Chapter 3
Most Recent Analysis of a Japanese Nationwide Survey of Pancreaticobiliary Maljunction over a Quarter of a Century

Yuji Morine, Mitsuo Shimada, and Hiroki Ishibashi

Abstract We herein present the most recent data on pancreaticobiliary maljunction (PBM) from a nationwide survey, which 3,303 individuals with PBM were registered at over 100 medical institutions in Japan for over 25 years. In this analysis, clinical features of eligible patients (n = 3,184) were compared according to age and presence of biliary dilatation (BD), and key points of this analysis were the coexistence of associated cancers and the surgical procedure including postoperative complication. Of the adults with CBD, 7.0 and 13.5% had gallbladder or bile duct cancers, whereas 4.0 and 37.2% of those with PBM without BD had these cancers. Three children with congenital biliary dilatation (CBD) had bile duct cancers (0.24%). As to individuals without asociated cancers, cholecystectomy combined with extrahepatic bile duct resection had been performed on 94.3% of children with CBD and on 90.7% of those with PBM with BD. In contrast, this procedure had been performed on 29.8% of adults with PBM without BD but on 87.1% of those with CBD. Postoperative complication rates of this procedure ranged from 10 to 20%. Thus, this largest and most recent series could be widely used to assist in making decisions about treatment strategies and understanding the pathophysiology of PBM.

Keywords Nationwide survey · Biliary dilatation · Biliary tract cancer Extrahepatic bile duct resection

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Abbreviations

BD	Biliary dilatation
CBD	Congenital biliary dilatation
JSPBM	Japanese Study Group on Pancreaticobiliary Maljunction
PBM	Pancreaticobiliary maljunction

3.1 Introduction

Pancreaticobiliary maljunction (PBM), in which the junction of the pancreatic and biliary ducts is located outside the duodenal wall [1–3], has been defined as a congenital anomaly by the Japanese Study Group on Pancreaticobiliary Maljunction (JSPBM). This condition was first described by Komi et al. in Japan in 1976 [4] and is now widely recognized as an anomalous arrangement or abnormal junction of the pancreaticobiliary ductal system. The JSPBM was developed at a small conference and founded in 1983 to discuss the diagnosis and treatment of this anomaly. The JSPBM has classified this anomaly into two categories according to the presence of biliary dilatation (BD). Until now, PBM with BD has been recognized as the congenital biliary dilatation (CBD) worldwide. Almost all individuals with CBD of Todani Type I (except for Type Ib) and Type IV-A have associated PBM [5]. The principal project of the JSPBM has been to collect clinical data on patients with PBM from 1990, and they have twice reported the clinical characteristics of this anomaly [6, 7]. as well as publishing Japanese clinical practice guidelines for this condition [5].

The most important clinical feature of this condition is the high frequency of associated biliary tract cancers, which was revealed by the JSPBM nationwide survey. Furthermore, biliary carcinogenesis in individuals with PBM arises as a result of reflux and stasis of bile mixed with pancreatic fluid in the bile duct and gallbladder and is associated with various epithelial gene mutations, such as *K-ras* and *p53* [5, 8–12]. Another important issue investigated by the JSPBM is the optimal surgical strategy for PBM without BD, which may not strongly associated with bile duct cancers, because the treatment strategy differs between CBD and PBM without BD in adults [7]. A worldwide consensus has been reached that CBD without associated cancers is best treated by cholecystectomy combined with extrahepatic bile duct resection. However, for PBM without BD and no associated biliary tract cancer, the prophylactic combined resection of the extrahepatic bile ducts is generally not recommended because of the comparatively low risk of bile duct cancer.

The JSPBM has continued to collect data on PBM in its nationwide survey, 3,303 individuals with PBM in this Japan having been registered during the 25 years from 1 January 1990 to 31 December 2014. This chapter presents the most recent analysis of this large cohort of individuals with PBM.

3.2 Methods

3.2.1 Patients and Methods

As reported previously, the JSPBM via its Registration Committee enrolled 3,303 individuals who had been diagnosed with PBM and treated for it from 1 January 1990 to 31 December 2014 at over 100 institutions throughout Japan. The registration system did not have a definition of dilatation of the extrahepatic bile duct throughout the period of data collection, the diagnostic criteria for CBD having been established only in 2015 [13]. Therefore, the attending doctors at each institute had determined whether the bile duct was dilated according to their own criteria referring the Registration Committee recommended criteria for BD in 2006.

It is unknown whether 26 of the 3,303 individuals with PBM had BD; additionally, the ages on initial diagnosis of a further 93 cases are unknown because of loss of detailed registration records. In this registry, adults are defined as aged 15 years or more. Consequently, after exclusion of those with unknown BD status or age, 3,184 individuals were analyzed after allocating them to one of four groups (Fig. 3.1a).

To facilitate registration, the JSPBM Registration Committee has designated three types of PBM according to the type of confluence between the terminal common bile duct and pancreatic duct (Fig. 3.1b) [6] as follows: in Type A (known as C-P, choledochal, or right-angle type), the common bile duct seems to join the pancreatic duct; in Type B (known as P-C, pancreatic, or acute-angle type), the pancreatic duct seems to join the common bile duct; and in Type C (known as complex type) junction of the pancreaticobiliary ductal system is complex.

Using the above criteria, the clinical features of PBM, including biliopancreatic disease and associated biliary tract cancers, were evaluated in individuals with and without BD. Additionally, the pancreatic enzymes in the bile were examined when available and the surgical procedures and postoperative complications investigated in individuals without associated cancers.

3.2.2 Statistics

All statistical analysis was performed using statistical software (JMP 8.0.1, SAS Campus Drive, Cary, 27513 NC, USA). The significance of differences between groups in clinical features was analyzed with the χ^2 test. Amylase, lipase, and phospholipase A2 concentrations in bile juice are expressed as median and range and analyzed using one-way ANOVA and the Bonferroni correction. $P \leq 0.05$ was considered to denote significance.

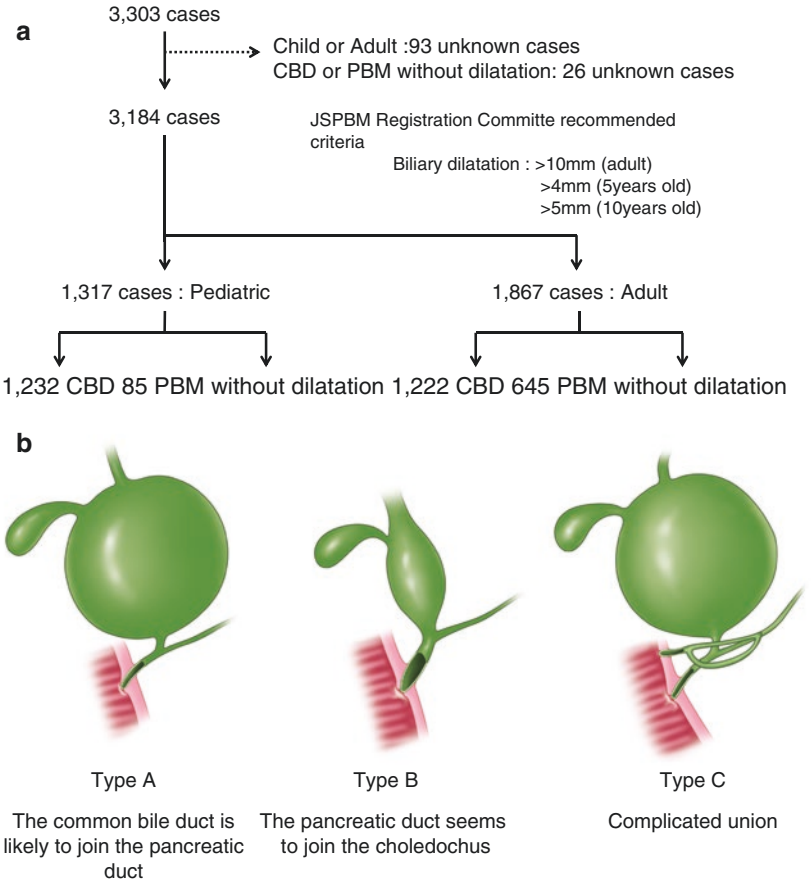

Fig. 3.1 (**a**) Flow chart showing patient enrollment and grouping according to age and presence of biliary dilatation. (**b**) Classification of pancreaticobiliary maljunction

3.3 Results

3.3.1 Patients' Distribution and Clinical Features

Using the specified cutoff age of 15 years, there were 1,317 pediatric and 1,867 adult patients. Of the pediatric patients, 1,232 had CBD (PBM with BD) and 85 PBM without BD. Of the adult patients, 1,222 had CBD and 645 PBM without BD; thus, BD was more frequently absent in adult than in pediatric patients. Figure 3.2 shows the age distribution of the registered PBM patients and that the adults frequently had PBM without BD.

Clinical features according to age and presence of BD are summarized in Table 3.1. Regarding confluence type, Type A (C-P type) occurred more frequently in individuals with CBD and Type B in those with PBM without BD, regardless of age. Pediatric patients more frequently had clinical symptoms than adults regardless

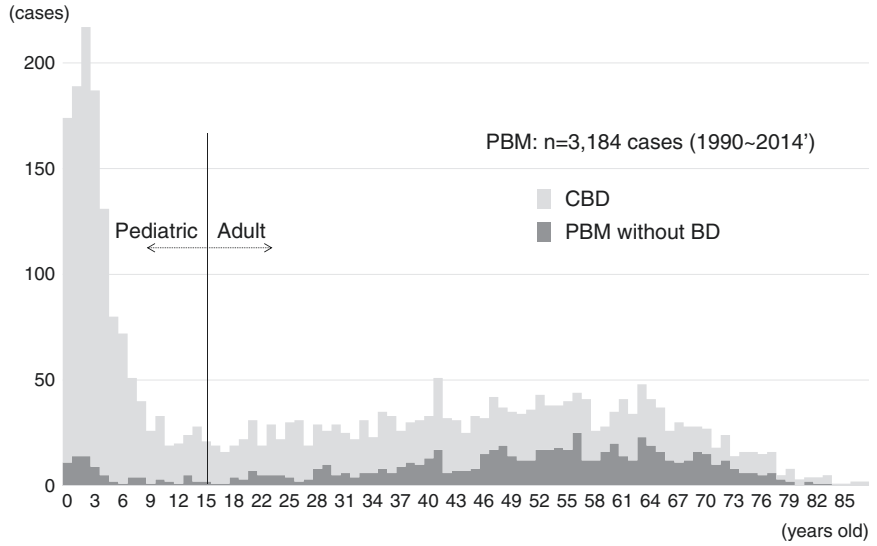

Fig. 3.2 Age distribution of registered individuals with PBM

Table 3.1 Clinical features of PBM according to age and presence of BD

	Pediatric (n = 1,018)		Adult (n = 1,511)	
Factors	CBD (n = 1,232)	PBM without BD (n = 85)	CBD (n = 1,222)	PBM without BD (n = 645)
Gender male:female (unknown)	298:924 (10)	23:62	310:894 (18)	173:463 (9)
PBM type A:B:C (unknown)	708:390:53 (81)	26:44:10 (5)	677:431:76 (38)	201:387:31 (26)
Common channel dilatation	354 (28.73%)	19 (22.35%)	317 (25.94%)	112 (17.36%)
Clinical symptom	1144 (92.86%)	77 (90.59%)	869 (71.12%)	441 (68.37%)
Abdominal pain	1140 (92.53%)	61 (71.76%)	726 (59.41%)	348 (53.95%)
Back pain	40 (3.25%)	3 (3.53%)	139 (11.37%)	82 (12.71%)
Jaundice	339 (27.52%)	19 (22.35%)	132 (10.80%)	90 (13.95%)
Tumor palpation	148 (12.01%)	6 (7.06%)	28 (2.29%)	14 (2.17%)
Fever	295 (23.94%)	17 (20.00%)	158 (12.93%)	73 (11.32%)
Vomiting	629 (51.06%)	47 (55.29%)	114 (9.33%)	42 (6.51%)
Nausea	435 (35.31%)	28 (32.94%)	143 (11.70%)	57 (8.84%)
Whitish stool	190 (15.42%)	11 (12.94%)	28 (2.29%)	12 (1.86%)
Preoperative complication				
Acute pancreatitis	327 (26.54%)	22 (25.88%)	100 (8.18%)	52 (8.06%)
Chronic pancreatitis	21 (1.70%)	3 (3.53%)	32 (2.62%)	6 (0.93%)
Biliary perforation	44 (3.57%)	3 (3.53%)	3 (0.25%)	1 (0.16%)

(continued)

Table 3.1 (continued)

Factors	Pediatric (n = 1,018)		Adult (n = 1,511)	
	CBD (n = 1,232)	PBM without BD (n = 85)	CBD (n = 1,222)	PBM without BD (n = 645)
Cholangitis	174 (14.12%)	8 (9.41%)	140 (11.47%)	48 (7.44%)
Liver dysfunction	410 (33.28%)	16 (18.82%)	162 (13.26%)	62 (9.61%)
Biliary stone	136 (11.04%)	7 (8.24%)	268 (21.93%)	152 (23.57%)
Gall bladder	26 (2.11%)	1 (1.18%)	112 (9.17%)	114 (17.67%)
Extrahepatic	96 (7.79%)	4 (4.71%)	161 (13.18%)	26 (4.03%)
Intrahepatic	10 (0.81%)	0 (0%)	24 (1.96%)	13 (2.02%)
Pancreatic stone	164 (13.31%)	12 (14.12%)	65 (5.32%)	10 (1.55%)
Calcium calculus	3 (0.24%)	0 (0%)	23 (1.88%)	3 (0.47%)
Protein plug	152 (12.34%)	10 (11.76%)	39 (3.19%)	4 (0.62%)

of the presence of BD (pediatric CBD, 92.8%; pediatric PBM without BD, 90.6%; adult CBD, 71.1%; adult PBM without BD, 68.4%). Also, there was no difference in the incidence of clinical symptoms according to the presence of BD regardless of age. The most common clinical symptom in all patients was abdominal pain, whereas nausea and vomiting occurred more frequently in pediatric than adult patients, regardless of the presence of BD.

The main preoperative complications were liver dysfunction, acute pancreatitis, and biliary perforation. In particular, acute pancreatitis and liver dysfunction were more frequent complications in pediatric than in adult patients, regardless of the presence of BD. Over 20% of adults had coexisting biliopancreatic stones, regardless of the presence of BD, whereas only about 10% of pediatric patients had such stones, regardless of whether they had CBD or PBM without BD. Conversely, coexistence of pancreatic stone was more frequent in pediatric than in adult patients, the stones most often comprising a protein plug in the former.

Regarding pancreatic enzymes in bile, amylase, lipase, and phospholipase A2 concentrations were investigated (Table 3.2). Amylase and lipase concentrations were significantly higher in both the gallbladder and bile duct in adults with CBD than in children with CBD; no other significant relationships were identified.

3.3.2 Prevalence of Associated Cancers

The prevalence of associated cancers according to patient group is shown in Table 3.3. Only three pediatric patients with CBD developed associated biliary tract cancers, and there were no other types of associated cancer. However, in adults, the prevalence of associated biliary tract cancers was extremely high, being 21.9% in those with CBD and 43.7% in those with PBM without BD; this difference was significant ($p < 0.0001$). Meanwhile, the prevalence of liver cancer was 0.65% in adults with CBD and 1.9% in those without BD ($p < 0.05$), whereas the prevalence of pancreatic cancer was 0.82% in adults with CBD and 1.4% in those with PBM without BD.

Table 3.2 Pancreatic enzymes in bile in individuals with PBM

Factors	Pediatric		Adult	
	CBD	PBM without BD	CBD	PBM without BD
Amylase: IU/L				
Gallbladder (range)	32,903 (0–6,633,000) $n = 772$	24,235 (0–1,266,399) $n = 42$	87,850 (0–6,920,000)* $n = 542$	55,977 (0–5,845,900) $n = 237$
Bile duct (range)	15,800 (0–958,000) $n = 631$	16,069 (0–592,000) $n = 30$	76,000 (0–6,730,000)** $n = 609$	53,400 (0–6,600,500) $n = 183$
Lipase: IU/L				
Gallbladder (range)	8,350 (0–1,059,156) $n = 453$	16,000 (2–841,400) $n = 21$	39,424 (0–1,332,500)** $n = 213$	55,006 (1–650,025) $n = 98$
Bile duct (range)	6,000 (0–2,149,688) $n = 335$	35,470 (138–606,810) $n = 16$	41,050 (0–1,873,000)* $n = 222$	60,550 (0–3,087,315) $n = 56$
Phospholipase A2: ng/dl				
Gallbladder (range)	888,758 (0–5,927,000) $n = 226$	283,650 (100–4,470,000) $n = 14$	431,000 (0–4,150,000) $n = 87$	747,200 (0–5,250,000) $n = 40$
Bile duct (range)	255,419 (0–1,000,897,000) $n = 166$	1,159,000 (698,000–1,620,000) $n = 2$	620,000 (0–5,630,000) $n = 97$	43,650 (0–2,110,000) $n = 18$

*$p < 0.001$ vs. pediatric CBD, **$p < 0.0001$ vs. pediatric CBD

Table 3.3 Prevalence of associated cancer according to patient group

Factors	Pediatric ($n = 1,018$)		Adult ($n = 1,511$)	
	CBD ($n = 1,232$)	PBM without BD ($n = 85$)	CBD ($n = 1,222$)	PBM without BD ($n = 645$)
Biliary cancers	3 (0.24%)	0 (0%)	268 (21.93%)	282 (43.72%)*
Liver cancer	0 (0%)	0 (0%)	8 (0.65%)	12 (1.86%)**
Pancreatic cancer	0 (0%)	0 (0%)	10 (0.82%)	9 (1.40%)
Others	0 (0%)	0 (0%)	31 (2.54%)	18 (2.79%)

*$p < 0.0001$ vs. adult CBD, **$p < 0.05$ vs. adult CBD

3.3.3 Locations of Associated Biliary Tract Cancers

Locations of associated biliary tract cancers are summarized in Table 3.4. All three associated biliary tract cancers in children with CBD were located in a dilated bile duct, one having progressed into an intrahepatic bile duct.

Bile duct cancer was identified in 7.0% ($n = 86$) and gallbladder cancer in 13.5% ($n = 165$) of adults with CBD and in 4.0% ($n = 26$) and 37.2% ($n = 240$), respectively, of adults with PBM without BD, the difference in prevalence of bile duct cancer

Table 3.4 Locations of associated biliary cancers

Factors	Pediatric (n = 1,018)		Adult (n = 1,511)	
	CBD (n = 1,232)	PBM without BD (n = 85)	CBD (n = 1,222)	PBM without BD (n = 645)
Gallbladder	0 (0%)	0 (0%)	165 (13.50%)	240 (37.21%)
Extrahepatic bile duct	2 (0.16%)	0 (0%)	82 (6.71%)	21 (3.26%)
Intrahepatic bile duct	0 (0%)	0 (0%)	2 (0.16%)	2 (0.31%)
Extrahepatic bile duct + intrahepatic bile duct	1 (0.08%)	0 (0%)	2 (0.16%)	3 (0.47%)
Gallbladder + extrahepatic bile duct	0 (0%)	0 (0%)	11 (0.90%)	13 (2.02%)
Gallbladder + intrahepatic bile duct	0 (0%)	0 (0%)	1 (0.08%)	0 (0%)
Gallbladder + extrahepatic bile duct + intrahepatic bile duct	0 (0%)	0 (0%)	3 (0.25%)	1 (0.16%)
Unknown	0 (0%)	0 (0%)	2 (0.16%)	2 (0.31%)

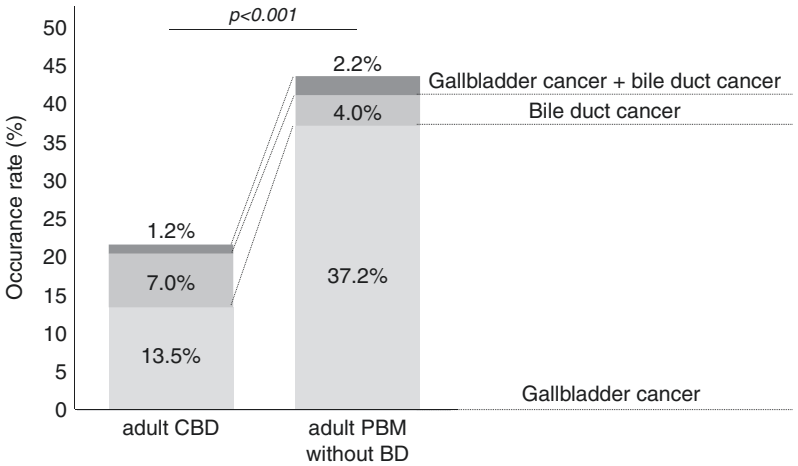

Fig. 3.3 Rates of associated biliary tract cancers in adults with PBM

being significant ($p < 0.001$) (Fig. 3.3). Additionally, the overall combined rate of bile duct and gallbladder cancers was 1.2% (n = 15) in adults with CBD and 2.2% (n = 14) in those with PBM without BD. Hence, the location of biliary tract cancers differed between adult patients with and without BD; however, gallbladder cancer was significantly predominant in both groups.

3.3.4 Surgical Procedures for PBM without Associated Cancer

In this study, the type of surgical procedure preferred for patients without associated cancers was also investigated (Table 3.5) because the prophylactic procedure of combined extrahepatic bile duct resection in individuals with PBM without BD is

Table 3.5 Treatment of PBM in patients without associated biliary cancer and without previous surgery (1997–2014)

Treatment	Pediatric (n = 788)		Adult (n = 741)	
	CBD (n = 734)	PBM without BD (n = 54)	CBD (n = 543)	PBM without BD (n = 198)
Cholecystectomy alone	2 (0.27%)	2 (3.70%)	17 (3.13%)	122 (61.62%)
Cholecystectomy + hepatic resection	0 (0%)	0 (0%)	0 (0%)	5 (2.53%)
Cholecystectomy + extrahepatic bile duct resection	692 (94.28%)	49 (90.74%)	473 (87.11%)	53 (26.8%)
Cholecystectomy + extrahepatic bile duct resection + hepatectomy	1 (0.13%)	0 (0%)	11 (2.03%)	3 (1.52%)
Pancreatoduodenectomy	0 (0%)	0 (0%)	14 (2.58%)	2 (1.01%)
Pancreatoduodenectomy + hepatic resection	0 (0%)	0 (0%)	1 (0.18%)	0 (0%)
Other procedures	7 (0.95%)	0 (0%)	1 (0.18%)	0 (0%)
Unknown procedure	27 (3.68%)	2 (3.70%)	7 (1.3%)	0 (0%)
No treatment	5 (0.68%)	1 (1.85%)	19 (3.50%)	13 (6.57%)

Table 3.6 Reconstruction methods after cholecystectomy + extrahepatic bile duct resection in patients without associated biliary cancer

Treatment	Pediatric (n = 741)		Adult (n = 526)	
	CBD (n = 692)	PBM without BD (n = 49)	CBD (n = 473)	PBM without BD (n = 53)
Intrahepatic hepaticojejunostomy	4 (0.57%)	1 (2.04%)	5 (1.06%)	2 (3.77%)
Hilar hepaticojejunostomy	202 (29.19%)	8 (16.32%)	164 (34.67%)	14 (26.42%)
Hepaticojejunostomy	443 (64.02%)	36 (73.47%)	262 (55.39%)	18 (33.96%)
Choledochojejunostomy	4 (0.57%)	1 (2.04%)	7 (1.48%)	4 (7.55%)
Hilar hepaticojejunostomy	11 (1.59%)	0 (0%)	0 (0%)	0 (0%)
Hepaticoduodenostomy	23 (3.32%)	2 (4.08%)	26 (5.50%)	2 (3.77%)
Choledochoduodenostomy	0 (0%)	0 (0%)	0 (0%)	9 (16.98%)
Unknown procedure	5 (0.72%)	1 (2.04%)	9 (1.91%)	4 (7.55%)

still controversial given the comparatively low risk of associated bile duct cancer. Various surgical procedures, including pancreatoduodenectomy or hepatectomy, had been performed on both pediatric and adult patients for individualized reasons.

Cholecystectomy combined with extrahepatic bile duct resection was performed on 94.3% of pediatric patients with CBD and for 90.7% of those with PBM with BD, probably because of high rate of clinical symptoms and complications. In comparison, this procedure was performed on only 29.8% of adult patients with PBM without BD but on 87.1% of those with CBD (Table 3.6). Hence, BD status made a considerable difference to the surgical procedures performed on adult patients but not to those performed on pediatric patients.

There is as yet no consensus on the optimal reconstruction procedure after extrahepatic bile duct resection. Table 3.5 shows these reconstruction procedures; hepatico- or choledochojejunostomy was performed more often than hepatico- or choledochoduodenostomy.

3.3.5 *Comparison of Postoperative Complications According to Surgical Procedure Performed on Patients with PBM*

Figure 3.4 shows the rates of postoperative complications after cholecystectomy alone and cholecystectomy with extrahepatic bile duct resection for both pediatric and adult patients with PBM and without associated cancers. The details of these complications are shown in Table 3.7. Ten to twenty percent of patients who had undergone cholecystectomy with extrahepatic bile duct resection developed postoperative complications, these rates being higher than in patients who had undergone cholecystectomy alone. In adults with PBM without BD, cholecystectomy with extrahepatic bile duct resection tended to have a higher complication rate than cholecystectomy alone; however, this difference was not significant (p = 0.068). Additionally, this rate did not differ from the rate of complications after cholecystectomy with extrahepatic bile duct resection in adults with CBD.

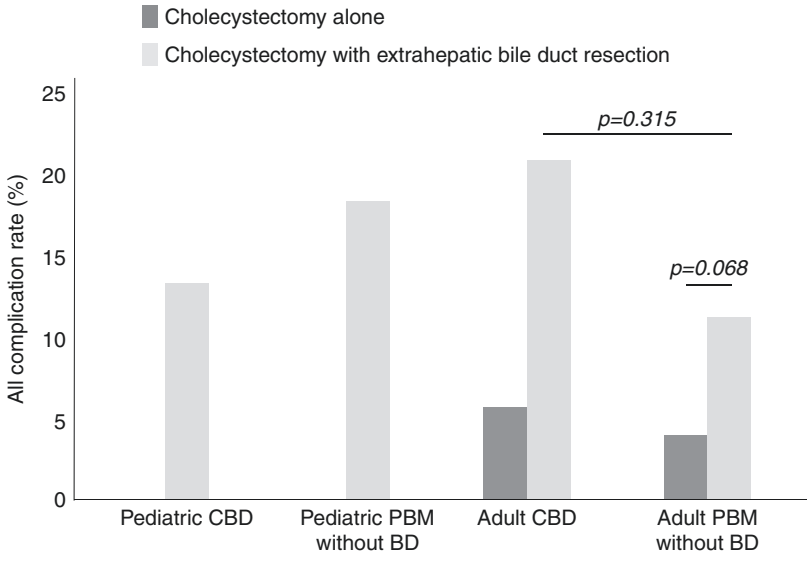

Fig. 3.4 Rates of postoperative complications in patients with PBM without associated cancers according to operative procedure and patient group

Table 3.7 Postoperative complications of cholecystectomy alone and cholecystectomy with extrahepatic bile duct resection (1997–2014)

	Pediatric (n = 4)		Adult (n = 140)	
Cholecystectomy alone	CBD (n = 2)	PBM without BD (n = 2)	CBD (n = 17)	PBM without BD (n = 123)
All complications	0 (0%)	0 (0%)	1 (5.8%)	5 (4.1%)
Cholangitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pancreatitis	0 (0%)	0 (0%)	0 (0%)	1 (0.81%)
Liver dysfunction	0 (0%)	0 (0%)	1 (5.8%)	1 (0.81%)
Ileus	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pancreatic fistula	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bile leakage	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)
Abdominal abscess	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Others	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)
Cholecystectomy + extrahepatic bile duct resection	Pediatric (n = 741)		Adult (n = 526)	
	CBD (n = 692)	PBM without dilatation (n = 49)	CBD (n = 473)	PBM without dilatation (n = 53)
All complications	93 (13.4%)	9 (18.4%)	99 (20.9%)	6 (11.3%)
Cholangitis	9 (1.3%)	1 (2.0%)	15 (3.2%)	1 (1.9%)
Pancreatitis	26 (3.8%)	3 (6.1%)	14 (3.0%)	0 (0%)
Liver dysfunction	30 (4.3%)	3 (6.1%)	26 (5.5%)	2 (3.8%)
Ileus	9 (1.3%)	0 (0%)	7 (1.5%)	0 (0%)
Pancreatic fistula	5 (0.72%)	0 (0%)	15 (3.2%)	1 (1.9%)
Bile leakage	14 (2.0%)	3 (6.1%)	13 (2.6%)	1 (1.9%)
Abdominal abscess	2 (0.29%)	0 (0%)	6 (1.3%)	1 (1.9%)
Others	17 (2.5%)	1 (2.0%)	19 (4.0%)	1 (1.9%)

3.4 Discussion

In this nationwide survey, we analyzed the updated registered data of a Japanese nationwide survey of PBM, which accumulated 3,303 patients with PBM at over 100 institutions for over 25 years, and here revealed the detail of clinical features, including associated cancers. We also investigated surgical procedures performed on patients without associated cancers and their postoperative complications. We have previously published the first and second versions of this Japanese nationwide survey of PBM [6, 7]. This most recent update includes the largest cohort of individuals with PBM reported thus far and may contribute to elucidating the pathophysiology of this disease according to the presence of BD and age.

Type A confluence between the terminal common bile duct and pancreatic duct was present significantly more frequently in individuals with CBD, whereas Type B was present significantly more frequently in those with PBM without BD, regardless of age. The incidence of clinical symptoms was significantly higher in pediatric than in adult patients. However, the incidence of clinical symptoms did not differ significantly between individuals with CBD and those with PBM without BD. We

identified no distinctive difference in symptoms according to BD status in either pediatric or adult patients. As to preoperative complications, acute pancreatitis and liver dysfunction tended to occur more frequently in individuals with CBD. Adult patients had a higher frequency of biliary stones, whereas pancreatic stones occurred more frequently in pediatric patients. Those findings did not differ substantially from those found at earlier stages of the Japan nationwide survey of PBM.

Our two previous Japanese nationwide surveys have highlighted the high frequency of associated biliary tract cancers and revealed that gallbladder cancer predominates regardless of the presence of BD in adults [6, 7]. We further analyzed the 3,184 eligible individuals with PBM in this study and here present the most detailed evaluation of associated biliary tract cancer distribution thus far. In this large study, we again found that the gallbladder was the most frequent site of cancer regardless of the presence of BD and that the rates of gallbladder versus bile duct cancers differed significantly between adults with CBD and those with PBM without BD. In particular, adults with PBM without BD had a much higher rate of gallbladder cancer than adults with CBD; conversely, the former's rate of bile duct cancer was lower. This cancer distribution is almost the same as that reported previously. However, the 4% rate of bile duct cancer in adults with PBM without BD found in the present study may be higher than the 3.1% of the second report. In 2009, the Japan Cancer Surveillance Research Group [14] reported the biliary tract (gallbladder and bile duct) cancer crude rates of 18.4 in male and 17.3 in female patients per 100,000 populations; thus, the overall incidence of associated bile duct cancer even in PBM without BD increased approximately 200-fold that of the general population. Additionally, we have reported the age at which individuals with PBM become susceptible to associated biliary tract cancers and suggested that they develop associated biliary tract cancers 15 or 20 years earlier than the general population. These data should be considered when making decisions on surgical strategy for individuals with PBM without BD and no associated biliary tract cancer. Additionally, our registry includes three pediatric patients with CBD and associated biliary tract cancer. Nine patients in Japan have reportedly developed associated biliary tract cancers as a complication of PBM, seven being bile duct cancers and two gallbladder cancers [5]; thus, their frequency may not be particularly high.

Given this background, we also investigated whether Japanese surgeons consider cholecystectomy combined with prophylactic extrahepatic bile duct resection a standard procedure for patients with PBM without associated biliary tract cancers. We found that this procedure is considered standard in pediatric patients. However, the treatment strategy differs considerably between adults with CBD and those with PBM without BD, cholecystectomy combined with extrahepatic bile duct resection not having been performed in the majority of adults with PBM without BD, probably because these individuals' risk of bile duct cancer is comparatively low. However, at 4.0%, this rate may be increasing, being about 200-fold that of the general population. The incidence of postoperative complications in adults with PBM without BD who had undergone cholecystectomy combined with extrahepatic bile duct resection was 11.3%, which we consider acceptable. Taken together, it may be necessary to reconsider whether this procedure should be the standard treatment.

Finally, to the best of our knowledge, over a quarter of a century, the JSPBM has registered the biggest cohort of individuals with PBM worldwide and investigated the clinical features, including associated cancers, in this study. Though it is necessary to continue to follow up these patients, data in this report could be widely used as a reference for understanding the pathophysiology and making decisions about treatment strategy for individuals with PBM.

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