Biliary disease progression in childhood onset autoimmune liver disease: A 30-year follow-up into adulthood

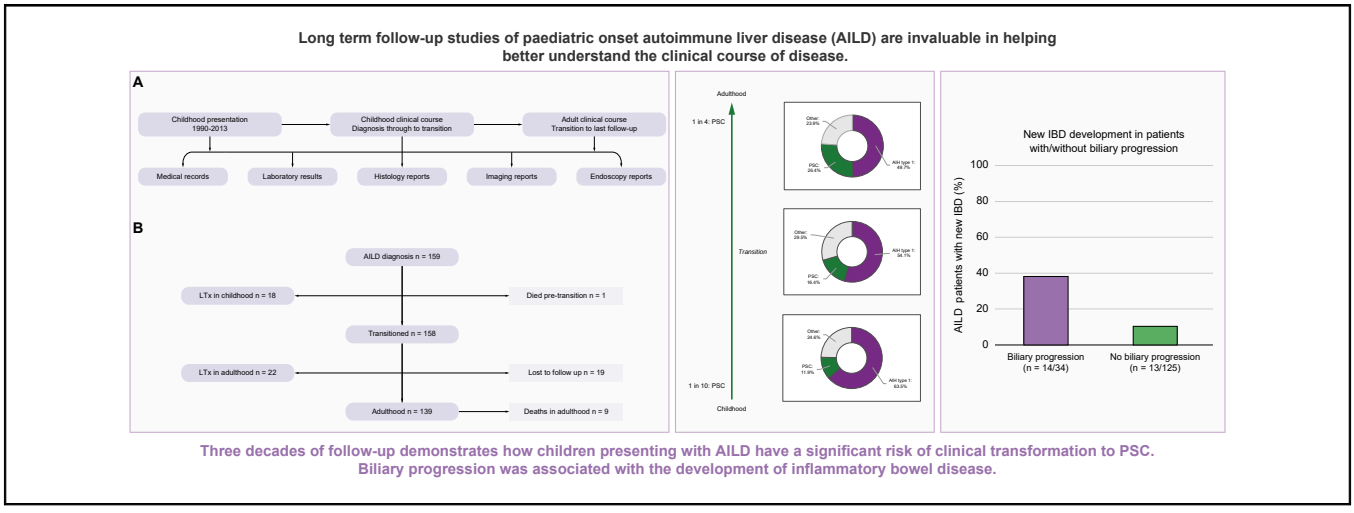
Authors

Suz Warner, Jeremy Rajanayagam, Emily Russell, Carla Lloyd, James Ferguson, Deirdre A. Kelly, Gideon M. Hirschfield

Correspondence

gideon.hirschfield@uhn.ca (G.M. Hirschfield).

Graphical abstract



Highlights

- Follow-up of paediatric onset AILD into adulthood is valuable.
- A total of 159 patients with childhood onset AILD between 1990 and 2013 were reviewed.
- Approximately 20% of patients with childhood onset AIH-1 developed biliary features by adulthood.
- Of these, 50% of patients phenotypically transitioned to PSC.
- Approximately 90% of patients with biliary progression developed ulcerative colitis during follow-up.

Impact and implications

Childhood onset autoimmune liver disease remains very impactful for patients and families. Disease nomenclature can however be confusing. Long-term follow up studies as children become adults is important to help understand how and why disease behaves over time. Understanding more about the long-term course of childhood autoimmune liver disease will help patients, families and doctors striving to improve care and reduce poor clinical outcomes. We followed over 150 patients with childhood onset autoimmune liver diseases into adulthood. We found that amongst patients with classical autoimmune hepatitis, 1 in 5 developed biliary disease over time, mostly consisting of primary sclerosing cholangitis. This was associated with developing inflammatory bowel disease. Our study design was retrospective and has relevant limitations. Defining phenotypes of autoimmune liver diseases is difficult and there is insufficient consensus, especially between adult and childhood physicians. Our data confirms the critical importance of careful long-term follow-up of patients, including safe transition to adult care, as well as robustly demonstrates, using real-world data, how disease nature can change over time. Our study affirms the need for investment in prospective cohort studies.

https://doi.org/10.1016/j.jhepr.2023.100901

Research article

JHEP|Reports

Biliary disease progression in childhood onset autoimmune liver disease: A 30-year follow-up into adulthood

Suz Warner,[1,2,3] Jeremy Rajanayagam,[1,2,3] Emily Russell,[1] Carla Lloyd,[2] James Ferguson,[1,3] Deirdre A. Kelly,[1,2,†] Gideon M. Hirschfield[3,4,†,*]

[1]*Centre for Liver and Gastrointestinal Research, University of Birmingham, Birmingham, UK;* [2]*Liver Unit, Birmingham Women's & Children's Hospital, Birmingham, UK;* [3]*NIHR Biomedical Research Centre, University Hospitals Birmingham, Birmingham, UK;* [4]*Toronto Centre for Liver Disease, Department of Medicine, University of Toronto, Toronto, Canada.*

JHEP Reports **2024.** https://doi.org/10.1016/j.jhepr.2023.100901

Background & Aims: Long-term follow-up studies of paediatric onset autoimmune liver disease (AILD) are invaluable in helping better understand the clinical course of disease. In day-to-day practice clinicians struggle with disease definitions whilst patients and parents lack clear prognostic information.
Methods: The clinical progression of 159 patients with childhood onset AILD between June 1990 and December 2013 was reviewed, capturing data up to adulthood (ending May 2021).
Results: Presentation with autoimmune hepatitis (AIH) was dominant (n = 119); biliary presentations accounted for 25%. During follow up, biliary disease progression confirmed by cholangiography and/or liver histology was observed frequently: 19.8% (20/101) patients with childhood onset AIH type 1 (AIH-1) developed biliary features by adulthood and of these 50% phenotypically transitioned to primary sclerosing cholangitis (PSC); the remaining transitioned to an overlap disease phenotype. No patients with AIH type 2 developed biliary progression. Two-thirds of patients with overlap features (14/21) in childhood had phenotypically progressed to PSC by adulthood. Approximately 43% (6/14) of AIH-1 patients requiring a liver transplant in adulthood had explant evidence of biliary disease compared with 11% (1/9) in childhood, whereas 35.7% (5/14) of patients had histology diagnostic of PSC in their explant liver and 7.1% (1/14) had overlap features. All patients with biliary phenotypes (PSC, autoimmune sclerosing cholangitis, overlap) who required a transplant (n = 18) were found to have explant histology consistent with PSC. Twelve of 14 patients with biliary progression developed ulcerative colitis during follow-up with 92% progressing to PSC.
Conclusions: Three decades of follow-up demonstrated how children presenting with AILD had a significant risk of clinical transformation to PSC. Biliary progression was significantly associated with the development of inflammatory bowel disease.
Impact and implications: Childhood onset autoimmune liver disease remains very impactful for patients and families. Disease nomenclature can however be confusing. Long-term follow up studies as children become adults is important to help understand how and why disease behaves over time. Understanding more about the long-term course of childhood autoimmune liver disease will help patients, families and doctors striving to improve care and reduce poor clinical outcomes. We followed over 150 patients with childhood onset autoimmune liver diseases into adulthood. We found that amongst patients with classical autoimmune hepatitis, 1 in 5 developed biliary disease over time, mostly consisting of primary sclerosing cholangitis. This was associated with developing inflammatory bowel disease. Our study design was retrospective and has relevant limitations. Defining phenotypes of autoimmune liver diseases is difficult and there is insufficient consensus, especially between adult and childhood physicians. Our data confirms the critical importance of careful long-term follow-up of patients, including safe transition to adult care, as well as robustly demonstrates, using real-world data, how disease nature can change over time. Our study affirms the need for investment in prospective cohort studies.

Introduction

Autoimmune liver diseases (AILD) are chronic immune mediated hepato-biliary disorders that damage hepatocyte and biliary epithelial cell function.[1–3] As a family of rare diseases, they often present in childhood and are usually lifelong.[4,5] The pattern of presentation differs between children and adults, with primary biliary cholangitis (PBC) in essence, exclusively defining an adult disease.[6,7] Whilst autoimmune hepatitis (AIH) is the dominant immune mediated disease in childhood, some children present with primary sclerosing cholangitis (PSC), and others will have

Keywords: Autoimmune hepatitis; Primary sclerosing cholangitis; Inflammatory bowel disease; Autoimmune sclerosing cholangitis; Overlap syndrome.
Received 20 March 2023; received in revised form 3 August 2023; accepted 24 August 2023; available online 9 September 2023
† Joint senior authors.
* Corresponding authors. Addresses: Lily and Terry Horner Chair in Autoimmune Liver Disease Research, Toronto Centre for Liver Disease, University Health Network and University of Toronto, Toronto, Canada
E-mail address: gideon.hirschfield@uhn.ca (G.M. Hirschfield).

features of both hepatocyte and biliary focused injury ("overlap" or "autoimmune sclerosing cholangitis [ASC])".[7–10] These mixed hepatitic-biliary phenotypes of overlap syndrome and ASC are more common in childhood, reportedly affecting 33% of children with AILD compared with 1.7–10% of adults.[11] In the absence of understanding disease aetiology definitions are driven by evolving consensus. ASC has been proposed as an overlap syndrome of AIH with features of sclerosing cholangitis, which affects males and females equally.[2,10,11] There is an association with inflammatory bowel disease (IBD), impacting 45% of children classified as having ASC. The majority will be positive for antinuclear antibody (ANA), smooth muscle antibody (SMA), and/or perinuclear anti-neutrophil cytoplasmic antibodies (pANCA). As with AIH, raised IgG levels have been reported and interface hepatitis is the predominant histological lesion. Biliary features include bile duct damage and proliferation, and cholangitis. Approximately 25% of children with ASC reportedly have no histological biliary features and are diagnosed based on cholangiography alone.[2,11] Overlap syndrome shares these features described in ASC but historically affects older children/adults.[11,12] Ultimately true validated definitions for both conditions do not exist, and terminology and practice continue to evolve.

AIH has two serologic patterns of presentation; type 1 (AIH-1) and type 2 (AIH-2), but treatment approaches are consistent, and are usually effective.[13–15] In contrast, treatment options for autoimmune biliary disease continues to lack the efficacy of AIH management, and often progressive biliary involvement portends a poorer outcome.[16–19] There remains variability in practice as regards to investigation approaches to children with AILD. Serology, histology, and imaging over time form the basis of clinical disease classification in practice, but marked heterogeneity exists with respect to interpretation of findings.

Long-term follow-up studies from AILD diagnosis in childhood through to established independent adult clinical practice remain relevant for patient care, treatment considerations, as well as for improving our understanding of disease.[20–22] To further our understanding, we have approached the problem by appraising the clinical narrative of management for children presenting with AILD to a single expert paediatric liver centre in the UK serving both a local and referral population. With 30 years of follow-up we provide clinical insights, highlighting biliary progression in AILD for a substantial proportion of children, as well as the importance of developing IBD in this phenotypic transition.

Patients and methods

Study population

This was a retrospectively analysed longitudinal study of all children aged <18 years of age who were diagnosed with AILD between 1 June 1990 and 31 December 2013 at The Liver Unit, Birmingham Women's & Children's Hospital, UK. The unit is a large paediatric liver centre in the UK, serving a combined secondary and tertiary referral base. The diagnosis and management of paediatric AILD was based on clinical consensus reached by multidisciplinary patient review by expert hepatologists, liver histopathologists and radiologists, and the authors allocated diagnosis for the study based on the overall clinical narrative. Assessments of each patient's liver histology and their clinical, biochemical, immunological, and radiological findings were considered. Clinical data was collected on each patient from childhood disease onset through to adulthood, up to and including 31 May 2021 (Fig. 1A).

The cohort for review was identified from within the clinical programme by searching prospectively collated diagnostic databases, for any of the following disease coding classifications: Autoimmune hepatitis (type 1 or 2), AIH, overlap syndrome, ASC, PSC, and/or AILD. Patients with other forms of hepatitis (*e.g.* viral hepatitis), drug induced liver injury, inherited and metabolic forms of chronic liver disease (*e.g.* Wilson's disease) and/or bile duct disease secondary to an alternative disease aetiology or surgery were excluded. The retrospective review was approved by the Research and Development Departments at Birmingham Children's Hospital and at the Queen Elizabeth Hospital, Birmingham, UK, where most of the patients were transitioned to adult specialist Hepatology care. Re-evaluation of historic imaging or pathology was not permitted.

Data collection and study definitions

The definitions of disease for reporting were (i) AIH (types 1 or 2), (ii) PSC, and patients with mixed hepatitic-biliary pathology, and (iii) overlap syndrome or ASC. The initial diagnosis for each patient was reached following a multidisciplinary discussion of their liver biopsy histology and consideration of their clinical, biochemical, and immunological characteristics including autoimmune serology and IgG values. As our aim was to describe the unadjusted clinical course of this cohort from the perspective of the patient, we elected to keep the two patient groups of ASC and overlap separate as per the clinical narrative from a detailed serial chart review.

Data was collected relating to the disease course of patients between the time of presentation through to adulthood. Investigators (SW, ER, and JR) collected demographic information, mode of presentation, personal and family history of other autoimmune diseases, clinical course and outcomes, laboratory results (including serum liver tests, full blood count, coagulation profile, immunoglobulins, and autoantibody profile), liver biopsy with or without explant histology reports, endoscopic, and radiological findings for patients at the time of their initial disease onset through to transition and from transition to adulthood, where available (Fig. 1A). Development of complications, treatment course, transplant status, graft survival, disease recurrence, onset of IBD, and/or other autoimmune conditions were recorded.

For patients who transitioned to adult Hepatology care at Queen Elizabeth Hospital, Birmingham, UK, clinical notes, and investigative results were available for review. This was supplemented by written correspondence from the patients' General Practitioner regarding their current clinical status. For patients lost-to-follow up, a last observation carried forward (LOCF) approach was used to impute their AILD phenotype and IBD status from transition. Long-term patient clinical outcomes and native liver survival/events were additionally assessed. As such, patients where these outcomes had not occurred were censored at the time of data collection.

Phenotypic biliary progression amongst the cohort was assessed based on a) cholangiography (magnetic resonance cholangiopancreatography [MRCP]) findings of biliary disease/progression and/or b) histological features of biliary ductular reaction (proliferation) and/or periductal concentric fibrosis (sclerosing lesions).

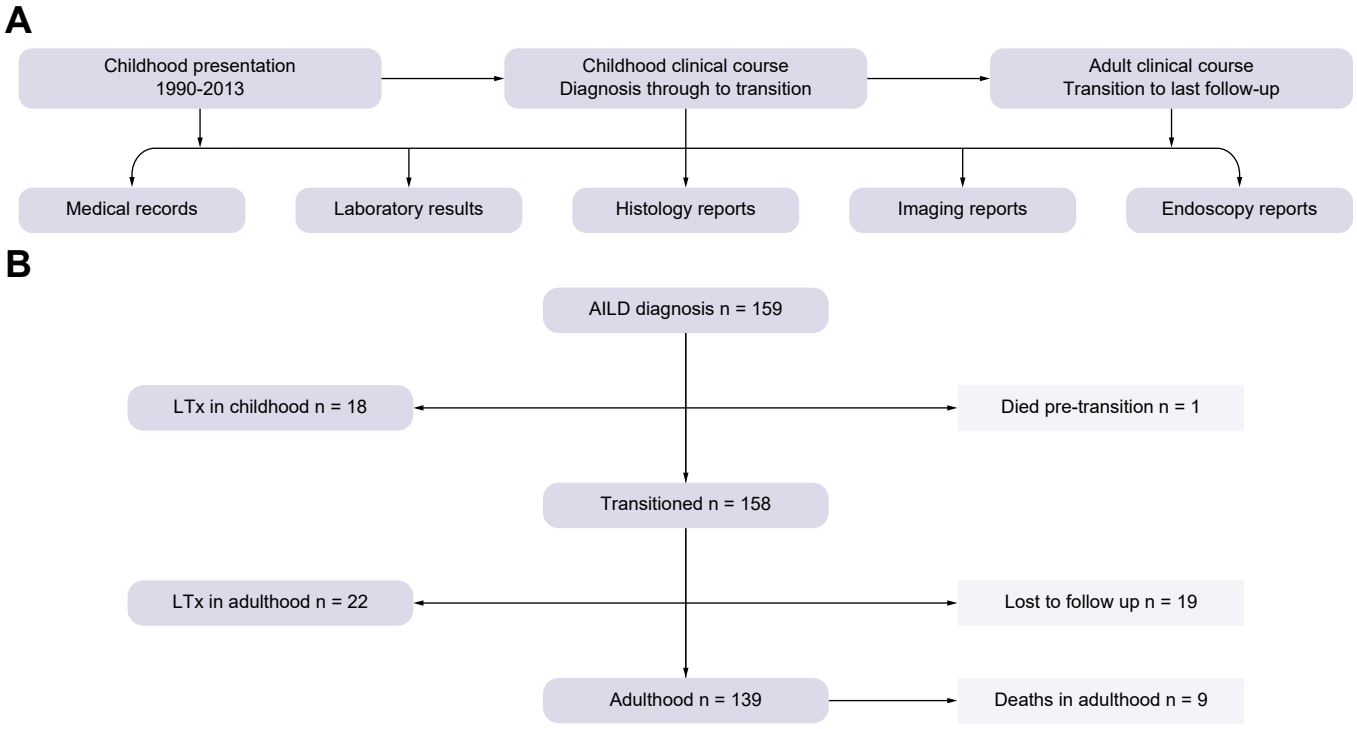


Fig. 1. Study overview. (A) Flowchart showing the method of data collection and (B) Patient follow-up flowchart: from childhood AILD diagnosis through to adulthood. A detailed review of the patients' electronic record archived medical notes and investigative results was undertaken. Data was obtained from the patients' paediatric presentation through to transition and from transition through to their last follow-up (ending 31 May 2021). A total of 159 patients were diagnosed with AILD between June 1990 to March 2013; one patient died in childhood and nineteen were lost to follow up. Data was captured for n = 159 patients at disease onset, n = 158 at transition, and n = 139 in adulthood. AILD, autoimmune liver disease.

AILD biliary phenotypic progression was defined as a change from either (i) AIH to disease with biliary features (PSC, ASC, overlap) or (ii) overlap/ASC progressing to PSC. Patients with biliary progression were re-assigned into their new phenotypic AILD subgroup at the timepoint when phenotypic change was identified.

Statistical methods

Patient demographics and disease-related factors were compared between groups defined by the AILD phenotypes at presentation. Continuous variables were reported as means ± standard deviations (SDs) for normally distributed data and as medians and the interquartile range (IQR) otherwise, with comparisons performed using Kruskal–Wallis tests. Ordinal variables were also analysed using Kruskal–Wallis tests, with Chi-square tests used for nominal variables. Post-hoc tests were then performed to further interrogate factors that differed significantly across the phenotypes. Initially, comparisons between AIH and non-AIH phenotypes (PSC, ASC, overlap) were conducted. Comparisons between the phenotypes within each of these subgroups were then performed and Bonferroni adjustment was applied for multivariate correction. Comparisons across groups included factors recorded at transition and adulthood. Analyses of disease complications and long-term outcomes were assessed using Kaplan–Meier curves, with *p*-values from log-rank tests. All analyses were performed using GraphPad Prism 9 (GraphPad Software Inc), with $p < 0.05$ deemed to be indicative of statistical significance throughout.

Results

Patient demographics and baseline characteristics

Data was collected for 159 patients at disease onset (paediatric presentation). Information on clinical outcomes and investigational results were collected firstly through to transition. The median follow-up to transition was 5 years from diagnosis (IQR 3.3–7.3 years). Secondly, data was collected from their first adult Hepatology clinic visit through to their current clinical status (up to 31 May 2021) with a median follow up of 16.7 years from diagnosis (IQR 12.6–21.6 years) (Fig. 1B). Across the cohort, the median age at presentation was 12.8 years (IQR 10.4–14.2 years); 44% patients were male and 87% were of Caucasian background. At the onset of disease, the most prevalent phenotype was AIH-1 (63.5%, n = 101). The remainder of the cohort consisted of patients with AIH-2 (11.3%; n = 18), PSC (11.9%; n = 19), overlap syndrome (7.6%; n = 12), and ASC (5.7%; n = 9) (Table 1 and Fig. 2).

Although the age at presentation was similar in AIH and non-AIH (biliary) patients overall (median: 12.8 *vs.* 12.9 years, $p = 0.668$), subgroup analysis within AIH found patients with AIH-1 to present significantly later than AIH-2 (median 13.0 *vs.* 8.8 years, $p = 0.001$), and a notable difference was also identified between PSC and ASC patients (13.1 *vs.* 10.2 years, $p = 0.024$) (Tables S1, and S2A,B). The duration of follow-up from disease onset through to transition differed by phenotype, being longest in the AIH-2 cohort on account of a younger age at presentation ($p < 0.0001$) (Table 2). At the end of the study, the median age patient of all patients was 27.9 years (IQR 24.8–33.6 years) (Table 3).

Table 1. Patient demographics at presentation.

	Autoimmune hepatitis		Autoimmune biliary phenotypes		
	AIH-1	AIH-2	PSC	Overlap	ASC
Patients, n	**101**	**18**	**19**	**12**	**9**
Age, years	13.0 (11.0–14.4)	8.8 (2.9–11.8)	13.1 (12.6–15.2)	12.8 (11.1–13.4)	10.2 (6.7–12.6)
Sex, %, male	37% (37/101)	33% (6/18)	74% (14/19)	75% (9/12)	33% (3/9)
Ethnicity					
White	87% (88/101)	83% (15/18)	84% (16/19)	92% (11/12)	100% (9/9)
Asian	10% (10/101)	6% (1/18)	11% (2/19)	8% (1/12)	0% (0/9)
Black	3% (3/101)	11% (2/18)	5% (1/19)	0% (0/12)	0% (0/9)
Laboratory values					
Total bilirubin, μmol/L	53 (26–93)	93 (22–216)	8 (6–12)	21 (11–55)	12 (7–22)
ALP, IU/L	681 (449-1036)	546 (38 –807)	753 (503–1130)	754 (463–1169)	841 (775-1081)
GGT, IU/L	107 (51–159)	87 (35–134)	175 (99–324)	245 (147–346)	258 (130–357)
ALT, IU/L	484 (145–819)	503 (171–968)	95 (56–130)	125 (68–419)	106 (54–216)
AST, IU/L	594 (154-1140)	465 (215–1018)	59 (44–109)	202 (127–395)	89 (82–186)
Albumin, g/L	34.7 ± 5.9	34.0 ± 6.8	40.7 ± 4.2	36.1 ± 7.2	39.8 ± 5.1
PT, sec	15 (12–17)	16 (13–33)	11 (11–12)	12 (11–13)	12 (12–14)
Platelets, × 10^9/L	187 (124–281)	183 (80–226)	354 (303–440)	350 (175-437)	368 (233–436)
IgG, g/L	29.0 (20.9–39.0)	17.8 (13.6–20.5)	15.6 (13.7–19.2)	25.6 (17.8–28.8)	18.9 (15.9–29.5)
Autoantibodies					
ANA	69% (65/94)	50% (10/18)	39% (7/19)	89% (8/9)	22% (2/9)
LKM	0% (0/94)	100% (18/18)	0% (0/19)	0% (0/9)	0% (0/9)
SMA	67% (62/93)	0% (0/18)	39% (7/19)	44% (4/9)	56% (5/9)
ANCA	54% (15/28)	0% (0/3)	69% (9/13)	100% (3/3)	80% (4/5)
Disease severity					
PELD*	4.1 (0.3–7.1)	7.1 (0–27.1)	0 (0–0)	0 (0–0)	0 (0–0)
MELD†	13 (8.5–17)	13 (13–13)	7 (7–8)	9.5 (8.8–11.8)	9 (8.5–9.5)
AIH score	7 (6–7)	7 (6–7)	–	7 (7-7)	5.5 (4.5-6)
PHT	23% (24/101)	28% (5/18)	11% (2/19)	33% (4/12)	22% (2/9)
Decompensated	25% (25/101)	22% (4/18)	5% (1/19)	8% (1/12)	11% (1/9)
Growth failure	13% (13/101)	22% (4/18)	11% (2/19)	17% (2/12)	22% (2/9)
IBD					
Total	4% (4/101)	0% (0/18)	53% (10/19)	25% (3/12)	44% (4/9)
Ulcerative colitis	3% (3/101)	0% (0/18)	37% (7/19)	17% (2/12)	44% (4/9)
Crohn's disease	1% (1/101)	0% (0/18)	16% (3/19)	8% (1/12)	0% (0/9)
Indeterminate	0% (0/101)	0% (0/18)	0% (0/19)	0% (0/12)	0% (0/9)

AIH-1, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine transaminase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; LKM, liver-kidney microsome; MELD, model for end-stage liver disease; PELD, paediatric end-Stage liver disease; PHT: portal hypertension; PT, prothrombin time; SMA, smooth muscle antibody.
Data for continuous variables are reported as mean ± SD or median (interquartile range), as applicable. Categorical variables are reported as percentage (%) (n/N).
* PELD, a disease severity scoring system for children <12 years of age.
† MELD, a predictor of survival in patients ≥12 years of age with cirrhosis. AIH score: simplified AIH score. Ethnicity as per https://www.ethnicity-facts-Fig.s.service.gov.uk/style-guide/ethnic-groups.

Patients presenting with non-AIH phenotypes were significantly more likely to be male (67% *vs.* 36%, $p = 0.001$); have IBD (36% *vs.* 3.5% $p < 0.0001$); and be asymptomatic (*e.g.* incidental abnormal liver chemistry, 64% *vs.* 30%, $p < 0.001$), compared with patients with AIH (Table S1). The latter was most marked in the PSC subgroup, with 89% of patients being asymptomatic at the time of diagnosis (Table S2A). Subgroup analysis found none of these factors differed significantly between patients with AIH-1 *vs.* AIH-2 (Table S2B).

Clinical outcomes for patients with autoimmune hepatitis

Liver disease progression and the development of complications amongst the AIH cohorts are presented in Tables 2 and 3. Patients with new onset or worsening cholestasis underwent disease reassessment by way of MRCP and/or liver biopsy evaluation. Over the time-course of the study, 19.8% (20/101) patients with childhood onset AIH-1 developed biliary features by adulthood and of these, 50% (10/20) phenotypically transitioned to PSC and the remaining 10 transitioned to an overlap disease phenotype. Fourteen of the 20 AIH-1 patients with biliary progression had both MRCP and histology features of biliary progression, with eight to overlap, two to ASC, and four to PSC. By adulthood, three of the AIH-1-overlaps progressed to PSC, and both AIH-1-ASC patients progressed to PSC.

Two of the remaining AIH-1 patients with biliary progression were diagnosed on MRCP alone, one patient had small duct disease, and three had biliary progression noted on repeated clinical correspondence but with an absence of access to the primary source observations.

The biochemistry findings for AIH-1 patients with biliary progression demonstrated significantly higher gamma-glutamyl transferase (GGT) values at diagnosis and transition when compared with AIH-1 children without biliary progression ($p < 0.001$) (Fig. 3).

Similar rates of portal hypertension (PHT) and liver decompensation were observed amongst both AIH subgroups with a greater proportion of AIH-2 patients developing PHT. Notably no patients with AIH-2 developed IBD.

There were seven deaths amongst patients with AIH-1 (69%, 7/101). Six were due to liver disease related complications with

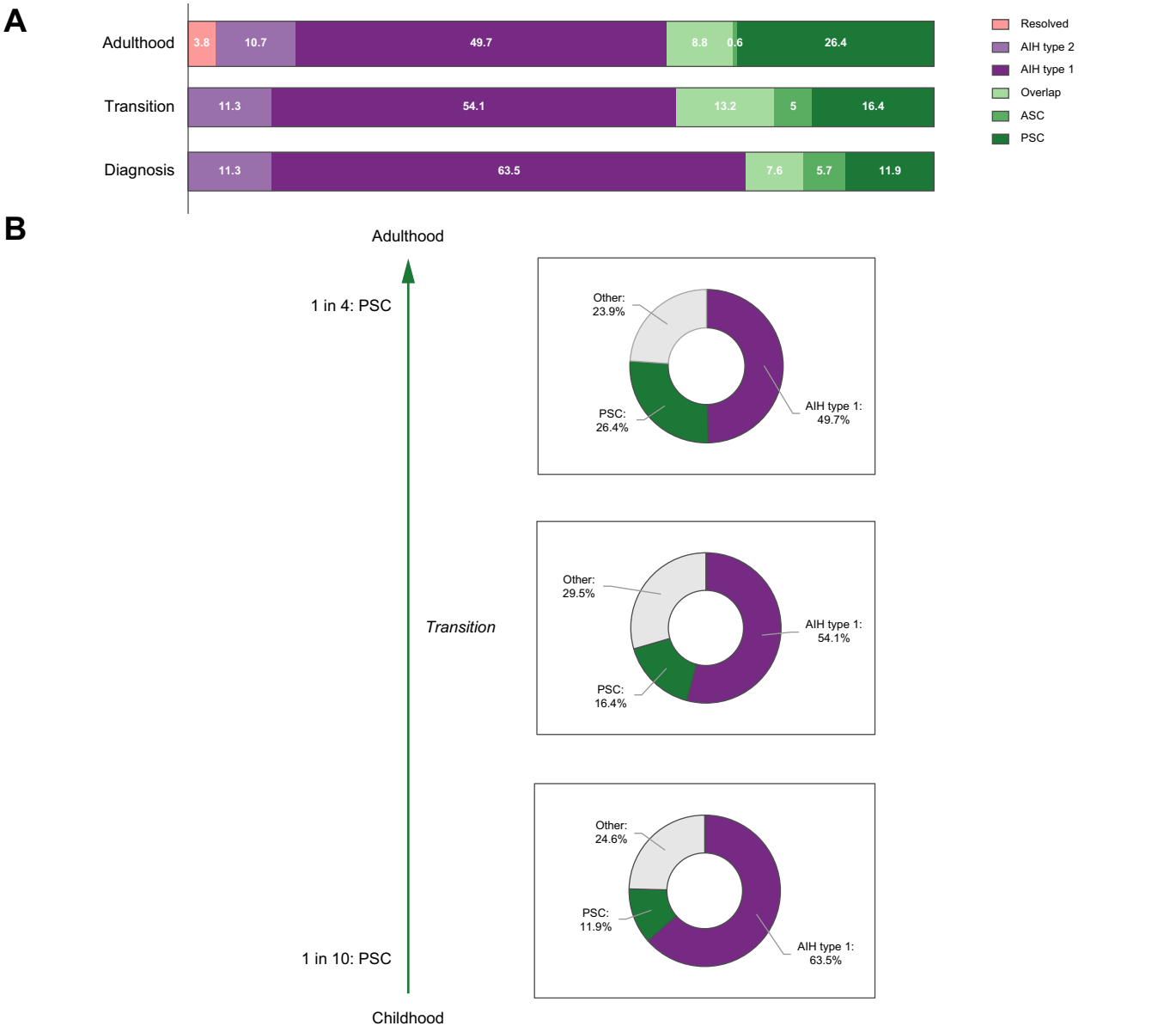


Fig. 2. AILD cohort distribution over time. (A) Horizontal bar chart showing phenotypic progression of our AILD cohort subgroups at diagnosis, transition and in adulthood. The last observation carried forward (LOCF) approach was used to impute AILD phenotype; this was applied to account for attrition bias. The prevalence of AIH-1 decreases over time whist the opposite trend is observed in PSC; (B) Pie charts showing the change in prevalence of AIH-1 and PSC in our cohort over time. The rate of PSC rises from one in 10 patients at diagnosis to one in four in adulthood by the end of the study period in May 2021). 'Others' include overlap, ASC, and AIH-2 patients. AIH-1, autoimmune hepatitis type 1; AIH-2, autoimmune hepatitis type 2; AILD, autoimmune liver disease; ASC, autoimmune sclerosing cholangitis; LOCF, last observation carried forward; PSC, primary sclerosing cholangitis.

hepatobiliary malignancy accounting for one patient. One AIH-1 patient died 9 months after their AILD diagnosis from an unrelated cause.

Unlike AIH-1, none of the autoimmune hepatitis type 2 patients (N = 18) developed evidence of biliary disease. Other distinct clinical differences were observed in the AIH-2 subgroup; aggressive clinical phenotype and a younger age at presentation, median 8.8 years (range 2.9–11.8 years), higher rates of acute severe hepatitis and/or liver failure (10/18), and transplantation. Disease recurrence and the need for regrafting were also higher compared with AIH-1 (Tables 2 and 3). There were two AIH-2 deaths (11.1%, 2/18), with 1 resulting from decompensated end-stage liver disease (ESLD).

Clinical outcomes in patients with autoimmune biliary disease phenotypes

At the outset, 13.2% (21/159) of the overall AILD cohort had mixed hepatitic and biliary phenotypes. Of these, 12 were classified as overlap and nine were ASC. There was a difference observed in the timeline of diagnostic terminology of these

Table 2. Disease course in childhood (up to transition).

	Autoimmune hepatitis		Autoimmune biliary phenotypes		
	AIH-1	AIH-2	PSC	Overlap	ASC
Patients, n	**86**	**18**	**26**	**21**	**8**
Age at transition, years	17.8 (17.2–8.4)	17.4 (16.7–18)	17.3 (16.3–18)	18.6 (18–19.3)	17.9 (17–19.5)
Sex, % male	34% (29/85)	33% (6/18)	73% (19/26)	57% (12/21)	38% (3/8)
Length of follow up, years	4.7 (3.3–6)	8.9 (6.3–12)	3.4 (2.6–4.8)	6.9 (5.7–11.6)	6.2 (4.3–11.6)
Disease severity					
MELD score	8 (7–10)	8 (7–9.8)	7.5 (7–8)	8 (7–10.5)	8 (7–10.5)
PHT	33% (28/86)	33% (6/18)	12% (3/26)	48% (10/21)	50% (4/8)
Ascites	13% (11/86)	11% (2/18)	0% (0/26)	5% (1/21)	13% (1/8)
Decompensated	12% (10/86)	17% (3/18)	12% (3/26)	5% (1/21)	25% (2/8)
Clinical cholangitis	2% (2/86)	0% (0/18)	4% (1/26)	0% (0/21)	13% (1/8)
IBD	2% (2/86)	0% (0/18)	54% (14/26)	33% (7/21)	38% (3/8)
Ulcerative colitis	1% (1/86)	0% (0/18)	38% (10/26)	29% (6/21)	38% (3/8)
Crohn's disease	1% (1/86)	0% (0/18)	15% (4/26)	5% (1/21)	0% (0/8)
Indeterminate colitis	0% (0/86)	0% (0/18)	0% (0/26)	0% (0/21)	0% (0/8)
Liver transplantation	9% (8/86)	28% (5/18)	12% (3/26)	5% (1/21)	13% (1/8)
Disease recurrence	38% (3/8)	80% (4/5)	33% (1/3)	0% (0/1)	0% (0/1)
Re-transplantation	13% (1/8)	40% (2/5)	33% (1/3)	0% (0/1)	0% (0/1)
Deaths	1% (1/86)	0% (0/18)	0% (0/26)	0% (0/21)	0% (0/8)

Data for continuous variables are reported as mean ± SD or median (interquartile range), as applicable. Categorical variables are reported as % (n/N). AIH-1, autoimmune hepatitis type 1; AIH-2, autoimmune hepatitis type 2; ASC, autoimmune sclerosing cholangitis; IBD, inflammatory bowel disease; MELD, model for end-stage liver disease; PHT, portal hypertension; PSC, primary sclerosing cholangitis.

subgroups which may reflect a change in practice over time; ASC patients were largely classified at an earlier timeline of 1992–1994 with a few recorded between 2008-2010. The overlap classification was used from 2002 onwards.

Two-thirds of these patients experienced phenotypic progression to PSC by adulthood: overlap (8/12) and ASC (6/9). Of the eight overlap patients, five had both MRCP and liver histology evidence of biliary progression to PSC, and two had small duct disease confirmation of PSC. One overlap patient was diagnosed with PSC progression by magnetic resonance imaging alone. Of the six ASC patients who progressed to PSC, five had MRCP and histological biliary progression and one was diagnosed by classical features on MRCP.

One overlap patient (1/12) developed dominant hepatitic features on histology and was reclassified as AIH-1. An ASC patient also had a rise in hepatitic activity and a quiescence of their biliary disease and was reclassified as AIH-1.

On review of laboratory results, GGT values at diagnosis from children with ASC/overlap who would progress to classic PSC were found to be significantly higher than those of overlap/ASC patients without biliary progression (p = 0.0017) (Fig. 3). No other laboratory or clinical features differed.

Patients diagnosed with PSC at disease onset primarily retained their original phenotype (94.7%; 18/19); one patient (5.3%; 1/19) was reclassified as overlap by adulthood given increasing hepatitic activity. Overall, 15% (24/159) patients had

Table 3. Disease course in adulthood.

	Autoimmune hepatitis		Autoimmune biliary phenotypes	
	AIH-1	AIH-2	PSC	Overlap
Patients, n	**65**	**14**	**42**	**13**
Current age, years	27.8 (25.3–34.2)	27.6 (23.0–31.0)	27.6 (24.7–31.4)	25.8 (23.6–32.9)
Sex, % male	38% (23/64)	21% (3/14)	67% (28/42)	46% (6/13)
Length of follow-up, years	15.3 (12.8–21.5)	21.9 (18.0–24.3)	15.4 (12.2–20.3)	15.5 (9.9–24.7)
Disease severity				
MELD score	8 (6-10)	8 (8-9)	7 (6-8.5)	7.5 (6-9.5)
PHT	25% (16/65)	36% (5/14)	31% (13/42)	15% (2/13)
Ascites	13% (8/65)	14% (2/14)	10% (4/42)	8% (1/13)
Decompensated	14% (9/65)	21% (3/14)	26% (11/42)	8% (1/13)
Clinical cholangitis	3% (2/65)	0% (0/14)	31% (13/42)	0% (0/13)
IBD	9% (6/65)	0% (0/14)	81% (34/42)	38% (5/13)
Ulcerative colitis	8% (5/65)	0% (0/14)	69% (29/42)	15% (2/13)
Crohn's disease	2% (1/65)	0% (0/14)	12% (5/42)	8% (1/13)
Indeterminate colitis	0% (0/65)	0% (0/14)	0% (0/42)	15% (2/13)
LT overall	25% (16/65)	43% (6/14)	38% (16/42)	15% (2/13)
LT in adulthood	12% (8/65)	7% (1/14)	28% (12/42)	8% (1/13)
Disease recurrence overall	19% (3/16)	83% (5/6)	31% (5/16)	0% (0/2)
Re-LT overall	19% (3/16)	67% (4/6)	25% (4/16)	0% (0/2)
Deaths	9% (6/64)	21% (3/14)	0% (0/42)	8% (1/13)

Data for continuous variables are reported as mean ± SD or median (interquartile range), as applicable. Categorical variables are reported as % (n/N).
AIH-1, autoimmune hepatitis type 1; AIH-2, autoimmune hepatitis type 2; IBD, inflammatory bowel disease; LT, liver transplant; MELD, model for end-stage liver disease; PHT, portal hypertension; PSC, primary sclerosing cholangitis.
*Six patients have had disease resolution (symptom free and off medications). Nineteen patients are lost to follow up.

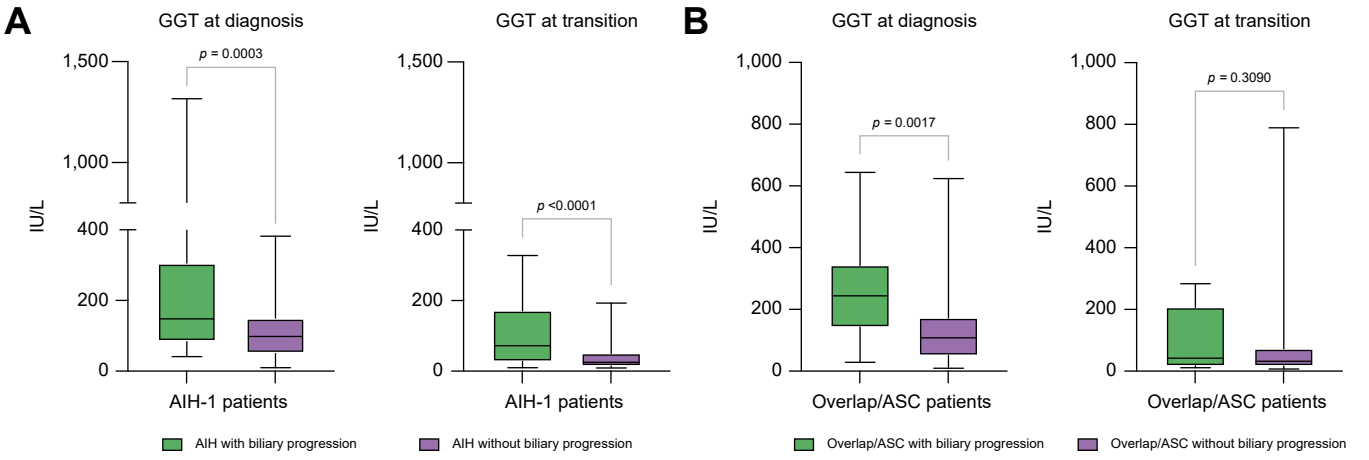


Fig. 3. GGT values and biliary disease progression. (A) Higher values of GGT in AIH-1 patients with biliary progression at diagnosis and at transition were found to be statistically significant compared with AIH-1 patients without progression; (B) Higher values of GGT in overlap/ASC patients with biliary progression at diagnosis were found to be statistically significant compared with overlap/ASC patients without progression. AIH-1, autoimmune hepatitis type 1; ASC, autoimmune sclerosing cholangitis; GGT, gamma-glutamyltransferase; HPS, hepatopulmonary syndrome.

phenotypically progressed to PSC by adulthood: 10 were originally AIH-1 (9.9%, 10/101), eight were overlap (66.7%; 8/12), and six were ASC (66.7%; 6/9) patients as described above.

In terms of disease related complications, episodes of cholangitis were much higher in patients with PSC compared with the other cohorts in adulthood (p <0.0001) (Table 3); 31% (13/42) PSC patients experienced cholangitis. Of these, 10 were patients with biliary progression to PSC; three were overlaps, four ASC, and three were AIH-1. Similar rates of PHT and decompensated liver disease were observed amongst the biliary phenotypes. One overlap patient died from decompensated cirrhosis and sepsis. There were no deaths amongst the PSC and ASC patients.

Approximately 3.8% (6/159) of patients in our AILD cohort had apparent disease resolution by adulthood; all were currently clinically well with normal liver chemistry and were off long-term immunosuppression at the last follow up. All six patients had mild disease and benign clinical courses: AIH-1 (n = 4), ASC (n = 1), and AIH-2 (n = 1).

Liver explant evaluation and biliary pathology

Over the course of the study, a total of 40 patients received a liver transplant (LT): 18 in childhood and 22 in adulthood (Fig. 4). The highest LT rate in childhood was observed in patients with AIH-2 and of the five patients (28%, 5/18) needing a LT, three were a result of acute liver failure (ALF) at initial presentation and one LT occurred within 2 years of diagnosis for acute on chronic liver failure. LT rates for the other subgroups were more gradual, spanning across the three decades of the study period (Fig. S1).

Patients with PSC had the highest LT rate overall, with 38% (16/42) progressing to LT, of which, 75% (12/16) occurred in adulthood. Four (20%, 4/20) of the PSC LT cohort were patients with biliary progression: three were originally overlap, and one was ASC at diagnosis (Tables 2 and 3).

Biliary disease was identified in the liver explants of AIH-1 and overlap/ASC patients. In 11% (1/9) of AIH-1 patients who required a LT in childhood, there was explant evidence of biliary disease. This rose to 43% (6/14) of AIH-1 patients in adulthood: 35.7% (5/14) had histology diagnostic of PSC in their explant liver and 7.1% (1/14) had overlap features. All patients with biliary phenotypes (PSC, ASC or overlap) who required LT in the duration of the study, had explant histology diagnostic of PSC. No AIH-2 patients were found to have biliary disease on explant histology.

Impact of IBD on liver disease clinical phenotype

Rates of IBD at presentation differed significantly between AIH and non-AIH phenotypes (p <0.0001): 53% (10/19) PSC patients, 25% (3/12) overlap, and 44% (4/9) ASC compared with 4% (4/101) in AIH-1 patients and none in those with AIH-2. Ulcerative colitis (UC) accounted for 76% of all IBD cases at liver disease onset (16/21), with Crohn's disease making up the remaining cases (24%; 5/21) (Table 1). Similar rates of IBD were observed by transition: 54% (14/26) PSC, 33% (7/21) overlap. and 38% (3/8) ASC patients had IBD compared with 2.5% (2/86) of AIH-1 patients. UC was the dominant phenotype (20/26) (Table 2).

By adulthood, there was a rise in the number of PSC patients with IBD, affecting 81% (34/42) of PSC patients compared with 38% (5/13) with overlap and 9% (6/65) of AIH-1 patients (p <0.0001) (Table 3). No AIH-2 patients developed IBD throughout the study. UC accounted for 80% of overall IBD cases (36/45) by adulthood (Fig. 5).

On review of the 34/159 patients with biliary disease progression, six had IBD at diagnosis and 14 developed IBD on follow-up (five by transition and nine in adulthood). Of the six patients with IBD at AILD diagnosis, all progressed to PSC except for one patient: 3/6 were ASC patients, all with UC, 2/6 were overlap patients with UC, and the last was an UC patient with AIH-1. This AIH-1 patient was reclassified as overlap syndrome by transition.

Of the 14 patients with biliary progression and new IBD development during follow-up, all also progressed to PSC except for one patient: 57% (8) were AIH-1 patients, 29% (4) overlap and 14% (2) had ASC. UC was the predominant IBD subtype in patients with biliary progression, accounting for 86% (12/14).

Approximately 78.6% (125/159) of AILD patients did not have biliary progression. Of these 15 had IBD at diagnosis and 13 developed IBD over follow-up (Fig. 5). UC accounted for 70–80%

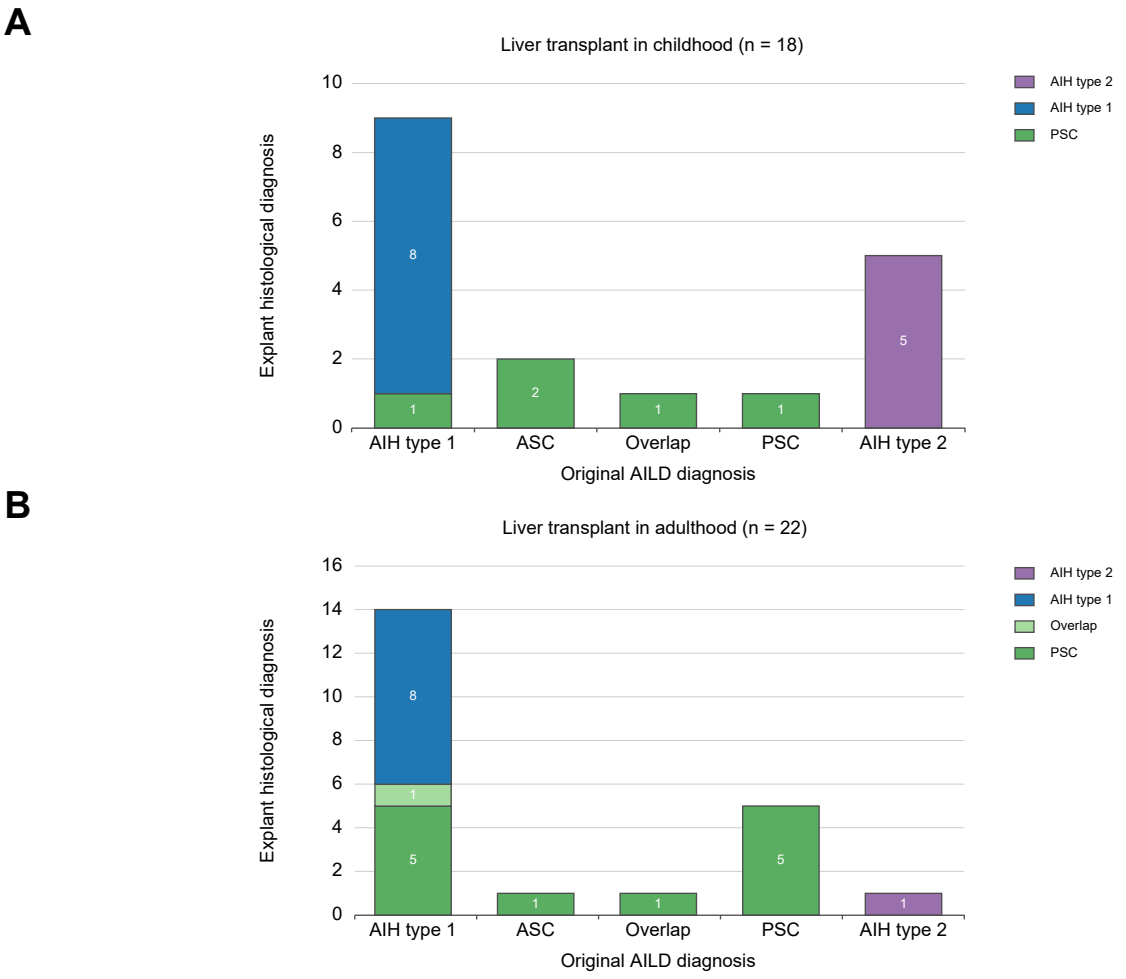


Fig. 4. Liver explant histology highlighting biliary findings. Explant histology for patients transplanted in (A) childhood or (B) as adults. AIH-1 patients (11% [1/9]) who needed a liver transplant in childhood had explant evidence supporting biliary disease. This rose to 43% (6/14) of AIH-1 patients in adulthood; 35.7% (5/14) had histology diagnostic of PSC in their explant liver and 7.1% (1/14) had overlapping features; all transplanted patients with biliary phenotypes (PSC, ASC, overlap) were found to have explant histology consistent with PSC. AIH-1, autoimmune hepatitis type 1; ASC, autoimmune sclerosing cholangitis; PSC, primary sclerosing cholangitis.

of cases. Approximately 66.7% (10/15) of patients with IBD had PSC at AILD diagnosis, whereas 46% (6/13) of those developing IBD subsequently also had PSC at diagnosis.

Discussion

Children presenting with AILD often face lifelong impactful disease with prognostic uncertainty. Managing patients requires careful attention to the risks and benefits of treatments in a longitudinal manner, and recognition that the clinical phenotype at presentation may change over time. Our objective was to examine the clinical course and pattern of AILD from childhood through to adulthood. We describe the clinical course of a large patient cohort, followed for 30 years, which mirrored the lived experience of patients and the decision-making and coding practises of their treating clinicians. Whilst acknowledging the methodologic limitations of this retrospective narrative approach, we nonetheless reviewed 159 patients, which given the nature of paediatric hepatology service provision in the UK is a substantial cohort. One in five AIH-1 patients developed biliary disease, with half of patients progressing to an overlap syndrome and the other half to PSC. A gradual evolution from a mixed picture of overlap/ASC to PSC was observed in the latter. In addition, two-thirds of overlap and ASC patients phenotypically progressed to PSC by adulthood. In contrast, virtually all PSC patients retained their original diagnosis. No patients with AIH-2 experienced biliary transition clearly suggesting a biological distinction from AIH-1. The development of IBD was a key factor associated with biliary progression. For most patients' clinical outcomes were good.

The dominant progression towards PSC was reflected in the native liver explant histology of AIH-1, with overlap and ASC patients requiring transplant. Almost half of native liver explants from AIH-1 patients presented biliary pathology in adulthood, and of these, the majority were of PSC. This finding was much lower in childhood, supporting the observation of a slowly evolving biliary pattern in this subgroup. Of the overlap and ASC patients who were transplanted (in childhood or adulthood), all had PSC confirmed in their explants. Our study additionally highlights the significance of IBD development in patients with AILD biliary progression who were four times more likely to develop new-onset IBD compared with those without biliary

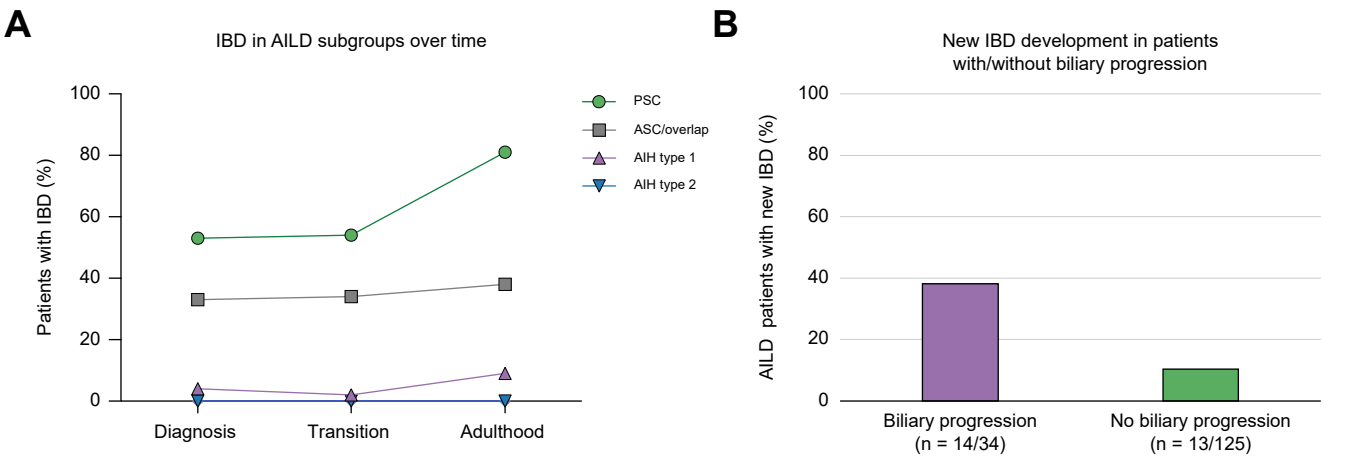


Fig. 5. Inflammatory bowel disease in AILD patients over time. (A) Line graph showing the prevalence of IBD in the AILD subgroups at the three timepoints; diagnosis, transition and in adulthood (end of study period). At diagnosis, 53% (10/19) PSC patients, 25% (3/12) overlap and 44% (4/9) ASC compared with 4% (4/101) in AIH-1 patients had IBD. Ulcerative colitis (UC) accounted for 76% of all IBD cases at liver disease onset. Similar rates of IBD were observed by transition; 54% (14/26) PSC, 33% (7/21) overlap and 38% (3/8) ASC patients had IBD compared with 2% (2/86) of AIH-1 patients. In adulthood, 81% (34/42) of PSC patients compared with 38% (5/13) overlap and 9% (6/65) AIH-1 patients had IBD (p <0.0001). No AIH-2 patients developed IBD throughout the study. UC accounted for 80% of overall IBD cases (36/45) by adulthood. (B) Bar chart showing the percentage (%) of patients with new-onset IBD with biliary progression (41.2%, n = 14/34) and without biliary progression (10.4%, n = 13/125). A total of 34 patients had biliary progression out of a total AILD cohort of 159 patients. Of these, 14 had new IBD development over follow up (duration of study). 125 of the 159 patients did not have biliary progression of their IBD and of these, 13 had new IBD during follow-up. AIH-1, autoimmune hepatitis type 1; AILD, autoimmune liver disease; ASC, autoimmune sclerosing cholangitis; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

progression. In patients with new-onset IBD, all but one had phenotypic progression to PSC. Furthermore, half of these were originally AIH-1 patients. UC accounted for nine of 10 new-onset IBD in patients with biliary progression. In patients who already presented IBD at AILD diagnosis, two-thirds also had with PSC, and in those who evolved to biliary progression, more than three-quarters were to PSC.

As well as new-onset IBD, patients with biliary progression of their AILD in our cohort were noted qualitatively to have had biliary ductular reaction identified in their diagnostic liver biopsies in childhood. This included AIH-1 patients in addition to those with ASC and overlap. Thus, although biliary ductular reaction is an expected histological finding in ASC and overlap, its presence in AIH-1, however minor, should alert physicians of the possibility of biliary disease progression and be considered as a prognostic indicator.[22–24]

The biliary cohort (PSC, overlap, or ASC) in our study were more likely to be (i) male; (ii) asymptomatic; and (iii) have IBD at disease onset, which is consistent with the disease phenotype described in the literature.[2,25] Importantly, none of the AIH-2 patients had biliary progression nor did they develop IBD in the duration of our study. There were well-defined expected differences in the AIH-2 cohort compared with the other AILD subgroups: younger age at presentation, aggressive clinical phenotype, higher rates of acute liver failure, and LT.[15,26] Disease recurrence and the need for re-grafting also surpassed other AILD phenotypes.

No statistical significance was identified in the development of complications (PHT, ascites, decompensation) amongst the AILD subgroups. PSC patients were observed to have higher rates of PHT and cirrhotic decompensation in adulthood compared with childhood.[24,27] This difference may be attributed to the later age of PSC onset in older children and hence a shorter duration in paediatric care. Patients with PSC were more likely to experience cholangitis in adulthood on account of the severity of stricture formation. Small duct disease is more common in childhood onset PSC in which there is histological evidence of biliary disease in the presence of a normal cholangiogram (*e.g.* MRCP).[4,10,24] The higher incidence of cholangitis observed in adulthood in our cohort reflects this natural disease progression and large bile duct involvement.

Transplantation was highest amongst the AIH-2 and PSC patient subgroups, with the majority occurring in childhood in the former and adulthood in the latter. The most common indication for LT was ESLD. Patient survival rates were similar to those published in the literature.[27,28] There were no patient deaths in the PSC subgroup despite the high cumulative rate of LT. Progression to transplantation was related to the length of time from AILD diagnosis on account of development of complications; a recent study highlighted an accelerated risk in patients with PHT, 68% of which consisted of PSC patients with UC,[29] a finding comparable to our cohort. Liver-related deaths were mostly from complications of decompensated cirrhosis and sepsis.

Overall, fewer than 5% of AILD patients presenting in childhood had disease resolution, largely from the AIH-1 subgroup. This was lower than the reported 10–40% of AIH-1 patients who stay in remission upon treatment withdrawal.[30–32] All patients with disease resolution had mild disease at presentation and a benign clinical course through to adulthood.

In choosing an observation approach to this study, inevitably bias amongst the treating clinical teams was a possibility, and earlier diagnosis of biliary disease might have been missed. However, the goal of this study was not to ascertain new ways to define disease or apply definitions that cannot be generalised across clinical programmes, but rather to describe what transpired for patients from the clinical observations made during their follow-up. Whilst there is value to a dedicated review of imaging and pathology (something particularly relevant to future prospective research), this was not possible given the

extended time course of our study, nor was it the primary purpose or permitted by the Institutional ethics approval. Our lost-to-follow up rate is low, and although a tertiary programme will inevitably have a referral bias, the childhood liver disease programme described herein equally provides a comprehensive secondary care service to a very large, representative, and diverse UK conurbation. Finally, the response to treatment and clinical outcomes cannot be addressed in a qualitative retrospective evaluation such as this study. Table S3 provides an overview of treatment approaches, but dedicated analysis of approaches to care with the greatest patient impact will require prospective research protocols, given the variability in how (and why) clinicians adjust treatments, and hence the risk of retros pective analysis may provide misleading insights. For example, why treatment is changed varies (response, adherence, side effects), and treatment choices may include decisions based on extra-hepatic disease (*e.g.* IBD, systemic lupus erythematosus, etc.)

In conclusion, we report a robust, as-observed, follow-up series of children who presented with AILD. We found that two-thirds of children with overlap/ASC, and one in five children with AIH-1, ultimately phenotypically progressed to PSC. Such patients were four times more likely to develop new-onset IBD than those without biliary progression. Clinical findings and outcomes from this longitudinal follow-up of patients over a 30-year period, offers important insights for patients, families, and treating physicians. Future multicentre prospective research remains important to pursue.

Abbreviations

AIH-1, autoimmune hepatitis type 1; AIH-2, autoimmune hepatitis type 2; AILD, autoimmune liver disease; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine transaminase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; ASC, autoimmune sclerosing cholangitis; AST, aspartate transaminase; ESLD, end-stage liver disease; GGT, gamma-glutamyltransferase; HPS, hepatopulmonary syndrome; IBD, inflammatory bowel disease; IgG, immunoglobulin G; LKM, liver-kidney microsome; LOCF, last observation carried forward; LT, liver transplant; MELD, model for end-stage liver disease; MRCP, magnetic resonance cholangiopancreatography; pANCA, perinuclear antineutrophil cytoplasmic antibodies; PBC, primary biliary cholangitis; PELD, paediatric end-stage liver disease score; PHT, portal hypertension; PSC, primary sclerosing cholangitis; PT, prothrombin time; SMA, smooth muscle antibody; UC, ulcerative colitis.

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interest

Unrelated to this study GMH has received consultancy and speaker fees from Intercept, Cymabay, GSK, Dr. Falk, Ipsen, Mirum, Escient, HighTide, and Gilead. DK provides consultancy for Intercept, Mirum, Alberio, Astra Zeneca, and Takeda. The remaining authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept: GMH, DK. Study supervision and execution: SW, DK, GMH. Study analysis: SW. Data collection and review: SW, ER, JR. Manuscript preparation and revisions: SW and GMH. Manuscript finalisation: all authors. Study guarantors: DK, GMH.

Data availability statement

Not applicable (retrospective patient data collection).

Acknowledgements

We thank all the patients for their ongoing support of academic studies in autoimmune liver disease. We thank Prof Ye Oo for his supervision of SW during her unrelated laboratory science studies. We thank Prof D Adams and Dr P Trivedi for clinical care of patients in this study. We thank all the Paediatric Hepatologists, Nursing and Administrative staff for the help and support given to SW throughout this study and for the duration of her training at the Liver Unit, Birmingham Children's Hospital. This paper presents independent research supported by the Birmingham NIHR BRC based at the University Hospitals Birmingham National Health Service Foundation Trust and the University of Birmingham. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100901.

References

[1] Mack CL, Adams D, Assis D, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020;72:671–722.
[2] Mieli-Vergani G, Vergani D, Baumann U, Czubkowski P, Debray D, Dezsofi A, et al. Diagnosis and management of pediatric autoimmune liver disease: ESPGHAN Hepatology Committee position statement. J Pediatr Gastroenterol Nutr 2018;66:345–360.
[3] Harrington C, Krishnan S, Mack CL, Cravedi P, Assis DN, Levitsky J. Noninvasive biomarkers for the diagnosis and management of autoimmune hepatitis. Hepatology 2022;76:1862–1879.
[4] Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011;54:374–385.
[5] Di Giorgio A, Hadzic N, Dhawan A, Deheragoda M, Heneghan MA, Vergani D, et al. Seamless management of juvenile autoimmune liver disease: long-term medical and social outcome. J Pediatr 2020;218:121–129 e3.
[6] Montano-Loza A, Allegretti JR, Cheung A, Ebadi M, Jones D, Kerkar N, et al. Single topic conference on autoimmune liver disease from the Canadian Association for the Study of the Liver. Can Liver J 2021;4:401–425.
[7] Ricciuto A, Kamath BM, Hirschfield GM, Trivedi PJ. Primary sclerosing cholangitis and overlap features of autoimmune hepatitis: a coming of age or an age-ist problem? J Hepatol 2023;9:567–575.
[8] Kerkar N, Chan A. Autoimmune hepatitis, sclerosing cholangitis, and autoimmune sclerosing cholangitis or overlap syndrome. Clin Liver Dis 2018;22:689–702.
[9] Mataya L, Patel N, Azzam RK. Autoimmune liver diseases in children. Pediatr Ann 2018;47:e452–e457.
[10] Beretta-Piccoli T, Vergani D, Mieli-Vergani G. Autoimmune sclerosing cholangitis: evidence and open questions. J Autoimmun 2018;95:15–25.
[11] Kumar N, Poddar U, Yadav R. Autoimmune sclerosing cholangitis in children: a prospective case-control study. Pediatr Gastroenterol Hepatol Nutr 2021;24:154–163.
[12] Di Giorgio A, Vergani D, Mieli-Vergani G. Cutting edge issues in juvenile sclerosing cholangitis. Dig Liver Dis 2022;54:417–427.
[13] Ramonet M, Ramirez-Rodriguez N, Álvarez Chávez F, Arregui MC, Boldrini G, Botero Osorio V, et al. Autoimmune hepatitis in pediatrics, a review by the working group of the Latin American society for pediatric gastroenterology, hepatology, and nutrition. Arch Argent Pediatr 2022;120:281–287.
[14] Sebode M, Hartl J, Vergani D, et al. Autoimmune hepatitis: from current knowledge and clinical practice to future research agenda. Liver Int 2018;38:15–22.
[15] Sokollik C, McLin VA, Vergani D, Lohse AW. International Autoimmune Hepatitis Group (IAIHG). Juvenile autoimmune hepatitis: a comprehensive review. J Autoimmun 2018;95:69–76.
[16] Chapman MH, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM, Alexander G, et al. British Society of Gastroenterology and UK-PSC

guidelines for the diagnosis and management of primary sclerosing cholangitis. Gut 2019;68:1356–1378.
[17] Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. Gut 2021;70:1989–2003.
[18] European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol 2015;63:971–1004.
[19] Milkiewicz P, Krawczyk M, Wunsch E, Trivedi PJ. Primary sclerosing cholangitis with features of autoimmune hepatitis: exploring the global variation in management. Hepatol Commun 2020;4:399–408.
[20] Maggiore G, Bernard O, Mosca A, Ballot E, Johanet C, Jacquemin E. Long-term outcomes of patients with type 1 or 2 autoimmune hepatitis presenting in childhood. J Hepatol 2023;78:979–988.
[21] Wiecek S, Wojtyniak A, Pindur B, Machnikowska-Sokołowska M, Gruszczyńska K, Grzybowska-Chlebowczyk U. Analysis of the clinical course of primary sclerosing cholangitis in paediatric population-single center study. Medicina 2021;57:663.
[22] Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 2001;33:544–553.
[23] Di Giorgio A, D'Adda A, Marseglia A, Sonzogni A, Licini L, Nicastro E, et al. Biliary features in liver histology of children with autoimmune liver disease. Hepatol Int 2019;13:510–518.
[24] Deneau M, Kyle Jensen M, Holmen J, Williams MS, Book LS, Guthery SL, et al. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. Hepatology 2013;58:1392–1400.
[25] Nayagam JS, Mandour MO, Taylor A, Heneghan MA, Dubois PC, Hayee B, et al. Clinical course of inflammatory bowel disease and impact on liver disease outcomes in patients with autoimmune sclerosing cholangitis. Clin Res Hepatol Gastroenterol 2022;46:101980.
[26] Roepe IG, Vierling JM, Goss JA, Miloh T. Presentation and outcomes of autoimmune hepatitis type 1 and type 2 in children: a single-center study. J Pediatr Gastroenterol Nutr 2021;72:101–107.
[27] Carbone M, Neuberger JM. Autoimmune liver disease, autoimmunity and liver transplantation. J Hepatol 2014;60:210–223.
[28] Couchonnal E, Jacquemin E, Lachaux A, Ackermann O, Gonzales E, Lacaille F. Long-term results of pediatric liver transplantation for autoimmune liver disease. Clin Res Hepatol Gastroenterol 2021;45:101537.
[29] Rocha HC, Vilela EG. Clinical aspects and prognosis of patients with inflammatory bowel disease associated with autoimmune liver diseases. Gastroenterol Hepatol 2022;45:83–90.
[30] Çavuş B, Akyuz F, Iliaz R, Atasoy A, Akyuz U, Demir K, et al. Is there any predictor for relapse after treatment withdrawal in autoimmune hepatitis patients in the real life? Int J Immunopathol Pharmacol 2022;36:3946320221077860.
[31] Volk ML, Reau R. Diagnosis and management of autoimmune hepatitis in adults and children: a patient-friendly summary of the 2019 AASLD Guidelines. Clin Liver Dis (Hoboken) 2021;17:859.
[32] Deneau M, Book LS, Guthery SL, Jensen MK. Outcome after discontinuation of immunosuppression in children with autoimmune hepatitis: a population-based study. J Pediatr 2014;164:714–719.