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Epidemiology, clinical features and management of autoimmune hepatitis in Switzerland: a retrospective and prospective cohort study

Christine Ludz[a], Guido Stirnimann[b], David Semela[c], Joachim Mertens[d], Andreas E. Kremer[e], Magdalena Filipowicz Sinnreich[f], Christiane Sokollik[g], Christine Bernsmeier[h], Solange Bresson-Hadni[i], Valérie McLin[j], Nathalie Rock[j], Christian Braegger[k], Carsten Posovszky[l], Pascal Müller[m], Matthias Cremer[n], Andrea De Gottardi[o], Antonio Galante[o], Raoul Furlano[p], Franziska Righini-Grunder[q], Björn Becker[r], Stephan Böhm[s], Klaas Heyland[t], Andreas Nydegger[u], Costanzo Limoni[v], Diego Vergani[w], Giorgina Mieli-Vergani[w], Claudia Di Bartolomeo[x], Andreas Cerny[x], Benedetta Terziroli Beretta-Piccoli[awx]

[a] Facoltà di Scienze Biomediche, Università della Svizzera Italiana, Lugano, Switzerland
[b] Universitätsklinik für Viszerale Chirurgie und Medizin, Inselspital Bern, Bern, Switzerland
[c] Klinik für Gastroenterologie und Hepatologie, Kantonsspital St. Gallen, St. Gallen, Switzerland
[d] GastroZentrum Hirslanden, Zürich, Switzerland
[e] Klinik für Gastroenterologie und Hepatologie, Universitätsspital Zürich, Zürich, Switzerland
[f] Clinic for Gastroenterology and Hepatology, Medizinische Universitätsklinik, Kantonsspital Baselland, Liestal, Switzerland
[g] Departement Pädiatrische Gastroenterologie, Hepatologie und Ernährung, Kinderklinik Inselspital Bern, Bern Switzerland
[h] Gastroenterologie/Hepatologie, Universitäres Bauchzentrum Basel Clarunis, Basel, Switzerland
[i] Service de Gastroentérologie & Hépatologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland
[j] Département de l'Enfant et de l'Adolescent, Centre Suisse des Maladies du Foie de l'Enfant, Hôpitaux Universitaires de Genève, Geneva, Switzerland
[k] Division of Pediatric Gastroenterology and Nutrition, University Children's Hospital Zurich, Zurich, Switzerland
[l] INutrition Research Unit, University Children's Hospital Zurich, Zurich, Switzerland
[m] Departement pädiatrische Gastroenterologie und Hepatologie, Ostschweizer Kinderspital, St. Gallen, Switzerland
[n] Departement für Kinder- und Jugendmedizin, Kantonsspital Graubünden, Chur, Switzerland
[o] Servizio di Gastroenterologia, Ente Ospedaliero Cantonale Ospedale Regionale di Lugano, Lugano, Switzerland
[p] University Children's Hospital Basel, Paediatric Gastroenterology & Nutrition, Basel, Switzerland
[q] Departement pädiatrische Gastroenterologie, Luzerner Kantonsspital/Kinderspital, Lucerne, Switzerland
[r] Departement Innere Medizin, Klinik für Gastroenterologie und Hepatologie, Kantonsspital Winterthur, Winterthur, Switzerland
[s] Departement Gastroenterologie und Hepatologie, Klinik Innere Medizin, Spital Bülach, Bülach, Switzerland
[t] Departement Kindergastroenterologie, Kantonsspital Winterthur, Winterthur, Switzerland
[u] Département femme-mère-enfant, Centre hospitalier universitaire Vaudois, Lausanne, Switzerland
[v] University of Applied Sciences and Arts of Southern Switzerland, Lugano, Switzerland
[w] MowatLabs, Faculty of Life Sciences & Medicine, King's College London, King's College Hospital, London, UK
[x] Epatocentro Ticino, Lugano, Switzerland

Summary

BACKGROUND AND AIMS: The Swiss Autoimmune Hepatitis Cohort Study is a nationwide registry, initiated in 2017, that collects retrospective and prospective clinical data and biological samples from patients of all ages with autoimmune hepatitis treated at Swiss hepatology centres. Here, we report the analysis of the first 5 years of registry data.

RESULTS: A total of 291 patients with autoimmune hepatitis have been enrolled, 30 of whom were diagnosed before 18 years of age and composed the paediatric cohort. Paediatric cohort: median age at diagnosis 12.5 years (range 1–17, interquartile range (IQR) 8–15), 16 (53%) girls, 6 (32%) with type 2 autoimmune hepatitis, 8 (27%) with autoimmune sclerosing cholangitis, 1 with primary biliary cholangitis variant syndrome, 4 (15%) with inflammatory bowel disease and 10 (41%) with advanced liver fibrosis at diagnosis. Adult cohort: median age at diagnosis 54 years (range 42–64, IQR 18–81), 185 (71%) women, 51 (20%) with primary biliary cholangitis variant syndrome, 22 (8%) with primary sclerosing cholangitis variant syndrome, 9 (4%) with inflammatory bowel disease and 66 (32%) with advanced liver fibrosis at diagnosis. The median follow-up time for the entire cohort was 5.2 years (IQR 3–9.3 years). Treatment in children: 29 (97%) children were initially treated with corticosteroids, 28 of whom received combination treatment with azathioprine. Budesonide was used in four children, all in combination with azathioprine. Mycophenolate mofetil was used in five children, all of whom had previously received corticosteroids and thiopurine. Treatment in adults (data available for 228 patients): 219 (96%) were treated with corticosteroids, mostly in combination with azathioprine. Predniso(lo)ne was the corticosteroid used in three-quarters of patients; the other patients received budesonide. A total of 78 (33%) patients received mycophenolate mofetil, 62 of whom had previously been treated with azathioprine. Complete biochemical response was achieved in 13 of 19 (68%) children and 137 of 182 (75%) adults with available follow-up data. All children were alive at the last follow-up, and none had undergone liver transplantation. Five (2%) adults underwent

Benedetta Terziroli Beretta-Piccoli
Epatocentro Ticino
Via Soldino 5
CH-6900 Lugano
benedetta.terziroli[at]usi.ch

liver transplantation, two of whom had a fulminant presentation. Four (2%) adults with autoimmune hepatitis died (two from liver-associated causes).

CONCLUSION: Patients with autoimmune hepatitis in Switzerland had clinical features similar to those in other cohorts. The proportion of patients diagnosed with primary biliary cholangitis variant syndrome was higher than expected. Autoimmune hepatitis was managed according to guidelines, except for the use of budesonide in a small proportion of paediatric patients. The outcomes were excellent, but the findings must be confirmed over a longer follow-up period.

Introduction

Autoimmune hepatitis is a rare, chronic inflammatory liver condition of unknown origin, affecting people of all ages. This condition is characterized by circulating autoantibodies, high serum transaminase and immunoglobulin G (IgG) levels, female preponderance, liver histology indicating interface hepatitis and a rapid response to corticosteroid treatment [1].

The Swiss Autoimmune Hepatitis Cohort Study, initiated in 2017, is a longitudinal collection of retrospective and prospective clinical data and prospective biological samples from patients with autoimmune hepatitis of all ages managed at Swiss hepatology centres; 19 centres currently enrol patients, including nine paediatric centres. The Swiss Autoimmune Hepatitis Cohort Study aims at standardized longitudinal collection of clinical data and biological samples to gain insights into the epidemiology, pathogenesis, natural history, response to treatment and outcomes of autoimmune hepatitis in Switzerland. These indices had not previously been investigated in Switzerland. In this study, we report the analysis of data collected by the Swiss Autoimmune Hepatitis Cohort Study from 2017 to March of 2022.

Autoimmune hepatitis is subdivided into two types: (a) type 1 autoimmune hepatitis, characterized by positive anti-nuclear (ANA) and/or anti-smooth muscle antibodies (ASMA), affecting both children and adults and (b) type 2 autoimmune hepatitis, characterized by positive anti-liver kidney microsomal antibody type 1 (anti-LKM1) and/or anti-liver cytosol antibody (anti-LC1), affecting primarily children and adolescents [2]. Anti-soluble liver antigen antibody (anti-SLA) is detected in 10–20% of patients with type 1 and type 2 autoimmune hepatitis, and is the only autoantibody specific for autoimmune hepatitis and associated with more aggressive disease [2, 6, 9].

A subgroup of adult patients with autoimmune hepatitis presents with clinical, serological and histological features of primary biliary cholangitis, or of primary sclerosing cholangitis; such features more rarely may appear later in the disease course [3]. These conditions are referred to as primary biliary cholangitis and primary sclerosing cholangitis variant syndromes, respectively [4]. In childhood, as many as half of all patients with autoimmune hepatitis type 1 have abnormal cholangiography findings at presentation and are therefore diagnosed with autoimmune sclerosing cholangitis, a condition often associated with inflammatory bowel disease and with anti-neutrophil cytoplasmic antibody (ANCA) positivity [5, 6].

Although autoimmune sclerosing cholangitis reportedly has a poorer prognosis than classical autoimmune hepatitis, a systematic diagnostic and therapeutic approach to paediatric autoimmune liver diseases has been shown to be associated with favourable long-term outcomes in both conditions, and is included in the paediatric guidelines [6–8].

The aim of this publication is to report the epidemiology, clinical features and management of autoimmune hepatitis in Switzerland, on the basis of data collected by the Swiss Autoimmune Hepatitis Cohort Study.

Methods

Contributing centres

The following hepatology centres contribute to the Swiss Autoimmune Hepatitis Cohort Study, including all Swiss transplant centres and nine of the ten Swiss university hospitals:

Transplant centres: Hôpitaux Universitaires de Genève, Pediatric Liver Centre at Hôpitaux Universitaires de Genève, Inselspital Bern and Universitätsspital Zürich

University hospitals: Inselspital Kinderklinik Bern, Universitäres Bauchzentrum Clarunis Basel, Universitäts-Kinderspital beider Basel, Universitäts-Kinderspital Zürich and Centre Hospitalier Universitaire Vaudois, Lausanne

Secondary referral centres: Ente Ospedaliero Cantonale, Epatocentro Ticino, Kantonsspital Baselland, Kantonsspital Graubünden, Kantonsspital St. Gallen, Luzerner Kinderspital, Ostschweizer Kinderspital, Kantonsspital Winterthur and Spital Bülach

The study is endorsed by the Swiss Association for the Study of the Liver (SASL study number 38, https://sasl.unibas.ch/7studies.php).

Study protocol

The study protocol (available for download as separate file at https://doi.org/10.57187/smw.2023.40102) followed the Swissethics template for research projects involving human participants (https://swissethics.ch/en/templates/studienprotokolle).

Clinical data and blood samples are collected at the time of cohort inclusion, at 6 months after diagnosis and on a yearly basis thereafter. The diagnosis of autoimmune hepatitis is made according to well established criteria [10]; however, such criteria can miss atypical cases [8], which are of particular interest in this cohort. Consequently, patients not meeting such criteria but still diagnosed with autoimmune hepatitis in a hepatology referral centre are included. Both previously and newly diagnosed patients are enrolled. Each included patient, or guardian in the case of minor patients, must sign an informed consent form approved by the local ethics committee (CE TI 3112). Participant confidentiality is ensured by the use of six-digit identification numbers when personal data are entered in the electronic case report forms or biological samples are stored in the biobank. Duplicate enrolments are excluded by identifying each patient according to sex and height (for participants >18 years of age) in addition to the six-digit code.

Data quality and completeness are verified at least yearly by the clinical trial unit of the Fondazione Epatocentro Ticino. Any identified inconsistencies are communicated and resolved through queries within the electronic case report form. The study was conducted according to the 1975 World Medical Association Declaration of Helsinki and the legally applicable local requirements.

Definitions used in the present report

Complete biochemical response is defined by normalization of transaminase and IgG levels [11].

Advanced fibrosis is defined by a modified Ishak score ≥3.

Statistical analysis

Statistical analysis was performed in GraphPad Prism 9.4.1. Continuous variables are expressed as medians, interquartile ranges (IQRs) and ranges; categorical variables are expressed as numbers and percentages. Fisher's exact test was used to compare categorical data between two groups. The Mann-Whitney U test was used to compare quantitative data between two groups. Two-tailed p-values <0.05 were considered significant in all analyses.

Results

Demographics and variant syndrome diagnosis

A total of 293 patients were enrolled from 1 January 2017 to 31 December 2021, 30 of whom were diagnosed before 18 years of age and composed the paediatric cohort. Two adult patients were diagnosed with autoimmune hepatitis after liver transplantation (de novo autoimmune hepatitis) and were excluded from the data analysis. Four paediatric patients and six adult patients were diagnosed before 1 January 2000. Clinical features of the study population are shown in table 1. Half the paediatric patients were boys: this high proportion might have been because nearly one-third of these patients had autoimmune sclerosing cholangitis, which affects males and females equally [5]. Non-white ancestry was significantly more common in the paediatric cohort than the adult cohort (p = 0.006). Three of the eight patients with autoimmune sclerosing cholangitis did not undergo cholangiography at the time of diagnosis and were initially diagnosed with autoimmune hepatitis but were subsequently found to have abnormal cholangiograms at follow-up. One-fifth (51 patients) of the adult autoimmune hepatitis population had a diagnosis of primary biliary cholangitis variant syndrome: seven (14%) of these patients were initially diagnosed with autoimmune hepatitis but subsequently developed primary biliary cholangitis after a median follow-up of 4.8 years. In four patients, the primary biliary cholangitis diagnosis predated the autoimmune hepatitis diagnosis by a median time of 5.2 years. In the remaining 40 patients (78%), primary biliary cholangitis variant syndrome was the initial diagnosis. The proportion of adult patients with advanced histological fibrosis was similar between those with autoimmune hepatitis and primary biliary cholangitis variant syndrome (p = 0.26).

One 17-year-old girl presented with primary biliary cholangitis variant syndrome. The adult patients with primary sclerosing cholangitis variant syndrome, composing 5% of the adult autoimmune hepatitis cohort, were significantly younger (median age 37 vs 55 years, p = 0.0269) and had a significantly higher percentage of men (61.5% vs 29.4%, p = 0.0031) than the patients with autoimmune hepatitis. Five of the 14 adult patients with primary sclerosing cholangitis variant syndrome were initially diagnosed with autoimmune hepatitis and had developed primary sclerosing cholangitis by follow-up (median time 5.9 years, range 10.5 months to 11.5 years); however, only one patient had normal magnetic resonance cholangiopancreatography findings documented (MRCP) at diagnosis. Three of the 14 patients with primary sclerosing cholangitis variant syndrome were initially diagnosed with primary sclerosing cholangitis and had developed autoimmune hepatitis by follow-up (median time 2 years, range 1.1–4.8 years).

Magnetic resonance cholangiopancreatography at diagnosis was performed in 40% of paediatric patients (12 of 30) but only 7% of adult patients.

Follow-up time

The median time from diagnosis to enrolment (retrospective data collection) was 3.6 years (IQR 0.3–7.7, range 0–44 years). The median time from enrolment to the last follow-up visit (prospective data collection) was 2.2 years (IQR 1.2–3.2, range 0–5 years). The median time from diagnosis to the last follow-up was 5.2 years (IQR 3–9.3, range 0–46 years). Fifteen patients discontinued study participation: four because of personal choice, four because of moving abroad, one because follow-up was transferred to a hepatology centre not participating in the present study, one because of loss to follow-up, and four because of death (two from liver-associated causes). The follow-up time between diagnosis of autoimmune hepatitis and death due to liver-associated causes in the two patients was 14.2 and 31.1 years, whereas the follow-up time in the two patients who died of other causes was 3.1 and 10 years.

Extrahepatic autoimmune diseases

In line with findings from other autoimmune hepatitis cohorts, the most prevalent extrahepatic autoimmune disease in our population was autoimmune thyroiditis (table 1). Concomitant inflammatory bowel disease was more common in children than adults, probably because screening for inflammatory bowel disease is routinely performed for all newly diagnosed patients at most paediatric centres (p = 0.034).

A substantial proportion of adults (32%) and children (41%) had advanced histological liver fibrosis at the time of diagnosis.

Laboratory values

Laboratory values at diagnosis are shown in tables 2 and 3. Statistical analysis of the paediatric cohort was limited by the small number of patients. In the adult cohort, the median alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin and international normalized ratio (INR) were higher in the autoimmune hepatitis group than the primary biliary cholangitis variant group. IgG levels were similar among the three adult groups but were significantly higher in children than adults with clas-

sical autoimmune hepatitis (p = 0.0003). Children with autoimmune hepatitis had higher INR (p = 0.0027) and lower gamma-glutamyltransferase (GGT) levels (0.0074) than adults with autoimmune hepatitis.

Autoantibody profiles are shown in table 4. One-third of the children and 3% of the adults were classified as having autoimmune hepatitis type 2 with anti-LKM1 positivity. Thirteen (11%) of the 120 tested adults, and three of the nine tested children, were anti-SLA positive. ANCA and AMA were rarely tested in children; one paediatric patient with primary biliary cholangitis variant syndrome was AMA positive. Eight (9%) of the 86 adults with autoimmune hepatitis tested for AMA had positive findings; only half the adults with primary biliary cholangitis variant syndrome were reportedly tested for AMA, and 56% were positive.

Treatment

Data on autoimmune hepatitis treatment were available for all children and for 233 of the 261 adults (table 5). Twenty-nine children were treated with corticosteroids (25 received predniso(lo)ne, median initial dose 1.08 mg/kg/day, IQR 0.78–1.33 mg/kg/day, range 0.13–2.07 mg/kg/day). Twenty-eight patients were also treated with azathioprine, nine of whom also received steroids as an initial treatment. Budesonide was used in four patients, all in combination with azathioprine, including one patient with autoimmune sclerosing cholangitis and the patient with primary biliary cholangitis variant syndrome. Mycophenolate mofetil was used as a second line treatment in five children, all of whom had previously received corticos-

Table 1:
Demographic and clinical characteristics of the Swiss Autoimmune Hepatitis Cohort. *Italic numbers in brackets* indicate the numbers of patients with available data.

		Children (n = 30)		Adults (n = 261)		Total (n = 291)	
Age at diagnosis (median [IQR, range]) *(children = 30, adults = 259)*		12.5	(8–15, 1–17)	54	(42–64, 18–81)		
Sex *(children = 30, adults = 261)*							
Female		16	(53%)	185	(71%)	201	(69%)
Ancestry *(children = 30, adults = 261)*							
White		24	(80%)	245	(94%)	269	(92%)
Asian		2	(7%)	10	(4%)	12	(4%)
Black		1	(3%)	2	(0.8%)	3	(1%)
American Indian/Alaskan Native		–		1	(0.4%)	1	(0.3%)
Other*		3	(10%)	3	(1%)	6	(2%)
BMI (median (IQR)) *(children = 24, adults = 193)*		37.5 percentile	(25–72)	24.9	(22.2–29)		
PBC variant *(children = 30, adults = 261)*		1	(3%)	51	(20%)	52	(18%)
PSC variant *(children = 30, adults = 261)*		8	(27%)	14	(5%)	22	(8%)
MRCP performed at diagnosis		12	(40%)	19	(7%)	31	(11%)
Type 2 AIH (anti-LKM-1 positive)*(children = 19, adults = 149)*		6	(32%)	5	(3%)	11	(7%)
Autoimmune co-morbidities *(children = 28, adults = 241)*							
Autoimmune thyroiditis		3	(11%)	23	(10%)	26	(10%)
Rheumatoid arthritis		–		13	(5%)	13	(5%)
Coeliac disease		1	(4%)	8	(3%)	9	(3%)
Sjögren syndrome		–		5	(2%)	5	(2%)
Systemic lupus erythematosus		–		4	(2%)	4	(1%)
Autoimmune skin diseases		–		4	(2%)	4	(1%)
	Cutaneous lupus erythematosus	–		1	(0.4%)	1	(0.4%)
	Neurodermatitis	–		1	(0.4%)	1	(0.4%)
	Psoriasis	–		1	(0.4%)	1	(0.4%)
	Pyoderma gangrenosum	–		1	(0.4%)	1	(0.4%)
Multiple sclerosis		–		3	(1%)	3	(1%)
Antiphospholipid syndrome		–		1	(0.4%)	1	(0.4%)
Autoimmune gastritis		–		1	(0.4%)	1	(0.4%)
Behçet disease		–		1	(0.4%)	1	(0.4%)
Complex autoimmune syndrome		–		1	(0.4%)	1	(0.4%)
IgA glomerulonephritis		–		1	(0.4%)	1	(0.4%)
Sarcoidosis		–		1	(0.4%)	1	(0.4%)
Systemic sclerosis		–		1	(0.4%)	1	(0.4%)
Inflammatory bowel disease *(children = 28, adults = 241)*							
Ulcerative colitis		3	(11%)	9	(4%)	12	(4%)
Crohn disease		1	(4%)	–		1	(0.4%)
Histological fibrosis at diagnosis *(children = 24, adults = 206)*							
No fibrosis		5	(21%)	74	(36%)	79	(34%)
Mild fibrosis		9	(38%)	66	(32%)	75	(33%)
Advanced fibrosis/cirrhosis		10	(41%)	66	(32%)	76	(33%)

AIH: autoimmune hepatitis; BMI: body mass index (kg/m^2); IgA: immunoglobulin A; IQR: interquartile range; anti-LKM-1: anti-liver kidney microsomal type 1 antibody; MRCP: magnetic resonance cholangiopancreatography; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis.

*includes the categories “two or more races”, “other” and “unknown”.

teroids and thiopurine (azathioprine or 6-mercaptopurine). Both children treated with infliximab had concomitant inflammatory bowel disease. One child with type 1 autoimmune hepatitis in the context of a pathogenic homozygous nonsense mutation (c.1054C>T) of the RBCK1 gene was treated with methotrexate, after initial treatment with prednisone and azathioprine.

Ninety-three percent of the adult patients with autoimmune hepatitis were initially treated with corticosteroids, most of whom received combination treatment with azathioprine. Predniso(lo)ne was the corticosteroid used in three-quarters of patients (median initialpredniso(lo)ne dose 40 mg/day, IQR 40–60 mg/day, range 2.5–125 mg/day), and the remaining patients received budesonide. The proportion of patients with ALT normalization was similar between patients treated with predniso(lo)ne and with budesonide (84.2% vs. 84.6%). No correlation was observed between the initial prednisone dose, which was known for 124 patients, and the bilirubin, ALT or INR levels at diagnosis. Similarly to the autoimmune hepatitis group, the primary biliary cholangitis and primary sclerosing cholangitis variant groups were typically initially treated with steroids and azathioprine. In both groups, the corticosteroid was budesonide in half the patients. Budesonide was administered significantly more often in patients with primary biliary cholangitis variant syndrome than in patients with autoimmune hepatitis ($p = 0.019$). A total of 78 patients received mycophenolate mofetil, 62 of whom had previously been treated with azathioprine. The third line treatments included primarily calcineurin inhibitors; anti-tumour necrosis factor alpha agents were used in three patients, one of whom had concomitant Behçet disease. Two patients with concomitant rheumatoid arthritis received abatacept and methotrexate.

All paediatric patients with autoimmune sclerosing cholangitis, 82% of the adults with primary sclerosing cholangitis variant syndrome and 94% of the patients with primary biliary cholangitis variant syndrome were treated with ursodeoxycholic acid. Five patients with primary biliary cholangitis variant syndrome additionally received bezafibrate, one of whom had previously received obeticholic acid and one of whom received fenofibrate. One patient with primary sclerosing cholangitis variant syndrome received bezafibrate.

Of the 20 patients (18 adults and 2 children) who received 6-mercaptopurine, 16 had previously received azathioprine.

Outcomes

Complete biochemical response was achieved in 62% of children and 78% of adults with classical autoimmune hepatitis (table 6, supplementary table S1). Among adults, similar proportions of patients with autoimmune hepatitis and primary biliary cholangitis variant syndrome achieved a complete biochemical response ($p = 0.67$). In adults with autoimmune hepatitis, no correlation was observed between the initial predniso(lo)ne dose and ALT normalization (data available for 102 patients). All children were alive at the last follow-up, and none had undergone liver transplantation. Five adult patients had undergone liver transplantation: two underwent transplantation 3 and 16 days after diagnosis, because of fulminant presentation, whereas three underwent transplantation 9, 10 and 17 years

Table 2:
Laboratory values (median and [IQR]) at diagnosis in paediatric patients. *Italic numbers in brackets* indicate the numbers of patients with available data.

	AIH		**PBC variant**		**ASC**		**Comparison of AIH and ASC**
	(n = 21)		**(n = 1)**		**(n = 8)**		
Age at diagnosis (years)	13	(7–14)	17	(17–17)	11.5	(8–15)	*p = 0.66*
	(n = 21)		*(n = 1)*		*(n = 8)*		
Female	13	(62%)	1	(100%)	2	(25%)	*p = 0.11*
ALT U/l	521	(311–1172)	213		341	(191–852)	*p = 0.49*
	(n = 19)		*(n = 1)*		*(n = 7)*		
AST U/l	440	(252–858)	117		240	(174–740)	*p = 0.56*
	(n = 19)		*(n = 1)*		*(n = 7)*		
ALP U/l	207	(155–285)	113		454	(423–556)	*p = 0.01**
	(n = 16)		*(n = 1)*		*(n = 5)*		
GGT U/l	80	(59–108)	–		371	(371–371)	
	(n = 6)		*(n = 0)*		*(n = 1)*		
Total bilirubin µmol/l	26	(14–57)	17		10	(5–20)	*p = 0.07*
	(n = 16)		*(n = 1)*		*(n = 6)*		
Albumin g/l	38	(35–42)	31		37	(35–39)	*p = 0.77*
	(n = 14)		*(n = 1)*		*(n = 6)*		
INR	1.31	(1.23–1.37)	0.9		1	(1–1)	
	(n = 16)		*(n = 1)*		*(n = 3)*		
Platelets × 10^9/l	155	(127–234)	293		425	(360–513)	
	(n = 17)		*(n = 1)*		*(n = 4)*		
IgG g/l	30	(23–40)	16		24	(18–24)	*p = 0.29*
IgG >ULN (n)	13	(87%)	1		4	(80%)	
	(n = 15)		*(n = 1)*		*(n = 5)*		

AIH: autoimmune hepatitis; ALT: alanine aminotransferase; ASC: autoimmune sclerosing cholangitis; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; IgG: immunoglobulin G; INR: international normalized ratio; IQR: interquartile range; PBC: primary biliary cholangitis; ULN: upper limit of normal.

* = statistically significant

after autoimmune hepatitis diagnosis, because of end-stage liver disease.

Discussion

The present study provides the first report of the clinical features, treatments and outcomes of autoimmune hepatitis in Switzerland, on the basis of data from the Swiss Autoimmune Hepatitis Cohort Study, a registry including all

Table 3:
Laboratory values (median and [IQR]) at diagnosis in adult patients. *Italic numbers in brackets* indicate the numbers of patients with available data.

	AIH		**PBC variant**		**Comparison of AIH and PBC variant**	**PSC variant**		**Comparison of AIH and PSC variant**
	(n = 197)		**(n = 51)**			**(n = 13)**		
Age at diagnosis (years)	55	(42–65)	53	(46–65.5)	*p = 0.76*	37	(28–46)	*p = 0.003**
	(n = 195)		*(n = 51)*			*(n = 13)*		
Female	139	(71%)	41	(80%)	*p = 0.22*	5	(38%)	*p = 0.03**
ALT U/l	455	(135–1031)	128	(64–370)	*p = 0.001**	369	(230–604)	*p = 0.80*
	(n = 168)		*(n = 43)*			*(n = 8)*		
AST U/l	343	(113–865)	99	(58–186)	*p = 0.0003**	224	(126–371)	*p = 0.55*
	(n = 166)		*(n = 43)*			*(n = 8)*		
ALP U/l	133	(88–184)	167	(108–248)	*p = 0.07*	229	(183–356)	*p = 0.002**
	(n = 167)		*(n = 43)*			*(n = 8)*		
GGT U/l	234	(115–406)	176	(106–315)	*p = 0.69*	934	(862–1005)	
	(n = 88)		*(n = 20)*			*(n = 2)*		
Total bilirubin µmol/l	31	(15–115)	16.5	(13–30)	*p = 0.002**	30	(18–41)	*p = 0.45*
	(n = 166)		*(n = 42)*			*(n = 8)*		
Albumin g/l	36	(30–39)	36	(34–41)	*p = 0.18*	40	(37–41)	*p = 0.09*
	(n = 156)		*(n = 40)*			*(n = 8)*		
INR	1.12	(1–1.3)	1	(1–1.18)	*p = 0.001**	1	(1–1.08)	*p = 0.09*
	(n = 135)		*(n = 34)*			*(n = 7)*		
Platelets × 10^9/l	218	(160–268)	247	(186–314)	*p = 0.09*	237	(206–284)	*p = 0.52*
	(n = 151)		*(n = 40)*			*(n = 8)*		
IgG g/l	19	(13–26)	17.5	(13–23)	*p = 0.45*	21	(16–25)	*p = 0.63*
IgG >ULN (n)	90	(63%)	22	(61%)		4	(67%)	
	(n = 143)		*(n = 36)*			*(n = 6)*		

AIH: autoimmune hepatitis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; IgG: immunoglobulin G; INR: international normalized ratio; IQR: interquartile range; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; ULN: upper limit of normal. Italic numbers in brackets indicate the numbers of patients with available data.

* = statistically significant

Table 4:
Autoantibody profiles at diagnosis. Numbers (percentages) of positive patients are shown. *Italic numbers in brackets* indicate the numbers of patients with available data.

	Children					**Adults**					
	AIH		**PBC variant**	**ASC**		**AIH**		**PBC variant**		**PSC variant**	
	(n = 21)		**(n = 1)**	**(n = 8)**		**(n = 197)**		**(n = 51)**		**(n = 13)**	
ANA ≥1:80	11	(85%)	1	3	(60%)	137	(88%)	37	(93%)	7	(100%)
ANA ≥1:160	6	(46%)	1	2	(40%)	110	(71%)	30	(75%)	6	(86%)
	(n = 13)		*(n = 1)*	*(n = 5)*		*(n = 155)*		*(n = 40)*		*(n = 7)*	
ASMA ≥1:40	11	(79%)	–	4	(100%)	85	(59%)	13	(54%)	4	(57%)
ASMA ≥1:80	6	(43%)	–	4	(100%)	72	(50%)	10	(41%)	2	(28%)
	(n = 14)		*(n = 0)*	*(n = 4)*		*(n = 144)*		*(n = 24)*		*(n = 7)*	
Anti-LKM1 ≥1:10	6	(43%)	–	0	(0%)	5	(4%)	0	(0%)	0	(0%)
	(n = 19)		*(n = 0)*	*(n = 5)*		*(n = 113)*		*(n = 30)*		*(n = 6)*	
Anti-LC1 ≥1:10	0		0	0		0		0		0	
	(n = 7)		*(n = 1)*	*(n = 0)*		*(n = 29)*		*(n = 0)*		*(n = 0)*	
ANCA ≥1:10	1	(25%)	–	4	(100%)	28	(36%)	5	(25%)	1	(20%)
	(n = 4)		*(n = 0)*	*(n = 4)*		*(n = 77)*		*(n = 20)*		*(n = 5)*	
AMA ≥1:40	0	(0%)	1	–		8	(9%)	14	(56%)	0	(0%)
	(n = 3)		*(n = 1)*	*(n = 0)*		*(n = 86)*		*(n = 25)*		*(n = 3)*	
Anti-SLA	3	(33%)	0	1	(50%)	13	(11%)	1	(3%)	1	(16%)
	(n = 9)		*(n = 1)*	*(n = 2)*		*(n = 120)*		*(n = 30)*		*(n = 6)*	

AIH: autoimmune hepatitis; AMA: anti-mitochondrial antibody; ANA: anti-nuclear antibody; ANCA: anti-neutrophil cytoplasmic antibody; ASC: autoimmune sclerosing cholangitis; anti-LKM1: anti-liver kidney microsomal antibody type 1; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; anti-SLA: soluble liver antigen; ASMA: anti-smooth muscle antibody; anti-LC1: anti-liver cytosol type 1 antibody.

consenting patients with autoimmune hepatitis managed at 19 Swiss hepatology centres. Assuming a prevalence of 15–20 cases per 100,000 inhabitants [12,13], we estimate that the registry currently includes approximately one-quarter of the Swiss population with autoimmune hepatitis. This estimate is corroborated by the high number of patients recruited in the Italian speaking part of Switzerland, where the coordination centre is located, and where the enrolment in the registry is likely to be relatively high, owing to the small size of the region, awareness of the registry, and close contact between family physicians and hepatologists, thus leading to a high referral rate of patients with suspected liver disease. Fifty-six patients were recruited from this region, accounting for 1/25 of the Swiss population (8.5 million inhabitants). If a similar autoimmune hepatitis prevalence across Switzerland is assumed, the estimated total number of patients with autoimmune hepatitis in the country is 1400, corresponding to a prevalence of approximately 16.5 per 100,000 inhabitants, in line with recent European epidemiological studies [12,13]. Our study included only patients managed at secondary and tertiary referral centres, thus potentially introducing a selection bias toward patients with more severe disease. However, only a minority of adult patients with autoimmune hepatitis and virtually no paediatric patients with autoimmune hepatitis are managed in the primary care setting. The median age at diagnosis, sex distribution and proportion of patients with advanced liver fibrosis at di-

Table 5:
Treatments. Thiopurines include azathioprine and 6-mercaptopurine. *Italic numbers in brackets* indicate the numbers of patients with available data.

	Children						**Adults**					
	AIH		**PBC variant**	**ASC**			**AIH**		**PBC variant**		**PSC variant**	
	(n = 21)		**(n = 1)**	**(n = 8)**			**(n = 197)**		**(n = 51)**		**(n = 13)**	
First line treatment												
Predniso(lo)ne	1		(5%)	–	–	(0%)	19	(11%)	1	(2%)	–	(0%)
Predniso(lo)ne + thiopurines	17		(80%)	–	7	(88%)	97	(54%)	19	(44%)	6	(55%)
Azathioprine	1		(5%)	–	–	(0%)	7	(4%)	2	(5%)	–	(0%)
Budesonide	–		(0%)	–	–	(0%)	4	(2%)	3	(7%)	1	(9%)
Budesonide + thiopurines	2		(10%)	1	1	(13%)	47	(26%)	18	(42%)	4	(36%)
	(n = 21)			*(n = 1)*	*(n = 8)*		*(n = 174)*		*(n = 43)*		*(n = 11)*	
Second line treatment												
Mycophenolate	2		(10%)	1	2	(25%)	55	(31%)	16	(37%)	7	(63%)
	(n = 21)			*(n = 1)*	*(n = 8)*		*(n = 179)*		*(n = 43)*		*(n = 11)*	
Third line treatment												
Tacrolimus	–		(0%)	–	–	(0%)	8	(4%)	3	(7%)	3	(27%)
Cyclosporin A	2		(10%)	–	1	(13%)	8	(4%)	2	(5%)	1	(9%)
Infliximab	–		(0%)	–	2	(25%)	1	(0.6%)	2	(5%)	–	(0%)
Methotrexate	1		(5%)	–	–	(0%)	–		–	(0%)	–	(0%)
Abatacept	–		(0%)	–	–	(0%)	1	(0.6%)	–	(0%)	–	(0%)
	(n = 21)			*(n = 1)*	*(n = 8)*		*(n = 179)*		*(n = 43)*		*(n = 11)*	
UDCA	3		(15%)	1	8	(100%)	21	(12%)	45	(94%)	9	(82%)
	(n = 21)			*(n = 1)*	*(n = 8)*		*(n = 179)*		*(n = 48)*		*(n = 11)*	

AIH: autoimmune hepatitis; ASC: autoimmune sclerosing cholangitis; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; UDCA: ursodeoxycholic acid.

Table 6:
Normalisation of transaminase and immunoglobulin G levels, mortality and liver transplantation. Median follow-up time 5.2 years (IQR 3–9.3, range 0–46 years). *Italic numbers in brackets* indicate the numbers of patients with available data.

	Children						**Adults**					
	AIH		**PBC variant**		**ASC**		**AIH**		**PBC variant**		**PSC variant**	
	(n = 21)		**(n = 1)**		**(n = 8)**		**(n = 197)**		**(n = 51)**		**(n = 13)**	
Normal ALT	12	(92%)	1	(100%)	4	(80%)	118	(87%)	31	(84%)	7	(70%)
	(n = 13)		*(n = 1)*		*(n = 5)*		*(n = 135)*		*(n = 37)*		*(n = 10)*	
Normal IgG	12	(75%)	1	(100%)	6	(100%)	137	(91%)	37	(86%)	9	(82%)
	(n = 16)		*(n = 1)*		*(n = 6)*		*(n = 150)*		*(n = 43)*		*(n = 11)*	
Normal ALT + IgG	8	(62%)	1	(100%)	4	(80%)	105	(78%)	25	(68%)	7	(70%)
	(n = 13)		*(n = 1)*		*(n = 5)*		*(n = 135)*		*(n = 37)*		*(n = 10)*	
Alive	21	(100%)	1		8	(100%)	193	(98%)	51	(100%)	13	(100%)
Dead	0	(0%)	0		0	(0%)	4	(2%)	0	(0%)	0	(0%)
Dead because of liver disease	–		–		–		2	(50%)	–		–	
Liver transplantation	0		0		0		4		0		1	
One liver transplantation	–		–		–		2		–		1	
Two liver transplantations	–		–		–		2		–		–	
	(n = 21)		*(n = 1)*		*(n = 8)*		*(n = 197)*		*(n = 51)*		*(n = 13)*	

AIH: autoimmune hepatitis; ALT: alanine aminotransferase; ASC: autoimmune sclerosing cholangitis; IgG: immunoglobulin G; IQR: interquartile range; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis.

agnosis in our cohort are consistent with findings in other published cohorts [14–16]. Moreover, our study confirmed that autoimmune hepatitis affects people of all ages, because the age at diagnosis ranged from 1 to 81 years. One-third of the paediatric population had type 2 autoimmune hepatitis, but information on anti-LKM1 status was available for only 19 children. The frequency of concomitant extrahepatic autoimmune diseases was low in our cohort, probably because of underreporting.

Twenty percent of the adult population with autoimmune hepatitis was diagnosed with primary biliary cholangitis variant syndrome; this proportion was twice that reported in other series [17]. Overdiagnosis of primary biliary cholangitis variant syndrome is a well-recognized phenomenon, which probably results from the presence of interface hepatitis on liver biopsy in patients with untreated primary biliary cholangitis [3]; this phenomenon is also likely to occur in Switzerland. As expected, in our population, patients with primary biliary cholangitis variant syndrome had lower transaminase levels than patients with autoimmune hepatitis; interestingly, they also had lower bilirubin and lower INR at presentation, thus indicating less severe disease. Although patients with primary biliary cholangitis variant syndrome have been reported to have poorer outcomes than patients with autoimmune hepatitis [3], this finding was not observed in our cohort, possibly because of overdiagnosis of primary biliary cholangitis variant syndrome.

The frequency of primary sclerosing cholangitis variant syndrome in our cohort was 5%, a value similar to the lower end of the 7–14% range reported in the literature [16]. Of note, we report one adult with autoimmune hepatitis and normal cholangiogram findings at diagnosis who had developed primary sclerosing cholangitis by follow-up, similarly to paediatric case reports [5]. The proportion of paediatric patients with autoimmune sclerosing cholangitis in our cohort was similar to that in the King's College Hospital cohort (27% vs 34%, $p = 0.14$), thus suggesting that paediatric patients in Switzerland are diagnosed according to the paediatric guidelines, which are largely based on the King's College Hospital protocol [7].

The autoimmune serological profile of our cohort indicated that the whole liver autoantibody panel is not consistently tested in Switzerland and therefore represents a missed opportunity for more accurate diagnosis.

According to our data, adult autoimmune hepatitis treatment in Switzerland is consistent with the guidelines, and is based on corticosteroids and azathioprine. In contrast, budesonide is occasionally used as the initial treatment in children despite not being recommended by the paediatric guidelines [7].

The rate of complete biochemical response in our cohort was lower than that generally reported in the literature, particularly in children: this finding warrants further investigation and longer follow-up times, also because we report a low (1.7%) liver transplantation rate. Fulminant presentation requiring liver transplantation was rare, affecting 2/261 (0.8%) adults and none of the 30 children.

Our study indicated that the data completeness of the Swiss Autoimmune Hepatitis Cohort Study requires improvement, because the observed low frequency of concomitant autoimmune diseases or positive serological results was most probably due to underreporting. Data completeness is a frequently encountered issue in registries, because data entry is time-consuming and requires knowledge of the disease. Therefore, registries are expensive, and acquiring funding for cohort studies is often difficult. Consequently, the main limitation of our study is associated with missing data in the electronic clinical report forms. These missing data prevented us from answering the highly relevant clinically question of whether the cohort included patients who discontinued immunosuppressive treatment.

In conclusion, analysis of the first 5 years of data from the Swiss Autoimmune Hepatitis Cohort Study showed that autoimmune hepatitis in Switzerland has clinical features in line with those observed in other cohorts; the proportion of patients diagnosed with primary biliary cholangitis variant syndrome was higher than expected; and autoimmune hepatitis was managed according to guidelines, except for the use of budesonide in a small proportion of paediatric patients. Moreover, the mortality and liver transplantation outcomes were excellent. We will follow up on this finding in future years during the Swiss Autoimmune Hepatitis cohort study. To obtain a complete, detailed picture of autoimmune hepatitis in Switzerland, patient recruitment and the data completeness of our registry should be improved; additional resources will be needed to achieve this goal.

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Potential competing interests

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Appendix: Supplementary table

Table S1:
Time from diagnosis to ALT normalisation. *Italic numbers in brackets* stand for the number of patients with normalised ALT.

	Children AIH *(normal ALT = 12)*	Children PBC variant *(normal ALT = 1)*	Children ASC *(normal ALT = 4)*	Adults AIH *(normal ALT = 118)*	Adults PBC variant *(normal ALT = 31)*	Adults PSC variant *(normal ALT = 7)*
Median in years	6.13	12.49	1.1	2.55	2.87	6.57
Range in years	1.02-36.07		0.57-1.6	0.12-23.05	0.35-20.5	1.72-26.66
IQR in years	4.73-7.9		0.61-2.44	1.17-6.16	1.12-7.92	4.13-9.35

AIH: autoimmune hepatitis; ASC: autoimmune sclerosing cholangitis; IQR: interquartile range; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis.