The natural history of primary sclerosing cholangitis in 781 children: a multicenter, international collaboration

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Abstract

Background:

There are limited data on the natural history of primary sclerosing cholangitis (PSC) in children. We aimed to describe the disease characteristics and long-term outcomes of pediatric PSC.

Methods:

We retrospectively collected all pediatric PSC cases from 36 participating institutions and conducted a survival analysis from the date of PSC diagnosis to dates of diagnosis of portal hypertensive or biliary complications, cholangiocarcinoma, liver transplantation, or death. We analyzed patients grouped by disease phenotype and laboratory studies at diagnosis to identify objective predictors of long-term outcome.

Results:

We identified 781 patients, median age 12 years old, with 4277 person-years of follow-up; 33% with autoimmune hepatitis (AIH), 76% with inflammatory bowel disease (IBD), and 13% with small duct PSC. Portal hypertensive and biliary complications developed in 38% and 25%, respectively, after 10 years of disease. Once these complications developed, median survival with native liver was 2.8 and 3.5 years, respectively. Cholangiocarcinoma occurred in 1%. Overall event-free survival was 70% at 5 years and 53% at 10 years. Patient groups with the most elevated total bilirubin, GGT and AST:platelet ratio index (APRI) at diagnosis had the worst outcomes. In multivariate analysis PSC-IBD and small duct phenotypes were associated with favorable prognosis (Hazard ratio 0.6 (95%CI 0.5-0.9) and 0.7 (95%CI 0.5-0.96), respectively). Age, gender and AIH overlap did not impact long-term outcome.

Conclusions:

PSC has a chronic, progressive course in children. Nearly half of patients develop an adverse liver outcome after 10 years of disease. Elevations in bilirubin, GGT and APRI at diagnosis can identify patients at highest risk. Small duct PSC and PSC-IBD are more favorable disease phenotypes.

Introduction

Primary Sclerosing Cholangitis (PSC) is a rare disease in pediatric patients, with an incidence of 0.2 cases per 100,000 children(1). Existing descriptions of the natural history and characteristics of PSC are largely from small, single center case series with limited long-term follow-up(1-8). Objective predictors of patient outcome are lacking. We created an international consortium of pediatric liver disease centers to collect a large number of children with PSC and overcome these problems. We sought to describe the natural history of PSC in children and to identify early laboratory, demographic and phenotypic predictors of long-term outcome.

Methods

Study population:

We retrospectively reviewed medical records on all known PSC patients at 36 different institutions throughout Europe, North America, the Middle East, and Asia. Potential PSC patients were identified from local clinical databases, regional research registries, ICD-9 and ICD-10 code searches, nationwide provider surveys and/or electronic medical record queries. 11 institutions providing data were non-transplant referral centers, 13 institutions providing data were large, tertiary referral liver transplant centers, and 12 institutions provided population-based data that captured all patients in a defined geographic region. We included all patients diagnosed with PSC before the age of 18 years. We excluded patients with cholangiopathy secondary to surgical complications or alternative systemic diseases(9) such as histocytosis, Wiscott-Aldrich or hyper IgM syndromes. Several centers had overlapping geographic referral areas and patients could potentially have been cared for at multiple locations. To account for this, we searched for and deleted duplicate instances of patients who were seen and enrolled at multiple study institutions.

Definitions and variables:

Diagnoses were confirmed using detailed records review by physician co-investigators at the individual centers. Data was abstracted and de-identified at local study sites, and reviewed and stored centrally. Any questions or discrepancies were reviewed between the local co-investigator and the first and senior authors. The diagnosis of PSC was based on a cholestatic biochemical profile with either cholangiography showing multifocal stricturing and segmental dilations of the biliary tree or liver histopathology showing periductal, concentric fibrosis, fibro-obliterative cholangitis, or primary ductular involvement(9). Patients with abnormal cholangiograms were labeled as large duct PSC. Patients with normal cholangiograms but abnormal liver biopsy were labeled as small duct PSC. Autoimmune hepatitis (AIH) was diagnosed in patients who met the simplified AIH criteria that have been validated in children (10), based on histopathology, positive autoantibodies, elevated serum globulins and exclusion of viral hepatitis. All patients with a 'probable' or 'definite' score were included as AIH.

For each patient, we collected basic demographics, general laboratory data at liver disease diagnosis including complete blood counts, serum chemistries, coagulation, serum globulins and autoantibody titers, the presence and type of associated inflammatory bowel disease (IBD), the presence of autoimmune hepatitis, large vs. small duct phenotype, any other co-existing immune-mediated diseases diagnosed at any time during available follow-up, and chronic treatment of ursodeoxycholic acid. We observed that all cases of UC refractory to oral aminosalicylate monotherapy, all cases of Crohn disease, and all cases of AIH received systemic immunosuppression. Physicians generally followed established practice guidelines for these diseases(11-13). Patients with PSC generally did not receive immunosuppression outside of that mandated by coexisting IBD, AIH or other immune-mediated diseases. Individual therapeutic regimens varied, and were not recorded.

We identified several clinical endpoints: 1. the development of portal hypertensive complications (ascites, hepatic encephalopathy, or esophageal varices with or without bleeding), 2. biliary complications (a cholangitis clinical picture with a biliary stricture requiring an intervention in the form

of endoscopic or percutaneous stenting, balloon dilation, or drainage), 3. cholangiocarcinoma (CCA), 4. liver transplantation, or 5. death from liver disease. Co-investigators reported the dates these clinical endpoints were first identified.

Analysis:

We created a retrospective cohort of all patients and followed them from time of PSC diagnosis to each of endpoints 1-5 above. A composite outcome of time free of all of 1-5 above was termed event-free survival. We also analyzed survival from diagnosis of portal hypertensive or biliary complications to liver transplantation or liver disease-related death. All observations were censored at the date of the last known clinical encounter. We used the Kaplan-Meier method to determine 5-year and 10-year outcome probabilities.

To identify early, objective laboratory predictors of long-term adverse outcomes, we compared event-free survival, and survival with native liver in patients grouped by tertile of values of each of AST:platelet ratio index (APRI)(14), total bilirubin, alkaline phosphatase (ALKP), and gamma glutamyl transferase (GGT) at liver disease diagnosis. Due to the wide range of normal ALKP values in children at different ages, we normalized all values for age using Mayo Medical Laboratories reference values(15). We excluded patients who presented with portal hypertensive or biliary complications within 3 months of PSC diagnosis from this analysis since their baseline laboratory studies were likely reflective of the outcome of interest already being present. The log-rank test assessed survival differences between laboratory tertiles.

We performed multivariate Cox regression to examine the association between outcome and patient gender, age at PSC diagnosis (<50th percentile vs. ≥50th percentile), the presence of large duct PSC, the presence of AIH, and the presence of IBD. The proportional hazards assumption was assessed graphically. All calculations were done using Stata version 13.0 (StataCorp, College Station, TX). The protocol of the study was approved by the institutional review and/or research ethics board of each collaborating institution.

Results:

Demographics and phenotype:

We identified 781 patients with pediatric-onset PSC; 420 patients (54%) came from non-transplant centers or population-based cohorts, and 361 patients (46%) were identified from single-center liver transplant programs. Patients were a median age of 12 years [interquartile range (IQR) 8-15] at diagnosis, and 39% female. Of 751 patients who underwent at least one endoscopy (96% of cohort), IBD was present in 76%, 83% as ulcerative colitis or indeterminate colitis, and 17% as Crohn disease. Large duct involvement was present in 87%, and 13% of patients had small duct disease. Overlap with autoimmune hepatitis was present in 33%, 97% as type 1 disease (smooth muscle antibody or antinuclear antibody positive), and 3% (n=9) as type 2 disease (liver kidney microsomal antibody positive). At least one additional comorbid immune-mediated disease was identified in 7% (52/781) of patients including: thyroiditis (n=11), celiac disease (n=10), type 1 diabetes (n=7), systemic vasculitis (n=6), juvenile idiopathic arthritis (n=5), epidermolysis bullosa (n=2), interstitial nephritis (n=2), uveitis (n=2), alopecia areata (n=2), and psoriasis, myasthenia gravis, and idiopathic thrombocytopenic purpura (n=1 each).

Long-term outcomes:

A total of 4277 person-years of follow-up was available. Individual patients were followed for a median of 4.4 years [IQR 2-7.9] after PSC diagnosis. Portal hypertensive complications occurred in 163 patients: present in 5% of patients at PSC diagnosis and 38% after 10 years of disease. Biliary complications occurred in 95 patients: present in 5% of patients at PSC diagnosis and in 25% after 10 years of disease. 73% (113/226) of patients with either complication were subsequently transplanted. The median survival with native liver after development of a portal hypertensive or biliary complication was 2.8 and 3.5 years, respectively.

CCA developed in 8 patients at an age range of 15-18 years, a median of 6 years after initial PSC diagnosis. Three patients had metastatic cancer and died under palliative care within 5 months of CCA diagnosis. Five patients had localized disease amenable to surgery; 4 underwent resection and chemotherapy and 1 underwent liver transplantation. All five were alive at last known follow-up, a median of 2.5 years after CCA diagnosis. All patients who developed CCA had PSC without AIH overlap (100% vs. 67% in the total cohort, p=0.04), and most were male (88% vs. 61% in the total cohort, p=0.16). CCA patients were otherwise similar to non-CCA patients in age of original liver disease diagnosis, IBD phenotype, and large vs. small duct phenotype.

Liver transplantation occurred in 14% of PSC patients overall (n=113) at a median age of 15 years [IQR 11.9-17.7], a median of 4 years [IQR 1.5-6.2] after initial liver disease diagnosis. Survival with native liver was 88% (95% CI 85-91) at 5 years and 70% (95% CI 64-75) at 10 years.

Death from liver disease occurred in 1.4% of PSC patients overall (n=11) at a median of 9 years after initial PSC diagnosis (range 0.4-13 years): 3 from metastatic CCA in the native liver, 2 from complications of end-stage liver disease in the native liver, and 6 after liver transplantation from complications of immunosuppression and infections.

Overall 221 patients experienced at least one adverse liver-related outcome. Event-free survival was 70% (95% CI 66-74) at 5 years and 53% (95% CI 47-59) at 10 years. Kaplan-Meier plots for each of the above survival outcomes are shown in **Figure 1.**

Laboratory values at PSC diagnosis and subsequent outcome:

APRI, GGT, ALKP and bilirubin data were available in 83% of patients. Tertile cutoff values at the 33rd and 66th percentile were: 1.4 and 2.2 times the upper limit of normal for ALKP, 142 and 309 U/L for GGT, 0.41 and 0.86 mg/dL for bilirubin, and 0.49 and 1.33 for APRI, respectively. Higher values of APRI, GGT and bilirubin were generally associated with worse long-term outcomes, shown in **Figure 2**.

PSC subtype characteristics and outcomes:

Demographics, initial laboratory studies, and long-term outcomes for each PSC subtype are compared in **Table 1**. Small duct PSC (compared to large duct PSC) patients were diagnosed at younger ages, and had more favorable event-free survival, primarily from less patients progressing to biliary complications. PSC-IBD (compared to PSC without IBD) patients were more likely male, and had a markedly lower proportion of AIH overlap. Patients without concomitant IBD presented with higher APRI and MELD, biomarkers of more advanced stages of liver disease, despite similar age at PSC diagnosis. The total proportion of patients with end stage liver disease and portal hypertensive complications at baseline was similar in PSC and PSC-IBD patients however. PSC-IBD patients had a slower progression to complications. PSC+AIH overlap patients were more likely to be female and to have additional non-IBD autoinflammatory diseases such as celiac disease. The baseline APRI was higher in patients with AIH, suggesting more hepatic fibrosis, but similar proportions of patients had end-stage liver disease at presentation and event-free survival was nearly identical in patients with and without AIH.

In multivariate regression analysis, patients with small duct PSC (vs. large duct PSC) or with PSC-IBD (vs. no IBD) generally showed favorable outcomes, detailed in **Table 2.**

Discussion:

We collaborated to create a multicenter, international cohort of pediatric PSC patients of unprecedented size. Our study was especially unique in that over half of patients were collected from smaller centers and population-based cohorts, eliminating much of the referral bias typical of rare disease research done only in the largest-volume, single tertiary care centers. There were three main findings from this study. First, we provided the clearest picture of the long-term outcomes in PSC

patients to date, with nearly half of all patients experiencing an adverse liver-related event within 10 years of diagnosis. Second, we showed that bilirubin, GGT and APRI at diagnosis correlate directly with a child's long-term clinical outcome. Third, we characterized the differences in presentation and outcome between PSC subtypes of PSC+AIH, PSC-IBD, and small duct PSC.

Natural History:

Pediatric PSC has a chronic, progressive, and relentless course. Nearly half of patients will develop an adverse liver outcome within 10 years of diagnosis. The identification of portal hypertensive or a biliary complication represents a tipping point in the natural history, with a subsequent median survival with native liver of only 3 years. These outcomes occurred despite treatment of the vast majority of patients with chronic ursodeoxycholic acid therapy. Effective treatments are needed to change the course of this disease.

Our study is unprecedented in size, and no other comparable pediatric data exist. Compared to descriptions of adult-onset PSC, pediatric disease appears milder. The 10-year survival with native liver in our series was better than what is reported in large adult studies (70% vs. 61%-64%, respectively)(16, 17). Approximately half of children with PSC experienced an adverse liver-related outcome by 10 years of disease, while a majority of adults with PSC have evidence of disease progression after 5 years(18). Up to one third of adults with PSC may have esophageal varices within a year of diagnosis(19, 20) (13% in our cohort), and symptomatic dominant strictures occur in the majority of adults within 5 years of diagnosis(21, 22) (16% in our cohort). Several factors may explain much of the difference in long-term outcomes between pediatric and adult-onset PSC. Lead-time bias may be an important contributor as adult patients may experience progressive, sub-clinical disease over a longer period of time than children, leading to a more advanced presentation of liver disease at diagnosis. General comorbidities such as obesity, fatty liver disease, alcoholic hepatitis, smoking, cardiovascular disease and diabetes are much more prevalent in adult patients, and may worsen overall outcomes compared to children. Many

studies of adults are more biased towards tertiary care, referral populations, a problem we attempted to control in our multicenter cohort inclusive of a broad spectrum of PSC patients. We speculate that children generally have an earlier stage of the same disease as adult patients, and if followed longer, their outcomes would become indistinguishable.

CCA is a rare, but serious complication in pediatric PSC. It occurred in 1% of children in follow-up, compared to 7-9% of adults(23, 24). All cases of CCA occurred in children aged 15 years or older. All children with CCA had previous or concurrent evidence of stricture requiring intervention (8% of all children who had treatment of a stricture at some point). There is currently no formal guidance on screening children with PSC for CCA. A combination of ultrasound and serum cancer antigen 19-9 detected 91% of CCA in adults(25). Practice guideline suggestions to screen PSC patients over the age of 18 with these studies at 6-12 month intervals(26) could reasonably be extended to PSC patients aged 15 and older, and those pediatric patients who require interventional procedures for biliary strictures.

Laboratory Predictors:

We showed that even small elevations in baseline total bilirubin, GGT and APRI at PSC diagnosis predict long-term clinical outcomes. Other surrogate investigations of fibrosis predict long-term outcome in adults with PSC. As the enhanced liver fibrosis(ELF) score or liver stiffness via transient elastography progressively increased, long-term survival in PSC progressively decreased similar to the trends shown with APRI in our series(27, 28). APRI, ELF and transient elastography have previously been shown to have similar accuracy in detecting significant fibrosis in chronic liver disease(29, 30). Elevated bilirubin is associated with a poor outcome in adult patients(17), and is included in prognostic models such as the Mayo score(31). We are not aware of data on elevated GGT as a prognostic marker in PSC. Alkaline phosphatase carries prognostic value in adults(32-34), but did not predict outcome in children even when normalized for age. ALKP is a less-reliable marker of liver disease in pediatrics due the wide

variability in isozyme originating from bone in growing children. GGT is a better biochemical marker of biliary disease in pediatrics.

It appears that APRI could be an indicator of hepatic fibrosis, while bilirubin and GGT are biomarkers of the degree of cholangiopathy present in pediatric PSC. Patients with even mild elevation of these markers at baseline have more advanced disease and are likely to experience a worse outcome. Bilirubin, GGT and APRI may be good biomarkers for future clinical trials in children, and could serve as the basis for future pediatric prognostic calculators.

PSC Phenotypes:

Small duct PSC and PSC-IBD were milder phenotypes of the disease. Disease progression was similar in patients regardless of gender, age at diagnosis and the presence of absence of AIH. Small duct PSC was a favorable phenotype in adult series as well(16, 35, 36). Some small duct PSC may be an earlier precursor to large duct PSC. Approximately 20% of adults with small duct disease will progress to large duct disease over time (36, 37). Some cases of small duct PSC may be genetically unique from large duct PSC(38). We saw a similar prevalence of portal hypertensive complications and similar APRI at diagnosis in both small and large duct PSC phenotypes. Despite a comparable degree of presumed fibrosis, small duct PSC patients progressed more slowly to end-stage disease complications.

PSC with AIH overlap experienced the same incidence of adverse outcomes as PSC patients without overlap. PSC and PSC+AIH had a similar transplant rate in a large adult series(16). Most cases of AIH in children are readily treated with standard immunosuppression and have excellent outcomes(12). The portal inflammation of AIH in PSC+AIH cases seems to respond to immunosuppressive therapy. A prospective study of immunosuppressive treatment of children with PSC+AIH overlap showed similar improvement in biochemistry and portal-based inflammation on histopathology compared to children with AIH alone(39). Immunosuppression did not appear to control progression of the bile duct disease

in these patients however, with half showing progressive cholangiopathy in follow-up. The 10-year survival with native liver was 65%, similar to the overall survival in PSC and PSC+AIH in our larger series. The similar progression to adverse outcomes between patients with and without AIH in our multicenter cohort suggests that it is the degree of underlying, untreatable cholangiopathy, not the degree of treatable portal-based inflammation related to AIH that independently determines outcome.

PSC-IBD carried a more favorable prognosis in our cohort as well. PSC patients with IBD had a lower rate of cirrhosis and higher survival with native liver in children(2). Adult PSC-IBD patients with a Crohn phenotype did markedly better in an adult series, though patients with ulcerative colitis did marginally worse(16). Many patients with IBD and PSC are on immunosuppressive medications though this is unlikely to be the reason for improved survival. Other studies have shown that corticosteroids, azathioprine, methotrexate and infliximab do not seem to affect PSC progression(9, 39-41). The prevalence of AIH overlap was much higher in patients without IBD. It is possible that concurrent immunosuppression for IBD masked the portal-based inflammation of AIH in some patients, incorrectly categorizing them as isolated cases of PSC. Multifactorial differences in microbiome, lymphocyte trafficking and immune regulation along the gut-liver axis between patients with and without IBD may explain different disease progression.

Strengths and Weaknesses:

The strengths of this study are its large size, and inclusion of a diverse patient mix from secondary as well as tertiary care sites, and from multiple population-based cohorts. Overall this is a more realistic representation of the full spectrum of PSC seen in children. We confirmed the diagnosis of PSC using detailed records review and did not rely on any administrative-level or coding data. The weakness of this study is its retrospective design, with the possibility of misclassification bias. Not all patients had all investigations, such as colonoscopy to look for IBD, and thus some patients have been incorrectly categorized. Differences in access to care in a variety of different health systems may have influenced

the timing and choice of diagnostic procedures. Our retrospective design limited the amount of data on the immunosuppression regimens used. A meaningful analysis of the effect of immunosuppression on these diseases requires complete and longitudinal data on varying drug doses and drug combinations, serum drug levels, and patient compliance that was not available. We presume that ill patients with advanced liver disease were more likely to receive regular follow-up and to be captured in this cohort. Unknown loss to follow-up of patients with mild disease may have artificially worsened the overall prognostic picture. We did not correlate laboratory studies with cholangiography or histopathology for this study, but hope to do this in the future.

Conclusions:

We collaborated to describe the disease characteristics and natural history of PSC in a large, global cohort of children. Adverse liver outcomes are common in children after 10 years of disease. Most patients who develop portal hypertensive or biliary complications require liver transplantation within 3 years. Small duct PSC and PSC-IBD are favorable disease phenotypes. Total bilirubin, GGT and APRI at PSC diagnosis are strongly-associated with long-term outcome.

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Table 1: Characteristics of PSC subtypes

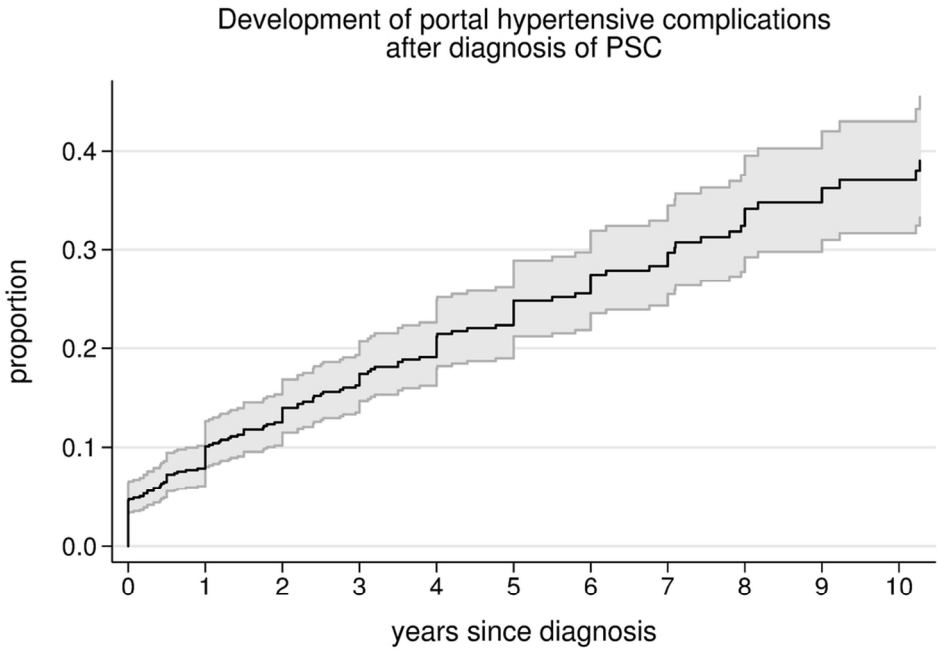
	Small duct (n=98)	Large duct (n=567)	No IBD (n=180)	PSC-IBD (n=571)	No AIH (n=521)	PSC+AIH (n=260)
Demographic and phenotypic characteristics:						
Female gender	35%	39%	**48%†**	**36%†**	**36%†**	**45%†**
Age at diagnosis (years)	**10.5†**	**11.7†**	10.9	11.6	11.5	11.3
PSC only	63%	69%	**49%‡**	**72%‡**	--	--
PSC + Autoimmune hepatitis	37%	31%	**51%‡**	**28%‡**	--	--
Inflammatory bowel disease	69%	78%	--	--	**82%‡**	**63%‡**
No IBD	31%	22%	--	--	**17%‡**	**37%‡**
Large duct disease	--	--	80%	86%	86%	83%
Small duct disease	--	--	20%	14%	14%	17%
Non-IBD, non-AIH autoimmune disease	7%	7%	4%	8%	**5%†**	**10%†**
Ursodeoxycholic acid treatment	77%	86%	84%	82%	84%	81%
Laboratory studies at diagnosis:						
Hemoglobin (g/dL)	12.1	12.1	12.1	12.1	12.1	12.1
Platelet count	323	330	**260‡**	**350‡**	328	320
INR	1.14	1.11	1.2	1.1	1.1	1.2
Total protein	7.9	7.8	7.9	7.8	**7.7‡**	**8.1‡**
Albumin	4.0	4.0	3.9	4.0	4.0	4.0
Total bilirubin	1.1	1.7	**2.5‡**	**1.2‡**	1.5	1.7
Alkaline phosphatase	552	590	637	546	599	495
ALKP (xULN)	1.3	1.4	1.6	1.3	1.5	1.2
GGT	286	302	281	294	290	290
ALT	222	199	**286†**	**176†**	**161‡**	**299‡**
AST	235	178	**293†**	**156†**	**142‡**	**290‡**
Globulins and autoantibodies:						
Globulin fraction	3.9	3.8	4.0	3.8	**3.7‡**	**4.1‡**
IgG	2041	1918	1996	1926	**1744‡**	**2319‡**
IgG4	153	132	118	154	133	190
ANA+	37%	52%	59%	47%	**41%‡**	**62%‡**
ANCA+	71%	66%	**53%†**	**69%†**	**60%†**	**74%†**
SMA+	48%	45%	**58%†**	**42%†**	**34%‡**	**61%‡**
LKM+	3%	1%	3%	1%	**0%‡**	**4%‡**
Disease severity at diagnosis:						
APRI	0.81	0.88	**1.57‡**	**0.68‡**	**0.71‡**	**1.25‡**
MELD score	0	1	**4‡**	**0‡**	1	2
Patients with MELD ≥ 12	3%	6%	**12%‡**	**3%‡**	4%	7%
Portal hypertensive complication at diagnosis	7%	5%	5%	5%	5%	5%
Biliary complication at diagnosis	1%	5%	5%	3%	5%	2%
Clinical endpoints:						
portal hypertensive complications at 5 years	22%	23%	**31%†**	**21%†**	21%	25%
biliary complications at 5 years	**1%‡**	**19%‡**	**24%†**	**12%†**	15%	12%
5-year survival with native liver	87%	88%	86%	89%	87%	90%
5-year event-free survival	77%	67%	**58%†**	**73%†**	71%	69%

† p<0.01 for pairwise comparison, ‡ p<0.001 for pairwise comparison

MELD = Model for End-stage Liver Disease, ANA = antinuclear antibody, ANCA = antinuclear cytoplasmic antibody, SMA = smooth muscle antibody, LKM = liver kidney microsomal antibody.

Table 2: proportional hazards analysis of phenotypic characteristics and event-free survival

Predictor	Reference	Univariate Hazard Ratio HR (95%CI)	p	Multivariate Hazard Ratio HR (95%CI)	p
Male gender	Female gender	0.88 (0.67-1.15)	0.342	0.90 (0.68-1.18)	0.450
Age ≥ 12 years	Age < 12 years	1.02 (0.79-1.34)	0.857	1.04 (0.80-1.36)	0.778
Small duct PSC	Large duct PSC	**0.71 (0.52-0.99)**	**0.042**	**0.69 (0.50-0.96)**	**0.028**
AIH	No AIH	1.00 (0.75-1.32)	0.990	0.89 (0.67-1.2)	0.461
IBD	No IBD	**0.66 (0.49-0.89)**	**0.006**	**0.63 (0.47-0.86)**	**0.004**



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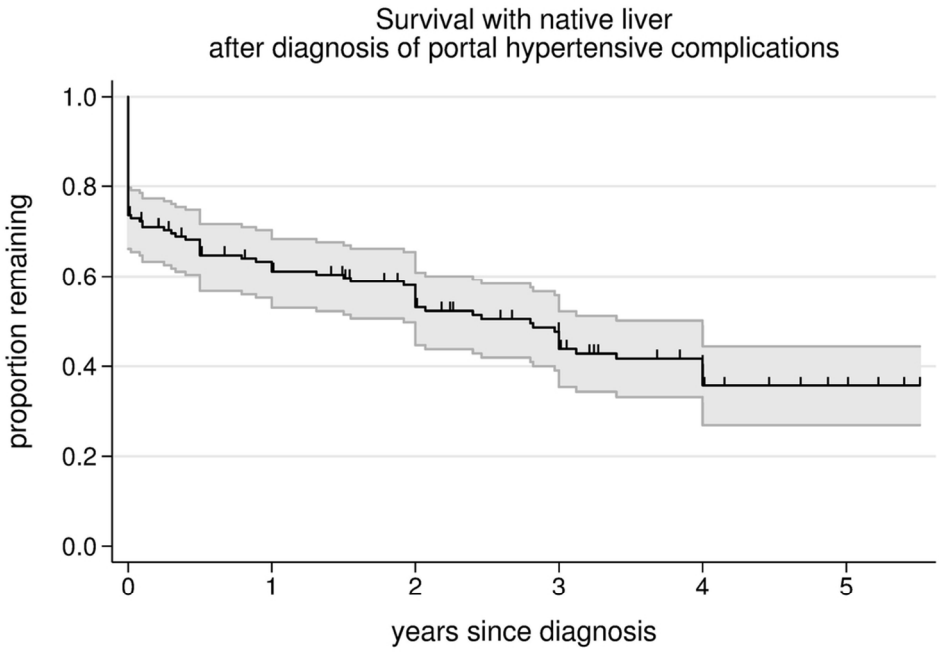

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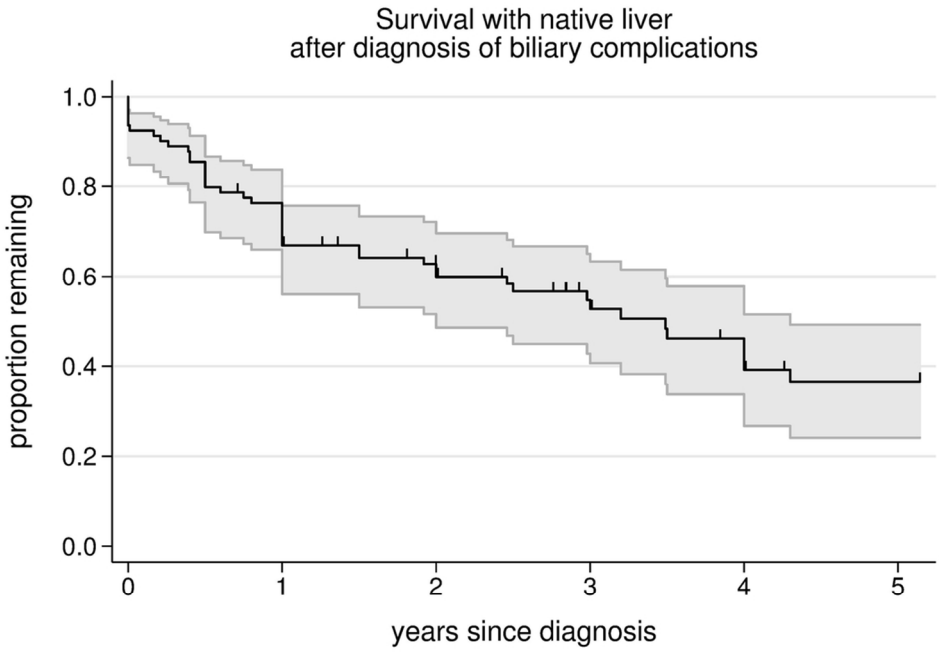

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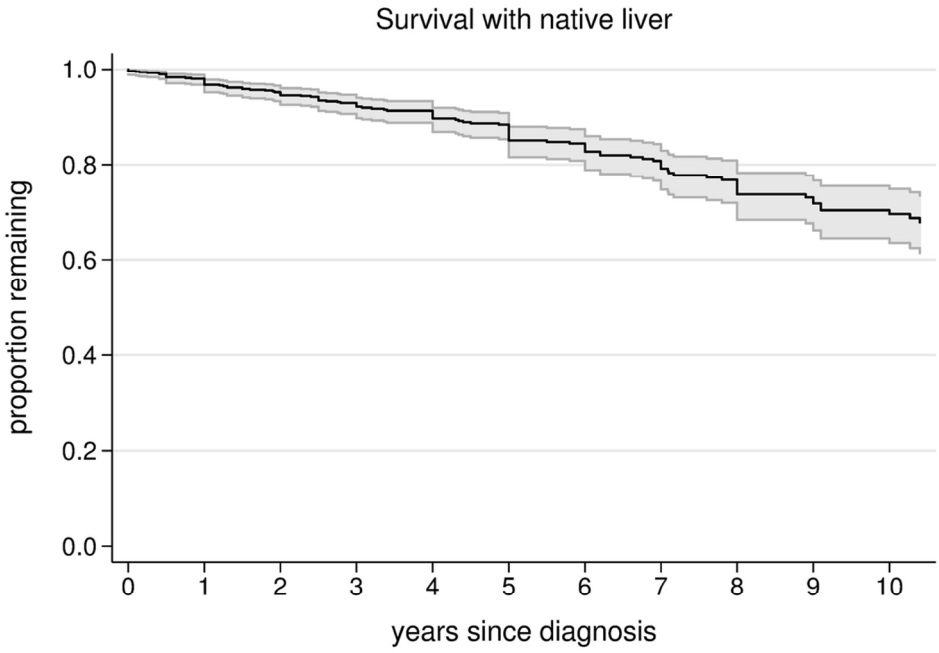

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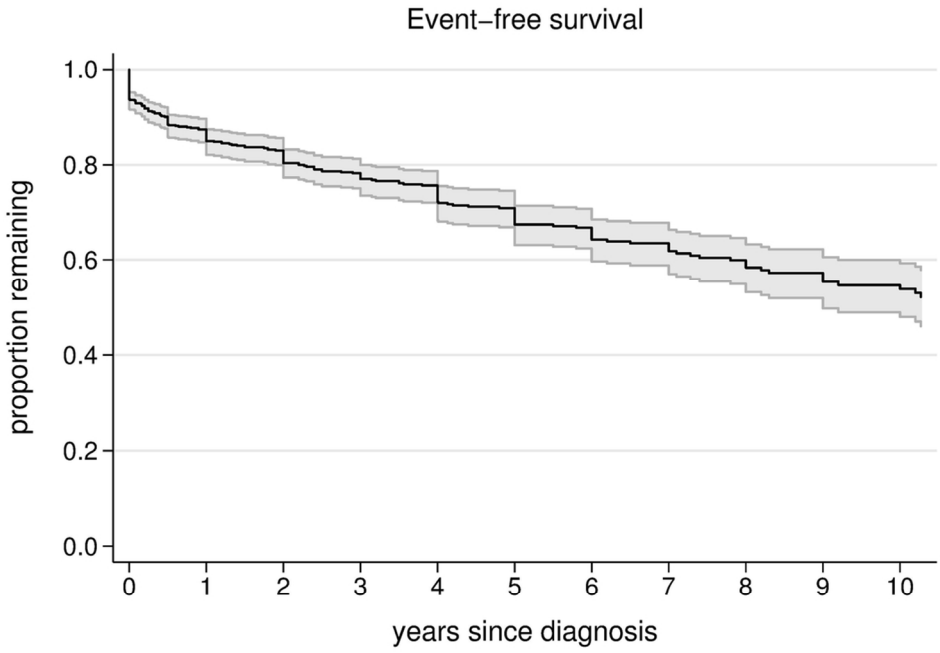

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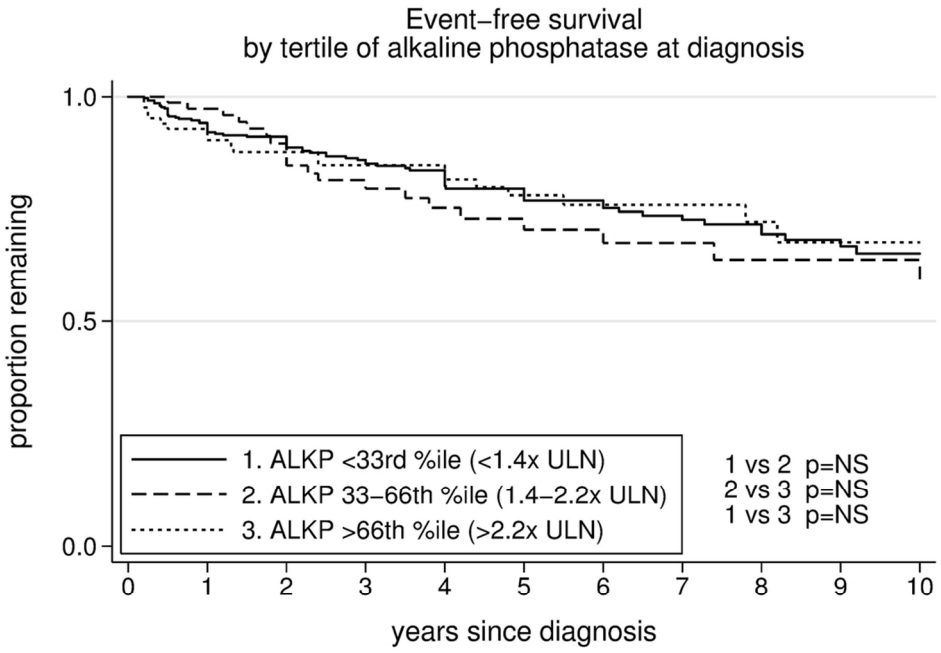

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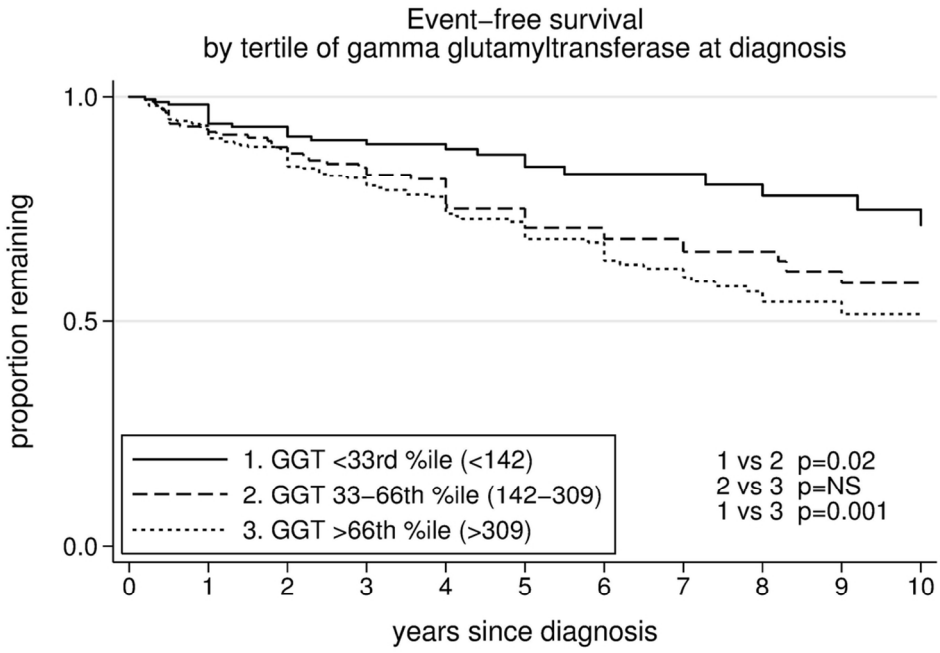

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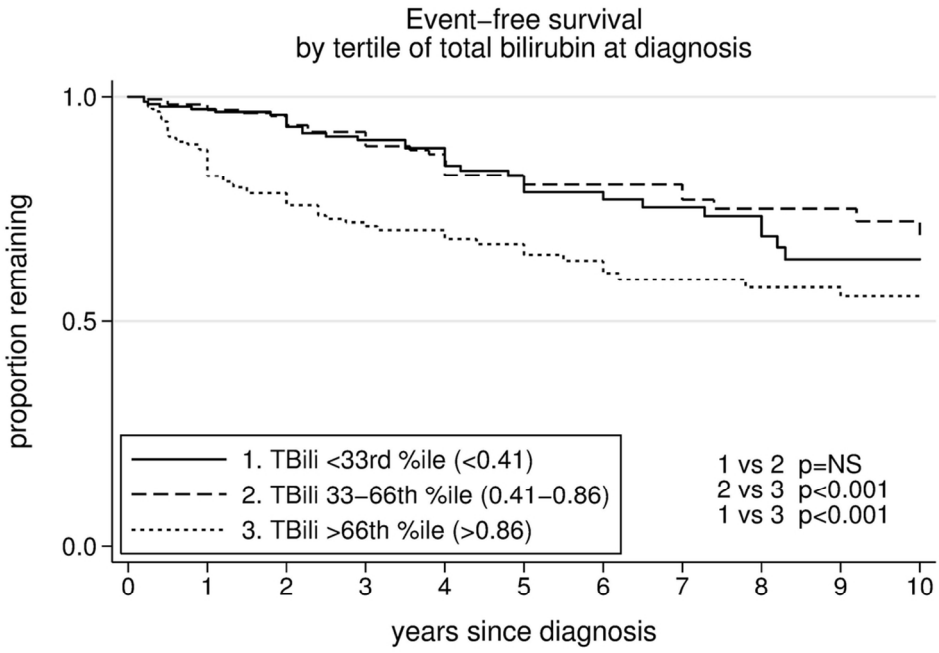

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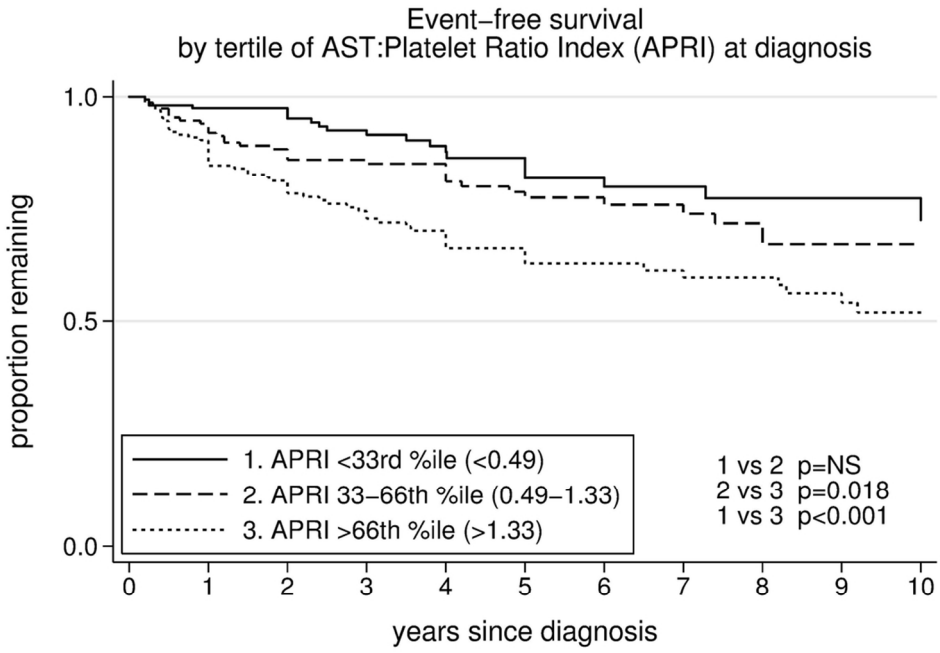

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