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Original Article

Characteristics and outcome of primary sclerosing cholangitis associated with inflammatory bowel disease in Asian children

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Key Words
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Abstract *Background:* Current knowledge on the clinical features and natural history of childhood primary sclerosing cholangitis — inflammatory bowel disease in Asia is limited. We described the presenting features and natural history of primary sclerosing cholangitis-inflammatory bowel disease seen in a cohort of Southeast Asian children.
Methods: We conducted a retrospective review of childhood primary sclerosing cholangitis-inflammatory bowel disease from three tertiary centers in Singapore and Malaysia.
Results: Of 24 patients (boys, 58%; median age at diagnosis: 6.3 years) with primary sclerosing cholangitis-inflammatory bowel disease (ulcerative colitis, n = 21; Crohn's disease, n = 1; undifferentiated, n = 2), 63% (n = 15) were diagnosed during follow-up for colitis, and 21% (n = 5) presented with acute or chronic hepatitis, 17% (n = 4) presented simultaneously. Disease phenotype of liver involvement showed 79% had sclerosing cholangitis-autoimmune hepatitis overlap, 54% large duct disease, and 46% small duct disease. All patients received immunosuppression therapy. At final review after a median [±S.D.] duration follow-up of

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4.7 [±3.8] years, 12.5% patients had normal liver enzymes, 75% persistent disease, and 12.5% liver failure. The proportion of patients with liver cirrhosis increased from 13% at diagnosis to 29%; 21% had portal hypertension, and 17% had liver dysfunction. One patient required liver transplant. Transplant-free survival was 95%. For colitis, 95% had pancolitis, 27% rectal sparing, and 11% backwash ileitis at initial presentation. At final review, 67% patients had quiescent bowel disease with immunosuppression. One patient who had UC with pancolitis which was diagnosed at 3 years old developed colorectal cancer at 22 years of age. All patients survived. *Conclusions:* Liver disease in primary sclerosing cholangitis-inflammatory bowel disease in Asian children has variable severity. With immunosuppression, two-thirds of patients have quiescent bowel disease but the majority have persistent cholangitis and progressive liver disease.

1. Introduction

Primary sclerosing cholangitis (PSC), a progressive, inflammatory, fibro-obliterative liver disorder, is the most challenging condition in clinical hepatology.[1,2] Persistent inflammation and fibrosis eventually leads to end-stage liver disease requiring liver transplantation (LT).[1,2] PSC associated with autoimmune hepatitis (AIH) is known as autoimmune sclerosing cholangitis (ASC).[1,2] The etiology and pathogenesis of PSC are unknown, although it is likely that the development of PSC represents a 'final common pathway' for multiple mechanisms of bile duct injury.[2] A recent genome-wide assay, identifying four new genome-wide significant loci, represents a substantial advance in the understanding of the genetics of PSC.[3] Recent evidence also suggests that intestinal microbiota play an important role in the etiopathogenesis of PSC.[4]

A large pediatric PSC series covering 781 patients confirmed progressive nature of PSC.[5] Children with portal hypertension and biliary complications were more likely to require LT.[5] Association between PSC and inflammatory bowel disease (IBD) is also well recognized.[1,6,7] Reports suggested that between 47 and 98% of PSC patients had IBD.[8,9] The IBD phenotype associated with PSC (PSC-IBD) is believed to be a distinct phenotype from IBD not associated with PSC.[6,7,10] Ulcerative colitis (UC) is found in 48%—86% of patients with PSC-IBD.[1] Crohn's disease, which is found in up to 13% of PSC-IBD, usually involves the colon (Crohn's colitis).[1] PSC-IBD is frequently characterized by rectal sparing and backwash ileitis and runs a mild or quiescent course.[1,7] However, there is an increased risk of colorectal neoplasia.[1,7]

To date, most of the published data on PSC-IBD are from adult patients.[6,7,9—14] Data from non-Caucasian population is scarce.[14] Ye et al. found that prevalence of PSC in Korean patients with UC was much lower than that of Western patients, but the endoscopic features were similar.[14] Similarly, most of the current knowledge on childhood PSC is from Caucasian population.[5,15—19] Little is known about its clinical features and natural history in Asian children.[20] The purpose of the present study was to describe clinical features and outcome of childhood PSC-IBD in South-east Asian children.

2. Patients and methods

This was a retrospective cohort study of patients diagnosed with PSC-IBD under the follow-up of three Paediatrics Liver Centers in Southeast Asia: National University Hospital and KK Women's and Children's Hospital, Singapore; and University of Malaya Medical Centre, Kuala Lumpur, Malaysia. All three hospitals are tertiary referral hospitals for pediatric liver diseases in Singapore and Malaysia, respectively. Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The present study was approved by the institutional review boards of all three centers.

2.1. Patient cohort and diagnosis

All patients younger than 18 years of age at the time of confirmed diagnosis between 1996 and 2014 in the three centers were included. Records of all patients with IBD and PSC in the three centers from the database were reviewed. Patients who fulfilled the inclusion criteria were included.

2.2. Diagnostic criteria of primary sclerosing cholangitis and autoimmune sclerosing cholangitis

Diagnosis of PSC was made based on presence of the following features: (a) cholestasis; (b) characteristic multifocal stricturing and dilatation of intrahepatic and/or extrahepatic bile ducts on cholangiography or abdominal ultrasound (US); (c) liver histology showing fibro-obliterative cholangitis or consistent with primary ductular involvement; and (d) absence of secondary causes of sclerosing cholangitis, such as Langerhans cell histiocytosis, cholangiocarcinoma, choledocholithiasis, and intrahepatic metastasis.[1,21] Presence of either cholangiographic or histological features was sufficient for diagnosis of PSC. Diagnosis of ASC was made in patients who had features of PSC and a positive antinuclear antibody (ANA) and/or anti-smooth muscle antibody (anti-SMA), anti-liver, kidney 1 (anti-LKM1) antibody, raised IgG and a liver histology consistent with AIH (interface hepatitis and portal lymphoplasmocytic infiltration).[1] No anti-liver cytosol (anti-

LC1) or IgG4 antibodies tests were performed in any of the centers. No additional IgG results were obtained during follow-up.

2.3. Classification of liver disease

PSC and ASC were classified as either large or small duct disease. 'Large' (macroscopic) duct disease was diagnosed in the presence of bile duct stenosis or dilatation, or attenuation of intraparenchymal arborization on magnetic resonance cholangiography (MRCP).[19] 'Small' (microscopic) duct disease was diagnosed when there was a positive histology report, including acute or chronic cholangitis associated with portal tract fibrosis, portal hepatitis, or cirrhosis, and concentric periductal fibrosis (onion skinning).[17] Diagnosis of small duct disease was made when histological features were present in the absence of characteristic cholangiographic findings.[17] Liver fibrosis was diagnosed when liver histology showed excessive accumulation of extracellular collagen fibers, while liver cirrhosis was defined as presence when there was demonstration of characteristic appearance of liver cirrhosis on imaging studies (ultrasound, CT scan or during MRCP examination) or histology showed regenerative nodules of hepatocytes surrounded by fibrous connective tissue which bridges between portal tract.[21]

2.4. Cholangiographic studies

Patients with initial IBD who developed laboratory features of cholestasis (raised conjugated bilirubin and/or gamma glutamyl-transpeptidase) during the course of disease were investigated for hepatobiliary disease. Cholangiography was performed by means of either MRCP or endoscopic retrograde cholangiography (ERCP). Some patients in the present cohort who did not have either MRCP or ERCP had abdominal US examination of the hepatobiliary system. Cholangiographic features suggestive of PSC in MRCP and ERCP include multifocal, short, annular strictures alternating with normal or slightly dilated segments, producing a 'beaded' pattern.[1,22] US features suggestive of PSC include bile duct wall thickening and/or focal bile duct dilatations, gallbladder wall thickening, gallbladder enlargement, presence of gallstones, and cholecystitis.[1]

2.5. Screening of PSC in children with IBD

Children with a confirmed diagnosis of IBD had regular monitoring of liver enzymes during their follow-up. In those with abnormally raised liver enzymes (alkaline phosphatase and/or γ-glutamyl transpeptidase) a diagnosis of PSC was excluded based on methods described above. No routine imaging of the hepatobiliary tree or liver biopsy was performed on diagnosis of IBD.

2.6. Definition of cirrhosis

Liver cirrhosis was confirmed by the presence of characteristic appearance on abdominal ultrasound and/or histologic appearance of liver fibrosis. Ultrasonic features of liver cirrhosis include nodularity and increased echogenicity.[23] Histological features of liver cirrhosis include parenchymal nodularity and fibrosis.[24]

2.7. Diagnosis, phenotype and outcome of IBD

The diagnosis of IBD was based on the presence of chronic symptoms, exclusion of infectious causes, and endoscopic and/or colonoscopic evidence of chronic mucosal inflammation and characteristic histology.[25] The patients were diagnosed to have CD, UC or IBD-unclassified (IBD-U) according to established clinical, biochemical, radiologic, endoscopic, and histologic criteria.[26] Briefly, UC is diagnosed based on presence of typical features: continuous mucosal inflammation of the colon, starting from the rectum with no small bowel involvement.[26] The mucosa shows erythema, friability, exudates and small ulcers. CD was diagnosed based on presence of mucosal aphthous ulcers, linear or serpentine ulceration and microscopic features of focal chronic inflammation, transmural inflammatory infiltrate, and submucosal fibrosis.[26] IBD-U was diagnosed in children with definite IBD where the inflammation was limited to the colon with features differentiating UC from CD being uncertain even after a complete workup.[26]

The final status of UC was determined by Pediatric Ulcerative Colitis Activity Index (PUCAI).[27] A PUCAI score of $<$10 was considered as in remission.[27]

2.8. Screening of IBD in children with PSC

After a patient was diagnosed with PSC, no routine colonoscopy to exclude IBD was performed. Colonoscopy was performed in the presence of symptoms suggestive of IBD, i.e., bloody diarrhea or abdominal pain. In the later part of the study, periodical stool screening with calprotectin was performed. In children with an elevated stool calprotectin level, IBD was excluded with colonoscopy.

2.9. Treatment protocol for PSC

For children with PSC, ursodeoxycholic acid was used a choleretic agent. In children also with autoimmune hepatitis (AIH), i.e., ASC, prednisolone and azathioprine were used as immunosuppression for AIH. In patients not responding to initial immunosuppression, mycophenolate mofetil, methotrexate, cyclosporin or tacrolimus was used as second line immunosuppression at the discretion of the clinician.

2.10. Data collection

Data were collected at the time of initial diagnosis (baseline) and at the latest review.

2.11. Statistics

Data were analyzed using IBM SPSS version 22.0. Statistical analysis included descriptive methods and standard tests of association. Percentages and means (or medians in non-

normally distributed data) were employed to describe clinical data. Statistical methods employed included Student's t-test for continuous data, and chi-square or Fisher exact tests for categorical data. Statistical significance was set at a P-value of <0.05.

3. Results

During the study period, 34 children were diagnosed to have PSC in the three participating centers (Fig. 1). Of these, 24 children (24/34; 71%) were found also to have IBD (PSC-IBD). There were 14 (58%) males. In total, during the study period, 257 patients were diagnosed to have IBD (Fig. 1). The proportion of patients with IBD who also had PSC (PSC-IBD) was 6.6% (17/257). Twenty-one children (87.5%) had UC, one (4%) had CD, while another two (8%) had IBD-U (Table 1).

3.1. Initial presentation

At initial presentation, 15 children (63%) had initial symptoms of IBD (Fig. 1). The PSC was diagnosed incidentally during follow-up of these patients. A further 5 (21%) had an initial presentation of PSC either as acute or chronic hepatitis necessitated further investigation, leading to diagnosis of PSC. The remaining 4 (17%) had an initial diagnosis of both IBD and PSC (Table 1).

3.2. Age distribution at initial diagnosis

The median age at onset of IBD was 5.0 years (mean 7.1 years; range 2—18 years). Thirteen of 24 (54%) had onset of IBD $\leq$ 5 years of age. The median ($\pm$SD) age at diagnosis of the 24 patients with PSC-IBD was 6.3 ($\pm$4.3) years (Table 1).

3.3. Family history

None of the patients in the present cohort had a positive history of IBD or PSC in the immediate family.

3.4. Other autoimmune diseases

None of the patients had other autoimmune diseases. One patient, an 18-year-old girl, had ankyloses of the temporomandibular joint. The condition responded to treatment. No other joints were involved.

3.5. Autoimmune sclerosing cholangitis at diagnosis

Nineteen (79%) of the 24 patients had ASC: 16 (67%) had a positive ANA (titers of $>$1:100); seven (29%) had a positive anti-SMA; and 16 (67%) patients had elevated serum IgG levels. Information on anti-LKM antibody was available for 12 patients and was negative in all patients.

3.6. Presenting clinical features

The presenting features of these 24 patients are shown in Table 1. At first diagnosis of PSC, 15 patients (71%) had hepatomegaly while five patients (22%) had splenomegaly. Only one (4%) had pruritus. At initial diagnosis, three patients (12.5%) had liver cirrhosis; these patients exhibited the features of bleeding esophageal varices (n = 1), ascites (n = 1), and both esophageal varices and ascites (n = 1). In all three patients, the onset of PSC preceded the diagnosis of IBD.

All patients had deranged liver function tests of varying severity with significant elevation of GGT at initial diagnosis (Table 2). Six patients (25%) also had hyperbilirubinemia at presentation.

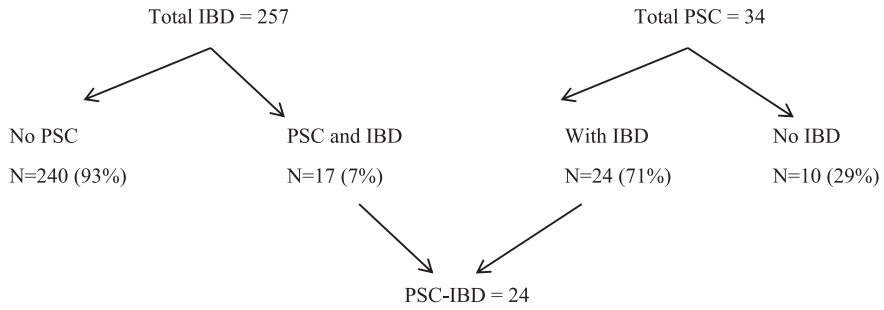

Figure 1 Proportion of primary sclerosing cholangitis patients with and without inflammatory bowel disease and proportion of inflammatory bowel disease with and without primary sclerosing cholangitis in the three centers during the study period.

Table 1 Demographic and clinical features of 24 Southeast Asian children with primary sclerosing cholangitis associated with inflammatory bowel disease.

Patient characteristics	No. of patients where information available	N (%)
Gender (Male)	24	14 (58%)
Family history of IBD	24	0 (0%)
Ethnicity	24	
Chinese		9 (37.5%)
Malays		8 (33%)
Indians		4 (16.7%)
Others		3 (12.5%)
Median age of diagnosis of PSC (year; ± SD)	24	6.3 ± 4.3
Current age (median, year; ± SD)	24	11.8 ± 5.2
Duration of follow-up (median, year; ± SD)	24	3.7 ± 3.8
Initial diagnosis	24	
IBD first		15 (63%)
PSC first		5 (21%)
Simultaneous		4 (17%)
Type of PSC	24	
Intrahepatic ducts only		3
Extrahepatic ducts only		3
Both intra- & extrahepatic ducts		7
Small duct (normal cholangiographic studies)		11
Autoimmune sclerosing cholangitis (ASC)		19 (79%)
IBD phenotype	24	
Ulcerative colitis		21 (87.5%)
Crohn's disease		1 (4%)
IBD-undetermined		2 (8%)
IBD location and disease behavior		
Involvement of colitis — pancolitis	24	23 (95%)
Rectal sparing	22	6 (27%)
Backwash ileitis	18	2 (11%)
Perianal disease	24	0 (0%)
First symptoms and signs of PSC		
Fatigue	23	20 (87%)
Hepatomegaly	23	15 (65%)
Jaundice	23	5 (22%)
Splenomegaly	24	5 (22%)
Liver cirrhosis	24	3 (12.5%)
Anorexia	23	2 (9%)
Variceal bleeding	23	2 (9%)
Ascites	23	2 (9%)
Pruritus	23	1 (4%)

Note: IBD — inflammatory bowel disease, PSC — primary sclerosing cholangitis.

3.7. Cholangiography

Nineteen of the 24 patients in the present cohort had MRCP, one had ERCP, and the remaining four had abdominal US examination. Eleven of the 20 patients either had MRCP or ERCP showed cholangiographic abnormalities. Of the four patients who had abdominal US, one had a dilated common bile duct while another had thickening of the gallbladder wall. Thus, in total of 13 (54%) patients had large duct disease (11 from MRCP/ERCP; two from abdominal ultrasound). Of these, seven had both extra- and intrahepatic biliary abnormalities; three had only intrahepatic abnormalities; and three one had only extrahepatic abnormalities. The remaining eleven (46%) had normal cholangiographic findings (small duct disease). None of the patients in the present cohort had any stent placement or balloon dilatation of the biliary tract.

3.8. Liver histology of PSC/ASC

Twenty-two (92%) patients had liver biopsy. Major histological findings were periductal fibrosis (n = 11; 50%), periductal inflammation (n = 8; 36%), portal edema (n = 6; 27%), duct proliferation (n = 6; 27%), fibro-obliterative cholangitis (n = 1; 5%), and cholestasis (n = 1; 5%). Nine of 22 (41%) biopsies had interface hepatitis with overall histology supporting a diagnosis of associated autoimmune hepatitis (AIH).

3.9. Medical therapy of PSC

All patients received ursodeoxycholic acid and immunosuppression for PSC. Prednisolone was the first line of immunosuppression (Table 3). Second-line therapy included azathioprine, mycophenolate mofetil, methotrexate, cyclopsorin and tacrolimus (Table 3).

3.10. Liver-related outcome

The median (±SD; range) follow-up duration was 4.7 (±3.8; range: 0.2—15.4) years. At final clinic review, three of the 24 patients (13%) showed normalization of liver enzymes and serum bilirubin. Eighteen (75%) patients had persistent cholangitis with stable liver function. Three (13%) patients had progressive worsening of PSC. Five patients (21%) had portal hypertension while four (17%) had impaired synthetic liver function.

One child with ASC with an associated UC had severe portal hypertension and severe synthetic liver function failure soon after diagnosis and underwent LT. Two years after LT, there was recurrence of AIH but no evidence of PSC in the graft, necessitating enhanced immunosuppression. Another 23 (95%) patients survived with their native livers. At final review, two patients were being assessed for LT because of decompensation of liver function. After a median duration of follow-up of 4.7 years, the overall survival rate with native liver was 95%.

There was no statistically significant relationship between the presence of large duct disease at initial diagnosis

of PSC and presence of liver cirrhosis at final review (4 of the 13 patients who had large duct disease had eventual liver cirrhosis [31%] vs. 3 of the 11 patients who had small duct disease had cirrhosis [27%]; P = 0.85).

3.11. Progression of liver disease

At initial diagnosis, three patients (12.5%) had cirrhosis and its complications (1 each for esophageal varies and ascites; 1 had both; Table 1). At final review (median duration of follow-up, 4.7 years), seven patients (29%; Table 3) had liver cirrhosis (2 had portal hypertension; 1 had synthetic liver dysfunction; 3 had both portal hypertension and synthetic liver dysfunction).

3.12. IBD phenotype, location and disease behavior at associated PSC

Twenty-one (87.5%) of the 24 patients had UC. The only one who have CD had pancolitis phenotype (L2 according to Paris classification of Pediatric IBD).[22] Two (8%) patients who had IBD-U also had pancolitis at initial diagnosis. Twenty-one of the 23 patients (93%) with complete information on disease location had pancolitis. Rectal sparing was observed in six of 22 patients (27%) where information was available. Backwash ileitis was observed in two (11%; 2/18) of 18 patients. None of the patients had anal disease in the present cohort, including the one patient with CD.

Table 2 Laboratory investigations results of 24 Southeast Asian children with primary sclerosing cholangitis associated with inflammatory bowel disease.

	N	Normal reference	Mean ± S.D.
Total bilibubin (μmol/L)	24	<34	28.6 ± 64.2
Albumin (g/L)	24	35–55	37.8 ± 6.4
International normalized ratio	21	1.0–1.2	1.09 ± 0.23
Alkaline phosphatase (IU/L)	24	150–400 (4–10 y) 180–450 (11–16 y) 50–250 (17–18 y)	535.9 ± 346.7
Alanine aminotransferase (IU/L)	24	<40	286.7 ± 301.4
Aspartate aminotransferase (IU/L)	23	<40	301.9 ± 349.0
Gamma glutamyl-transpeptidase (IU/L)	24	<55	328.3 ± 196.3
Ig G (mg/L)	21	450–900 (1–3 y) 500–1500 (4–19 y)	2420 ± 1100

Y: year.

Table 3 Management and outcome of 24 Southeast Asian children with primary sclerosing cholangitis associated with inflammatory bowel disease.

	No. with information available	Number (%)
Medical therapies for both PSC and IBD	24	
Ursodeoxycholic acid		23 (96%)
Prednisolone		18 (75%)
Azathioprine		18 (75%)
Mycophenolate mofetil		6 (25%)
Methotrexate		3 (13%)
Cyclosporine		2 (8%)
Tacrolimus		2 (8%)
Infliximab		2 (8%)
Disease status of IBD on final review	24	
Remission; on immunosuppression		16 (67%)
Partial response or no response to immunosuppression		8 (33%)
Complications of PSC on final review		
Liver cirrhosis (either histology and/or imaging studies)		7 (29%)
Portal hypertension		5 (21%)
Decompensated liver function		4 (17%)
Failure to thrive[a] (n = 23)	23	5 (22%)
Disease status of PSC on final review	24	
Normalization of liver enzymes		3 (13%)
Partial normalization of liver enzymes		18 (75%)
Not responding to therapy		3 (13%)
Liver transplant		1 (4%)
Awaiting liver transplant		2 (8%)

[a] Failure-to-thrive is defined as the weight-for-age z score ≤ -2.0.

3.13. Medical therapy of IBD

In addition to medical treatment for PSC, three patients were also given biologics (infliximab) for persistent severe IBD. All had severe UC with pancolitis.

3.14. IBD-related outcome

At the final review, the IBD of 16 (67%) patients was in remission (Table 3). The remaining 8 (33%) patients had persistent disease. No patient had IBD-related surgery.

3.15. Malignancy

One patient with UC with pancolitis was diagnosed at three years of age. The disease was easily controlled with azathioprine. This patient developed PSC at ten years of age. At 22 years of age, the disease was complicated by multi-focal adenocarcinoma involving the cecum, transverse and sigmoid colon. He had total colectomy and chemotherapy. No other patient in the present cohort developed cholangiocarcinoma or other malignancies.

3.16. Death

No patients in present cohort died as a result of PSC, IBD or their complications.

4. Discussion

The present study reviews the phenotype, presenting clinical features and outcome of a cohort of Asian children with PSC-IBD from Southeast Asia. To our knowledge, this is the first study on childhood PSC-IBD from non-Caucasian population.[6,28] The present study shows that 70% of Asian childhood PSC was associated IBD. The commonest IBD phenotype was UC (87.5%). In most (70%) patients with PSC the IBD preceded onset of PSC with the majority of PSC patients diagnosed during the follow-up of IBD. Similar to studies in Caucasian children, 80% of cases of PSC also had features of AIH.[17]

PSC is characterized by progressive cholangitis. Despite immunosuppression, the majority of PSC cases (87%, 21/24) in the present study had persistent or progressive disease. At final review, normalization of liver enzymes was seen in only 13% (3/24). Three patients (12.5%) either had or were awaiting LT because of end-stage liver disease. In addition, the proportion of children with liver cirrhosis increased from 12.5% (3/24) at initial presentation to 29% (7/24) after a median follow-up of 4.7 years. This could be an underestimate, as serial liver biopsies were not performed. On the other hand, for IBD, 67% of children had a quiescent disease at the end of review.

The current study confirms that a combination of ursodeoxycholic acid and immunosuppression is ineffective to control progressive cholangitis in PSC.[1,2] However, a recent study using norUrsodeoxhycholic acid showed promising preliminary results in adults with PSC, demonstrating improvement of cholestasis.[29] Currently, no similar study has been conducted in pediatric PSC.

Large duct disease has been associated with a worse prognosis in both adult and pediatric studies.[5,9] In the current study, 54% (13 of 24) of the patients with PSC had 'large duct disease' at initial diagnosis. This is lower compared to 87% in the studies by Deneau et al.[5] and 76% by Valentino et al.[17] However, this could be an under estimate as 4 patients who did not have either MRCP or ERCP had abdominal US. Liver US is known to underestimate cholangiographic abnormalities in children with PSC.[17]

Cholangiocarcinoma is the most common malignancy associated with PSC in adult study.[9] However, it is rare in childhood PSC.[5] It was not observed in the current study. Nevertheless, it is important to monitor for the presence of this complication in all children with PSC.

Several studies, particularly from the adult population, showed that IBD associated with PSC is a distinctive phenotype as compared to IBD without PSC.[7,9,30] A systematic review showed that IBD associated with PSC had a more quiescent disease course, with frequent pancolitis and infrequent rectal sparing and backwash ileitis.[7] In the current study, the clinical features of children with IBD without PSC were not available for comparison. Nevertheless, the phenotype and outcome of IBD in the current study are similar to those reported in the literature.[30] For instance, two-thirds (67%) of patients with IBD in this study had a quiescent disease course. Pancolitis was seen in 95% of patients and rectal sparing was noted in only 27% of patients. This is very similar to Lascurain et al.'s study.[30] One possible explanation for this difference in behavior is difference in stool microbiome between patients with and without PSC.[4]

PSC is highly associated with IBD. In adult studies, approximately 50%—80% of PSC patients had concomitant IBD, predominantly UC.[7,31] The reported prevalence of IBD in childhood PSC was 76%.[5] The proportion of children with PSC and IBD in the current study was 71%. The true prevalence is unclear as different studies reported different methods for diagnosis. Some authors routinely screen all patients with PSC for IBD with colonoscopy and histology, while others will only confirm the diagnosis with colonoscopy if the patient is symptomatic.[7] Thus, there is a possibility of under diagnosis of IBD in patients with PSC without a standard routine surveillance, particularly in the early course of illness.[31]

There is even less consensus on screening for PSC in children with IBD.[31] In the adult population, the reported prevalence of PSC in IBD ranges from 0.8% to 5.6% in patients with UC, and 0.4%—6.4% in patients with CD.[31] This discrepancy in the reported prevalence may be due to methodologic differences, selected patient populations, and non-uniform diagnostic criteria.[31] A major issue is a lack of objective reference standard for the diagnosis of PSC on MRCP, especially in pediatric PSC. The significance of detection of subclinical lesions on MRCP is not well defined.[31] A lack of effective therapy to reverse the progressive nature of PSC also renders routine screening for early PSC in patients with IBD doubtful. Nevertheless, it is likely that PSC may be under-diagnosed in patients with IBD.

Colorectal cancer developing in patients with PSC-IBD is a major concern, especially in Asian patients.[14,15,20] In addition to cholangiocarcinoma, an increased risk of other cancers such as pancreatic cancer has been noted in patients with PSC-IBD as compared with IBD without PSC.[28] In Korea, risk of developing colorectal cancers was about 15%.[14,20] It is mandatory to monitor for of colorectal cancers in patients with PSC-IBD, especially in those with long standing disease. A vigorous endoscopic surveillance for colorectal adenocarcinoma has been recommended, even in children.[5,17] In the current study, one patient developed adenocarcinoma of the rectum.

Several limitations of the present study include its retrospective nature with no uniform protocol on imaging, liver biopsies or screening of other liver- or IBD-related

complications. Secondly, data on clinic reviews may be incomplete. Thirdly, recently diagnosed patients with a relatively short duration of follow-up were also included. The median duration of follow-up was 4.7 years. Finally, there was no estimate on the population prevalence of PSC since the present study was based on three referral centers from Malaysia and Singapore.

However, the advantage of this study was that it originated from Asia where the prevalence of IBD is much lower as compared to the Caucasian population. The only other study on childhood PSC-IBD in Asia was a case series from Korea describing 13 children with PSC-IBD.[20] After a median follow-up of 6.4 years, two patients (15%) underwent LT and two (15%) had colorectal cancer, 13 and 20 years after the onset of UC, respectively.[20] An adult study from Korea showed the incidence of colorectal cancer to be 14.3%.[14]

In conclusion, the present study confirms the progressive nature of childhood PSC-IBD in Asian children. The majority of children were incidentally diagnosed during review for IBD. Two-thirds of patients could only achieve partial disease control. Liver disease was progressive over time, with the distinct possibility of developing liver cirrhosis and end-stage liver disease necessitating liver transplantation. On the other hand, two-thirds of patients had a quiescent course of colitis. This highlights not only the need for regular monitoring of liver function tests on a periodic basis in IBD patients but also the need to have a low threshold for utilizing radiological investigations in addition to liver biochemistry to diagnose PSC early.

Conflict of interest

None of the authors has any personal or funding interests to be declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2018.09.007.