 4. Average surgical age of patients without gallbladder (GB) cancer for all types.

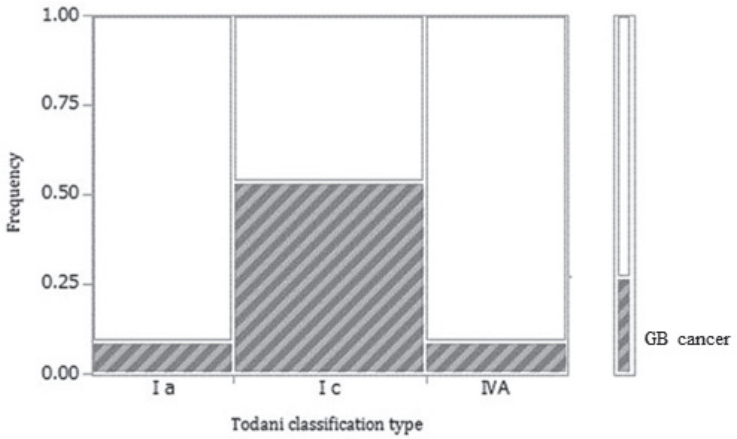

Figure 5. Gallbladder (GB) cancer rate for each type.

Table 3. Comparison of each parameter between patients with and without GB cancer

Variable	GB cancer		p value
	Yes (n=10)	No (n=27)	
Cb (mm^2)	19.12±11.82	1.89±1.61	<0.01
Cp (mm^2)	3.58±1.13	3.23±1.13	0.29
cosθ	0.87±0.15	0.35±0.47	<0.01
MCBD (mm)	20.9±8.70	30.4±18.6	0.32
MCBD/Db	4.48±1.96	25.60±21.09	<0.01
Lc (mm)	20.38±4.04	15.82±6.49	0.15
AMY ($\times 10^5$ U/L)	1.32±1.05	1.81±1.64	0.81

GB, gallbladder; Cb, bile duct cross-sectional area; Cp, pancreatic duct cross-sectional area; θ, junction angle between the pancreatic and bile ducts; MCBD maximum diameter of the congenital biliary dilatation; Lc, length of the common channel; and AMY, amylase.

patients with and without GB cancer, the values were respectively 19.12±11.82 and 1.89±1.61 mm^2 for Cb, 0.87±0.15 and 0.35±0.47 for cosθ, and 4.48±1.96 and 25.60±21.09 for MCBD/Db. These parameters all significantly differed between groups ($p<0.05$). On the other hand, Cp, MCBD, length of the common channel (Lc), and AMY were not significantly different.

Next, we generated scatter diagrams to determine which parameters are associated with the onset age. Figure 6 shows that the Cb of patients with GB cancer was higher than that of patients without GB cancer in all age groups. Figure 7 shows that cosθ had a wide range in the patients without GB cancer, while the values were greater than 0.84 for all patients with GB cancer except one ($\cos\theta=0.5$). This exception was an advanced gallbladder cancer case, which had highly infiltrated the common biliary tract. We suggest that the low value may not reflect the precise junction angle θ before carcinogenesis. Figure 8 shows that MCBD/Db took a wide range of values in the patients without GB cancer, while only low values were observed in patients with GB cancer. A low value indicates that the common bile duct is in a spindle-like or unexpanded form. Table 4 presents the examination result of the correlation with AMY and other parameters. The correlation coefficient between AMY

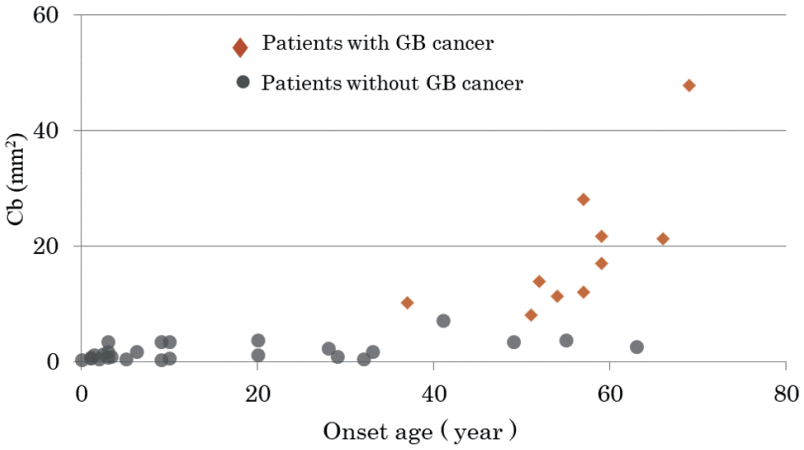

Figure 6. Scatter diagram showing the relationship between junctional bile duct cross-sectional area (Cb) and onset age.

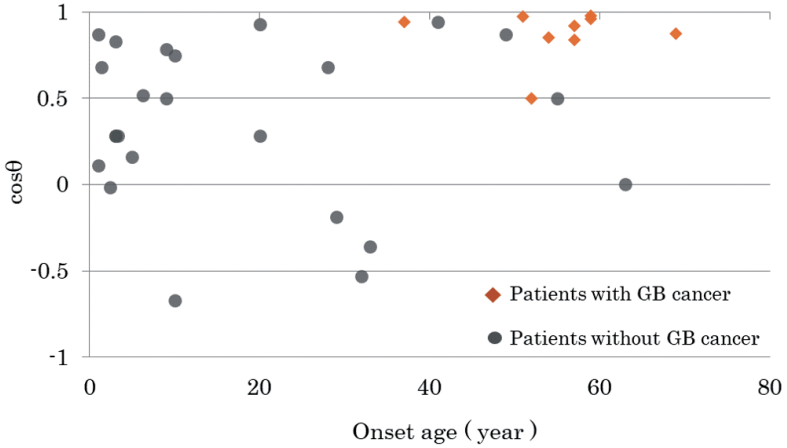

Figure 7. Scatter diagram showing the relationship between cosθ and onset age.

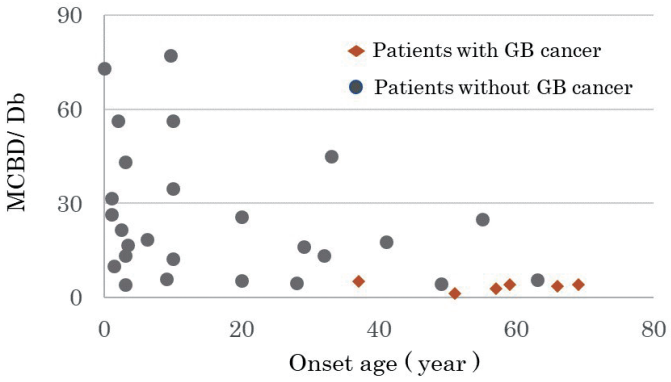

Figure 8. Scatter diagram showing the relationship between the ratio of the maximum diameter of the congenital biliary dilatation to the diameter of the bile duct (MCBD/Db) and onset age.

and cosθ was 0.50 ($p=0.02$), and that between AMY and Lc was 0.47 ($p=0.046$). The other parameters were not correlated with AMY, showing that refluxing pancreatic enzymes were influenced by cosθ and Lc.

Discussion

PBM is a single malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall, but there are several varieties in terms of their clinical courses and prognosis, owing to differences between the various forms of confluence. Therefore, we chose parameters to quantitatively evaluate these confluence forms, and then evaluated them as carcinogenic predictors.

Patients without GB cancer showed no differences in the surgical age between types (Fig. 4). In addition, the carcinogenic rate clearly differed between each type (Fig. 5). If there had been a type with a low surgical age, curative treatment would be completed before carcinogenesis, so the carcinogenic rate would be expected to decrease. However, since we did not find such a difference in surgical age, it can be inferred that there is a wide range of carcinogenic risk within each type. This means that variations in the connection between bile duct and the pancreatic duct strongly influences GB carcinogenesis.

Next, when comparing each parameter between patients with and without GB cancer, Cb, cosθ and MCBD/Db showed significant differences between patients with and without GB cancer (Table 3). In addition, these parameters behaved differently between patients with and without GB cancer (Figs. 6-8). These findings indicated that these parameters play important roles in carcinogenesis.

Specifically, the Cb of all patients with GB cancer exceeded 8.0 mm^2 (Fig. 6). We believe 8.0 mm^2 is an important boundary value that promotes an increased reflux of pancreatic juices to the biliary tract, and eventually contributes to carcinogenesis.

In addition, most values of cosθ in the patients with GB cancer were greater than 0.84 (Fig. 7), which was correlated with AMY (Table 4). These findings indicate that pancreatic juices may more easily reflux to the biliary tract when the junction angle is smaller, and a value of 0.84 may be an important boundary value that promotes the reflux of pancreatic juices to the biliary tract.

Finally, MCBD/Db reflects the degree of biliary tract dilatation and may be an indicator of the stagnation of bile and refluxed pancreatic juices.

MCBD/Db had values less than 4.3 in all patients with GB cancer, while it ranged widely in the patients without GB cancer MCBD/Db (Fig. 8). This different behavior of MCBD/Db seemed to indicate an important clue of carcinogenesis, and a value of 4.3 may be an important boundary value that controls the reflux of pancreatic juices to the biliary tract.

By examining the parameters listed above, we conclude that cosθ, Cb, and MCBD/Db can be

Table 4. Correlation between AMY and other parameters

Combination of parameters	Correlation coefficient	p value
AMY and Cb	−0.03	0.87
AMY and Cp	0.09	0.69
AMY and cosθ	0.50	0.02
AMY and MCBD	−0.08	0.75
AMY and MCBD/Db	−0.18	0.35
AMY and Lc	0.47	0.046

AMY, amylase; Cb, bile duct cross-sectional area; Cp, pancreatic duct cross-sectional area; θ, junction angle between the pancreatic and bile ducts; MCBD maximum diameter of the congenital biliary dilatation; Db, diameter of the bile duct; and Lc, length of the common channel.

defined as carcinogenic predictors. In addition, from the results of Figures 6-8, the prediction criteria for carcinogenesis are defined as follows.

(1) $\cos\theta \geqq 0.84$

(2) $Cb \geqq 8.0$

(3) $MCBD/Db \leqq 4.3$

While it is impossible to actually evaluate the degree of reciprocal flow of bile and pancreatic juice in vivo, the cutoff values above can be important indicators of the carcinogenic risk of GB cancer in patients with PBM.

Because of the small number of cases, we could not use multiple logistic regression analysis on Cb, $\cos\theta$, and MCBD/Db to determine which is the most useful parameter for carcinogenesis prediction. We therefore plan to accumulate additional cases in the future and evaluate more appropriate carcinogenesis prediction factors.

Acknowledgement

All authors have no COI to declare regarding the present study.

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