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Liver, Pancreas and Biliary Tract

Paediatric-onset autoimmune liver disease: Insights from a monocentric experience

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ABSTRACT

Background: Autoimmune liver disease (AILD) encompasses autoimmune hepatitis (AIH), autoimmune sclerosing cholangitis (ASC) and primary sclerosing cholangitis (PSC). A unified disease process evolving over time through these entities has been recently suggested. From this perspective, this study aimed to compare the characteristics of childhood-onset AILD at baseline and after a medium-to-long term follow-up period.

Methods: Paediatric-onset cases of AILD diagnosed between 1992 and 2023 at a tertiary-care centre were reviewed. Patients transitioned to adult-care by the time of data collection were asked for clinical updates.

Results: Fifty-five patients were included (AIH = 20, ASC =22, PSC =13). AIH, ASC and PSC exhibited increasing age at the onset (AIH to PSC, $p < 0.01$). The area under the receiver operating characteristic curve for gamma-glutamyltranspeptidase (GGT) combined with alkaline phosphatase/aspartate aminotransferase (ALP/AST) ratio in predicting sclerosing cholangitis was 0.94, with a sensitivity of 86 % and a specificity of 94 %. At the last follow-up (median duration 5,8 years, interquartile range [IQR] 2,9–10,2, $n = 45$), 15 patients (33 %) developed portal hypertension, 2 patients (4 %) underwent liver transplantation, no patient died.

Conclusion: A cohort of childhood-onset AILD managed at a single centre reveals a temporal trend in the onset of AIH, ASC and PSC, with progressively older ages. Elevated GGT levels combined with a high ALP/AST ratio predict the diagnosis of sclerosing cholangitis. The occurrence of liver-related adverse events in one-third of patients highlights the progressive nature of paediatric-onset AILD.

1. Introduction

The classification of autoimmune liver disease (AILD) is complex and continuously evolving and notable discrepancy exists between classifications used in adults and children, often leading to confusion in the field. Paediatric autoimmune liver disease (AILD) currently includes two disorders in which chronic inflammation of native liver is likely to arise from autoimmune mechanisms: autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC) [1]. Primary sclerosing cholangitis (PSC) remains delineated as a separate entity, being "primary" by definition, and thus lacking a known etiology [2]. However, among various theories proposed to explain PSC pathogenesis, the observation that most of susceptibility genes for PSC are involved in adaptive immunity, the predominance of T-cells in the portal infiltrate, along with the strong association with inflammatory bowel diseases (IBD), suggest potential involvement of immune-mediated phenomena [3,4]. Indeed, AILD in adults encompasses AIH, PSC and primary biliary cholangitis (PBC), the latter being a disease entity virtually affecting exclusively adults [5–7]. Additionally, according to the working definitions endorsed by the International PSC Study Group, PSC is further categorized into large duct PSC, small duct PSC and PSC with features of AIH, conceptually aligning with ASC [8].

Overcoming the boundaries of classifications, Ricciuto et al. recently proposed that AIH, ASC and PSC may not represent distinct pathological entities, but rather different phases of a

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continuous unified disease process that evolves over time, with biliary derangement progressively superseding the inflammatory features, ultimately converging into the phenotype of PSC [5].

From this perspective, the primary objective of this study is to compare the demographic, clinical and laboratory characteristics of children and adolescents diagnosed with AILD at a single tertiary care referral centre, at baseline and after a medium-to-long term follow-up period. The secondary aim is to assess whether any biochemical findings at presentation may aid in predicting the differential diagnosis.

2. Patients and methods

Children and adolescents (age <18 years) diagnosed with AIH, ASC and PSC as defined below, at the Liver Unit of Istituto di Ricerca e Cura a Carattere Scientifico (IRCCS) Meyer Children's Hospital in Florence between March 1992 and September 2023 were included in the study. Patients with small duct disease (SDD) were excluded. A retrospective analysis of data collected from clinical records was conducted. Patients who had transitioned to adult care services by the time of data collection (October 2023) were reached by telephone or e-mail, following ethics board approval. They were asked for major clinical updates, including current therapy, occurrence of clinically evident portal hypertension (CEPH) and liver transplantation.

Diagnostic criteria are reported in Supplementary Table 1. AIH diagnosis was established in the presence of elevated aminotransferase levels, positive autoantibodies with or without increased IgG levels, histological evidence of interface hepatitis and after exclusion of hepatitis A, B, C, E virus infection, Wilson's disease, metabolic (dysfunction)-associated steatotic liver disease (MASLD) and drug-induced liver disease. AIH was classified into type 1 (AIH-1) or type 2 (AIH-2) based on the profile of autoantibodies. Patients meeting criteria for AIH and exhibiting alterations of the intra- and/or extra-hepatic biliary tree as identified by magnetic resonance cholangiopancreatography (MRCP), including dilatation, narrowing or obliteration, were diagnosed with ASC. PSC was diagnosed in the presence of cholangiographic anomalies at MRCP, in the absence of interface hepatitis with or without histological biliary features and after exclusion of known causes of secondary sclerosing cholangitis (see Supplementary Table 2).

Clinical presentation was classified as:

- insidious: history of progressive fatigue, relapsing jaundice, amenorrhea, headache, anorexia, joint and abdominal pain, diarrhea, weight loss;
- asymptomatic: incidental finding of deranged liver function tests during investigations for extrahepatic conditions;
- acute: rapid onset of nonspecific (malaise, nausea, vomiting, anorexia, abdominal pain, arthralgia) and/or specific symptoms (jaundice, dark urine and pale stools);
- acute liver failure (ALF): impaired liver function tests with international normalized ratio (INR) $\geq$ 1,5 (with encephalopathy) or $\geq$ 2 (without encephalopathy) not corrected after vitamin K parenteral administration, in a subject without previously recognised liver disease [1,9].

Occurrence of CEPH was identified by the presence of at least one of the following indirect signs of portal hypertension:

- splenomegaly (bipolar diameter of the spleen above the upper limit of normal for age, assessed by ultrasound) [10] with or without low platelets count (< 150,000/µl),
- endoscopic demonstration of oesophageal and/or gastric varices [11].

At the end of follow-up, the events of interest under consideration encompassed withdrawal of immunosuppressive therapy and the occurrence of liver-related adverse events, including CEPH, liver transplant and death.

Statistics were performed using MedCalc® Statistical Software, version 20.104 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables are expressed as median and interquartile range (IQR), categorical variables are expressed as count and percentage. Comparisons were made using T-test or Mann-Whitney U test for continuous variables and chi-squared test for nominal ones. A 2-tailed p-value < 0.05 was considered significant. A receiver operating characteristic (ROC) analysis of gamma-glutamyltranspeptidase (GGT) and alkaline phosphatase (ALP)/aspartate aminotransferase (AST) ratio in predicting sclerosing cholangitis (both ASC and PSC) was conducted. To combine GGT and ALP/AST ratio, a binary logistic regression was performed, followed by a ROC analysis of the obtained predicting probabilities.

3. Results

Fifty-five patients were included (32 males, 58 %). Twenty had received a diagnosis of AIH (n = 17 AIH-1, 85 %), 22 ASC and 13 PSC. Two patients were diagnosed with AIH between March 1992 and September 2002, with no diagnosis of ASC or PSC during this period. From October 2002 to March 2013, 16 diagnoses were made, including 6 cases of AIH, 9 of ASC and 1 of PSC. Between April 2014 and September 2023, a total of 37 patients were diagnosed, comprising 12 with AIH, 13 with ASC and 12 with PSC.

3.1. Demographic and clinical features at baseline

Table 1 reports demographic and clinical characteristics at baseline, along with prevalence of autoimmune (AI) family history and association with other AI disorders. Children diagnosed with AIH, ASC, and PSC exhibited a trend of increasing age at the time of diagnosis, with a significant difference observed when comparing AIH to PSC, the latter being older ($p < 0.01$) (Fig. 1). Female predominance was observed in AIH (65 %), while patients with ASC and PSC were more often male (73 % and 69 %, respectively). None of the patients presented with ALF. Acute clinical presentation was most common among children with AIH (45 %), whereas the majority of children with ASC and PSC were asymptomatic (64 % and 69 %, respectively). Thirteen patients (24 %) exhibited splenomegaly on ultrasound at the time of diagnosis. Among them, 2 patients diagnosed with AIH also presented with low platelet counts. Seventeen patients (29 %) had at least one first degree family member affected by AI disorders and 35 patients (64 %) had at least one associated AI comorbidity. The majority of patients with ASC and PSC were also affected by IBD (55 % and 70 %, respectively), which had been diagnosed at the same time of liver disease in 58 % and 56 % of the cases, respectively. Six patients (29 %) had received IBD diagnosis prior to the onset of liver disease. Among the 4 patients with ASC, 3 had ulcerative colitis (UC) and 1 had unclassified IBD (IBD-U). Among the 2 patients with PSC, 1 had Crohn's disease (CD) and 1 had UC. The median interval between IBD and liver disease diagnosis was 1.5 years (IQR 1–1.5) for patients with UC or IBD-U, and 9.1 years for the patient with CD. Regarding immunomodulatory treatments received prior to diagnosis of liver disease, two patients with ASC had received short-courses of prednisone, one patient with ASC had received three doses of infliximab (discontinued due to ineffectiveness) and one patient with ASC was under therapy with azathioprine. The patient with CD had started adalimumab treatment 9 months before being diagnosed with PSC. All patients with UC or IBD-U were being treated with mesalazine and none underwent colectomy. No patients with AIH exhibited associated IBD.

Table 1
Baseline demographic and clinical characteristics.

Variable	All (n = 55)	AIH (n = 20)	ASC (n = 22)	PSC (n = 13)	p value[d]
Age (years), median (range)	11,5 (1,5–16,7)	8,3 (1,5–15,8)	11,3 (3–16,1)	13,5 (8,3–16,7)	0,12* < 0,01† 0,06§
Female, n (%)	23 (42)	13 (65)	6 (27)	4 (31)	0,02* 0,06† 0,83§
Clinical presentation					
Acute, n (%)	14 (24)	9 (45)	4 (18)	0	0,06* <0,01† 0,11§
Insidious, n (%)	12 (21)	4 (20)	4 (18)	4 (31)	0,88* 0,5† 0,4§
Asymptomatic, n (%)	32 (55)	7 (35)	14 (64)	9 (69)	0,07* 0,06† 0,74§
Splenomegaly, n (%)	13 (24)	5 (25)	3 (14)	5 (38)	0,4* 0,4† 0,1§
AI family history (first degree), n (%)	17 (29)	5 (25)	7 (32)	4 (31)	0,6* 0,7† 0,9§
AI comorbidity (IBD included)[a], n (%)	35 (64)	9 (45)	16 (73)	10 (77)	0,07* 0,07† 0,8§
Celiac disease	4	3	0	1	
Diabetes mellitus type 1	3	2	1	0	
Thyroiditis	2	2	0	0	
AI polyendocrinopathy	1	1	0	0	
Rheumatologic disorders[b]	6	2	3	1	
AI pancreatitis	1	0	0	1	
Selective IgA deficiency	1	0	1	0	
Cogan syndrome	1	1	0	0	
IBD, n (%)	21 (38)	0	12 (55)	9 (70)	0,4§
Ulcerative cholitis (UC)	19	0	11	8	
Crohn disease (CD)	1	0	0	1	
Unclassified (IBD-U)	1	0	1	0	
IBD time diagnosis before liver disease, n (%)	6 (29)	–	4 (33)	2 (22)	
with liver disease, n (%)	12 (57)	–	7 (58)	5 (56)	
after liver disease, n (%)	3 (14)	–	1 (9)	2 (22)	

[a] Some patients have more than one disorder.
[b] Including juvenile idiopathic arthritis, connectivitis, dermatomyositis, psoriasis.
[c] AI=autoimmune; IBD= inflammatory bowel disease.
[d] * AIH vs ASC; † AIH vs PSC; § ASC vs PSC.

3.2. Laboratory, biliary imaging and liver histology at the time of diagnosis

Liver biochemistry, autoimmune profile and histological findings at the time of diagnosis are summarized in Table 2. Patients with AIH had higher transaminases and lower GGT levels, compared to patients with sclerosing cholangitis ($p < 0.01$). Transaminase levels were higher in ASC than in PSC ($p < 0.05$). ALP/AST ratio was higher in both ASC and PSC, compared to AIH ($p < 0.01$). Fig. 2 represents the ROC analysis in predicting sclerosing cholangitis for GGT, ALP/AST ratio and for the predicting probabilities obtained from a binary logistic regression of GGT and ALP/AST ratio. The combined cut-off values for GGT and ALP/AST ratio corresponding to the best cut-off predicting probability value (0.5169, area under the ROC curve 0.938) were GGT 200 IU/L and ALP/AST ratio 0.7.

Patients with fibrosis or cirrhosis on liver histology exhibited a lower white blood cell count, with a median value of 6830 cells/mm^3 (IQR 5530–9075) compared to 11,440 cells/ mm^3 (IQR 6590–11,940) in those without fibrosis or cirrhosis ($p = 0.038$). This finding was not confirmed in any diagnostic subgroup. There was no difference in the prevalence of splenomegaly, platelet count and serum albumin levels between patients with or without fibrosis or cirrhosis.

Patients diagnosed with AIH, ASC and PSC showed similar levels of immunoglobulin type G (IgG), as well as prevalence of positive antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA), along with their titers. Positive perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) were predominantly detected in patients with ASC and PSC compared to AIH.

Baseline MRCP detected anomalies in the intrahepatic biliary ducts in similar proportions of patients with ASC and PSC ($p = 0.12$). Specifically, eleven patients with ASC (50 %) and 10 patients with PSC (77 %) exhibited intrahepatic biliary involvement, which was reported as marked in two patients with PSC.

Twelve patients underwent baseline transient elastography using Fibroscan®. Two of these patients (17 %) had cirrhosis detected by liver histology, with liver stiffness measurements of 15 kPa and 36.3 kPa, respectively. The remaining patients, all but one of whom had fibrosis on liver biopsy, had a median liver stiffness of 6.75 kPa (IQR 6.3–7.2).

Liver histology revealed more frequent occurrence of fibrosis in children with ASC and PSC compared to AIH ($p < 0.01$). Biliary changes (including cholangiocytes degeneration and atrophy, duc-

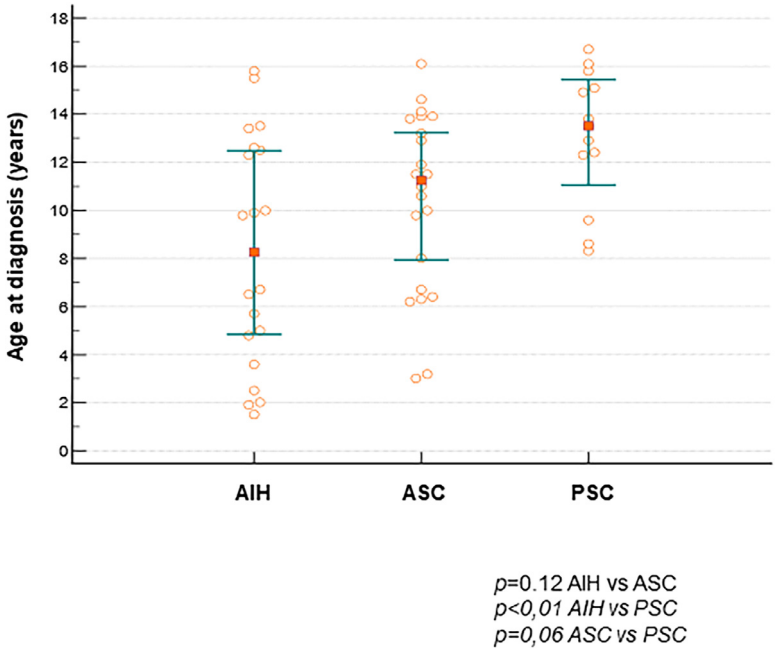

Fig. 1. Age at diagnosis of AILD (AIH=autoimmune hepatitis; ASC=autoimmune sclerosing cholangitis; PSC=primary sclerosing cholangitis).

tular proliferation, ductular metaplasia, copper-associated proteins deposition) were detected in 68 % and 100 % of children diagnosed with ASC and PSC, respectively, and in 20 % of those diagnosed with AIH ($p < 0.01$).

3.3. Medical therapy and response to treatment

Patients diagnosed with AIH or ASC underwent immunosuppressive therapy. Forty out of 42 patients (95 %) received high dose oral prednisone. Cyclosporine was utilized as a steroid-sparing agent in two patients (5 %) with type 1 diabetes, one with AIH and one with ASC respectively. The latter switched to low-dose prednisone combined with azathioprine after 6 months. Fifteen patients with AIH (75 %) and 13 with ASC (59 %) necessitated adding azathioprine during prednisone tapering, at a starting dose of 0.5 mg/kg/day and escalated to a median dose of 1.8 mg/kg/day (IQR 1,5–2). One patient treated with prednisone was already under mycophenolate at the time of diagnosis of AIH due to coexisting Cogan syndrome. Patients with sclerosing cholangitis (both ASC and PSC, $n = 35$) received ursodeoxycholic acid (UDCA), at a median dose of 15 mg/kg/day (IQR 13–17).

Normalization of transaminase levels was achieved in 15 patients (75 %) with AIH, after a median time of 53 days (IQR 27–169), while immunological remission, defined by both normal IgG levels and negative or low-titre autoantibodies, was not observed in any patients with AIH before transitioning to adult care. Six patients (30 %) with AIH, including 3 with AIH-2, experienced at least one relapse (one patient with AIH-2 had 2 episodes), attributed to low-adherence to therapy in 2 cases, de-escalation of prednisone to 2.5 mg/day in one case, and unexplained in the remaining cases.

3.4. Outcome

Table 3 summarizes the cumulative incidence of the principal events of interest at the end of follow up ($n = 45$, median duration 5.8 years, IQR 2,9–10,2). At the time of data collection, 27 patients (49 %) had transitioned to adult care services. Of these, 17 (median age 22 years, IQR 20–24) were reachable by telephone or email and agreed to provide clinical updates. Withdrawal of immunosuppressive therapy was achieved in 3 patients with AIH (19 %) and in 2 patients with ASC (13 %). Two out of the 3 patients with AIH and both the patients with ASC ceased immunosuppression under medical supervision following transition to adult care services. Liver biopsy before attempting immunosuppression withdrawal was performed in one patient with ASC. Fifteen patients (33 %) developed CEPH at a median time of 1.9 years after diagnosis (IQR 0–3.7). Patients who had splenomegaly at the time of diagnosis did not have worse outcomes compared to those without splenomegaly at presentation, in terms of upper gastrointestinal bleeding episodes and the need for liver transplantation.

Two patients with AIH underwent follow-up MRCP which confirmed normal findings. Among the 22 patients with ASC, 10 repeated MRCP. Biliary progression was detected in 9 cases (41 % of total cases) at a median time from diagnosis of 5.2 years (IQR 2–6.7). Three out of 13 patients with PSC underwent follow-up MRCP, which revealed worsening of biliary findings in 2 cases (15 % of total cases) after 1.4 and 4.9 years from diagnosis, respectively. There was no significant difference in baseline GGT, ALP and ALP/AST ratio values between patients who experienced biliary progression and those who did not.

One patient with ASC (6 %) developed choledocholithiasis and stenosis, requiring stent placement at the age of 18.4 years and received liver transplantation at 19 years. Two patients with PSC (15 %) developed major biliary strictures necessitating interventional management, at 18.7 and 20.4 years of age, respectively. The latter of these patients had also exhibited marked intrahepatic biliary anomalies at diagnosis. Another patient with PSC with baseline marked intrahepatic biliary alterations received liver transplantation at the age of 15 years. Overall, no patient died.

4. Discussion

We conducted a retrospective analysis of a cohort of patients diagnosed with AIH, ASC and PSC during childhood and then followed-up at a single tertiary care referral centre. Unlike most of previous studies that focused solely on cohorts of paediatric AIH and ASC or cohorts of paediatric ASC and PSC, respectively, our study encompasses all three clinical entities. This choice has been

Table 2
Laboratory and histological features at diagnosis.

Variable	All (n = 55)	AIH (n = 20)	ASC (n = 22)	PSC (n = 13)	p value[d]
Biochemical features[a]					
AST (IU/L)	230 (88–830)	897 (362–1615)	192 (106–341)	78 (43–152)	<0,01* <0,01† 0,03§
ALT (IU/L)	289 (125–960)	1007 (443–2149)	287 128–520)	125 (92–179)	<0,01* <0,01† 0,02§
GGT (IU/L)	133 (79–283)	91 (53–127)	276 (101–433)	241 (138–347)	<0,01* <0,01† 0,8§
ALP (IU/L)	368 (304–524)	351 (304–533)	476 (307–739)	396 (264–459)	0,6* 0,8† 0,3§
Total bilirubin (mg/dl)	0,9 (0,4–1,6)	1,3 (0,6–5,9)	0,9 (0,4–1,4)	0,5 (0,4–1)	0,1* 0,01† 0,1§
Bile acids (µmol/L)	26 (9–67)	16 (11–158)	37 (12–61)	11 (5–56)	0,9* 0,1† 0,1§
ALP/AST ratio	1,9 (0,5–5,3)	0,6 (0,3–1)	3,5 (1,1–6,3)	5,2 (4,2–10,5)	<0,01* <0,01† 0,1§
INR	1,1 (1,04–1,18)	1,2 (1,1–1,4)	1,1 (1–1,2)	1,1 (1–1,1)	0,01* <0,01† 0,3§
Albumin (g/L)	4,3 (4–4,5)	4,3 (4,1–4,5)	4,3 (3,9–4,5)	4,1 (4–4,3)	0,9* 0,3† 0,3§
Immunological profile					
IgG (mg/dL)[a]	1685 (1295–2297)	1665 (1415–2387)	1700 (1242–2509)	1655 (1038–1722)	0,9* 0,2† 0,3§
ANA positive, n (%)	41 (75)	13 (65)	17 (77)	11 (85)	0,4* 0,2† 0,6§
Reciprocal of ANA titer[a]	320 (160–800)	320 (160–1280)	320 (80–640)	320 (200–1120)	0,6* 0,8† 0,6§
ASMA positive, n (%)	41 (75)	15 (75)	18 (82)	8 (62)	0,6* 0,4† 0,2§
Reciprocal of ASMA titer[a]	80 (40–160)	80 (80–160)	40 (40–160)	40 40–80)	0,1* 0,2† 0,7§
LKM-1 positive, n (%)	3 (5)	3 (15)	0	0	
Reciprocal of LKM-1 titer[a]	160 (160–1960)	160 (160–1960)	–	–	
pANCA positive, n (%)	29 (53)	5 (31)	16 (76)	8 (67)	<0,01* 0,07† 0,6§
Liver histology					
Interface hepatitis, n (%)	42 (76)	20 (100)	22 (100)	0	–
Fibrosis, n (%)	38 (69)	10 (50)	15 (68)	13 (100)	0,004* 0,006† 0,7§
Cirrhosis, n (%)	5 (9)	3 (15)	2 (9)	0	0,7* 0,13† 0,19§
Biliary changes[b], n (%)	32 (58)	4 (20)	15 (68)	13 (100)	<0,001* <0,001† 0,2§

[a] Values are expressed as median (interquartile range).
[b] including cholangiocytes degeneration and atrophy, ductular proliferation, ductular metaplasia, copper-associated proteins deposition
[c] AST=aspartate aminotransferase, ALT=alanine aminotransferase, GGT=gamma-glutamyltranspeptidase, ALP=alkaline phosphatase, INR= international normalized ratio. ANA= antinuclear antibodies, ASMA=anti-smooth muscle antibodies, LKM-1=anti-liver kidney microsomal type 1 antibody, pANCA=perinuclear anti-neutrophil cytoplasmic antibodies.
[d] * AIH vs ASC; † AIH vs PSC; § ASC vs PSC.

driven by the hypothesis that AIH, ASC and PSC in childhood may represent different phases of a unified spectrum of disease. Furthermore, it reflects our attempt to transcend the boundaries of classifications and shift the scientific debate back to clinical practice, where, in facing a young patient presenting with suspected AILD, the diagnostic pathway moves through each of these entities. A recently published retrospective study including a cohort of 159 patients with childhood-onset AILD has revealed that approximately 20 % of individuals diagnosed with AIH-1 during childhood progress to either ASC or PSC within a follow-up period up to 30

Table 3
Outcome at the end of follow-up (information available for 45 total patients).

Variable	All ($n = 45$)	AIH ($n = 16$)	ASC ($n = 16$)	PSC ($n = 13$)	*p value*[c]
Follow up duration, median (IQR)	5,8 (2,9–10,2)	8,9 (4,9–12,7)	6,2 (3,2–11,4)	4,3 (2,5–5,8)	0,6* 0,05† 0,14§
Age at the end of follow up (years), median (IQR)	17,7 (14,4–20)	16,3 (12,7–22,2)	17,5 (9,7–26,4)	18,8 (10,6–23,1)	0,7* 0,6† 0,8§
Stop immunosuppressive (IS) therapy, n (%)	5 (16)	3 (19)	2 (13)	–	0,7
Time stop IS therapy since diagnosis, median (IQR)	11,9 (6,8–12)	7,8	12	–	
CEPH, n (%)[a]	15 (33) [1]	3 (19)	6 (38)	6 (46)	0,25* 0,12† 0,64§
Time first detection CEPH, median (IQR)	1,9 (0–3,7)	0	4,3	0 (0–2,7)	0,018* 0,29† 0,03§
Biliary complications	3 (7)	0	1 (6)	2 (15)	0,28§
Liver transplant, n (%)	2 (4)	0	1 (6)	1 (8)	
Time liver transplant		–	6,1	3,5	
Dead, n (%)	0	0	0	0	

[a] All had splenomegaly (with or without low platelet count), one patient with ASC also developed oesophageal varices.
[b] CEPH=Clinically Evident Portal Hypertension
[c] * AIH vs ASC; † AIH vs PSC; § ASC vs PSC.

years. Furthermore, it was found that two-thirds of paediatric cases of ASC progress to PSC through adulthood [12]. It could be hypothesized that as-yet-unidentified individual characteristics may play a role in determining the risk of progression between these pathological entities for a given patient. In our cohort, no patient with AIH progressed to ASC, and follow-up liver histology data were not available to assess the evolution of ASC to PSC. However, the limited number of patients included and the brevity of the median follow-up prevent any definitive conclusions from being drawn in this regard.

During the observation period, a notable increase in the number of diagnoses was observed, rising from a total of 2 cases in the first decade to 37 cases in the last decade. Although the literature reports an increase in the incidence of AILD, it is reasonable to hypothesize that an overall increase in the referral of patients with suspected liver disease to our centre over time has influenced this trend [13–15].

In our cohort, patients with AIH presented at a significantly younger age than those with PSC, whereas patients with ASC tended to present at an intermediate age. This observation conceptually aligns with the assumption proposed by Ricciuto et al., suggesting a temporal progression of juvenile immune-mediated liver disease, transitioning from AIH to PSC, through the intermediate phenotype of ASC [5].

Consistent with findings from other studies [16–18], AIH demonstrated a higher prevalence among females (2 out of 3 cases), whilst sclerosing cholangitis affected more often males (almost 7 out of 10 cases). A positive family history of autoimmune disorders was reported in approximately 30 % of our patients, consistent with the variable association documented in other cohorts ranging from 21 % to 40 % [18,19]. Notably, a stronger association with extrahepatic autoimmune disorders, including inflammatory bowel disease (IBD), was observed: 64 % of our patients either presented with at least one non-hepatic autoimmune disease at the time of diagnosis or developed it during follow-up, whilst previous studies report an association ranging from 21 % to 48 % [16,18,19]. This result may reflect the higher representation of patients affected by sclerosing cholangitis in our cohort: notably, 55 % of patients diagnosed with ASC and 70 % of those with PSC were also affected by IBD, with predominance of UC. This is consistent with the prevalence rates reported in the literature, reaching up to 81 % [16–18,20]. In contrast, AIH was predominantly associated with celiac disease, autoimmune thyroiditis and diabetes type 1. None of the patients with AIH received a diagnosis of IBD in our experience, whereas other studies report associations ranging from 5 to 18 % of cases [16,18,19]. It is noteworthy that the majority of patients diagnosed with sclerosing cholangitis in our cohort did not exhibit symptoms indicative of hepatic disease. Liver involvement was unveiled during investigations for IBD-related gastrointestinal symptoms. In the remaining cases of sclerosing cholangitis the presentation was insidious, often becoming apparent after a variable period characterized by subtle and nonspecific symptoms. A close temporal relationship between the diagnosis of UC or IBD-U and sclerosing cholangitis emerged in our cohort. In fact, 86 % of sclerosing cholangitis cases were diagnosed concurrently with or within a median of 1.5 years following the diagnosis of UC/IBD-U. In contrast, the only patient with CD developed PSC after approximately 9 years. In our cohort, immunosuppression for IBD prior to the diagnosis of ASC, did not appear to prevent the detection of inflammatory infiltrate on liver histology, while it is unclear whether the PSC phenotype in the patient with CD may have been influenced by the treatment with adalimumab.

AIH presented acutely in 45 % of patients, consistent with findings reported in previous cohorts [16,18,19]. Interestingly, despite the more frequent subtle onset of sclerosing cholangitis, the prevalence of clinically evident portal hypertension (CEPH) at the time of presentation – and in particular splenomegaly – was similar across our three groups.

As expected, serum transaminases were significantly higher in AIH, compared to both types of sclerosing cholangitis. Higher levels of transaminases were also observed in ASC in comparison to PSC. This could be partly attributed to the absence of acute presentation among patients diagnosed with PSC. GGT levels were significantly higher in patients with sclerosing cholangitis compared to those with AIH. There was no difference in ALP levels, likely due to the inability to distinguish the hepatic isoenzyme from the bone one. Interestingly, the ALP/AST ratio was significantly lower in AIH compared to sclerosing cholangitis. As previously suggested by other authors [16,18], the ALP/AST ratio could serve as useful additional marker for the differential diagnosis and, after validation in larger series, it may be potentially incorporated into the scoring system. We propose to combine the ALP/AST ratio with GGT levels. Intuitively, the accuracy in distinguishing sclerosing cholangitis from AIH should increase, as demonstrated in our cohort.

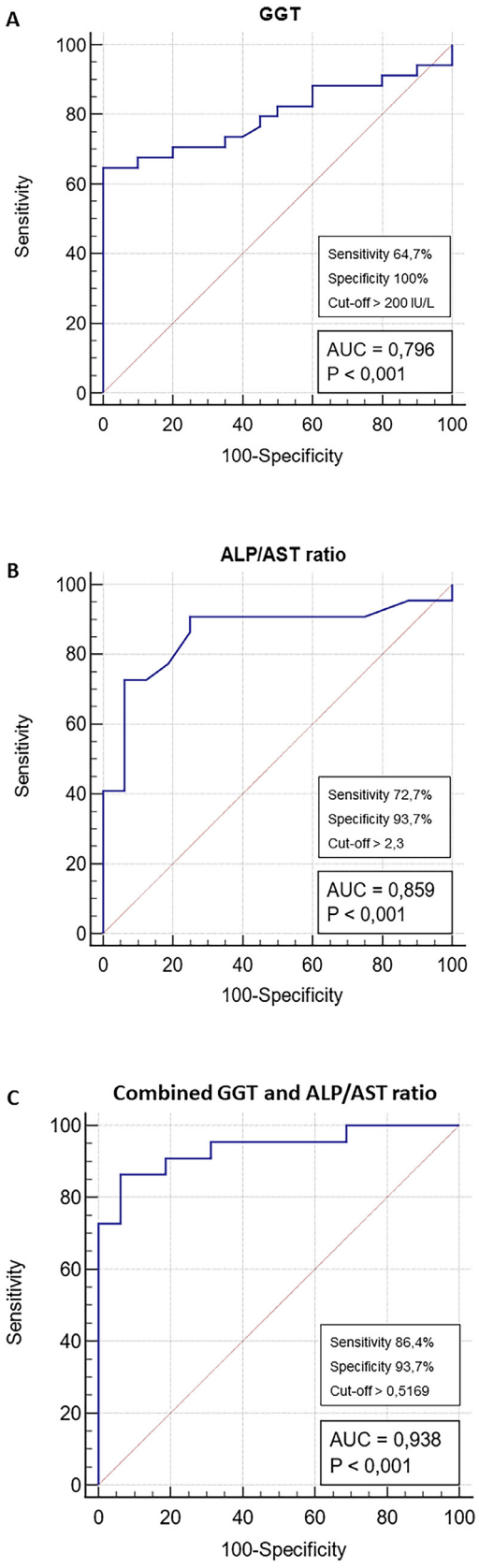

Fig. 2. ROC analysis in predicting sclerosing cholangitis: **A**, GGT; **B**, ALP/AST ratio; **C**, predicting probabilities obtained from binary logistic regression of GGT and ALP/AST ratio (GGT=gamma-glutamyltranspeptidase, ALP=alkaline phosphatase, AST=aspartate aminotransferase).

As for the immunological profile, neither autoantibodies and their titers, nor the serum levels of IgG exhibited the capability to differentiate between the proper AILD (AIH and ASC) and PSC. The only significant difference lies in the prevalence of perinuclear anti-neutrophil cytoplasmic antibody (pANCA), which is lower in AIH. These findings are consistent with the ESPGHAN scoring system [1].

Liver histology showed a higher frequency of fibrosis in sclerosing cholangitis compared to AIH. As expected, features indicative of biliary duct damage are more frequently detected in liver biopsies from patients diagnosed with sclerosing cholangitis [18].

We assessed the clinical outcome after a median follow-up time of approximately six years. The median age at the end of the observation period was around 18 years. This relatively short follow-up duration, compared to the overall length of the observation period, can be attributed to the occurrence of two-thirds of the diagnoses in the last decade. Notably, patients affected by PSC tended to have a shorter follow-up duration. This is consistent with the heightened frequency of PSC diagnoses documented in the literature, which may be attributed to the growing utilization of biliary imaging techniques, particularly the noninvasive modality of MRCP [21]. Among patients who transitioned to adult care and provided clinical updates, an overall low rate of deterioration was observed, with only one patient requiring liver transplantation. However, the relatively short follow-up period after transitioning, with a median age of 22 years, may explain the overall lack of deterioration.

In our experience, fewer than one in five patients were able to discontinue immunosuppressive therapy, after a median duration of approximately 11 years since diagnosis. It is noteworthy that one in three patients experienced at least one adverse liver-related event, such as portal hypertension or liver transplantation, within two years following diagnosis. Additionally, one out of ten patients with sclerosing cholangitis experienced biliary complications approximately 6 years after diagnosis, whereas Denau and collaborators reported a proportion of 15 % over the same period [17]. Furthermore, patients with ASC seemed more likely to experience biliary progression over time compared to those with PSC, with rates of 41 % and 15 % of total cases, respectively. It could be hypothesized that the inflammatory component may facilitate biliary worsening in patients with ASC. However these findings should be interpreted with caution, as follow-up MRCP was not performed in all patients, and the degree of biliary alterations was not formally assessed.

These findings underscore the progressive nature of these conditions and emphasize the importance for clinicians, families and patients themselves to prioritize strict adherence to medical therapy in the attempt to mitigate the progression of the disease.

5. Conclusions

AIH, ASC and PSC constitute a spectrum of disorders that, while distinguishable from each other, share many clinical and pathological characteristics. PSC may represent the final phenotype of a dynamic process involving immune-mediated aggression of the liver during earlier phases. Prospective collaborative studies are needed to assess the long-term evolution of these disease entities. Advances in understanding the pathogenesis of AILD are necessary to identify potential therapeutic targets. The combination of ALP/AST ratio and GGT levels may aid in distinguishing between AIH and sclerosing cholangitis, but cholangiographic studies remain necessary to assess the extent of biliary damage.

Author contributions

Study concept: FC, GI. Study supervision and execution: FC, EB, GI. Data collection and review: FC, CR, MS, SC. Data analysis: FC, GI. Manuscript writing and revisions: FC, GI, ST.

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Conflict of interest

Unrelated to this study GI has received consultancy and speaker fees from Mirum and IPSEN. The remaining authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.09.020.

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