CHAPTER 7

DISEASE PROGRESSION IN PAEDIATRIC- AND ADULT- ONSET SCLEROSING CHOLANGITIS: RESULTS FROM TWO INDEPENDENT DUTCH REGISTRIES

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ABSTRACT

Background & Aims: Sclerosing cholangitis (SC) is a severe liver disease leading to destruction of bile ducts. It is believed to run a milder course in children than in adults. To test this assumption, we evaluated time-to-complication curves in two independent pediatric-onset cohorts from the same geographical area.

Methods: Short-term disease outcomes were evaluated with an online clinical registry that was filled with data on children with SC diagnosed between 2000 and 2017 and who were followed bi-annually thereafter. Long-term disease outcomes were evaluated in a pediatric-onset subcohort derived from a previously published population-based study from the Netherlands. Time-to-complication in the first cohort was defined as the time from diagnosis until portal hypertension, biliary obstructions and infections, development of malignancy, or liver transplantation, whichever came first. In the second cohort time-to-complication was defined as the time until liver transplantation or PSC-related death.

Results: Median age at diagnosis in the first cohort (n=86) was 12.3 years. In the first 5 years post-diagnosis 23% of patients developed complications. The patients in the population-based study (n=683) were stratified into those diagnosed before the age of 18 years ("pediatric-onset" subcohort, n=43) and those diagnosed after the age of 18 years ("adult-onset" subcohort, n=640). Median age at diagnosis was 14.6 and 40.2 years, respectively. Median time-to-complication in the pediatric-onset and adult-onset subcohorts were not statistically different.

Conclusion: Pediatric and adult-onset SC run a similar long-term disease course. Pediatricians who treat children with SC should monitor them closely to recognize early complications and control long-term sequelae.

KEY POINTS BOX

- It is thought that pediatric-onset SC has a milder phenotype and therefore a more favourable outcome compared to adult-onset SC, but the time horizon of earlier studies was restricted due to transfer to adult-oriented care.
- We evaluated time-to-complication curves in two independent Dutch cohorts.
- A total of 23% pediatric-onset patients developed biliary and portal hypertensive complications in the first five years after SC diagnosis.
- No differences were seen between pediatric-onset SC and adult-onset SC with regard to long-term liver-related outcomes and survival.

INTRODUCTION

Sclerosing cholangitis (SC) is a rare cholestatic disease characterized by fibrosis of the intra- and/or extrahepatic bile ducts and is strongly associated with inflammatory bowel disease (IBD). The disease presents in most patients between the age of 25 and 40 years1, 2, though it is recognized as an important cause of chronic liver disease in children. Patients with SC carry an ongoing and disproportionate high clinical need because of the association with poor clinical outcomes including end-stage biliary cirrhosis and hepatopancreatobiliary and colorectal malignancies.3, 4
In the early stages bile duct disease may be easily overlooked, as symptoms are initially nonspecific and intestinal disease is frequently more prominent in patients with concomitant IBD.5
It is suggested by several authors that pediatric-onset SC runs a milder course and has a more favourable outcome compared to adult-onset PSC.6, 7 The time horizon in these papers could have been restricted by transfer of patients to adult-oriented care. To test the assumption of a relatively benign disease course in pediatric-onset SC, we evaluated time-to-complication curves in two independent Dutch cohorts. The first cohort contained data of children with SC who were followed bi-annually until transfer to adult-oriented care, the second cohort consisted of adults with pediatric-onset SC derived from a previously published population-based study from the Netherlands.

METHODS

Objectives

Our objectives were to [1] describe short-term outcomes, for which we created an online registry filled with closely followed data on pediatric-onset SC patients in the Netherlands during the first five years after diagnosis, and [2] compare long-term disease outcomes between pediatric- and adulthood-onset SC patients, for which we used data from a second, independent, previously published population-based study from the Netherlands. [2]

Short-term disease outcomes (cohort 1)

Setting

We used longitudinal data on pediatric-onset SC patients who were diagnosed between 2000 and 2017 at five tertiary hospitals in the Netherlands, including one referral pediatric liver transplant center. The data were derived from local clinical databases and International Classification of Diseases code searches.
We assessed clinical, biochemical, radiological and histological parameters at SC diagnosis, and followed the patients at least bi-annually until transfer to adult-oriented care. We created an online clinical registry using Castor Electronic Data Capture (Amsterdam, The Netherlands8), which was filled with retrospective data for this specific research project. After this project, the registry will be maintained and regularly updated to serve as a prospective registry.
The ethical committee of the Erasmus MC in Rotterdam reviewed the study protocol and waived the need for informed consent due to the anonymous and non-interventional fashion of the study (MEC-2016-736). Secondary approval was obtained from all other participating centers.

Participants

Pediatric-onset SC is classified as primary SC (PSC) or autoimmune SC (ASC). The latter is also known as PSC-autoimmune hepatitis (AIH) overlap syndrome, due to concurrence of increased levels of transaminases, hypergammaglobulinaemia and autoantibodies. We included patients diagnosed with SC before the age of 18 years. Patients with cholangiopathies secondary to surgical complications or other liver diseases were excluded. We reviewed immunological, radiological and/or histological features to determine if patients were appropriately assigned a diagnosis of PSC, ASC or AIH (Figure

S1). The diagnosis of SC was based on a cholestatic biochemical profile (raised conjugated bilirubin levels and/or elevation of alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT)), in combination with bile duct irregularities on endoscopic retrograde cholangiography (ERC) or magnetic resonance cholangiography (MRC), and/or ductular reactions on liver histology. SC patients with at least one of the appropriate auto-antibodies in their serum (anti-nuclear antibodies (ANA); anti-smooth muscle antibodies (anti-SMA); anti-liver kidney microsome type 1 (anti-LKM-1); or antibody to liver cytosol (anti-LC-1)) were classified as ASC. SC patients with negative auto-antibodies were classified as PSC.9, 10 Patients were excluded from further analysis when they had isolated AIH,11, 12 or when both cholangiography (ERC or MRC) and liver biopsy were missing in the diagnostic work-up (Figure S1).

Variables

Baseline data included patient demographics, associated immune disorders and presence and type of inflammatory bowel disease (IBD), signs, symptoms and age at SC diagnosis; and detailed information on diagnostic work up. We used age- and sex-adjusted cut points for elevated ALP. Cut-offs were 424 U/L for boys and girls younger than 13 years, 454 U/L for boys 13 to 17 years, and 254 U/L for girls between 13 and 17 years.13 Hepatomegaly was defined as a liver length measured in the midclavicular line exceeding the upper limit of normal for height and age.14 Splenomegaly was defined as a splenic length measured in coronal section (passing through the splenic hilum) exceeding the upper limit of normal for age and gender.14

Follow-up data included the clinical endpoints (1) portal hypertensive complications, (2) biliary complications, (3) hepatobiliary malignancy, (4) liver transplantation, or (5) death from liver disease. Portal hypertensive complications included thrombocytopenia (<150 × 109/l), bleeding oesophageal varices and the need for placing a transjugular intrahepatic portosystemic shunt (TIPS). Biliary complications included cholangitis or bile duct obstruction, whether or not requiring endoscopic intervention. The composite outcome short-term disease progression was defined as occurrence of at least one of five clinical endpoints within the first five years following diagnosis of SC.

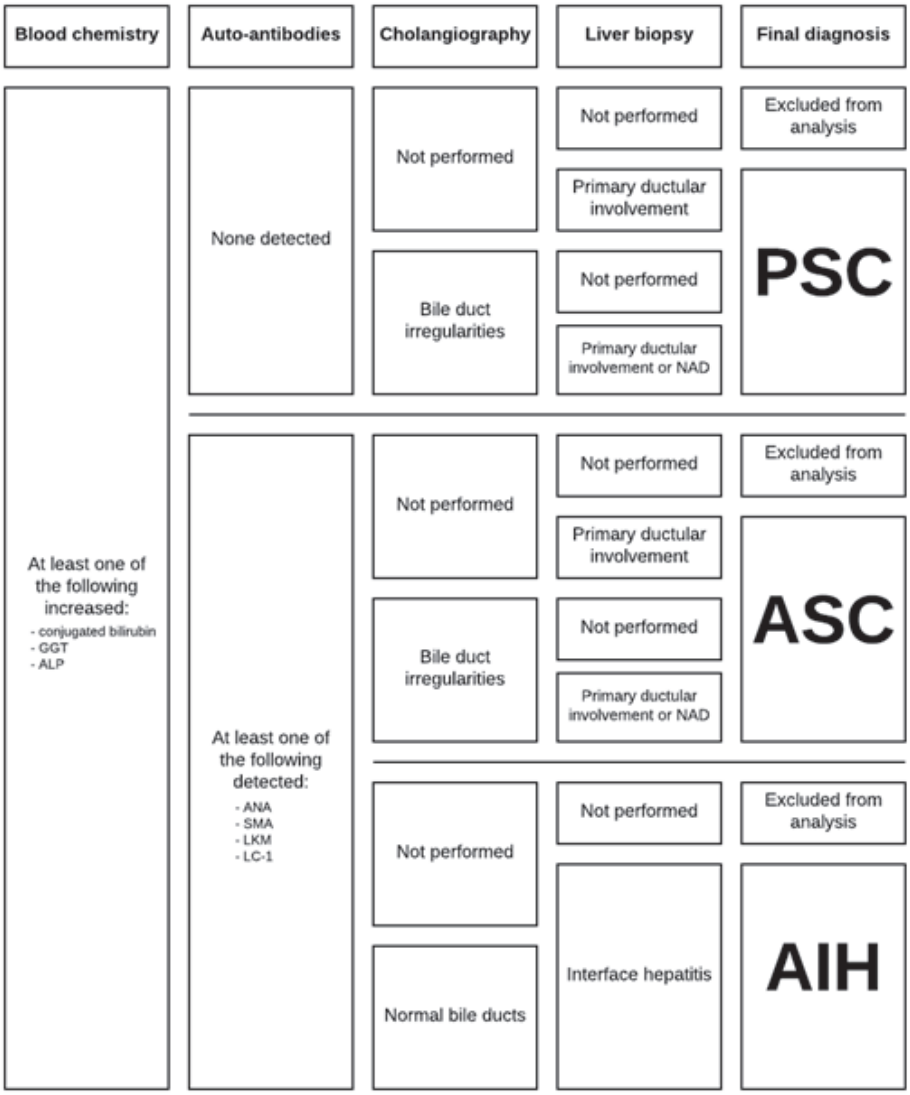

Figure S1. Diagnostic decision matrix. Immunological, radiological and/or histological features were reviewed to determine if patients were appropriately assigned a diagnosis of PSC, ASC or AIH. Patients were excluded from further analysis when they had isolated AIH, or when both cholangiography and liver biopsy were missing in the diagnostic work-up.

Predictors of short-term disease progression

To construct a prognostic model for short-term disease progression we carried out a backward stepwise elimination. Candidate predictors with $p<0.10$ in bivariate analysis were selected for use in the multivariate analysis. This level was chosen

because of the limited number of patients in the analysis. For patients with an incomplete follow-up (i.e. less than five years postdiagnosis) we calculated the Follow-Up Index (FUI), which is defined as the ratio between the actual observed follow-up period and the minimally preferred follow-up period.14 The FUI ranges from near 1.0 (almost 5 years follow-up) to near 0 (diagnosed just before the study closing date). The FUI is a simple measure to critically appraise the credibility of the prognostic model. Patients with isolated AIH were excluded from the survival and logistic regression analysis.

Long-term disease outcomes (cohort 2)

To obtain insight in long-term disease course of pediatric-onset SC patients after transition to adult care, we used a large comprehensive SC cohort that has been described before, and which came from the same geographical area of the Netherlands as cohort 1.2 Between January 2008 and December 2011, the researchers in this study identified all adult PSC patients in 44 hospitals in the Netherlands, that were diagnosed from 2000 onward. Data collection included patient demographics, disease characteristics at diagnosis and follow-up of clinical endpoints, as liver transplantation and SC-related death.
For our study, we performed an additional analyses of this cohort and stratified for age at diagnosis before 18 years ("pediatric-onset" cohort, n=43) or after 18 years ("adult-onset" cohort, n=640). We compared frequencies of liver transplantations, median time-to-complication, and SC-related death. Detailed information on the study design, participants, data collection and variables can be found in the original publication.2

Statistical methods

Data analyses were performed using IBM SPSS version 23 Baseline demographic and disease characteristics were evaluated for both SC registries using descriptive statistics. We summarized continuous variables as medians and interquartile ranges (IQR: 25th percentile, 75th percentile). For discrete variables, we calculated the 95% confidence interval in OpenEpi, Version 3, using the Wilson method for calculating confidence intervals for proportions. Differences in groups were compared by the Mann Whitney U test for continuous variables; for categorical outcomes the Chi square test and Fisher's exact test were used. P values <0.05 were considered statistically significant.
In cohort 1, we estimated the cumulative incidence of any of the

above-mentioned clinical endpoints, by performing Kaplan-Meier survival analysis. Time was defined as the moment of SC diagnosis until appearance of the first sign of early hepatic deterioration or until five years after SC diagnosis. Patients who did not have a complete follow-up of 5 years and did not develop signs of disease progression were censored. In cohort 2, a Kaplan-Meier survival analysis with Log rank test was performed to compare long-term disease outcomes between pediatric-onset and adult-onset SC patients. Event was defined as liver transplantation or death from liver disease. Time was defined as the moment of SC diagnosis until appearance of the event. Patients who were lost to follow-up without experiencing an event were censored.

RESULTS

Short-term disease outcomes in pediatric-onset SC

Patient demographics and characteristics

We identified 160 patients who were diagnosed between 2000 and 2017. A total of 17 children were excluded because of an incomplete diagnostic work-up, and 57 for isolated AIH. Thirty-two patients were classified as PSC and 54 as ASC (Table 1). Patients were diagnosed at a median age of 12.4 years (IQR 9.1-14.8) and the gender distribution was predominantly male (PSC 75% and ASC 61%). Comorbidities in patients with ASC included insulin-dependent diabetes mellitus (n=2), celiac disease (n=1), autoimmune hemolytic anemia (n=1), rheumatoid arthritis (n=1) and idiopathic thrombocytopenic purpura (n=1). Only one PSC patient had an associated autoimmune disease (celiac disease). Both PSC and ASC were strongly associated with IBD (respectively in 84% and 76% of cases). UC was the predominant type of IBD in both PSC and ASC with a high proportion of pancolitis (PSC, 70%; ASC, 83%).

Characterization of SC at diagnosis

Among the 54 patients with ASC, 25 were positive for ANA alone, 9 for both SMA and ANA, 19 for SMA alone and 1 for LKM1 alone. Diagnostic liver ultrasonography was performed in 65 of the 86 patients (76%). Splenomegaly was present at ultrasonography in 19 patients (26%) and hepatomegaly in 31 patients (43%). MRC or ERC was performed in 73 patients (85%) and liver biopsy in 75 patients (87%). All PSC patients received ursodeoxycholic acid (UDCA); 94%

of ASC patients received UDCA. Steroid tapering dose was given to 59% of PSC patients (n=19) and 85% of ASC patients (n=46), in the majority of cases (80%) as induction therapy for concomitant IBD. Thiopurines were used by 59% of PSC patients (n=19), of which 89% had concomitant IBD. 76% of the ASC patients (n=41) used thiopurines.

Short-term disease progression
Individual patients were followed for a median of 5.1 years (IQR 2.6-7.8) after SC diagnosis (Table 2). Figure 1 shows that the interval to hepatic deterioration was similar for patients with PSC and ASC (p=0.752, log-rank test, Figure 1). Portal hypertensive complications developed in 16% of PSC patients (n=5) and 17% of ASC patients (n=9). Biliary complications developed in 16% of PSC patients (n=5) and 17% of ASC patients (n=9). Four ASC patients (7%) developed both portal hypertensive as well as biliary complications. Liver transplantation was performed in three patients after a mean disease duration of 9.3 years (range 5.9-9.8). Two patients died; one patient with ASC and end-stage liver disease from massive upper gastrointestinal hemorrhage and one patient with PSC died in a traffic accident. No patients developed cancer within the follow-up period.

Predictors of short-term disease progression
Twenty patients (23%) developed disease progression in the first 5 years after diagnosis. Fifty-eight of 86 patients (67%) had a complete 5-year follow-up. The remaining 28 patients with an incomplete follow-up had a mean (SD) FUI of 0.41 (0.21). We measured candidate factors to construct a prognostic model for short-term disease progression. Table 3 shows the results of the bivariate logistic regression analysis and the multivariate model, selected with the maximum likelihood approach. Treatment with thiopurines, steroids or UDCA did not influence disease course. Elevated ALP, fibrosis in liver biopsy, hepatomegaly and splenomegaly on ultrasonography had a P-value <0.10 and were selected for use in the multivariate analysis. In the multivariate model elevated ALP (odds ratio [OR] 5, 95%CI 1-21) and hepatomegaly on ultrasonography (OR 9, 95%CI 2-47) remained significant predictors of short-term disease progression. The logistic regression coefficients (β) in the multivariate model allowed to construct a forecast for short-term disease progression in children at diagnosis of SC. The equation beneath table 3 indicates the mutually adjusted relative contribution of the

Table 1. Patient characteristics, clinical presentation at time of diagnosis and association with IBD.

	PSC (n = 32)	ASC (n = 54)
Median age at diagnosis in years (IQR)	13.3 (10.2-15.2)	11.4 (8.2-14.3)
Male gender	75% (58-87)	61% (48-73)
Liver-related symptoms at diagnosis		
■ Jaundice	16% (7-32)	13% (7-24)
■ Hepatomegaly	6% (2-21)	11% (5-22)
■ Splenomegaly	3% (1-16)	7% (3-18)
■ Ascites	0% (0-11)	0% (0-7)
■ Fatigue	34% (21-52)	50% (37-63)
■ Pruritus	22% (11-39)	17% (21-45)
■ Coagulopathy	0% (0-11)	4% (1-13)
Liver disease in first degree relatives	3% (1-16)	4% (1-13)
Associated autoimmune disease	3% (1-16)	11% (5-22)
Association with IBD	84% (68-93)	76% (63-85)
Median age at IBD diagnosis in years (IQR)	12.2 (9.2-15.2)	11.5 (8.6-14.4)
Type of IBD, % (n)		
■ CD	11% (4-28)	22% (12-37)
■ IBD-U	4% (1-18)	5% (1-16)
■ UC	85% (68-94)	73% (58-84)
■ Pancolitis	70% (49-84)	83% (66-93)
Timing of diagnosis of liver disease, % (n)		
■ Simultaneous with diagnosis of IBD	41% (25-59)	73% (58-84)
■ Before diagnosis of IBD	11% (4-28)	15% (7-28)
■ During follow-up of IBD	48% (31-66)	12% (5-26)

Values are percentages (95% confidence interval) unless otherwise stated. Abbreviations: PSC, primary sclerosing cholangitis; ASC, autoimmune sclerosing cholangitis; CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, IBD unclassified; IQR, interquartile range; PSC, primary sclerosing cholangitis; UC, Ulcerative colitis.

factors to the risk score. As an example of the use of this equation, consider a teenager with the SC phenotype, with elevated ALP and hepatomegaly. The total risk score of this patient amounts to 0.3, which corresponds to a probability of short-term disease progression of 57%, compared to a pre-test probability of 23%.

Long-term disease outcomes in pediatric-onset versus adult-onset SC

The large SC cohort by Boonstra et al. included a total of 697 SC patients. Fourteen patients were excluded from the analyses because the date of diagnosis was missing (Table 4). Mean age of liver disease diagnosis was 14.6 years in the pediatric-onset cohort

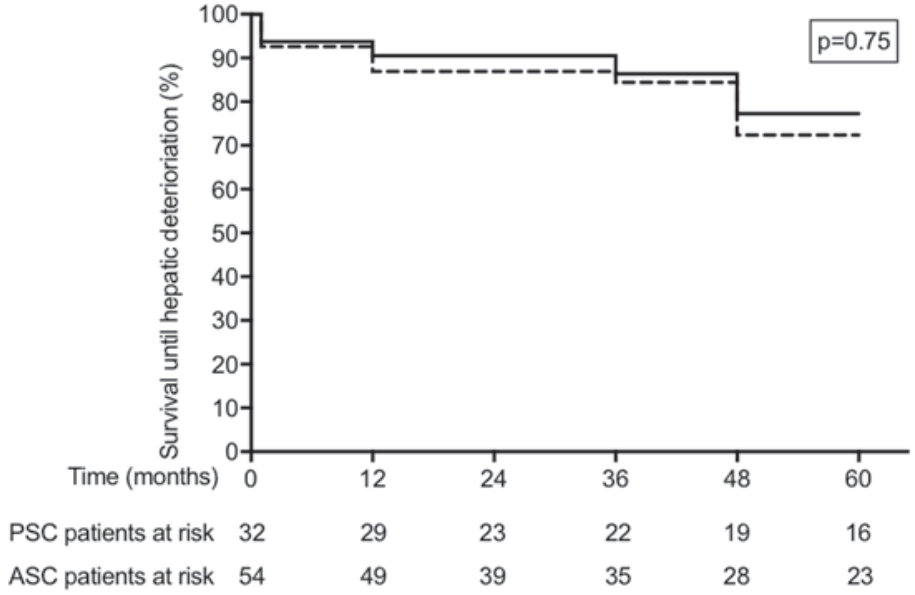

Figure 1. Short-term disease progression in children with SC. Kaplan-Meier plot demonstrating the percentage of patients with survival until disease progression after SC diagnosis. Adolescents with PSC (solid line) are compared with adolescents with ASC (dotted line). Event is defined as development of portal hypertensive complications, biliary complications, hepatobiliary malignancy, liver transplantation, or death from liver disease. Time is defined as the moment of SC diagnosis until the first complication, or five years postdiagnosis. Patients with no complete 5-year follow-up and who did not develop signs of disease progression were censored. The numbers on the lowest line indicate the number of patients being represented at that point in time.

(n=43) and 40.2 years in the adult-onset cohort (n=640). There were no baseline differences in sex, presence of AIH overlap, small duct disease, or concomitant diagnosis with IBD between the pediatric-onset and adult-onset SC patients. Median follow up was 10 years (IQR 7-17) for the pediatric-onset cohort and 8 years (IQR 4-13.8) for the adult-onset cohort. During follow-up two pediatric-onset SC patients (5%) and 59 adult-onset SC patients (9%) died. Median transplant-free survival was 21 and 23 years in pediatric-onset and adult-onset SC patients, respectively. Frequencies of liver transplantations (23% vs 17%) and mean disease duration until liver transplantation (11 years vs 9.3 years) were not statistically different between the pediatric-onset and adult-onset cohort, respectively. Figure 2 shows that there is no difference in time-to-liver transplantation or SC-related death between both sub cohorts (p=0.58, Log-rank test).

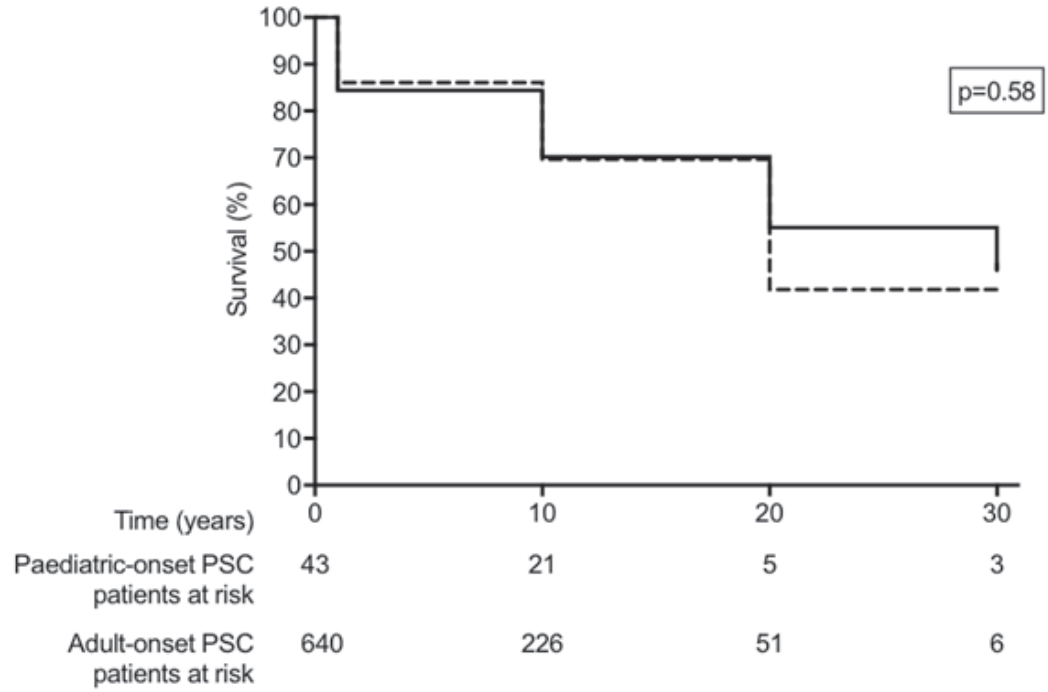

Figure 2. Time-to-transplantation or PSC-related death. Kaplan-Meier plot demonstrating the percentage of patients with time-to-liver transplantation or PSC-related death. Patients with adult-onset PSC (solid line) are compared with patients with pediatric-onset PSC (dotted line). Event is defined as liver transplantation or death from liver disease. Time is defined as the moment of PSC diagnosis until appearance of the event. Patients who were lost to follow-up without experiencing an event were censored. The numbers on the lowest line indicate the number of patients being represented at that point in time.

Table 2. List of clinical endpoints in patients with pediatric-onset SC in the first five years postdiagnosis.

	PSC (n = 32)	ASC (n = 54)
Median follow-up time in years (range)	4.7 (0.2-12.3)	5.5 (0.7-14.5)
Portal hypertensive complications	16% (6.9-31.8)	17% (9.0-28.7)
■ Thrombocytopenia	9% (3-24)	11% (5-22)
■ Bleeding oesophageal varices	6% (2-20)	6% (2-15)
■ Need for TIPS placement	3% (1-16)	4% (1-12)
Biliary complications	16% (6.9-31.8)	17% (9.0-28.7)
■ Episodes of cholangitis	9% (3-24)	13% (6-24)
■ Need for ERC	6% (2-20)	11% (5-22)
Liver transplantation	3% (0.6-15.7)	4% (1.0-12.5)
Hepatobiliary malignancy	0% (0-11)	0% (0-7)
Death from liver disease	3% (0.6-15.7)	2% (0.3-9.8)

Values are percentages (95% confidence interval) unless otherwise stated. Abbreviations: ASC, autoimmune sclerosing cholangitis; AIH, autoimmune hepatitis; IQR, interquartile range; ERC, endoscopic retrograde cholangiography; PSC, primary sclerosing cholangitis; TIPS, transjugular intrahepatic portosystemic shunt.

Table 3. Predictors of short-term disease progression in the first five years after diagnosing SC.

	Bivariate			Multivariate		
Prognostic markers at diagnosis of liver disease	*ß*	**P**	**Odds Ratio**	*ß*	**P**	**Odds Ratio (95%CI)**
ALP elevation (age and sex adjusted)*	1.0	0.057	2.8	1.6	0.034	4.8 (1.1 – 20.6)
Fibrosis in liver biopsy*	1.0	0.037	2.8			
Hepatomegaly at ultrasonography*	1.9	0.019	6.9	2.1	0.014	8.5 (1.5 – 46.5)
Splenomegaly at ultrasonography*	1.2	0.067	3.2			
Constant				-3.4	0.000	0.033

* Binary variables are coded 0 for no or 1 for yes.
Cox and Snell R = 0.203, Nagelkerke R (Max rescaled R) = 0.305.
Risk for early hepatic deterioration can be calculated from the following standard formula:
Risk score = -3.4 + 1.6 (ALP elevation) + 2.1 (Hepatomegaly at ultrasonography)
Predicted risk = 1/(1 + $^{\text{e-risk score}}$)

Abbreviations: ALP, alkaline phosphatase

Table 4. Comparison of long-term outcomes in pediatric-onset and adult-onset PSC.

	Pediatric cohort (N = 43)	Adult cohort (N = 640)	P value (Pediatric vs Adult)
Median age at diagnosis, yr (IQR)	16.0 (14-18)	40.0 (30-50)	-
Male, n (%)	67% (52-80)	65% (61-68)	NS
AIH overlap, n (%)	9% (4-22)	3% (2-5)	NS
Small duct PSC, n (%)	9% (4-22)	9% (7-11)	NS
Association with IBD, n (%)	79% (62-87)	69% (64-72)	NS
Mortality, n (%)	9% (4-22)	17% (14-20)	NS
Median age at PSC Related death, yr (IQR)	31.0 (1.0)	53.0 (20.25)	0.03
PSC-related death, n (%)	5% (1-15)	9% (7-12)	NS
CCA	1	26	NS
CRC	1	6	NS
Liver failure	0	16	NS
LTx related complications	0	9	NS
Gallbladder carcinoma	0	1	NS
Median transplant free survival, yr	21	23	NS
Liver transplantation, n (%)	23% (13-38)	17% (14-20)	NS
Median disease duration until LTx, months (IQR)	112.5 (155.25)	90.5 (107.75)	NS
Median age at LTx, yr (IQR)	22.5 (15-30)	48 (40-56)	<0.001

Data on a total of 697 SC patients is currently included in the Boonstra cohort. Fourteen patients were excluded from the analyses because the date of diagnosis was missing. Mann-Whitney U test (continuous variables)

or Fisher's exact test (categorical variables) was used to test differences between 2 groups. Log rank test was used to compare transplant free survival. Definition of abbreviations: PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; IBD, inflammatory bowel disease; CCA, cholangiocarcinoma; CRC, colorectal carcinoma; LTx, liver transplantation; yr, year; n, number of patients; NS, not significant; IQR, interquartile range.

DISCUSSION

Key findings

We described clinical outcomes in two independent Dutch pediatric-onset SC registries. In cohort 1, which was ideal for studying short-term disease progression, twenty-three percent of patients developed portal hypertension, biliary complications, or progressed to liver transplantation within 5 years after SC diagnosis. In cohort 2, which allowed us to study long-term disease outcomes beyond the age of transfer to adult-oriented care, we observed that pediatric and adult-onset SC run a similar disease course regarding time-to-transplantation and SC related death. Our findings contradict the current view that pediatric-onset SC runs a relatively benign disease course as compared to adult-onset SC.

Comparison with other studies

Disease progression

We identified ten observational studies from MEDLINE and EMBASE that described pediatric cohorts with SC.6, 7, 15-18 A recently published multicenter, international cohort study of children with SC (n=781) reported portal hypertensive and biliary complications in 30% of cases in the first five years postdiagnosis, and 12% of patients required a liver transplantation within 5 years after SC diagnosis.6 Similarly, 11% of children included in a single center cohort of pediatric PSC patients from the United States (n=120) was transplanted in the first five years postdiagnosis.7 Our data from cohort 1 demonstrates that 23% of patients develop short-term disease progression within 5 years after SC diagnosis. This is possibly an underestimation as indicated by the low FUI. Taken together, our data and earlier published information show that a quarter to a third of pediatric-onset SC patients have a progressively worsening liver condition before transfer to adult-oriented care. Recently, a more favorable outcome of SC in children is described in an Italian pediatric-onset SC cohort (n=45), with approximately 15% (n=7) of patients developing liver-related disease complications after a mean follow-up of 8.7 ± 5.6 years. 20 This is likely explained by the fact that most children in the Italian cohort had asymptomatic elevation of liver enzymes at disease diagnosis, as in Italy healthy children are often screened for liver function, illustrating that published series about pediatric SC indeed depend on the center and country where the study is performed.

Prognostic biomarkers
Low platelet count, prolonged pro-thrombin time and higher values of bilirubin and GGT have previously been identified as markers for progressive liver disease in children with SC.6, 15, 16 In our multivariate model that was based on cohort 1 these laboratory markers had no prognostic value. Instead we identified hepatomegaly on ultrasonography and elevated ALP at diagnosis as significant and independent predictors of short-term disease progression. Elevated ALP has not been identified as a prognostic marker in previous pediatric research, but is consistently associated with poor prognosis in adult SC literature.19-23 Some may argue that GGT is a more accurate diagnostic marker of SC in children than ALP, as ALP is also dependent on bone growth.15, 16 However, in our patient cohort GGT was already elevated in 94% cases at diagnosis, which explains its poor specificity to use it as an indicator for future disease progression.

Phenotype of pediatric- versus adult-onset SC
Some groups have suggested that pediatric-onset SC has a milder phenotype and therefore a more favourable outcome compared to adult-onset SC.6, 7 The international collaboration group that recently published the results of a large cohort of children with SC (n=781) reported a transplantation-free survival of 88% and 70% at 5 and 10 years respectively.6 In a large international cohort of adult patients with SC (n=7121) transplantation-free survival was 80%, 63% and 48% after 5, 10 and 15 years postdiagnosis.24 Variation in geographical backgrounds of these two large cohorts may have hampered a reliable comparison of transplantation-free survival. As far as we know this is the first time that long-term outcomes of pediatric-onset and adult-onset SC patients coming from the same geographical area were compared.2 The time-to-complication analysis showed that there was no difference between pediatric- and adult-onset SC. We therefore argue that pediatric-onset SC follows the same disease course as adult-onset SC.

Implications for pediatric practice
Despite the lack of current therapies that cure or halt disease progression, targeting and selecting children with a likelihood of short-term disease progression has several benefits, including appropriate counselling of the patient and family, close monitoring for potential severe complications (including hepatobiliary and colorectal malignancies) and timely referral to a

liver transplantation center. The prognostic biomarkers described in cohort 1 (hepatomegaly on ultrasonography and elevated ALP) may allow physicians involved in the care of children to more accurately predict disease progression in the early stages of SC. The robustness of these biomarkers needs to be evaluated in a validation cohort of patients with pediatric-onset SC.
Our findings provide an evidence base that the time-to-complication in pediatric-onset SC is not different from the adult-onset type. We call for a more rigorous follow-up of children with SC, including monitoring for symptoms from dominant strictures such as cholangitis, jaundice, pruritus, right upper quadrant pain or worsening cholestatic biochemical profile. Additionally, in those without concurrent IBD annual fecal calprotectin screening is warranted. A detailed handover letter including a clear timeline of diagnostic and therapeutic procedures should be written by the pediatric team prior to the transfer to adult-oriented care.

Strengths and limitations
The diagnostic criteria for pediatric-onset SC are not univocal. There is a need to develop an evidence-based guideline that brings more uniformity in the diagnostic criteria for SC in children. One of the strengths of this study was the confirmation of the diagnosis of PSC or ASC with a detailed record review and diagnostic decision matrix with strict definitions for PSC and ASC (Figure S1), instead of merely relying on the administration of the treating doctor or on coding data. This strategy reduced the risk of misclassification and misdiagnosis, and consequently type I errors. A limitation was that not all patients in cohort 1 had a complete 5-year follow-up. Although our study provides important insight regarding disease progression in pediatric-onset SC, potential drawbacks of this study relate to the retrospective nature of the study and the limited sample size.

Conclusion

In conclusion, our data provide new insights into the course of disease in pediatric-onset SC. The results strongly suggest that pediatric- and adult-onset SC run a similar short- and long-term disease course. Both pediatricians as well as adult-oriented specialists who treat patients with pediatric-onset SC should monitor them closely to recognize early complications and control long-term sequelae. Finally, our methodology in which we used two independent cohorts from the same geographical area for the evaluation of short-term and long-term disease outcome is valid and useful for the follow-up of young patients with rare diseases, whose disease course is blurred by transition to adult-oriented care.

REFERENCES

1. Molodecky NA, Kareemi H, Parab R, et al. Incidence of Primary Sclerosing Cholangitis: a Systematic Review and Meta-Analysis. Hepatology 2011;53:1590-1599.
2. Boonstra K, Weersma RK, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology 2013;58:2045-55.
3. Deneau M, Jensen MK, Holmen J, et al. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in utah children: Epidemiology and natural history. Hepatology 2013;58:1392-1400.
4. Schrumpf E, Boberg KM. Hepatic and extrahepatic malignancies and primary sclerosing cholangitis. Gut 2003;52:165.
5. Karlsen TH, Folseraas T, Thorburn D, et al. Primary sclerosing cholangitis - a comprehensive review. J Hepatol 2017;67:1298-1323.
6. Deneau MR, El-Matary W, Valentino PL, et al. The natural history of primary sclerosing cholangitis in 781 children: A multicenter, international collaboration. Hepatology 2017;66:518-527.
7. Valentino PL, Wiggins S, Harney S, et al. The Natural History of Primary Sclerosing Cholangitis in Children: A Large Single-Center Longitudinal Cohort Study. J Pediatr Gastroenterol Nutr 2016;63:603-609.
8. Castor Electronic Data Capture CB, Amsterdam, The Netherlands, 2018.
9. Liberal R, Vergani D, Mieli-Vergani G. Paediatric Autoimmune Liver Disease. Dig Dis 2015;33 Suppl 2:36-46.
10. Lindor KD, Kowdley KV, Harrison ME, et al. ACG Clinical Guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol 2015;110:646-59; quiz 660.
11. Mileti E, Rosenthal P, Peters MG. Validation and modification of simplified diagnostic criteria for autoimmune hepatitis in children. Clin Gastroenterol Hepatol 2012;10:417-21 e1-2.
12. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51:2193-213.
13. Derksen-Lubsen G MHA, Oudesluys-Murphy H M, Sprij A. Compendium kindergeneeskunde. Diagnostiek en behandeling, 5th edn. Stafleu van Loghum, 2018.
14. von Allmen RS, Weiss S, Tevaearai HT, et al. Completeness

of Follow-Up Determines Validity of Study Findings: Results of a Prospective Repeated Measures Cohort Study. PLoS One 2015;10:e0140817.
15. Feldstein AE, Perrault J, El-Youssif M, et al. Primary sclerosing cholangitis in children: a long-term follow-up study. Hepatology 2003;38:210-7.
16. Wilschanski M, Chait P, Wade JA, et al. Primary sclerosing cholangitis in 32 children: Clinical, laboratory, and radiographic features, with survival analysis. Hepatology 1995;22:1415-1422.
17. Miloh T, Arnon R, Shneider B, et al. A retrospective single-center review of primary sclerosing cholangitis in children. Clin Gastroenterol Hepatol 2009;7:239-45.
18. Rojas CP, Bodicharla R, Campuzano-Zuluaga G, et al. Autoimmune hepatitis and primary sclerosing cholangitis in children and adolescents. Fetal Pediatr Pathol 2014;33:202-9.
19. Watanabe T, Hirano K, Tada M, et al. Short-term prognostic factors for primary sclerosing cholangitis. J Hepatobiliary Pancreat Sci 2015;22:486-90.
20. de Vries EM, Wang J, Leeflang MM, et al. Alkaline phosphatase at diagnosis of primary sclerosing cholangitis and 1 year later: evaluation of prognostic value. Liver Int 2016;36:1867-1875.
21. Stanich PP, Bjornsson E, Gossard AA, et al. Alkaline phosphatase normalization is associated with better prognosis in primary sclerosing cholangitis. Dig Liver Dis 2011;43:309-13.
22. Al Mamari S, Djordjevic J, Halliday JS, et al. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. J Hepatol 2013;58:329-34.
23. Angulo P, Maor-Kendler Y, Lindor KD. Small-duct primary sclerosing cholangitis: a long-term follow-up study. Hepatology 2002;35:1494-500.
24. Weismuller TJ, Trivedi PJ, Bergquist A, et al. Patient Age, Sex, and Inflammatory Bowel Disease Phenotype Associate With Course of Primary Sclerosing Cholangitis. Gastroenterology 2017;152:1975-1984.e8.