Research Square

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The Impact of Pathological Cyst Wall Changes on Congenital Biliary Dilatation in Infancy

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Abstract

Purpose

This study aimed to evaluate the impact of pathological changes in bile duct cysts on the clinical and liver pathological findings in early infantile patients with congenital biliary dilatation (CBD).

Method

In patients with CBD who underwent definitive surgery ≤ 4 months of age, the clinical and liver pathological findings were analyzed according to the presence or absence of inflammatory and fibrotic changes on the luminal side of the bile duct cyst.

Results

Among the 14 patients with infantile CBD, 8 had inflammatory cell infiltration (iCBD), and 4 of these 8 patients showed the formation of a collagen layer together. In the remaining six patients, no infiltration of inflammatory cells or formation of collagen layers was observed (non-iCBD). In the iCBD group, the preoperative liver biochemistry levels were higher, the cyst amylase levels were lower, and the degree of liver fibrosis was more severe than those in the non-iCBD group, with significant differences. In comparisons of iCBD patients, there were no differences in the preoperative liver biochemistry levels, cyst amylase levels, and severity of liver fibrosis between the presence and absence of a collagen layer.

Conclusion

Inflammatory and fibrotic changes in the bile duct cysts due to obstructive cholestasis may affect the clinical and liver histopathological differences in early infantile CBD after birth.

Introduction

Congenital biliary dilatation (CBD) is characterized by extrahepatic bile duct dilatation with pancreaticobiliary maljunction (PBM), which in many cases causes pancreatic juice reflux into the bile duct [1, 2]. CBD diagnosed during infancy is identified as a cyst at the hepatic hilum in the prenatal period, or as symptoms of jaundice/acholic stool related to biliary obstruction after birth [3–5]. Pediatric patients with CBD may present with advanced liver fibrosis, and early surgical planning is recommended upon diagnosis [3, 5]. Hepaticojejunostomy (HJ) with appropriate resection of the external bile duct cyst is generally preferred as a definitive surgical method for pediatric CBD [6, 7]. Another surgical approach is hepaticoduodenostomy. However, there are concerns about the long-term adverse effects of bile juice flowing into the stomach [8] and intestinal contents flowing into the liver [9] after surgery. In recent years, laparoscopic HJ procedures including robotic assistance have become increasingly common [10, 11].

While its minimally invasive advantages should be actively adopted for pediatric CBD, cautions unique to laparoscopic techniques are warranted, such as the tendency toward anastomotic stricture at the hepatic hilum [12].

Although reports on the diagnosis, surgery, and liver histopathological stage for patients with CBD in the early infantile stage have been accumulated to date, there are few studies that have examined in detail the pathological changes in the bile duct cyst wall according to the pre- and post-operative course. In previous reports on the relationship between the histological findings of bile duct cysts and the physiological findings in pediatric patients with CBD, the inflammatory changes in bile duct cysts were influenced by the degree of choledochal pressure, negatively correlated with cyst amylase levels, and positively correlated with the liver biochemistry values [13]. The formation of a collagen layer with myofibroblasts that leads to lamellar sclerosis was also observed in patients with CBD < 12 months of age, as with cystic biliary atresia (BA) [14] which has a possibility to require liver transplantation due to progressive liver fibrosis [15] and it can be diagnosed as a bile duct cyst near the liver, similar to CBD during the fetal, neonatal, and infantile stages [16]. These reports suggest that the postnatal clinical course until definitive surgery in infants with CBD may result in inflammatory or fibrotic changes of the bile duct cyst related to the biliary obstructive pathology [13, 14].

We hypothesized that inflammatory or fibrotic changes in the bile duct cyst wall may cause clinical differences and liver histopathology after birth in early infantile CBD patients. We retrospectively studied this based on the pathological changes in the bile duct cysts of early infantile CBD patients, which need to be differentiated from cystic BA and sometimes require early surgery due to signs of cholestasis.

Patients and methods

We examined the clinical data and pathological specimens of liver biopsy specimens and the resected bile duct cyst wall, which were obtained at the first laparotomy definitive surgery (excision of the extrahepatic bile duct with Roux-en-Y HJ) in 14 patients who underwent surgery at ≤ 4 months of age from 107 pediatric patients with CBD followed for at least 5 years at Kyushu University between January 1991 and December 2025.

To evaluate the impact of inflammatory or fibrotic changes in the bile duct cyst wall on clinical and liver pathological findings, the analysis of the bile duct cyst wall focused on the presence of inflammatory cells, collagen layer, and myofibroblasts in the luminal side of the cyst using Hematoxylin and Eosin (HE) staining (Fig. 1) and immunohistochemical staining of anti-alpha-smooth muscle actin antibody (α-SMA, AT1202-1, pre-diluted working solution using Histostainer-AT [Nichirei Biosciences Inc., Tokyo, Japan]) (SI, Supplementary Information). We compared the clinical findings and liver pathology of patients with CBD depending on the presence or absence of inflammatory cells infiltration on the luminal side of cyst wall (iCBD, patients with inflammatory cell infiltration; non-iCBD, patients without inflammatory cell infiltration). As a subgroup analysis, we also conducted a comparison based on the presence or absence

of a collagen layer on the luminal side of the cyst wall. As the biliary epithelium was mostly denuded, it was not evaluated in the present study.

Liver specimens were analyzed using HE and Azan staining, as well as immunohistochemical staining for anti-cytokeratin-19 antibody (CK19, Dako, M0888, 1:50). Liver fibrosis was classified according to the New Inuyama classification as follows: F0, no fibrosis; F1, fibrous portal expansion; F2, bridging fibrosis; F3, bridging fibrosis with lobular distortion; and F4, cirrhosis [17], as previously reported [5]. The ductular reaction was graded according to the extent of lesions surrounding the circumference of the portal tract: none, mild, moderate (more than half), and severe (more than three-quarters) [5, 18]. The presence or absence of bile plugs in the intrahepatic bile duct and ballooning of hepatocytes were also evaluated.

A pathological examination of the hepatic tissue and bile duct cyst wall was jointly performed by pathologists. The resected liver tissues and bile duct cysts were cut into 4 μm sections for staining in this study. The sections were obtained from stored paraffin blocks that had been soaked in 10% formalin overnight. Images of stained sections were captured using a microscope (BZ-X710; Keyence, Osaka, Japan).

Preoperative blood tests and measurement of the cyst size in the horizontal plane using ultrasound or magnetic resonance cholangiopancreatography (MRCP) were performed within one week before definitive surgery. Sludge in the cyst was confirmed by imaging studies. The cyst amylase levels were measured when the catheter was inserted into the cyst before performing intraoperative cholangiography during the first definitive surgery. In patients with CBD, dilated or non-dilated intrahepatic bile ducts and PBM were confirmed by preoperative MRCP or intraoperative cholangiography, and the morphological type of the bile duct was classified based on the Todani classification [1]. Postoperative follow-up was performed using blood tests and imaging studies.

All statistical analyses were performed using the JMP® Pro 16.0.0 software program (SAS Institute Inc.). Continuous variables are presented as the median values with the interquartile range and were analyzed using Wilcoxon's rank sum test for two groups. Nominal variables were analyzed using Fisher's exact tests. Statistical significance was set at $P < 0.05$. Data were collected retrospectively from clinical records. This study was approved by the Institutional Review Board of Kyushu University (no. 22282-00).

Results

Pathological features of the cyst wall in patients with CBD who underwent definitive surgery at ≤ 4 months of age

In 14 patients with infant CBD ≤ 4 months of age, 8 patients (57%) had the infiltration of inflammatory cells (iCBD), and 4 patients (29%) of these 8 patients showed the formation of collagen layer together. In the remaining six patients (non-iCBD), no infiltration of inflammatory cells or formation of collagen layers was observed. Figure 1 shows the pathological features on the luminal side of the cyst wall in patients with non-iCBD (**A** and **B**), iCBD (**C** to **F**), and iCBD with a collagen layer (**E** and **F**). In iCBD patients,

inflammatory cell infiltration (▲) and collagen layer formation (▯) were observed on the luminal side of the cyst by HE staining. Myofibroblasts were widely observed in the collagen layer (SI).

Clinical and pathological differences regarding inflammatory changes in the bile duct cyst.

Table 1 shows the clinical and pathological features of 14 patients with infantile CBD who underwent definitive surgery at ≤ 4 months of age and comparisons among these features between patients with non-iCBD and iCBD. No differences were found in sex, birth weight, prenatal detection of cysts, and phototherapy for jaundice after birth between the groups. In the initial symptoms after birth, cholestatic symptoms such as jaundice or acholic stool were significantly observed in the patients with iCBD (88%). In contrast, four out of six non-iCBD patients were asymptomatic after birth until definitive surgery. These four patients were detected prenatally and underwent surgery due to the gradual enlargement of the bile duct cyst after birth.

Table 1
Comparisons of the clinical and pathological features between the patients with non-iCBD and iCBD.

Preoperative and intraoperative clinical findings		**Total, N = 14**	**non-iCBD, n = 6**	**iCBD, n = 8**	***p*-values**
Sex, number of females (%)		10 (71)	3 (50)	7 (88)	0.245
Prenatal diagnosis of the cyst, n (%)		9 (64)	5 (83)	4 (50)	0.301
Birth weight, kg (IQR)		3.1 (2.9–3.3)	3.2 (2.8–3.4)	3.0 (2.9–3.1)	0.401
Phototherapy for jaundice after birth, n (%)		2 (14)	0 (0)	2 (25)	0.473
Initial symptoms [Jaundice or acholic stool / Bleeding / None], n		8 / 2 / 4	1 / 1 / 4	7 / 1 / 0	**0.006**
Preoperative blood test (IQR)	TB, mg/dL	1.4 (0.4-6.0)	0.4 (0.3–4.4)	3.2 (1.2–7.9)	0.069
	DB, mg/dL	0.8 (0.1-3.0)	0.1 (0.1–0.4)	2.2 (0.7-5.0)	**0.017**
	AST, U/L	60 (33–138)	32 (27–43)	115 (66–406)	**0.002**
	GGT, U/L	526 (32-1382)	32 (20–455)	685 (456–1469)	**0.033**
	TBA, μmol/L	39 (5–82)	5 (5–9)	65 (60–99)	**0.003**
	APRi	0.47 (0.25–1.14)	0.25 (0.22–0.27)	0.77 (0.54–3.97)	**0.002**
Presence of sludge in the cyst, n (%)		10 (71)	2 (33)	8 (100)	**0.015**
Preoperative cyst size, mm (IQR)		45 (30–62)	31 (28–54)	51 (35–77)	0.155
Date of surgery, days (IQR)		106 (81–121)	118 (72–129)	96 (73–117)	0.333
Todani classification in type □a / □-A, n		8 / 6	4 / 2	4 / 4	0.640
Cyst amylase, U/L (IQR)		12 (3-520)	714 (81-1852)	3 (1–16)	**0.012**
Pathological findings of the cyst wall					

Normal upper limits of the blood test results: TB < 1.6 mg/dL, DB < 0.4 mg/dL, AST < 31 U/L, GGT < 65 U/L, and TBA < 9 μmol/L.

Preoperative and intraoperative clinical findings		Total, N = 14	non-iCBD, n = 6	iCBD, n = 8	*p*-values
Presence of inflammatory cells infiltration, n		8	0	8	-
Presence of collagen layer formation, n (%)		4 (29)	0 (0)	4 (50)	0.085
Pathological findings of the liver					
Liver fibrosis [F0 to F1 / F2 to F3], n		7 / 7	6 / 0	1 / 7	**0.005**
Ductular reaction [None to Mild / Moderate to Severe], n		8 / 6	6 / 0	2 / 6	**0.010**
Presence of bile plug in the intrahepatic bile duct, n (%)		7 (50)	1 (17)	6 (75)	0.103
Presence of ballooning of the hepatocytes, n (%)		5 (36)	1 (17)	4 (50)	0.301
Postoperative clinical findings					
Observation period after surgery, years (IQR)		14.5 (11.7–26.3)	13.2 (12.9–15.1)	20.8 (10.4–28.7)	0.852
Complications	Cholangitis, n (%)	0 (0)	0 (0)	0 (0)	1.000
	Ireus, n (%)	0 (0)	0 (0)	0 (0)	1.000
Latest blood test (IQR)	TB, mg/dL	0.6 (0.5–0.8)	0.6 (0.4–0.8)	0.7 (0.5–0.9)	0.602
	DB, mg/dL	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.471
	AST, U/L	24 (19–34)	31 (25–38)	20 (17–27)	0.070
	GGT, U/L	11 (10–15)	14 (10–41)	10 (10–11)	0.280
	TBA, μmol/L	8 (6–18)	7 (5–18)	8 (6–18)	0.897
	APRi	0.32 (0.29–0.36)	0.34 (0.30–0.40)	0.31 (0.28–0.34)	0.272

Normal upper limits of the blood test results: TB < 1.6 mg/dL, DB < 0.4 mg/dL, AST < 31 U/L, GGT < 65 U/L, and TBA < 9 μmol/L.

The preoperative serum values of liver biochemistry in direct bilirubin (DB), gamma glutamyl transpeptidase (GGT), and total bile acid (TBA) of iCBD patients showed higher levels with significant differences compared to the non-iCBD patients (2.2 mg/dL vs. 0.1 mg/dL, 685 U/L vs. 32 U/L, and 65 μmol/L vs. 5 μmol/L, respectively). Higher levels of aspartate aminotransferase (AST) (115 U/L vs. 32 U/L) and the AST to platelet ratio index (APRi) (0.77 vs. 0.25) were also observed in the patients with iCBD than in the non-iCBD patients. Sludge in the cyst was more frequently detected in patients with iCBD than in the non-iCBD patients, preoperatively. No differences were found in the preoperative cyst size, timing of definitive surgery, or Todani classification between the two groups. Conversely, the level of cyst amylase was lower, with marked differences (3 U/L vs. 714 U/L).

Regarding the pathological findings of the cyst wall, the presence of a collagen layer was more likely to be found in the iCBD patients than in the non-iCBD patients (50% vs. 0%, $p = 0.085$) (**E** and **F** in Fig. 1). In terms of the pathological features of the liver, iCBD patients had more severe liver fibrosis and ductular reactions than non-iCBD patients, with significant differences. Bile plugs in the intrahepatic bile duct were also more frequently recognized in iCBD patients (75%).

In the postoperative course, no significant differences were observed in complications and liver biochemistry between the two groups, and no patients with CBD showed any signs of progressive liver damage during the study period.

Impacts of inflammatory changes with fibrotic changes in the bile duct cyst.

A subgroup analysis was performed on the iCBD patients with and without a collagen layer (four patients each). Figure 2 shows a comparative review of representative data among non-iCBD (**a**), iCBD without a collagen layer (**b**), and iCBD with a collagen layer (**c**), and detailed data are shown in the SI.

In each group of iCBD patients, regardless of the presence or absence of a collagen layer, there were no differences in the preoperative liver biochemistry (DB, TBA, and APRi), cyst amylase, and pathological features of the liver. On the other hand, both iCBD groups had higher levels of preoperative liver biochemistry, lower values of cyst amylase, and more severe liver fibrosis (F2 to F3) with significant differences compared to the non-iCBD patients.

Discussion

This report is the first to investigate clinical and liver pathological features based on the histopathological changes in the bile duct cyst wall in early infantile patients with CBD. The present study revealed that infants with CBD who had inflammatory and fibrotic changes on the luminal side of the bile duct cyst more frequently showed cholestatic features, such as symptoms after birth, high levels of preoperative liver biochemistry in contrast to low levels of cyst amylase, and severe liver fibrosis than the patients without these pathological changes. Therefore, in early infantile CBD patients, inflammatory or fibrotic changes in the bile duct cyst wall, as an obstructive cholestasis, may impact both the clinical course and liver histopathological damage.

To date, some established surgical strategies for infants with CBD, including pre- and post-operative courses, have been reported, namely, early surgical planning [3, 4] based on clinical changes after birth, such as symptoms, laboratory data [5], cyst size, definitive surgery [6–8, 10–12], and pre- and post-operative evaluation by ultrasound or MRCP [3, 5, 7].

However, there have been very few reports on the pathological features of bile duct cysts in patients with infantile CBD. Turowski et al. reported a relationship between pathological changes in the bile duct and biliary pressure, including cyst amylase, in pediatric patients with CBD [13]. In their report, a negative correlation between the biliary pressure and cyst amylase levels was observed. Liver biochemistry was positively correlated with the biliary pressure, whereas cyst amylase was negatively correlated. Their cases with moderate to severe fibrotic changes with bile impregnation in the bile duct cyst showed a higher choledochal pressure with lower cyst amylase level. These findings suggest that the key factor in severe pathological changes in the cyst is distal bile obstruction rather than the reflux of pancreatic juice via PBM [13].

Slightly different from the bile duct cyst wall findings that we focused on, their findings [13] were in line with our study of the relationship between low levels of cyst amylase and the presence of bile duct inflammation and fibrotic changes. Todani et al. reported serum amylase levels in healthy infants with inguinal hernia and cyst amylase levels in infants with CBD [19]. Pancreatic exocrine production in healthy infants and the cyst amylase concentration via PBM in infants with CBD may be age-dependent [3, 19]. However, in this study, no difference was found in the age between the groups. In the present study, infants with CBD with inflammatory cell infiltration in the bile duct cyst had significantly lower cyst amylase levels, but more severe liver biochemistry and liver fibrosis than those without inflammation. Furthermore, sludge suspected to be biliary stasis in the cyst was confirmed preoperatively in all patients with inflammatory cell infiltration in the bile duct cyst. Therefore, our study also suggests that in early infancy CBD, the histological inflammatory and fibrotic changes in the bile duct cyst are more likely to be influenced by bile duct obstruction than by pancreatic reflux [3, 13].

Although we investigated the collagen layer in the bile duct cyst as fibrotic changes to evaluate its effect on the clinical and liver pathological findings in early infant CBD, there were no differences in these findings between the inflammation groups regarding the presence or absence of a collagen layer. In other words, both iCBD groups showed similar clinical and pathological features. The presence or absence of a collagen layer in the pathological examinations might depend on its shedding, similar to the mucosa within the bile duct cyst as sludge due to surgical conditions or sample processing. However, in another study concerning fibrotic changes in the bile duct cyst, Lobeck et al. reported that some patients with CBD under 12 months of age had fibrotic changes in the bile duct cyst wall, similar to those with cystic BA, such as myofibroblasts with a sclerotic collagen layer [14]. Cystic BA is an infantile disease that should be differentiated from CBD in the early postnatal period by imaging examinations. It is characterized by a small cystic lesion in the atrophic bile duct with obstruction. Previous reports on the bile duct cyst of cystic BA have shown pathological findings of a sclerotic collagen layer with myofibroblasts [14, 20–23].

As noted in their report, the formation of a collagen layer with inflammatory cells and myofibroblasts (SI) in the bile duct cyst wall was also observed in the present study of patients with CBD ≤ 4 months of age. There are similarities in the pathological findings of bile duct cysts between infant CBD and cystic BA, which Lobeck et al. described as an enigma [14]. However, it may result from obstructive cholangiopathy due to bile duct stenosis or an obstruction at the bottom of the cyst in patients with CBD, because of an elevated serum liver function data and severe liver fibrosis in our patients with inflammatory and fibrotic changes in the bile duct cyst wall. Therefore, these reports on the collagen layer of the bile duct suggest that the presence of an inflamed collagen layer indicates a pathological condition of cholestasis due to the bile duct obstruction, including the findings of our study.

The present study has some limitations. The study population included a small number of patients aged ≤ 4 months, and the data were collected at a single institution. These limitations may have resulted in some statistical bias. Our pathological data were limited to liver specimens and the bile duct of the cyst wall, which were jointly assessed by pathologists without using a method of interobserver agreement and they did not include the gallbladder or biliary epithelium. In this study, although no discrepancies were observed in the pathologist's assessments of the jointly evaluated specimens, the objectivity of the pathological data would be more appropriately ensured by a method of interobserver agreement. It was difficult to identify myofibroblasts in some bile duct cysts. A consistent and large database from multiple centers is required to make a more objective evaluation. Further studies with a quantitative analysis are needed to clarify the molecular mechanisms involving hepatocytes, bile ducts, and bile juice that contribute to pathological changes in pediatric CBD.

Conclusion

We evaluated the pathological changes in the bile duct cysts of patients with CBD. It is hypothesized that inflammatory and fibrotic changes in such bile duct cysts due to obstructive cholestasis may affect the clinical and liver histopathological differences in early infantile CBD after birth.

Abbreviations

CBD, congenital biliary dilatation; PBM, pancreaticobiliary maljunction; HE, Hematoxylin-Eosin; CK19, cytokeratin-19; MRCP, magnetic resonance cholangiopancreatography; IQR, interquartile range; TB, total bilirubin; DB, direct bilirubin; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; TBA, total bile acid; APRi, AST to platelet ratio index.

Declarations

Informed consent The patient and/or legal guardian consented to participate in this study. This study was approved by the Institutional Review Board of Kyushu University (no. 22282-00), and the information disclosure for consent was available publicly on the homepage of the IRB.

Declaration of Competing Interest

The authors declare no conflicts of interest in association with the present study.

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Author Contribution

Shirai T, Matsuura T, and Tajiri T wrote and revised the manuscript. Shirai T, Tamaki A, and Matsuura T designed and conducted the study. Shirai T, Tamaki A, Maeda S, Toriigahara Y, Takahashi Y, Yoshimaru K, Kohashi K, and Oda Y collected and analyzed the data. All authors have reviewed the manuscript.

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Supplementary Information.

Supplementary data are included with this article.

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Figures

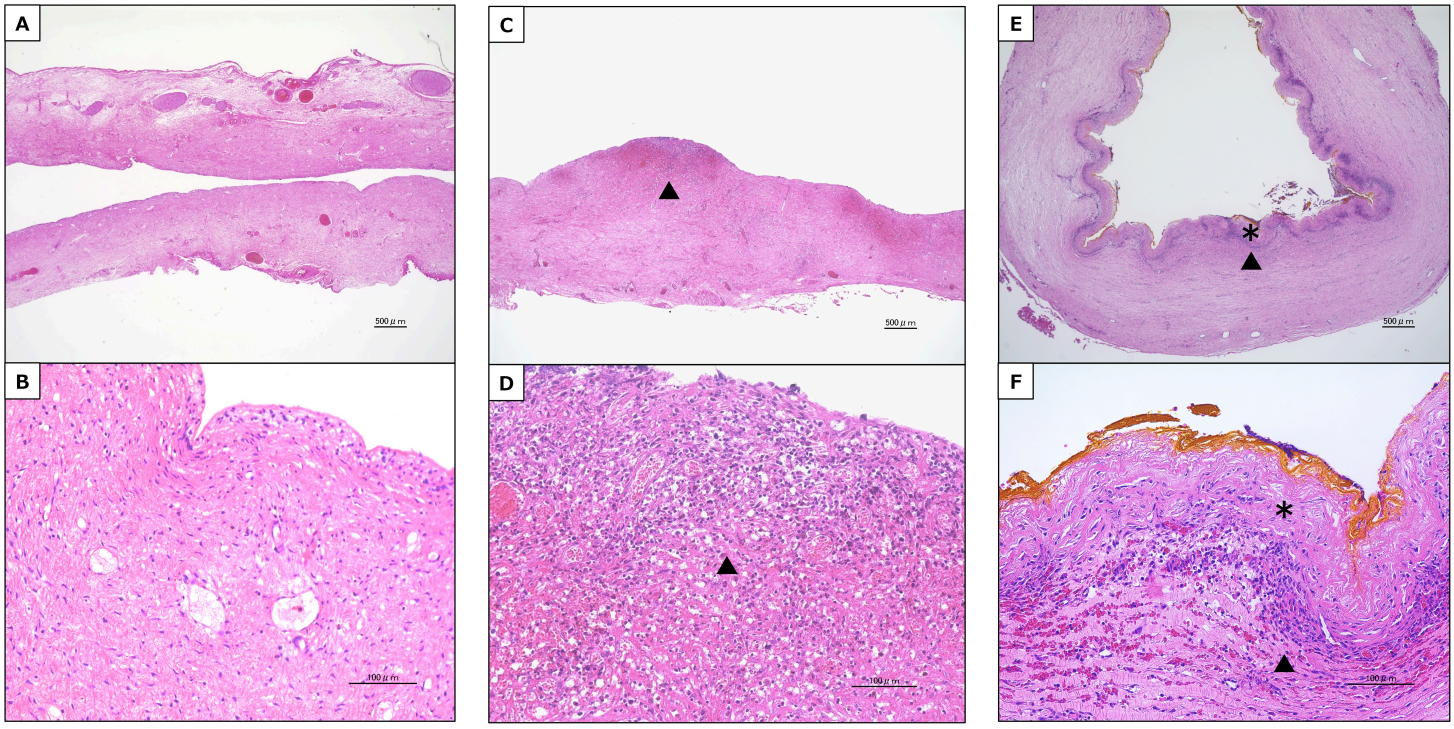


Figure 1

Pathological findings of the bile duct cyst wall in patients with congenital biliary dilatation.

Pathological findings of the luminal side of the cyst wall in patients with non-iCBD (**A**, **B**), iCBD without a collagen layer (**C**, **D**), and iCBD with a collagen layer (**E**, **F**). In patients with iCBD (**C** to **F**), infiltration of inflammatory cells (▲) and formation of collagen layer (□) were distributed on the luminal side of the cyst by HE staining. Lamellar fibrotic changes composed of a collagen layer (□) and infiltration of inflammatory cells (▲) were extensively observed on the luminal side of the cyst with bile impregnation in an iCBD case with a collagen layer (**E**, **F**). These findings were not observed in a non-iCBD patient (**A** and **B**). **A**, **C**, **E**: HE staining, magnification 2×. **B**, **D**, **F**: HE staining, magnification 20×.

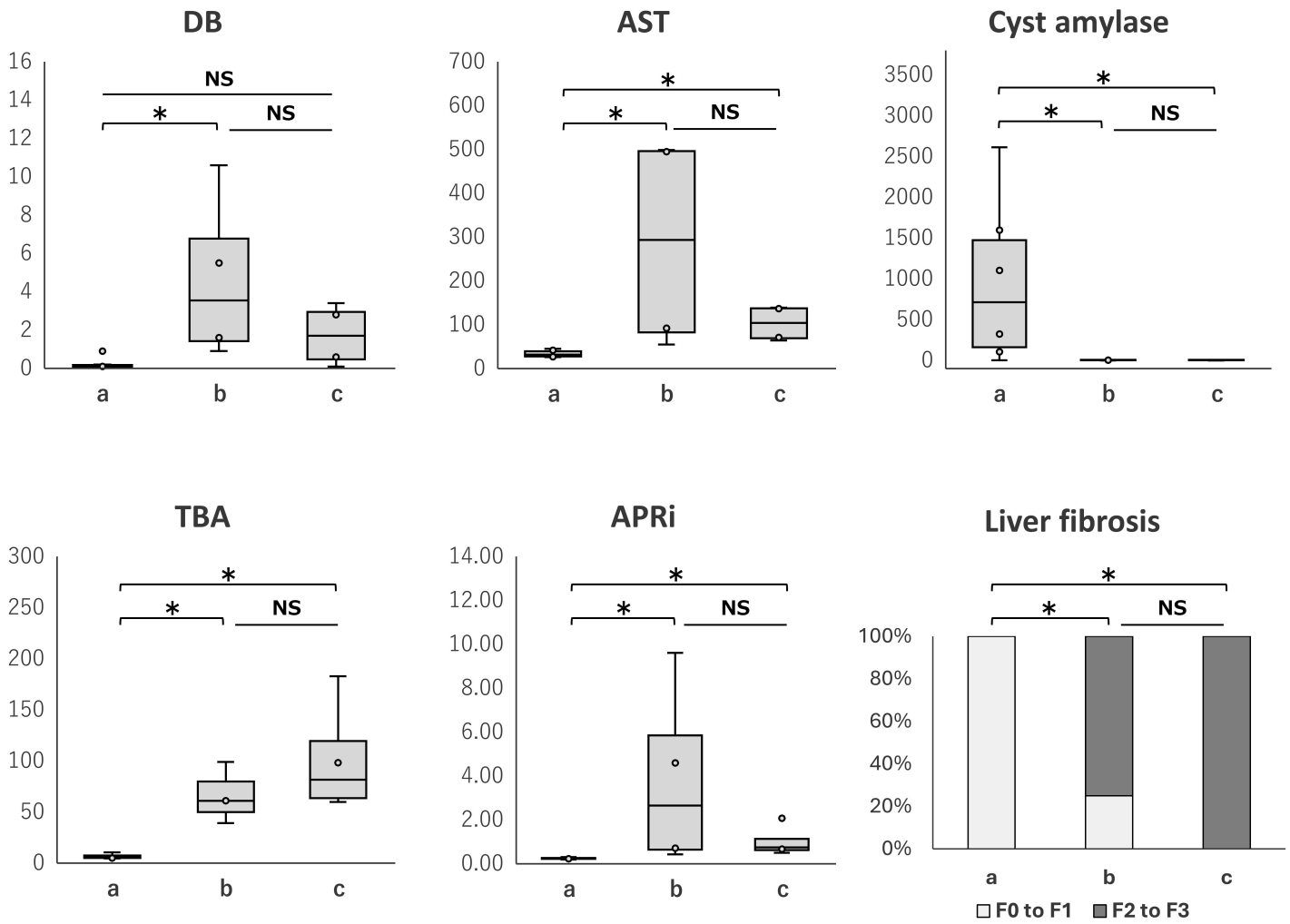


Figure 2

Comparisons of the clinical and pathological features in non-iCBD patients (**a**), iCBD patients without a collagen layer (**b**), and iCBD patients with a collagen layer (**c**).

No significant differences were found between the iCBD patients without collagen layer (**b**) and those with a collagen layer (**c**) in the preoperativelevels of DB (mg/dL), TBA (μmol/L), AST (U/L), APRi, and Cyst

amylase (U/L), and the degree of liver fibrosis. Both iCBD groups (**b**and **c**) had higher levels of preoperative liver biochemistry, lower values of cyst amylase, and more severe liver fibrosis with significant differences compared to the non-iCBD patients (**a**).

NS; Not Significant. □; p<0.050.

Supplementary Files

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