KOÇ UNIVERSITY

ALD-Örtüşme Sendromları

Cigdem Arıkan,MD

Pediatric GI/Hepatology/Transplantation

Koc University School of Medicine

Koc University Research Center for Translational Medicine (KUTTAM)

Koc University Health Sciences (GSHS) Immunology

KUTTAM

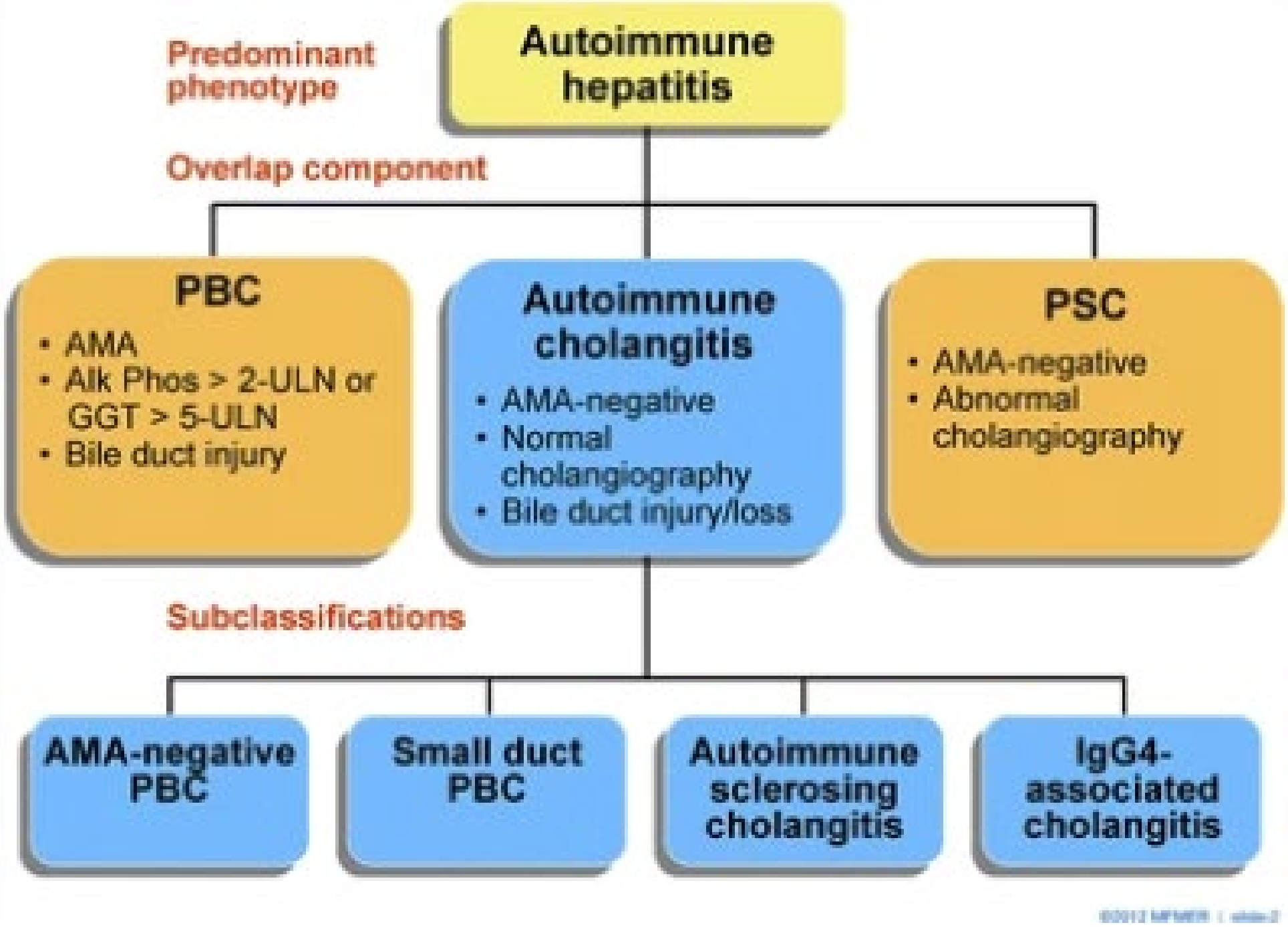
KOÇ UNIVERSITY RESEARCH CENTER FOR TRANSLATIONAL MEDICINE

Sunum planı

ALD-overlap tanımı
ALD-overlap patogenezi
ALD-overlap tanı
ALD-overlap tedavi

Neler biliyoruz

- Tanımlama
- Klinik ve doğal seyir bilinmiyor
- Portal HT, ölüm ve karaciğer nakli sıklığı OS'da sadece AIH'e göre daha yüksek
- Doğal seyir


Predominant phenotype
Autoimmune hepatitis
Overlap component
PBC
• AMA
• Alk Phos > 2-ULN or GGT > 5-ULN
• Bile duct injury
Autoimmune cholangitis
• AMA-negative
• Normal cholangiography
• Bile duct injury/loss
PSC
• AMA-negative
• Abnormal cholangiography
Subclassifications
AMA-negative PBC
Small duct PBC
Autoimmune sclerosing cholangitis
IgG4-associated cholangitis

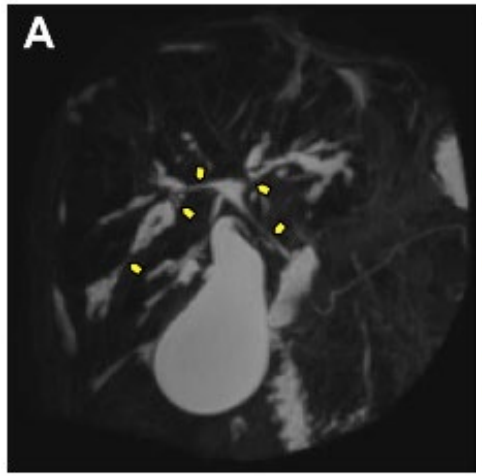
OS-Tanım

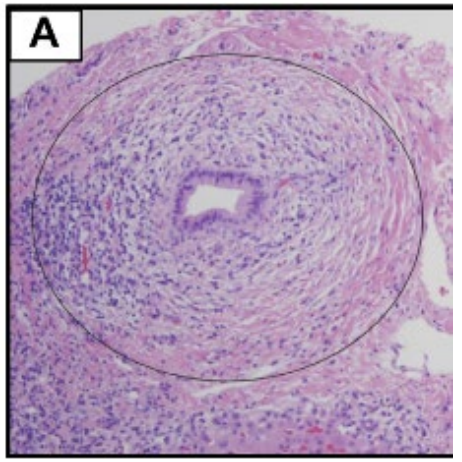
- Es zamanlı veya sekansiyel olarak klinik biyokimyasal, serolojik ve histolojik özeliklerin birarada bulunması
- Iyi tanımlanmış tanı kriterleri olmadığından prevalansı çok değişken
- AIH –PBS 1%-19%
- AIH-PSC 1%-54%

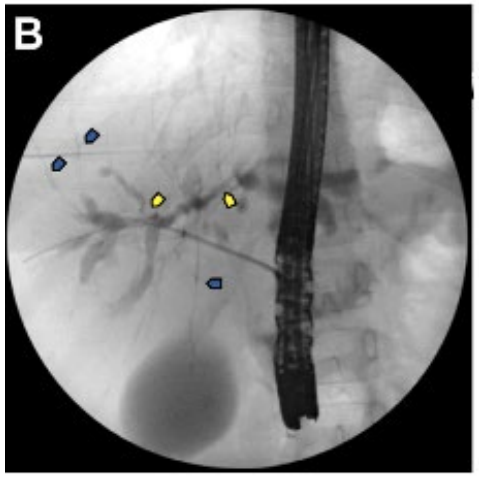
PSK'ya ne oldu?

Table 2
Criteria for defining large duct PSC and small duct PSC

Large Duct PSC	Small Duct PSC
1. Evidence of cholestasis on biochemistries (elevated bilirubin, GGT, and/or ALP)	1. Evidence of cholestasis on biochemistries (elevated bilirubin, GGT, and/or ALP)
2. Cholangiographic (MRCP, ERCP) findings of ≥1 of the following within large or medium sized bile ducts: • Focal stricturing of bile duct(s) • Dominant stricture of common bile duct[a] • Saccular dilatation of bile duct(s) • Beaded appearance of bile duct(s) • Pruning appearance of the distal bile duct branches	2. Liver histologic findings of: Definite small duct PSC • Periductal fibrosis/onion skinning around interlobular bile ducts or smaller profiles Probable small duct PSC: liver histology with ≥3 of 5 criteria: • Periductal edema • Periductal concentric inflammation • Bile duct epithelial injury • Ductular reaction • Neutrophils in bile ducts
3. Exclusion of secondary causes of sclerosing cholangitis (see Table 3)	3. Absence of cholangiographic abnormalities (ie, normal MRCP or ERCP)







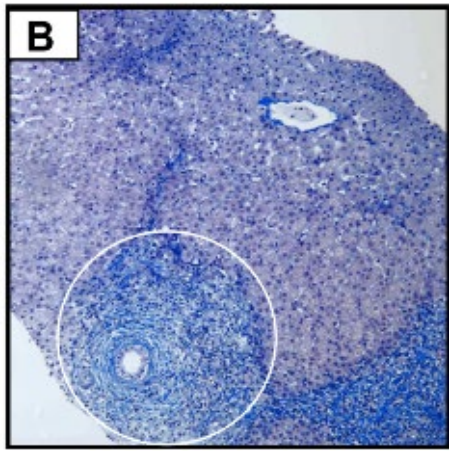


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Table 3
Causes of secondary sclerosing cholangitis

Anatomic	Choledocholithiasis (idiopathic, sickle cell disease, other) Choledochal cyst Congenital stricture of the common bile duct Trauma
Infection	Pyogenic cholangitis Septic shock *E coli* 0157:H7 enterocolitis Cryptosporidium
Immunodeficiency	X-linked hyper-IgM syndrome–CD40 ligand deficiency with concurrent Cryptosporidium Wiskott–Aldrich syndrome Natural killer cell deficiency with concurrent Trichosporon infection Agammaglobulinemia with Cryptosporidium Combined variable immunodeficiency with concurrent Cryptosporidium AIDS-associated cholangiopathy with concurrent cytomegalovirus or Cryptosporidium
Neoplastic	Langerhans cell histiocytosis Hodgkin lymphoma Ductal cancer, gallbladder cancer Reticulum cell sarcoma
Congenital	Cystic fibrosis Congenital hepatic fibrosis Caroli disease Caroli syndrome (congenital hepatic fibrosis with Caroli disease) Ductal plate abnormalities

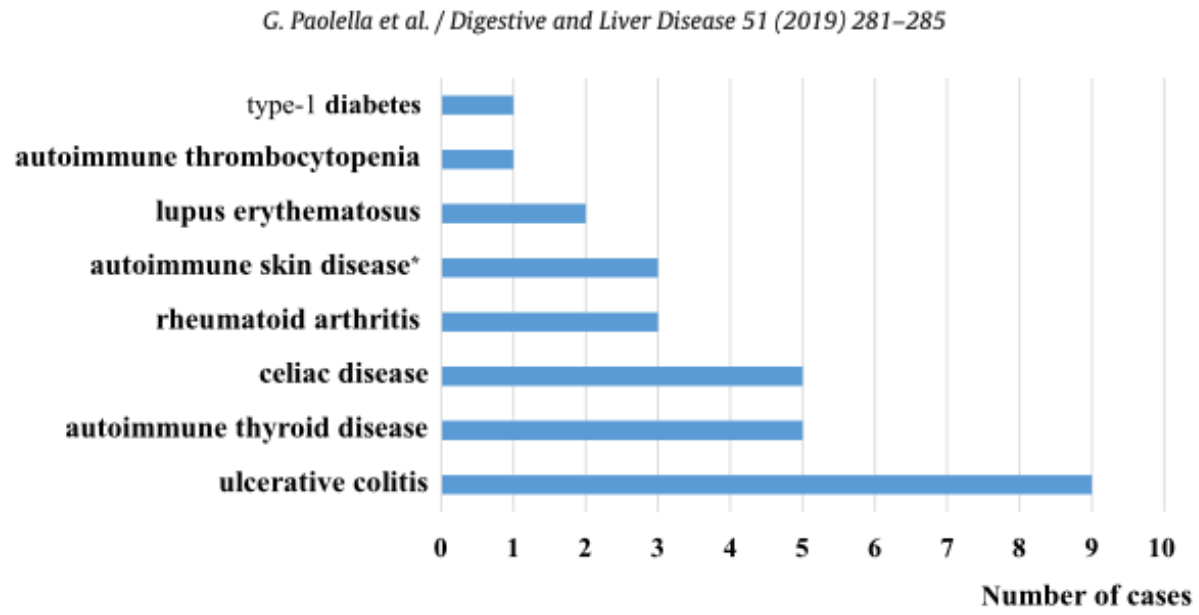
Components	Diagnostic criteria	Salient features	Frequency (%)
AIH/PBC	*AIH Group* (*2 of 3*) [102]: ALT ≥ 5 ULN IgG ≥ 2 ULN or SMA Interface hepatitis *PBC group* (*2 of 3*) [102]: Alk phos ≥ 2 ULN or GGT ≥ 5 ULN AMA Florid duct lesions	AIH predominant phenotype [32] IAIHG score for AIH [32] Alk phos ≥ 2 ULN [46, 82] AMA [32, 82] Bile duct destruction or loss [32, 128]	7–13
AIH/PSC	Predominant AIH [32] AMA-negative [32] Bile duct injury or loss [128] Biliary sclerosis [17, 32]	IAIHG score for AIH [32] Concurrent inflammatory bowel disease possible [17]	6–11
AIH/AC	Predominant AIH [32, 54] AMA-negative [32, 54] Bile duct injury or loss [54, 128] Normal cholangiography [32, 54]	IAIHG score for AIH [32, 54] Probably mixed syndrome including AMA-negative PBC and small duct PSC [54, 128]	5–11 [32, 67]
AIH/AMA-negative PBC	Same as autoimmune cholangitis [56, 63, 66]	IAIHG score for AIH [32]	5–8 [67]
AIH/Small duct PSC	Same as autoimmune cholangitis [69–71]	Poor response to ursodeoxycholic acid [71]	3 [71]
AIH/ASC	Same as AIH with PSC [72, 73]	Affects children [72, 73] Corticosteroid responsive [72]	50 [72]
AIH/IgG4 cholangitis	>5 $IgG4^+$ plasma cells per high power field in liver tissue [78, 80, 81] Abnormal biliary cholangiogram [79]	Corticosteroid responsive [78, 80, 81] Variable serum IgG4 level [80]	Uncertain [78, 80, 81]

OS-extrahepatik immun aracılı hastalıklar

- Tiroid hastalıkları
- Sjogren Hastalığı
- Psoriasis
- Romatoid artrit
- Hemolitik anemi
- Multiple sklerozis
- Temporal arterit
- Membranöz glomerulonefrit

AIH-PBC 'li hastalarda %44

otoimmunitenin mozaikliği



Primary Sclerosing Cholangitis in Childhood

Table 1. Clinical and Laboratory Features of 13 Children With Primary Sclerosing Cholangitis at Time of Diagnosis

Patient	Sex	CIBD	Age at onset of PSC (yr)	Presenting features of PSC	Serum bilirubin (μmol/L)	Alk phos (IU/L)	AST (IU/L)	γ GT (IU/L)	IgG (g/L)	IgM (g/L)	IgA (g/L)	ANF titer (reciprocal)	SMA titer (reciprocal)
1[a]	F	CUC	8	Hepatomegaly	10	181	94	203	11.0	2.10	1.50	Negative	Negative
2	F	CUC	2.17	Hepatomegaly	20	328	123	2360	24.0	5.60	2.10	160	Negative
3	F	CUC	5	Hepatomegaly and pruritus	<10	122	34	38	25.0	2.61	1.44	40	10
4	M	IC	2.33	Hepatomegaly and jaundice	17	1871	197	550	28.5	2.87	3.41	40	Negative
5	F	?	7	Hepatosplenomegaly and fever	12	3930	138	599	37.4	3.40	3.83	1600	160
6	F	?	4	Hepatosplenomegaly and fever	24	1082	190	162	22.3	1.90	1.90	160	40
7	F	CUC	2.42	Hepatosplenomegaly	13	864	352	93	23.3	1.60	2.10	Negative	40
8	M	CUC	2.5	Abnormal liver function tests	9	292	680	299	19.5	2.70	1.60	160	Negative
9	M	IC	13.58	Abnormal liver function tests	15	524	543	318	35.1	2.10	1.60	160	10
10	M	IC	13.83	Abnormal liver function tests	6	508	112	307	35.9	2.26	5.73	Negative	160
11	M	MC	3.67	Hepatomegaly and fever	5	1151	217	286	70.8	2.20	4.90	640	40
12	F	?	12	Jaundice	108	500	218	250	27.3	3.70	2.41	Negative	40
13	F	IC	9.25	Jaundice	328	172	2150	58	62.4	1.38	1.88	640	640

Alk phos, alkaline phosphatase; ANF, antinuclear antibody; AST, aspartate aminotransferase; CIBD, chronic inflammatory bowel disease; CUC, chronic ulcerative colitis; γ GT, γ-glutamyl transpeptidase; IC, indeterminate colitis; Ig, immunoglobulin; MC, microscopic colitis; PSC, primary sclerosing cholangitis; SMA, smooth muscle antibody. Upper limits of normal: Bilirubin, 20 μmol/L; alkaline phosphatase, 300 IU/L; aspartate aminotransferase, 45 IU/L; γ-glutamyl transpeptidase, 45 IU/L; IgG, 16.0 g/L; IgM, 2.1 g/L; IgA, 4.0 g/L. [a] On prednisolone, 5 mg twice daily, at time of diagnosis.

Table 2A
Paediatric series including patients with AIH/SC overlap (ASC). Baseline demographic characteristics and comorbidities.

	Country	Year	Study design	Total number of patients	AIH/SC overlap (ASC)	SDD	IBD	Age (years, median)
El-Shabrawi [10]	UK	1987	Retrospective	13	13	None	10	5
Debray [43]	France	1994	Retrospective, Single-centre	56	2	None	1/2	Not reported
Wilschanski [44]	Canada	1995	Retrospective, multicentre	32	9	None	17/30	13
Floreani [47]	Italy	1999	Retrospective, single-centre	9	37.5% ANA/SMA positive	None	6/9	10 (mean)
Gregorio [6]	UK	2001	Prospective, single-centre	55	27	1	12/27	11.8
Feldstein [48]	USA	2003	Retrospective, single-centre	52	14	None	42/52	14.7
Batres [49]	USA	2005	Retrospective, single-centre	20	Not reported	None	10/20	9.33 (mean)
Miloh [50]	USA	2009	Retrospective, single-centre	47	12	16	59% (50% of ASC patients)	12 (13.5 in over patients)
Deneau [29]	USA	2013	Retrospective, multi-centre	41	12	Not reported	9/12	11.3 (mean)
Rojas [42]	USA	2014	Retrospective, single centre	31 (AIH + overlap patients)	11	None	9/10	13 (mean)
Yoon [57]	Korea	2015	Retrospective, single-centre	13	Not reported	None	13/13	15.0
Tenca [55]	Finland	2015	Retrospective, single-centre	33	15	None	25/33	16
Valentino [56]	USA	2016	Retrospective, single-centre	120	31	24	21/31 (68%)	14.7 (patients in to age 20)
Rodrigues [46]	Brazil	2016	Retrospective, single-centre	134 AIH patients	28	None	1 patient out of 134	10.7
Smolka [58]	Czech republic	2016	Retrospective, single-centre	25	11	None	8/11 ASC 11/14 PSC	15 (14 in ASC pa
Deneau [51]	Europe, North America, Middle and Far East	2017	Retrospective, international	781	260 (33%) (3% LKM1-positive)	98	63%	11.3
Fagundes [59]	Brazil	2017	Retrospective, single-centre	21	0	1	5/21	6.7 (mean)

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Autoimmune sclerosing cholangitis: Evidence and open questions

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ARTICLE INFO

Keywords:
Sclerosing cholangitis
Autoimmune sclerosing cholangitis
Small duct disease
Inflammatory bowel disease
Cholangiography

ABSTRACT

Juvenile sclerosing cholangitis is a rare chronic hepatobiliary disorder characterized by inflammation of the intra- and/or extrahepatic bile ducts, bile duct dilatation, narrowing and obliteration, and, histologically, by inflammatory bile duct damage leading to periductular fibrosis. The diagnosis is based on endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography. In children, it may be associated to a variety of systemic and hepatic conditions: thus, the term "primary" sclerosing cholangitis should be reserved for the rare cases without a known cause. Small duct disease is diagnosed in the presence of histological features diagnostic of sclerosing cholangitis and normal cholangiography. Autoimmune sclerosing cholangitis (ASC) is a form of sclerosing cholangitis with strong autoimmune features overlapping with those of autoimmune hepatitis (AIH). It is a well-recognized nosological entity in paediatrics, where it accounts for the majority of sclerosing cholangitis cases. It is as prevalent as AIH in children, is equally frequent in males and females, half of the patients have concomitant inflammatory bowel disease, virtually all patients have raised immunoglobulin G levels and positive anti-nuclear and/or anti-smooth muscle antibodies. Half of the ASC patients respond well to standard immunosuppressive treatment for AIH with the addition of ursodeoxycholic acid, but the transplant rate is higher than in AIH, and post-transplant recurrence is frequent. A number of open questions remain: are ASC and AIH distinct entities or different manifestations of the same condition? What is the role of histology? Is small duct disease a specific entity? What is the relationship between ASC and adult primary sclerosing cholangitis? What is the role of inflammatory bowel disease? In addition, validated diagnostic criteria for ASC are needed.

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

- AIH n= 260 (33%)
- SDD n= 98 (12%)
- IBD n=571 (73%)

  Kolanjiokarsinoma n=8 (15-18 y)
- Nakilsiz 5-yıllık sağ kalım LD PSC ve SDD gruplarında benzer 87% ve 88%.
- AIH eşlik eden ve etmeyen gruplar arasında 5 yıllık olaysız sağ kalım aynı ancak overall sağ kalım belirtilmemiş.
- ASC ve OS sıklığı düşük. … tanı kriteri/IS tedavi

Hepatology 66 (2017) 518–527

Örtüşme sendromları- sıklık

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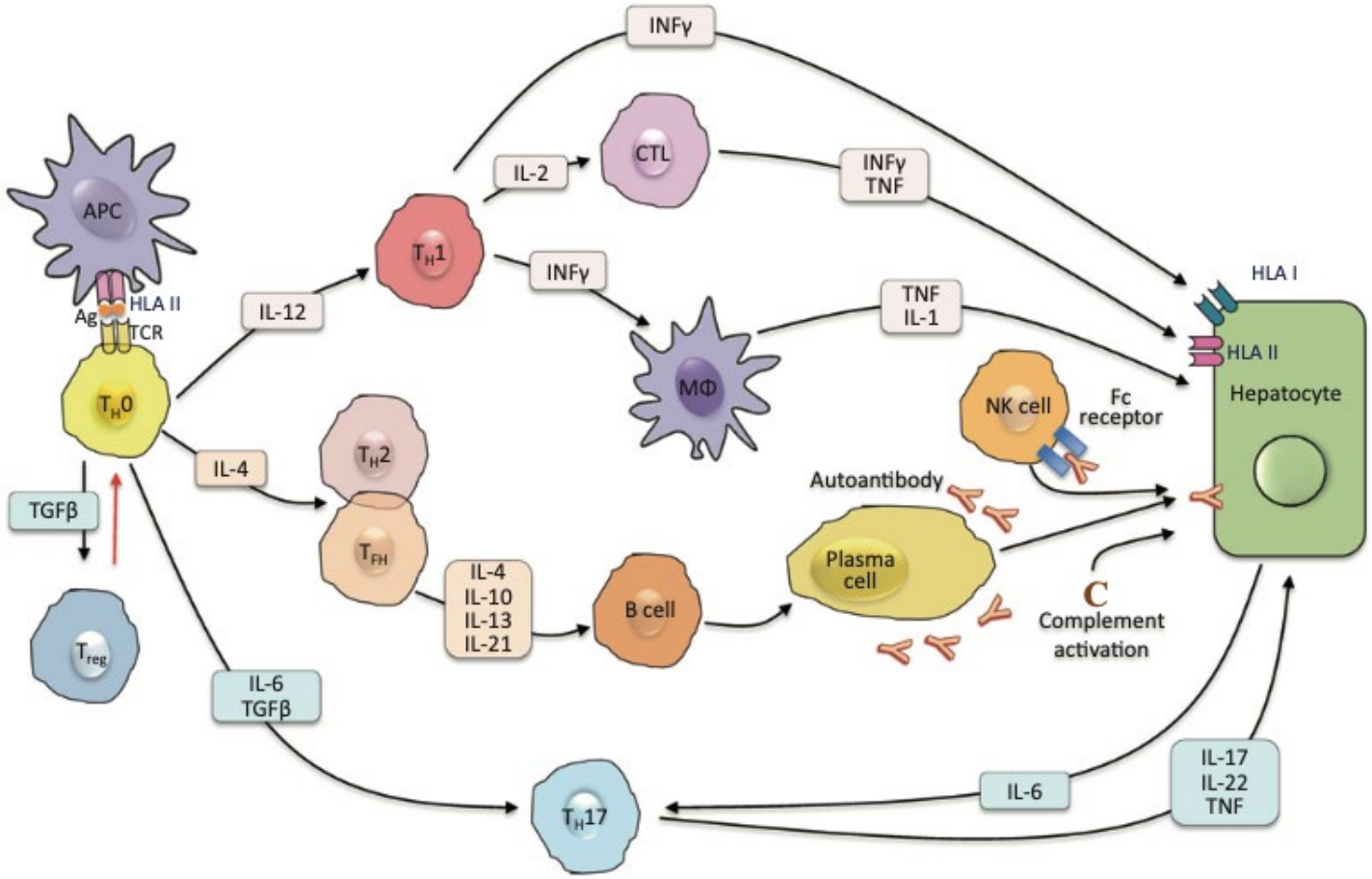
Çocukluk çağı OS özellikleri

1. 50% of the patients with ASC are male.
2. Abdominal pain, weight loss, and intermittent jaundice, are frequent presenting symptoms in both ASC and AIH-1.
3. IBD affects about 45% of children with ASC, and about 20% of those with AIH.
4. Virtually all ASC patients are seropositive for ANA and/ or SMA.
5. 90% of children with ASC have greatly increased serum IgG levels.
6. Standard liver function tests do not help in discriminating between AIH and ASC at presentation.
7. The IAIHG scoring systems do not discriminate between AIH and ASC.
8. pANCA is present in 75% of patients with ASC in comparison with 45% of patients with AIH type 1 and 10% of those with AIH type 2.

Patogenez


INFγ
IL-2
CTL
INFγ
TNF
APC
HLA II
Ag
TCR
IL-12
T_H1
INFγ
TNF
IL-1
MΦ
HLA I
HLA II
Hepatocyte
NK cell
Fc
receptor
T_H0
IL-4
T_H2
TGFβ
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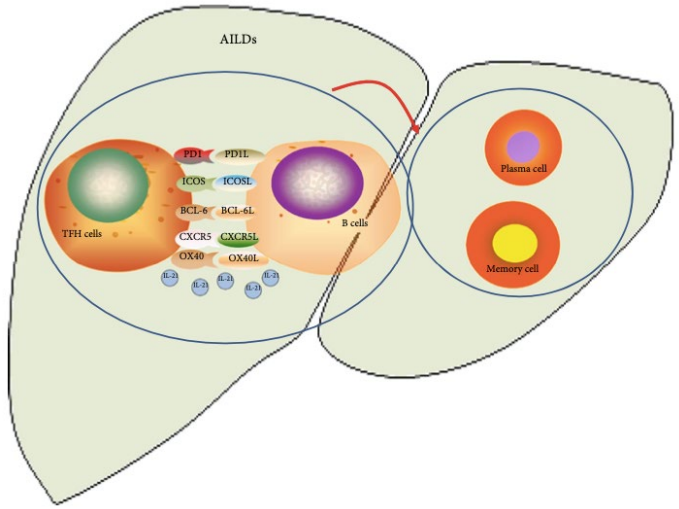
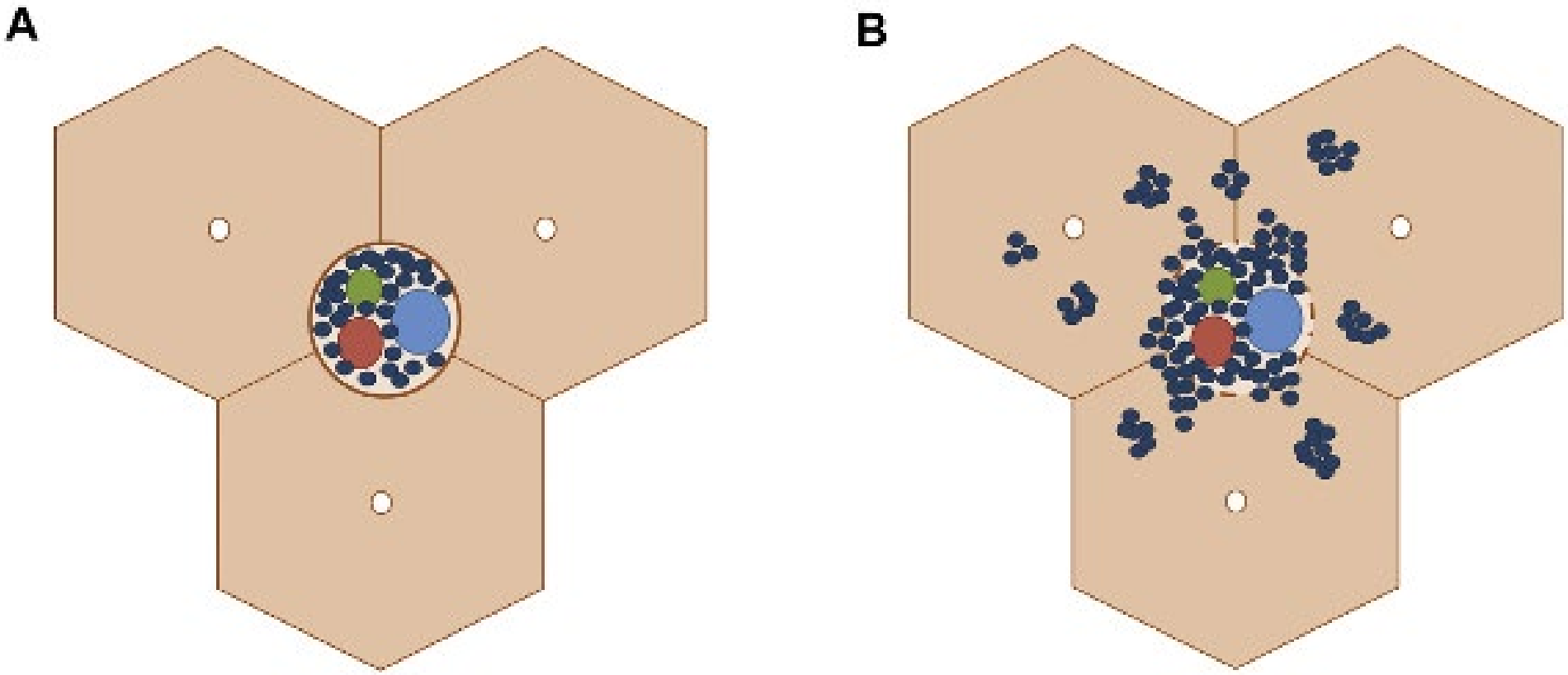
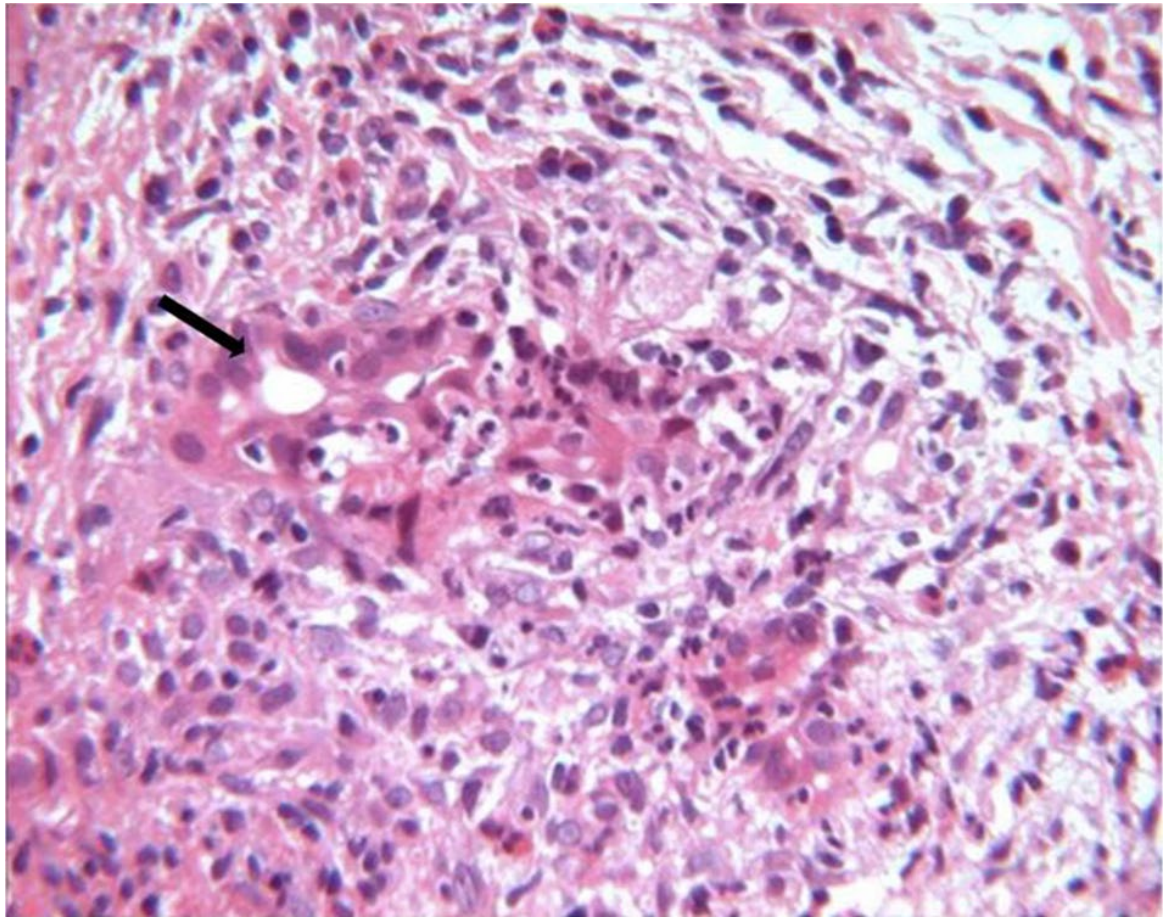
IL-17
IL-22
TNF


AILDs
PD1
PD1L
ICOS
ICOSL
BCL-6
BCL-6L
CXCR5
CXCR5L
OX40
OX40L
TFH cells
B cells
Plasma cell
Memory cell

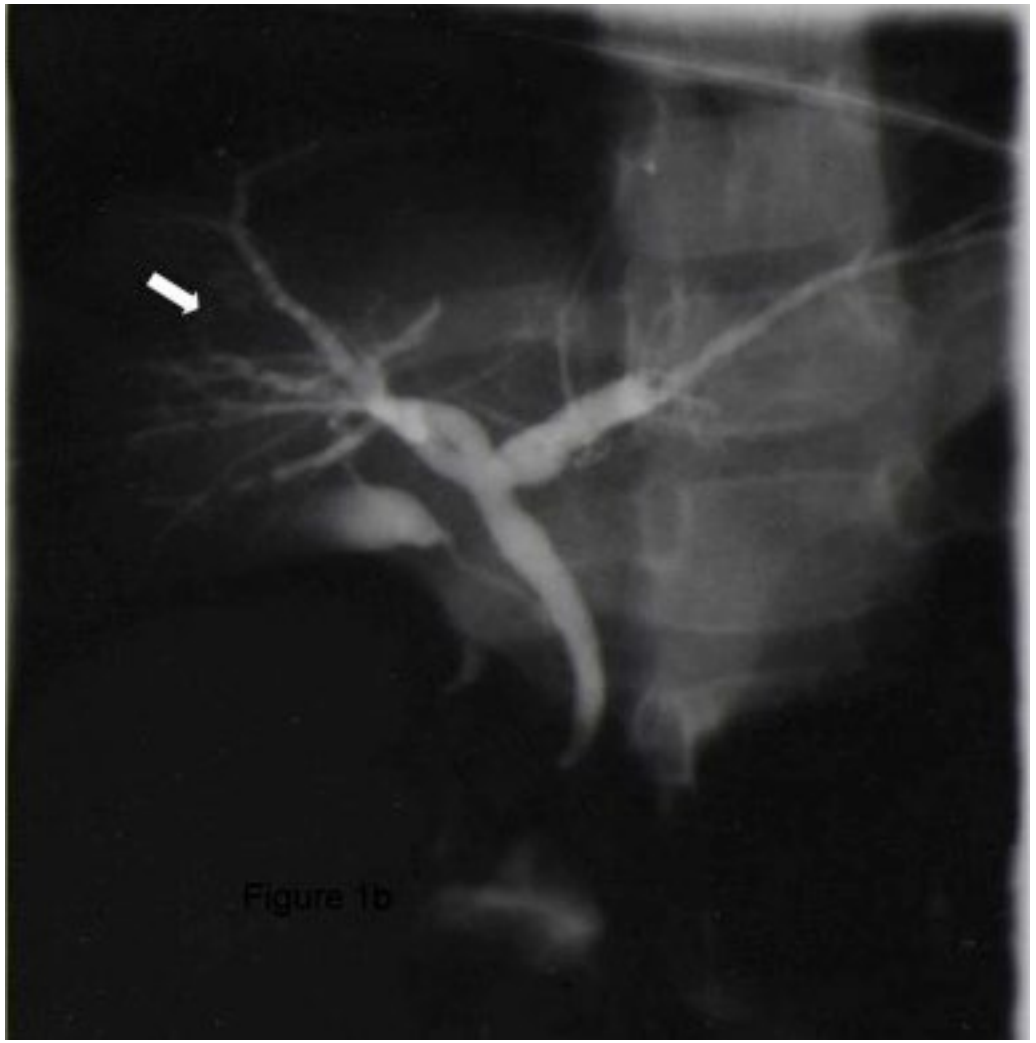
Patogenez



AIH-ASC



limiting plate uzanan ve parankimi bozan portal lenfosit ve plasma hücre infiltrasyonu-safra kanal hasarı



ERCP'de multiple striktür

Patogenez

Table 1 HLA associations of AIH presented in the previous literature

Disease	HLA type	Country/geographic area	Key reference
AIH type 1 in adults	B08*	Italy, northern Europe, northern America	7, 9
	DRB1*03	England, Italy, northern Europe, Brazil, Venezuela	7, 9, 10, 11, 12, 13
	DRB1*04:01	England, northern America, northern Europe	9, 10, 13
	DRB1*04:04	Mexico	14
	DRB1*04:05	Argentina, Japan	15, 16
	DRB1*13	Venezuela, Brazil	11, 12
AIH type 1 in children	B08*	England, Germany	8, 17, 18
	DRB1*03	France, Canada, England, Brazil, Germany	6, 8, 12, 18, 19
	DRB1*13	France, Germany, Canada, Brazil, Argentina	6, 12, 15, 19
AIH type 2 in adults and children	DRB1*03	France, Canada	20
	DRB4	Brazil	12
	DRB1*07	Germany, Brazil	12, 21
	DRB1*15	Germany	21
	DQB1*02	Brazil, France, Canada	12, 20

AIH = Autoimmune hepatitis; HLA = Human leucocyte antigen.

HLA PROFILE PREDICTS SEVERITY OF AUTOIMMUNE LIVER DISEASE IN CHILDREN OF EUROPEAN ANCESTRY

Background and Aims: Genetic predisposition to autoimmune hepatitis (AIH) in adults is associated with possession of HLA class I (*A*01*, *B*08*) and class II alleles (*DRB1*03*, *–04*, *–07* or *–13*), depending on geographic regions. Juvenile autoimmune liver disease (AILD) comprises AIH-1, AIH-2 and autoimmune sclerosing cholangitis (ASC), which are phenotypically different from their adult counterparts. We aimed to define the relationship between HLA profile and disease course, severity and outcome in juvenile AILD.

Methods: We studied 236 children of European ancestry [152 females (64%), median age 11.15 years, range 0.8–17], including 100 AIH-1, 59 AIH-2 and 77 ASC. The follow up period was from 1977 to June 2019 (median 14.5 years). Class I and II HLA genotyping was performed using PCR/sequence specific primers.

Results: HLA *B*08*, *-DRB1*03* and the *A1-B8-DR3* haplotype impart predisposition to all three forms of AILD. Homozygosity for *DRB1*03* represented the strongest risk factor (8.8). HLA *DRB1*04,* which independently confers susceptibility to AIH in adults, was infrequent in AIH-1 and ASC, suggesting protection, and *DRB1*15* (DR15) was protective against all forms of AILD. Distinct HLA class II alleles predispose to the different subgroups of juvenile AILD: *DRB1*03* to AIH-1, *DRB1*13* to ASC and *DRB1*07* to AIH-2. Possession of homozygous *DRB1*03* or of *DRB1*13* is associated with fibrosis at disease onset, and possession of these two genes in addition to *DRB1*07* is associated with a more severe disease in all three subgroups.

Conclusion: Unique HLA profiles are seen in each subgroup of juvenile AILD. HLA genotype might be useful in predicting responsiveness to immunosuppressive treatment and course.

Hepatology. 2021 October ; 74(4): 2032–2046

Human leucocyte antigens *B*08*, *DRB1*03* and *DRB1*13* are significantly associated with autoimmune liver and biliary diseases in Finnish children

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Keywords
Autoimmune biliary disease, Autoimmune liver disease, Cholangitis, Hepatitis, Human leucocyte antigen

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Received
15 June 2016; revised 5 September 2016; accepted 17 October 2016.

DOI:10.1111/apa.13641

ABSTRACT

Aim: The human leucocyte antigen (HLA) allele and haplotype frequencies of the Finnish population are unique because of the restricted and homogenous gene population. There are no published data on HLA genotype associations in paediatric autoimmune liver diseases in Scandinavia. This study characterised the HLA genotypes of children with autoimmune liver or biliary disease in Finland.

Methods: The study cohort comprised 19 paediatric patients (13 female) aged three years to 15 years treated for autoimmune liver or biliary disease at the Children's Hospital, Helsinki University Hospital, between 2000 and 2011, and followed up for four years and three months to 14.6 years. We genotyped HLA-B and HLA-DRB1 in the children, and the HLA antigen frequencies were compared with 19 807 records from the Finnish Bone Marrow Donor Registry.

Results: All paediatric patients with autoimmune liver or biliary disease had either autoimmune HLA haplotype *B*08;DRB1*03* or *DRB1*13*. These were significantly more common among patients with autoimmune hepatitis, primary sclerosing cholangitis and autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome than the Finnish control population. HLA *RB1*04* was not found in the study cohort.

Conclusion: Our study found that *B*08*, *DRB1*03* and *DRB1*13* were significantly associated with autoimmune liver and biliary diseases in Finnish paediatric patients.

Table 2b

Paediatric series including patients with AIH/SC overlap (ASC). Baseline biochemical, histological and serological characteristics, treatment and outcome.

	Biochemical cholestasis at presentation	Interface hepatitis at diagnosis	Periductular fibrosis at diagnosis	ANA positivity	SMA positivity	ANCA positivity	Treatment	Outcome
El- Shabrawi [10]	Elevated GGT in 12/13	4/13	12/13	9/13	9/13	Not reported	Prednisolone ± azathioprine in 12 patients	No death or LT reported on a median follow up of 2.5 years
Debray [43]	Elevated GGT in 2/2	Not reported	Not reported	2/2	2/2	Not reported	Not reported	Estimated 10-year survival rate 86%
Wilschanski [44]	16/30 (AP only)	5/30	Not reported	14/30	19/30	9/23	Immunosuppression in 6 of 9 ASC patients	9/30 listed for LT (mean follow up 3.8 years)
Floreani [47]	Not reported	50%	29%	4/10 ANA and/or SMA-positive		9/9	UDCA 600 mg/m^2 in all patients, prednisone, azathioprine in 8/9 patients	10-year survival: 100%
Gregorio [6]	20/27 (combined AP and GGT) AP	9/26	2/26	20/27	20/27	20/27	Prednisone/azathioprine/UDCA (second line: cyclosporin, penicillamine, colchicine)	Estimated 10 years transplant-free survival: 65% Survival rate 100% after a median follow-up of 7 years
Feldstein [48]	49/52 elevated GGT levels; 39/52 elevated AP levels	14/52 (12/14 patients diagnosed as overlap)	17/52	22/52	15/52	37/52	11/14 steroids ± azathioprine ± UDCA 1/14 UDCA 2/14 no treatment	Median survival free of transplant: 12.7 years
Batres [49]	Not reported	9/20	5/20	5/17	4/13	12/19	Not reported	45% required LT after a median time of 7.7 years
Miloh [50]	GGT elevated in all patients; AP increased in 38/47			5/9	7/9	10/52 (pANCA)	UDCA 20–30 mg/kg/day (+steroids and/or azathioprine in 9/12 overlap patients)	9-year transplant-free survival in overlap: about 60%
Deneau [29]	All (inclusion criterion)	Not reported	Not reported	7/9	2/6	8/10	Not reported	5-year survival rate with native liver: 90%
Rojas [42]	Not reported	9/11 (chronic hepatitis)	4/11	2/8	2/7	0/4	Not reported	2/11 patients underwent LT (follow-up time not reported)
Yoon [57]	GGT elevated in all tested patients (12/12)	0/2	2/2	Not reported	Not reported	Not reported	UDCA, immunosuppression for concomitant IBD	5/13 had LT, cancer or death over a median follow-up of 11.4 years
Tenca [55]	Not reported	15/15	5/15 (defined as "PSC alterations")	11/14 ANA and/or SMA positive		6/11	UDCA 20 mg/kg/day in 91%, steroids and/or azathioprine in 12/15 overlap cases	
Valentino [56]	Not reported	Not reported	88% (histopathology consistent with PSC)	10/17	11/16	No reported	57% on steroids one year after diagnosis	5-year survival with native liver: 89% (whole cohort)
Rodrigues [46]	Not reported	27%	Absence of biliary changes	18/28	20/28	Not reported	Steroids ± azathioprine	89% 5- and 10-year survival rate
Smolka [58]	GGT elevated in all patients, AP in 7/25			6/11	2/11[a]	11/11 ASC 11/14 PSC	UDCA 15–20 mg/kg/day, + steroids in 10/11 ASC patients (+azathioprine in 3 ASC patients)	100% 10-year survival in ASC 70% 10-year survival in PSC
Deneau [51]		Not reported	Not reported	62%	61%	74%	81% UDCA, 100% immunosuppressive treatment (no details available)	70% 10-year survival with native liver
Fagundes [59]	GGT and AP elevated in all	Not reported	2/15	3/21	Not reported	3/21	20/21 UDCA 15 mg/kg/day, 5/21 steroids ± azathioprine for IBD	2/21 died, 4/21 underwent LT over a mean follow-up of 4.8 years

Biliary features in liver histology of children with autoimmune liver disease

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Received: 17 January 2019 / Accepted: 20 April 2019 / Published online: 8 May 2019

Abstract

Objectives and study Various degrees of biliary changes are considered to be part of the histological picture of children with pediatrics autoimmune liver disease (AILD), but the literature is scarce and confusing. We aimed to describe the characteristics of children with AILD (autoimmune hepatitis, AIH, and autoimmune sclerosing cholangitis, ASC) focusing on the prevalence and type of biliary abnormalities on initial biopsy to see whether ASC was predictable on histological ground.

Methods The files of children diagnosed with AILD were reviewed. The Ishak score was used to grade inflammation and fibrosis on biopsy; a biliary score was built to grade bile duct injury. Demographic, laboratory and histological features at diagnosis were reported and compared between the two groups (AIH vs ASC).

Results Forty-one patients were diagnosed with AIH ($n=24$), ASC ($n=13$) and PSC ($n=4$) between 2009 and 2018. Twenty-nine patients [$F=76\%$, AIH = 20, ASC = 9, median age at diagnosis 11.7 (range 2.2–17.8)] were included in the study; 12 (4 with PSC) were excluded. Prevalence of inflammatory bowel disease was higher in ASC group (56% vs 10% in AIH, $p<0.05$). On histology 17% had cirrhosis. The grade of biliopathy with AILD was moderate in 72% and severe in 31%, and overall more prominent in ASC ($p=0.031$). The inflammation of the bile ducts was classified as "multifocal" or "diffuse" mainly in ASC patients (89% vs 45% in AIH, $p=0.043$). Periductular fibrosis was reported in 52% of AILD patients, with a higher mean score in ASC group ($p<0.05$). However, ductular reaction, biliary metaplasia and granulomatous cholangitis were equally reported in AIH and ASC, providing no clear-cut for the distinction of the two entities in the global histological evaluation.

Conclusions Majority of patients with pediatrics AILD have "moderate" or "severe" features of biliopathy; AIH and ASC are not easily distinguishable on histological ground at diagnosis, and therefore, the cholangiogram remains the only effective tool to differentiate patients with AIH from those with ASC. Further prospective studies are needed to better define histological biliary features in AILD, assess if the biliopathy responds to immunosuppressive treatment and evaluate its impact on long-term outcome.

Keywords Autoimmune hepatitis · Autoimmune sclerosing cholangitis · Overlap syndrome · Children

	All pts ($n=29$)	AIH ($n=20$)	ASC ($n=9$)	p value
Age (years)	11.7 (2.2–17.8)	11.7 (2.2–17.8)	14.3 (4.3–16.1)	0.370
Female prevalence	22 (76%)	16 (80%)	6 (67%)	0.642
AST (nv: < 50 IU/l)	330 (66–2037)	452 (66–2037)	155 (85–875)	**0.049**
ALT (nv: < 50 IU/l)	285 (71–2183)	671 (71–2183)	156 (116–890)	**0.049**
GGT (nv: < 40 IU/l)	158 (10–655)	110 (10–594)	287 (48–655)	**0.028**
Total bilirubin (nv: < 1 mg/dl)	2.3 (0.3–20.8)	3.0 (0.3–20.8)	1.2 (0.8–6.5)	0.205
Conjugated bilirubin (mg/dl)	1.6 (0.1–16.2)	1.9 (0.1–16.2)	0.4 (0.1–4.3)	0.155
ALP (nv: < 350 IU/l)	268 (107–1209)	265 (107–1209)	285 (173–817)	0.719
ALP/AST ratio	1.2 (0.1–9,3)	0.4 (0.1–5)	2.0 (0.3–9.3)	**0.047**
INR (nv: 0.8–1.2)	1.3 (0.9–2.9)	1.3 (1–2.9)	1.1 (0.9–1.4)	0.071
IgG (g/dl)	1.8 (0.6–4.0)	1.9 (0.6–4.0)	1.7 (1.3–3.4)	0.754
IgG > ULN, n (%)	19 (65%)	13 (65%)	6 (66%)	1.00
ANA ≥ 1:20	24 (83%)	15 (75%)	9 (100%)	0.152
SMA ≥ 1:20	21 (72%)	14 (70%)	7 (78%)	1.00
LKM-1 ≥ 1:10 (or LC1 positive)	5 (17%)	5 (25%)	0	0.152
pANCA positive	11 (38%)	6 (30%)	5 (56%)	0.231
Associated IBD	7 (25%)	2 (10%)	5 (56%)	**0.016**

- Tip1 AIH hastaların 1/3.nde kolanjiogram anormal—ASC
- LKM pozitifliği hiç bir ASC hastasında pozitif değil
- Ishak skorlamasına göre inflamasyon ve nekroz, fibrosis/siroz evreleri arasında anlamlı fark yok,
- Ancak

Long-term outcomes of pediatric-onset primary sclerosing cholangitis: A single-center experience in Japan

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Aim: Primary sclerosing cholangitis (PSC) is very rare in Japan. Although a large-scale cohort study of 781 pediatric-onset PSC patients in Europe and North America showed that the 5-year survival with native liver was 88%, the long-term outcomes of pediatric-onset PSC in Japan are unknown. Here, we evaluated the clinical outcomes of pediatric-onset PSC in Japan.

Methods: We carried out a retrospective cohort study with a medical records review of pediatric PSC patients diagnosed between 1986 and 2017 at a single center. The PSC diagnoses were based on cholangiography, liver histology, and biochemical findings. The patients' survival was analyzed using the Kaplan–Meier method. Prognostic factors were determined by univariate and multivariate analyses using the Cox proportional hazards regression model.

Results: We identified 39 pediatric-onset PSC patients (22 boys, 17 girls). The median age at diagnosis was 9 years (interquartile range 6.0–13.5 years). The median follow-up period was 5.5 years (interquartile range 3.4–8.7 years). The phenotypes of PSC-autoimmune hepatitis, PSC-inflammatory bowel disease, and small-duct PSC were diagnosed in 13 (33.3%), 36 out of 38 (94.8%), and three (7.7%) patients, respectively. The 5-year liver transplantation-free survival of the whole cohort was 93.5%. Nine patients underwent liver transplantation, and four of these nine cases resulted in death. Both the univariate and multivariate analyses showed that the phenotype of "PSC-autoimmune hepatitis overlap" was an independent poor prognostic factor.

Conclusions: The overall survival of pediatric-onset PSC in Japan was comparable to those in Western countries. The phenotype of PSC-autoimmune hepatitis was identified as a prognostic factor associated with a poorer long-term outcome.

Key words: autoimmune hepatitis, autoimmune sclerosing cholangitis, inflammatory bowel disease, liver transplantation, overlap syndrome

Hepatology Research 2019; **49**: 1386–1397

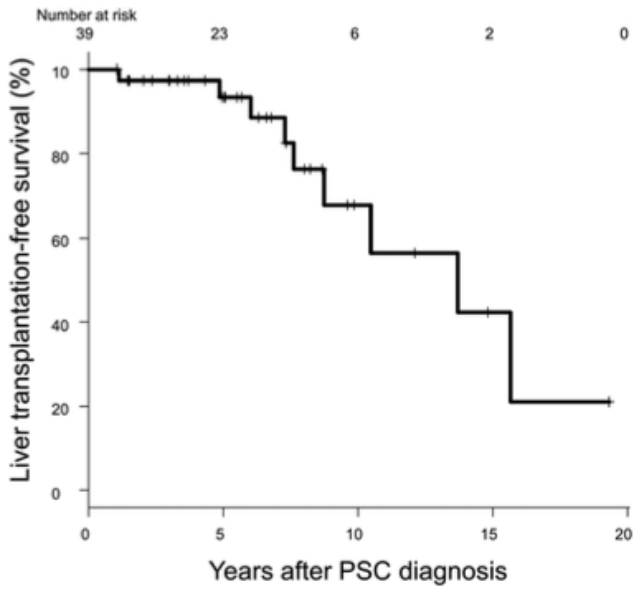

Figure 2 Liver transplantation-free survival of 39 patients with pediatric-onset primary sclerosing cholangitis (PSC) at a single center in Japan. The 5-year survival rate was 93.5%.

Table 2 Outcomes during follow-up for pediatric primary sclerosing cholangitis

	PSC $n = 26$		PSC-AIH overlap $n = 13$		P-value
Liver transplantation	2	(7.7)	7	(53.8)	<0.01
Esophagogastric varices	3	(11.5)	9	(69.2)	<0.01
Recurrent bacterial cholangitis	2	(7.7)	2	(15.4)	0.59
Hepatopulmonary syndrome	2	(7.7)	3	(23.1)	0.07
Cholangiocarcinoma	0	(0)	0	(0)	
Colorectal carcinoma	0	(0)	0	(0)	
Dead	0		4	(15.4)	<0.01

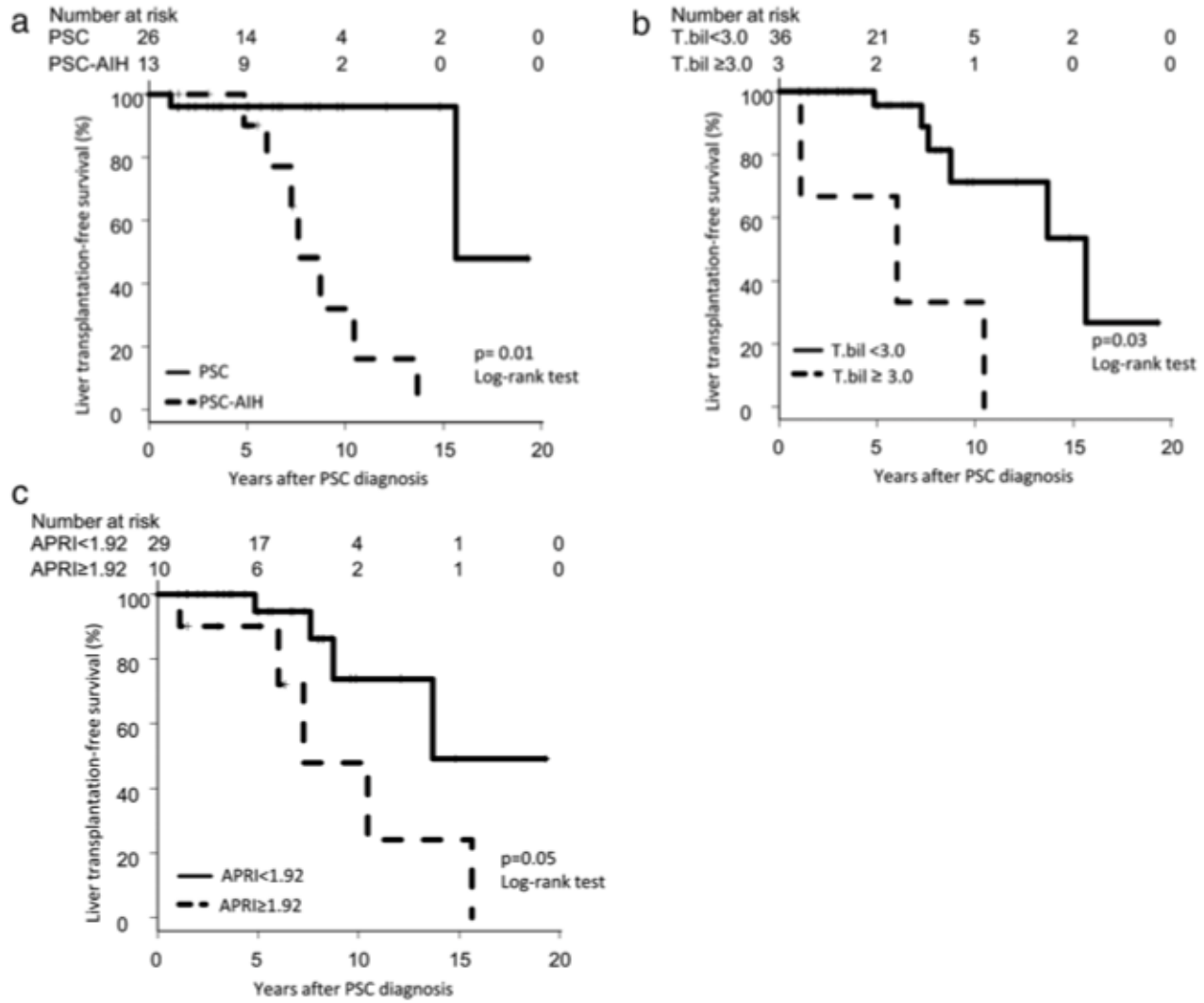

Figure 3 Factors associated with survival free of liver transplantation in Japanese patients with pediatric-onset primary sclerosing cholangitis (PSC). Kaplan–Meier curve suggesting the time to the development of survival free of liver transplantation (a) in pediatric-onset PSC patients with the phenotype PSC (black line) or PSC-autoimmune hepatitis (AIH) overlap (dashed line; log–rank test; $P = 0.01$); (b) in patients with total bilirubin (T. bil) at diagnosis <3.0 mg/dL (black line) or ≥3.0 (dashed line; $P = 0.03$); and (c) in the patients with an aspartate aminotransferase to platelet index (APRI) at diagnosis <1.92 (black line) or ≥1.92 (dashed line; $P = 0.05$).

Seamless Management of Juvenile Autoimmune Liver Disease: Long-Term Medical and Social Outcome

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Objectives To report baseline features and long-term medical/social outcomes of juvenile autoimmune liver disease, including autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC), managed in a single tertiary center.

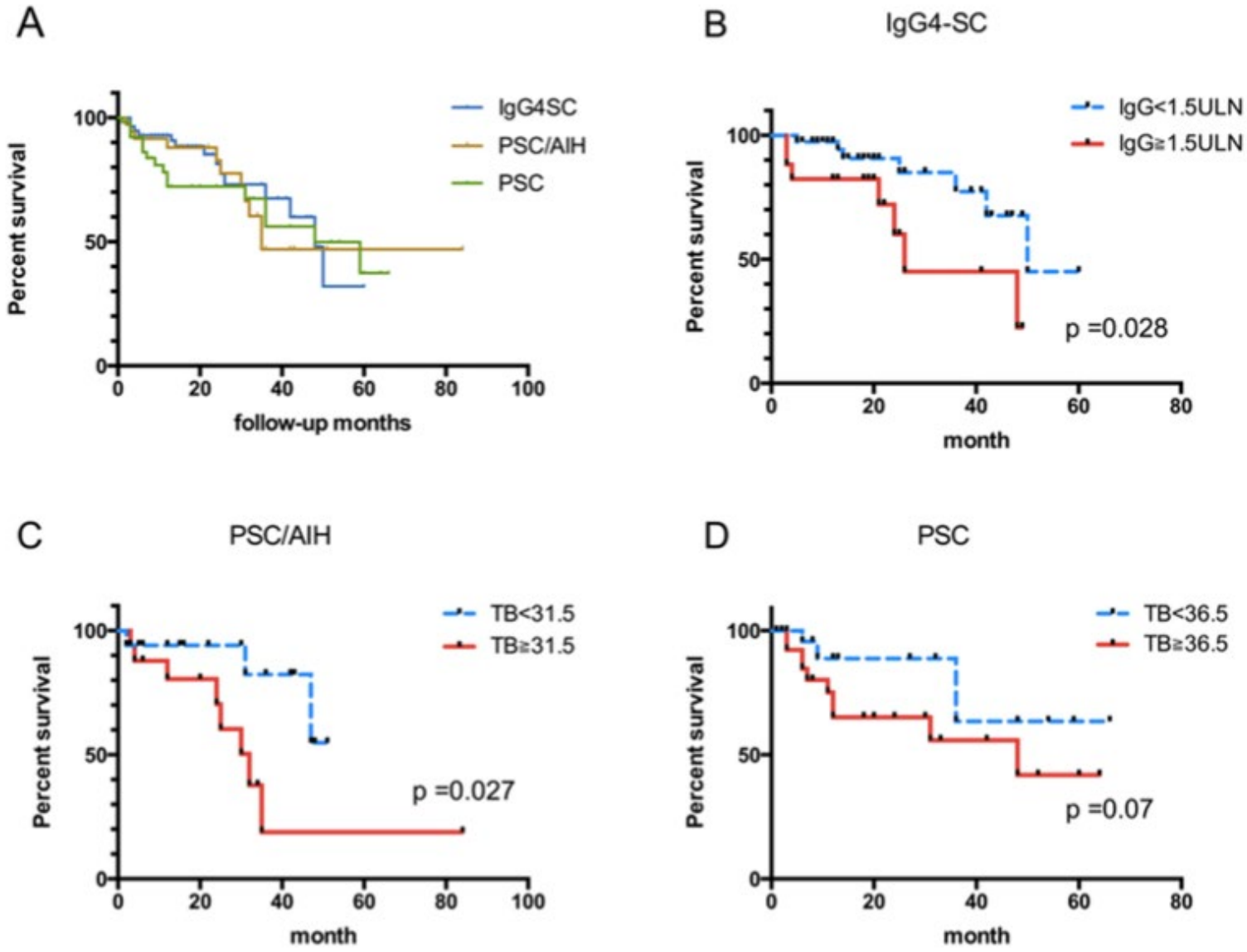
Study design Retrospective study of children diagnosed in 2000-2004 with AIH/ASC followed up to date. Patients with abnormal cholangiogram were classified as ASC. Presentation and outcome features were compared.

Results Eighty-three children were included (42 female, median age 12.1 years [8.5-14.1 years], AIH = 54, ASC = 29). Most (65%) had antinuclear and/or anti-smooth muscle autoantibodies; 6% presented with acute liver failure; 29% had histologic evidence of cirrhosis. The 1999 and simplified International Autoimmune Hepatitis Group criteria failed to diagnose up to 26% of patients with AIH and 48% with ASC, and the proposed the European Society for Pediatric Gastroenterology, Hepatology and Nutrition criteria were accurate. Response to treatment was excellent with 95% achieving normal transaminase levels. During follow-up, 31% had at least 1 relapse episode; 3 patients with AIH developed cholangiopathy and 5 patients with ASC developed progressive bile duct injury. At last follow-up (median of 14.5 years, 10.4-16.8), 99% were alive, 11 underwent transplantation and 1 is listed for transplant. Five-, 10-, and 15-year transplant-free survival rates were 95%, 88%, and 83%; patients with ASC and those relapsing being more likely to require transplant. Social outcome was excellent with 93% in employment/education.

Conclusions Seamless management of juvenile autoimmune liver disease leads to excellent clinical and social outcomes. Despite good response to immunosuppressive treatment, patients with ASC have a worse prognosis than those with AIH. Diagnostic models developed for adults are unsatisfactory to correctly diagnose juvenile autoimmune liver disease. (*J Pediatr* 2020;218:121-9)

Comparative clinical characteristics and natural history of three variants of sclerosing cholangitis: IgG4-related SC, PSC/AIH and PSC alone

There is increased interest and recognition of the clinical variants of Sclerosing Cholangitis (SC) namely IgG4-SC, PSC/AIH overlap and PSC. For most Centers, the characteristic of IgG4-SC has not been thoroughly clinically compared with other sclerosing cholangitis variants. Further there are relatively few PSC/AIH overlap patients and the clinical outcome is not well characterized, especially for the PSC/AIH overlap syndrome. Our objective herein is to clarify the differences and similarities of the natural history of IgG4-SC, the PSC/AIH overlap and PSC alone. We also place in perspective the diagnostic value of serum IgG4 for IgG4-SC and investigate biomarkers for predicting the prognosis of sclerosing cholangitis. In this study, we took advantage of our large and well-defined patient cohort to perform a retrospective cohort study including 57 IgG4-SC, 36 PSC/AIH overlap patients, and 55 PSC patients. Firstly, as expected, we noted significant differences among immunoglobulin profiles and all patients exhibited similar cholestatic profiles at presentation. Cirrhotic events were found in 20 of total 57 IgG4-SC, 15 of 36 PSC/AIH overlap, and 18 of 55 PSC patients. Serum IgG4 was elevated in 92.65% of IgG4-SC patients with an 86% sensitivity and 98% specificity for diagnosis. IgG4-SC patients had a better treatment response at 6-month and 1-year than PSC/AIH patients, while the latter responded better with steroids than PSC patients. Importantly the adverse outcome-free survival of IgG4-SC patients was reduced, unlike earlier reports, and therefore similar to the PSC/AIH overlap syndrome. Serum IgG and total bilirubin were useful to predict long-term survival of IgG4-SC and PSC/AIH, respectively. In conclusion, serum IgG4 ≧ 1.25 ULN shows an excellent predictability to distinguish IgG4-SC among SC patients. IgG4-SC appears to be immune-mediated inflammatory process, while PSC/AIH overlap more tends to be cholestatic disease.


A
IgG4SC
PSC/AIH
PSC
Percent survival
follow-up months
B
IgG4-SC
IgG<1.5ULN
IgG≥1.5ULN
p =0.028
month
C
PSC/AIH
TB<31.5
TB≥31.5
p =0.027
month
D
PSC
TB<36.5
TB≥36.5
p =0.07
month

The prognostic values of baseline features for adverse outcomes-free survival in PSC/AIH patients.

	Univariate			Multivariate		
	Relative risk	95% CI	p	Relative risk	95% CI	p
IgG ≧ 18.3	1.14	1.01–1.28	0.03	1.19	0.99–1.43	0.06
IgM ≧ 2.6	1.64	1.06–2.54	0.03			
IgA ≧ 2.1	1.05	0.51–2.16	ns			
IgG4 ≧ 0.314	1.8	0.38–8.47	ns			
IgG/IgG4 ≦ 0.02	0.99	0.96–1.02	ns			
CRP ≧ 8	1.04	0.95–1.15	ns			
Alb ≦ 39	0.86	0.75–0.99	0.04	1.15	0.9–1.45	0.26
Glb ≧ 35.4	1.07	0.97–1.18	ns			
TB ≧ 31.5	1.02	1–1.04	0.01	1.03	1–1.06	0.03
DB ≧ 21.7	1.01	1–1.02	ns			
ALT ≧ 108	1	1–1	ns			
AST ≧ 125	1	1–1.01	ns			
AKP ≧ 316	1	1–1.01	ns			
GGT ≧ 229	1	1–1	ns			
WBC ≧ 5.14	1.18	1–1.39	0.05			
PLT ≧ 194.5	1	0.99–1.01	ns			
APRI ≧ 1.87	1.07	0.9–1.27	ns			
FIB-4 ≧ 2.78	1.06	0.84–1.32	ns			
E% ≧ 1.2	0.56	0.2–1.58	ns			

E%, eosinophile percentage; ns, not significant; CI, confidence interval; P valu
tive risk were calculated by stepwise Cox regression analysis.

Take-home messages

- Serum IgG4 ≧ 1.25 ULN are recommended for prediction of IgG4-SC.
- The clinical outcome of IgG4-SC is not as benign as once believed and is similar to that of the PSC/AIH overlap.
- Corticosteroids are effective for the PSC/AIH overlap for short-term responses but have no or little benefit for long-term prognosis.
- High serum IgG and total bilirubin at presentation are predictive of poor outcomes for IgG4-SC and PSC/AIH overlap.

Bu çalışmaların gösterdikleri

- ASC AİH nadir değil
- AIH en çok eşlk eden hastalık ASC
- Hastaların yarısında IBH mevcut
- Serum IgG yüksek
- Otoimmun karaciğer serolojisi AIH tip 1, SMA pozitif
- Standart İS tedaviye yanıt oranı %50

Autoimmune Hepatitis and Autoimmune Hepatitis Overlap With Sclerosing Cholangitis: Immunophenotype Markers in Children and Adolescents

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ABSTRACT

Objective: The pathophysiology of autoimmune hepatitis (AIH) may involve the activation of immune cells and changes in the expression of cellular markers. The aim of the present study was to characterize the immunophenotype markers of lymphocytes and monocytes in the peripheral blood of children and adolescents with type 1 AIH and AIH overlap with sclerosing cholangitis (overlap syndrome [OS]).

Methods: This is a cross-sectional study of 20 children and adolescents diagnosed with type 1 AIH and 19 with OS. Fifteen healthy subjects were included as controls. Flow cytometric analysis was used to identify markers of inflammation and autoimmunity.

Results: The total number of $CD4^+$ T cells was higher in the AIH patients compared with the controls. The number of $CD4^+$ T cells expressing CCR3 and CD28 was higher in the AIH group than in the control group. CD45RO was more highly expressed in the AIH group, whereas CD45RA was more highly expressed in the OS group. In regard to $CD8^+$ T lymphocytes, the CCR3 expression was higher in both groups of patients. Patients with OS had the highest expression of CD45RA and CD25. In monocytes, human leukocyte antigen DR (HLA-DR) was less expressed in both groups of patients.

Conclusions: Complex phenotype features may be involved in the pathophysiology of AIH, accounting for changes in immune system regulation mechanisms. In conclusion, even after good response to treatment, patients still have immune activity signals at the cellular level.

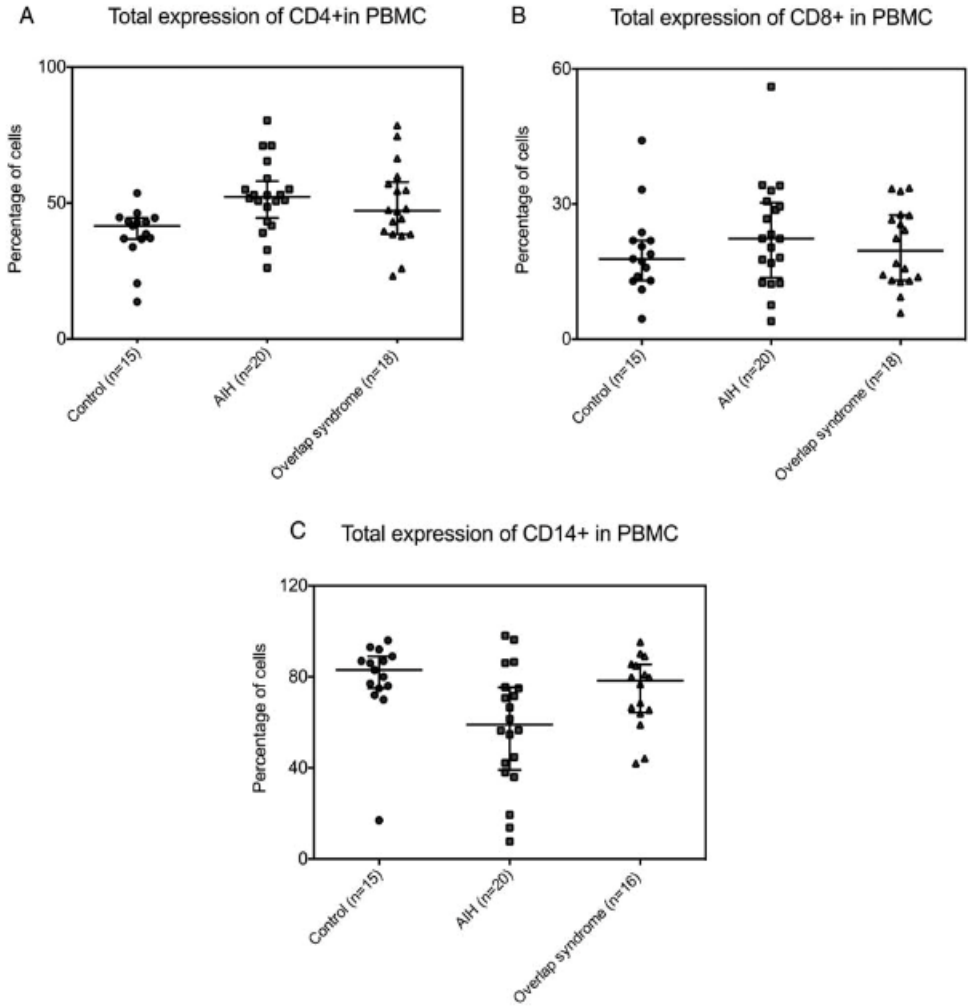
What Is Known

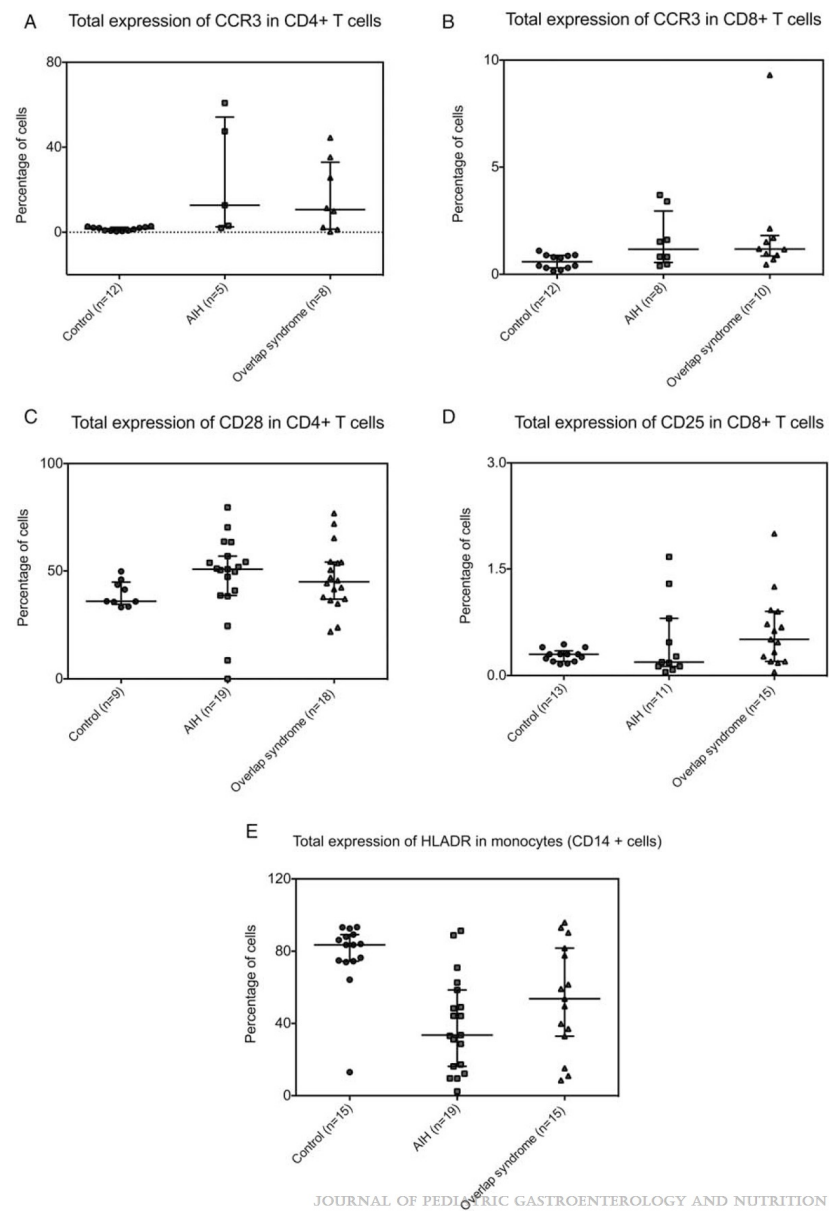
- The pathophysiology of autoimmune hepatitis and autoimmune hepatitis overlap with sclerosing cholangitis involves activation of immune cells and changes in the expression of cellular markers.
- Autoimmune hepatitis and overlap syndrome have genetic associations with HLADR subtypes.
- $CD4^+$ T cells have important role in the autoimmune mechanism.

What Is New

- Patients with autoimmune hepatitis and patients with overlap syndrome exhibit persistent activation of immune system cells despite clinical and laboratory response.

(JPGN 2018;66: 204–211)





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(JPGN 2018;66: 204–211)

Soluble PD1 levels are increased with disease activity in paediatric onset autoimmune hepatitis and inflammatory bowel disease

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ABSTRACT

Introduction: Immune mediated liver diseases entail a broad category which are associated with increased morbidity and mortality amongst the paediatric population. Programmed Death 1 (PD1) is an inhibitory receptor mainly expressed by T cells, and when activated shed into plasma as soluble PD1(sPD1). The AIM of this study was to evaluate sPD1 levels in plasma of paediatric patients with Autoimmune Hepatitis (AIH), Primary Sclerosing Cholangitis (PSC), AIH and PSC overlap, Inflammatory Bowel Disease (IBD) alone, and concurrent PSC/IBD and AIH/IBD in order to identify a biomarker to response or predict relapse verses remission.

Methods: Plasma samples were collected from 41 paediatric patients. AIH patients were further categorized into active, incomplete responders and responders, based on response to standard therapy. sPD1 levels were measured and compared between PSC, PSC/AIH, IBD alone, PSC/IBD and AIH/IBD patients and between active AIH, incomplete responders and responders. Flow cytometry was performed to further analyze CD45RA+, CD3CD4, CD8, CCR7, CXCR3, CD38 and PD1.

Results: In the AIH group, those with active disease demonstrated a significantly higher sPD1 levels in comparison to responders (*p>.001). However, the incomplete responders didn't show a reduction in sPD1 in comparison to active AIH and patients with IBD alone. Interestingly, patients with PSC showed significantly lower level of sPD1 compared to active AIH (*p<.002), whereas, patients with PSC in conjunction with AIH (*p<.006) or IBD (*p<.02) demonstrated a significant increase in sPD1. In addition, we have observed increased levels of circulating CD4 and CD8 bound PD1 in active AIH but not in PSC or responders suggesting T cells activation. CD4+ PD1 double positive cells demonstrated increased expression of CXCR3. Thus, suggesting the activation of PD1 +T cells is mediating through CXCR3 in Autoimmune hepatitis.

Conclusions: Our study demonstrates that sPD1 levels correlate with active disease state of AIH and IBD. sPD1 levels did not correlate with PSC. However, PSC in conjunction with AIH or IBD showed higher levels of sPD1. This suggests that T cell activation plays a critical role in active AIH and IBD but not in PSC. Soluble PDI levels could be used as a clinical biomarker to assess response in patients with AIH and for prospectively monitoring PSC patients for development of IBD or AIH.

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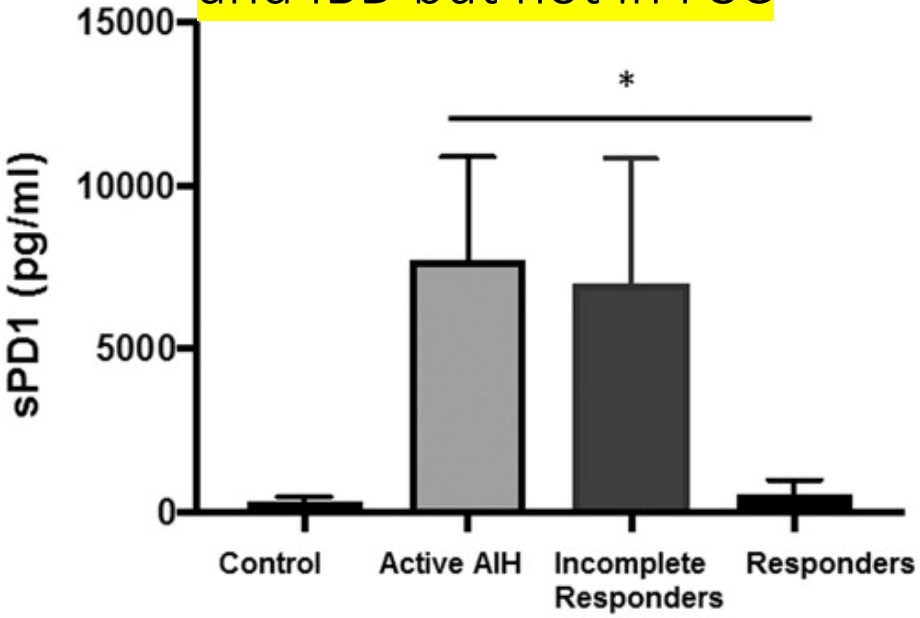

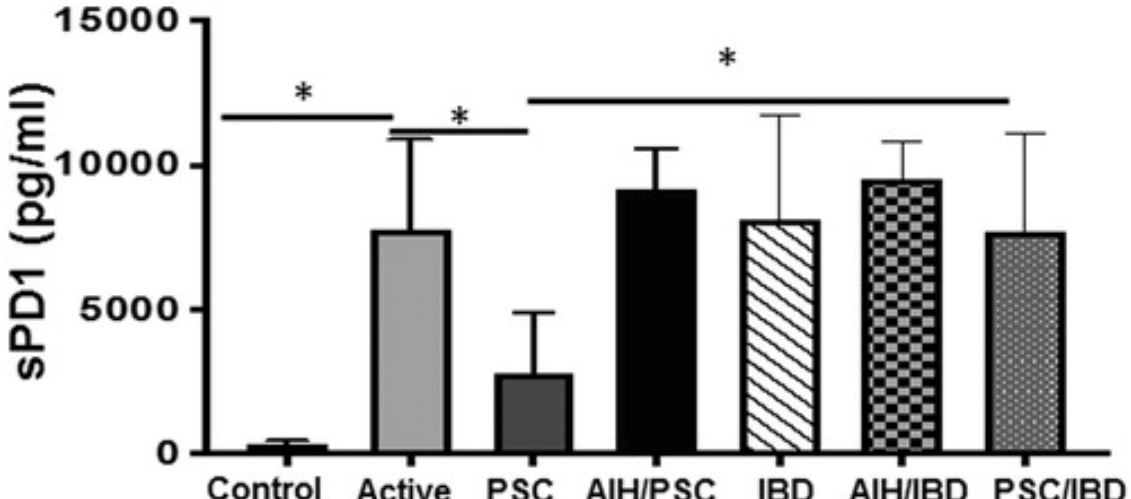

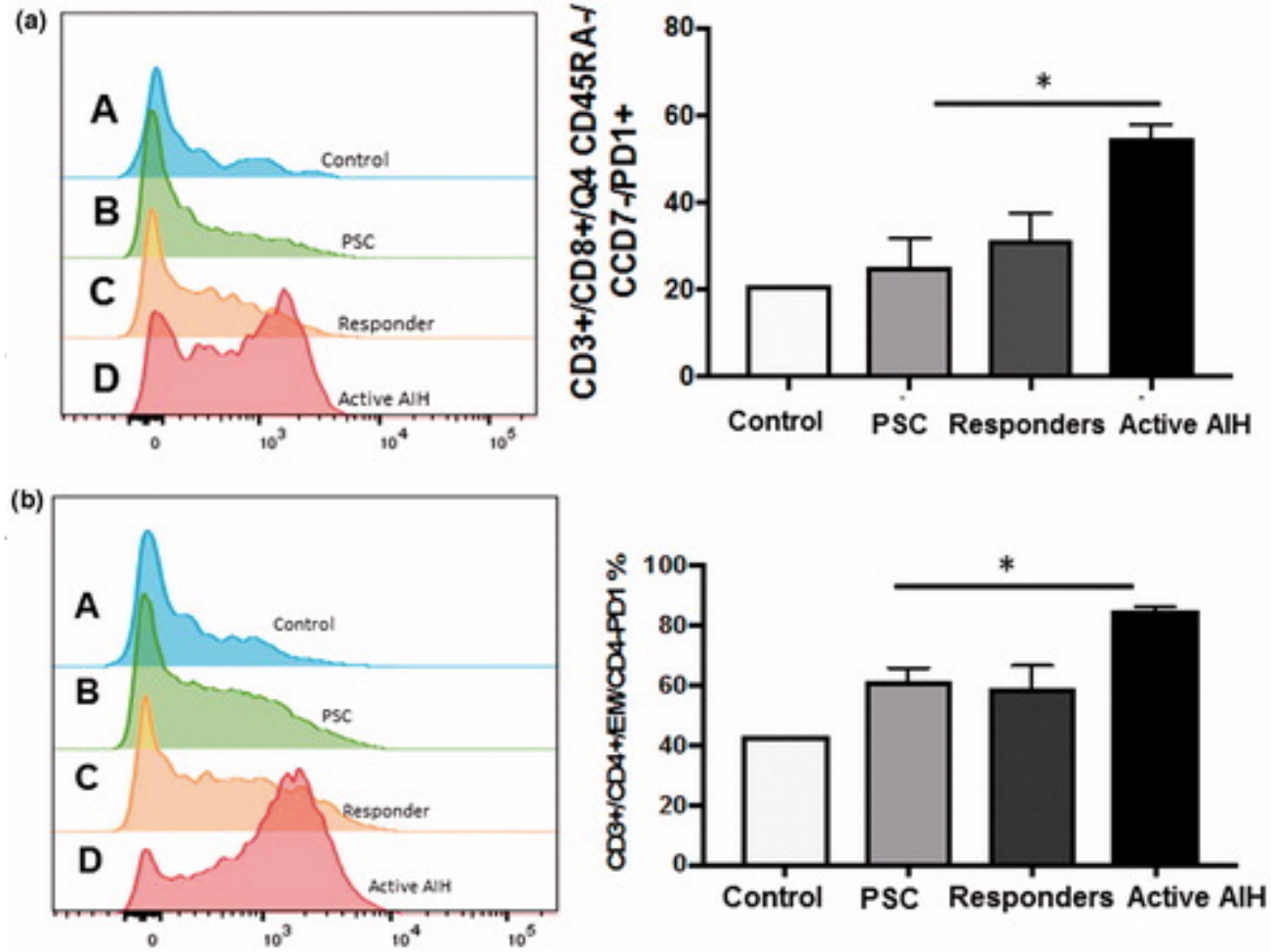

Autoimmunity 2020 Aug;53(5):253-260.

Serum Matrix Metalloproteinase 7 Is a Diagnostic Biomarker of Biliary Injury and Fibrosis in Pediatric Autoimmune Liver Disease

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In autoimmune liver disease (AILD), including autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and overlap syndrome of AIH and PSC (ASC), the presence of biliary injury portends a worse prognosis. We studied serum matrix metalloproteinase 7 (sMMP7) as a biomarker for pediatric sclerosing cholangitis (SC). We prospectively enrolled 54 children (median age, 16 years) with AILD (AIH, n = 26; ASC, n = 16; and PSC, n = 12) at our center. The sMMP7 concentrations were higher in patients with SC compared to those without cholangiopathy ($P < 0.001$). An sMMP7 concentration >23.7 ng/mL had a sensitivity and specificity of 79% and 96%, respectively, and outperformed alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) in segregating patients with SC. Serum concentrations correlated with liver gene expression levels for *MMP7* ($r = 0.70$; $P < 0.001$). Using immunofluorescence, MMP7 was localized primarily to the cholangiocytes of patients with SC. In 46 subjects with liver biopsy available for blinded review, elevation in sMMP7 concentrations segregated with the presence of lymphocytic and neutrophilic cholangitis and periductal fibrosis and correlated with Ishak, Ludwig, and Nakanuma scoring systems. Liver stiffness measured by magnetic resonance elastography also correlated with sMMP7 concentrations ($r = 0.56$; $P < 0.01$). Using magnetic resonance cholangiopancreatography plus (MRCP+), sMMP7 in 34 patients correlated with the number of biliary dilatations ($r = 0.54$; $P < 0.01$) and strictures ($r = 0.56$; $P < 0.01$). MMP7 as a marker of biliary injury was validated in an independent cohort of children with ulcerative colitis. Higher sMMP7 concentrations also correlated with a history of SC-related complication. *Conclusion*: MMP7 is a promising biomarker for pediatric SC that diagnostically outperforms ALP and GGT. sMMP7 may directly reflect biliary injury and fibrosis, the main drivers of disease progression in SC. (*Hepatology Communications* 2020;4:1680-1693).

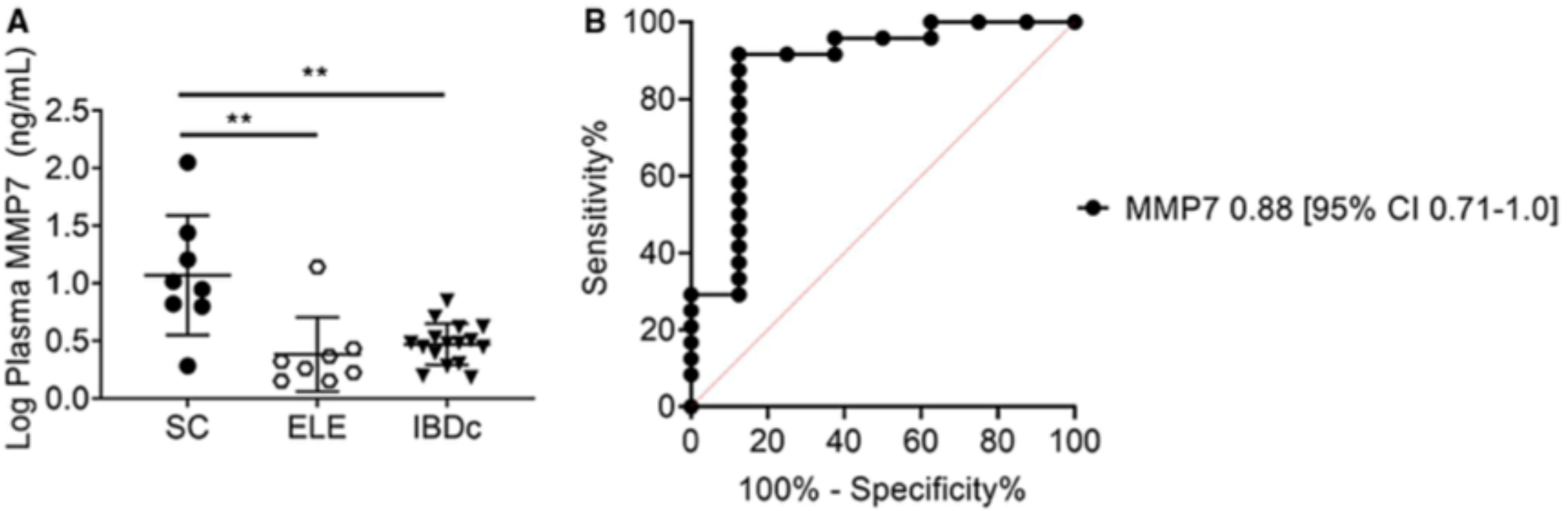

FIG. 2. Validation of plasma MMP7 as a diagnostic biomarker for concomitant PSC/ASC in an inception cohort of pediatric patients with UC. (A) MMP7 concentrations were measured by Luminex in archived plasma samples from patients with UC at the time of diagnosis. Results were grouped according to presence of ASC/PSC (n = 8), ELEs (n = 8), or IBDc (n = 16). Differences among groups were tested for statistical significance using a one-way ANOVA and Tukey's test; $^{**}P < 0.005$. (B) An ROC curve for pMMP7 concentrations in distinguishing ASC/PSC from ELEs and IBDc was constructed.

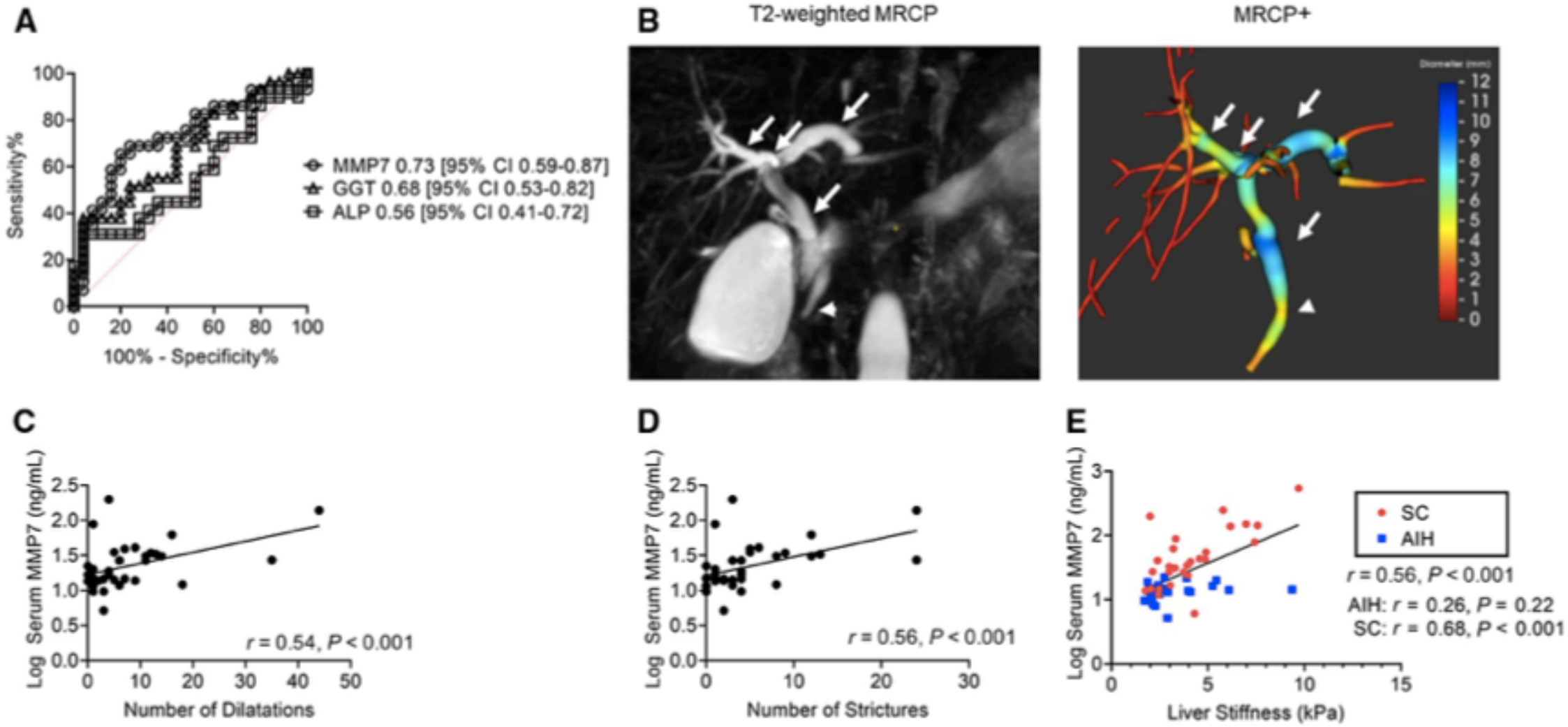

FIG. 4. Correlation between serum MMP7 concentrations and MRI-based determination of large bile duct damage and fibrosis. (A) Prediction of cholangiopathy on concomitant rMRCP by sMMP7, ALP, and GGT. (B) Biliary injury was quantitated on T2-weighted 3D rMRCP using the proprietary Perspectum MRCP+ software. sMMP7 concentrations were correlated with the numbers of candidate (C) dilatations and (D) strictures. (E) sMMP7 concentrations were correlated with liver stiffness as measured by MRE. *P* values represent Pearson's correlation coefficients.

IgG:IgM Ratios of Liver Plasma Cells Reveal Similar Phenotypes of Primary Biliary Cholangitis With and Without Features of Autoimmune Hepatitis

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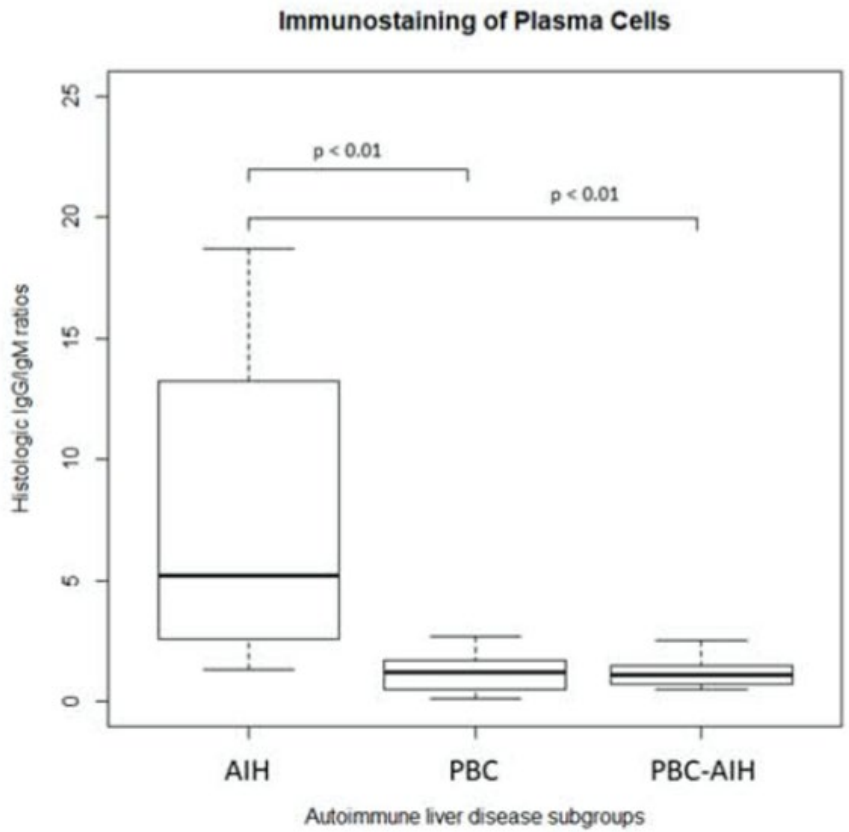

A total of 114 liver biopsies from patients with a diagnosis of AIH, PBC or PBC-AIH (55, 31, and 25 patients, respectively) were identified. Ninety-one percent were female and 87% were Hispanic with a mean age of 49 years. A total of 54 non-cirrhotic, non-fragmented liver biopsy specimens were randomly chosen for immunostaining for IgG and IgM (19 AIH, 22 PBC, and 13 PBC-AIH) (Figure 1A). The number of portal tracts did not differ across subgroups. The number of IgG-plasma cells per portal tract was similar amongst all groups. However, the number of IgM-plasma cells per portal tract was higher in PBC and PBC-AIH compared to AIH. The calculated IgG/IgM plasma cell ratio was lower in PBC and PBC-AIH compared to AIH (1.2 (IQR: 0.6-1.7) and 1.1 (IQR: 0.7-1.5) versus 5.2 (IQR: 2.6-13.3), respectively, $p<0.01$) (Figure 1B).

Tanı

Table 2
Clues to an overlap syndrome

Clinical Clue	Features	Implication
Serum AP >2-fold ULN at presentation	Present in only 21% with AIH[24] Rarely ≥4-fold ULN in AIH[24]	Unusual cholestatic component in AIH[17,24] Justifies histologic examination and AMA[24] Consider ERC or MRC[13,14,17,24]
Serum GGT > ULN unimproved or worse during therapy	Common in AIH at entry[25] Usually improves during therapy[26]	Consider cholestatic component if unchanged or worse during therapy[25,26] Justifies histologic examination and AMA[13] ERC or MRC if unchanged or worse[13,26]
AMA at presentation or later	Occurs in 6%–18% of AIH[11,24,27,46]	Requires histologic examination[1,11] Bile duct injury suggests PBC overlap[1,11] Could be serologic finding only[28,46]
Histologic findings of bile duct injury or loss	Liver tissue examination shows[1,19,31,53] Destructive cholangitis Ductopenia Periductal fibrosis Fibrous obliterative cholangitis	Justifies serologic test for AMA[1,13,24] ERC or MRC if AMA negative[13,14,21]
Concurrent inflammatory bowel disease	Abnormal ERC in 41%[32] May have no cholestatic findings[33]	Perform ERC or MRC in all patients[13,14,32] Focal strictures and dilations confirm PSC[20] Liver biopsy if normal cholangography[36,37]
Recalcitrance to corticosteroid therapy (treatment failure or incomplete response)	Treatment failure in 7% of AIH[42] Incomplete response in 14%[40]	Reevaluate original diagnosis[42] Perform liver biopsy, AMA, and MRC[42]

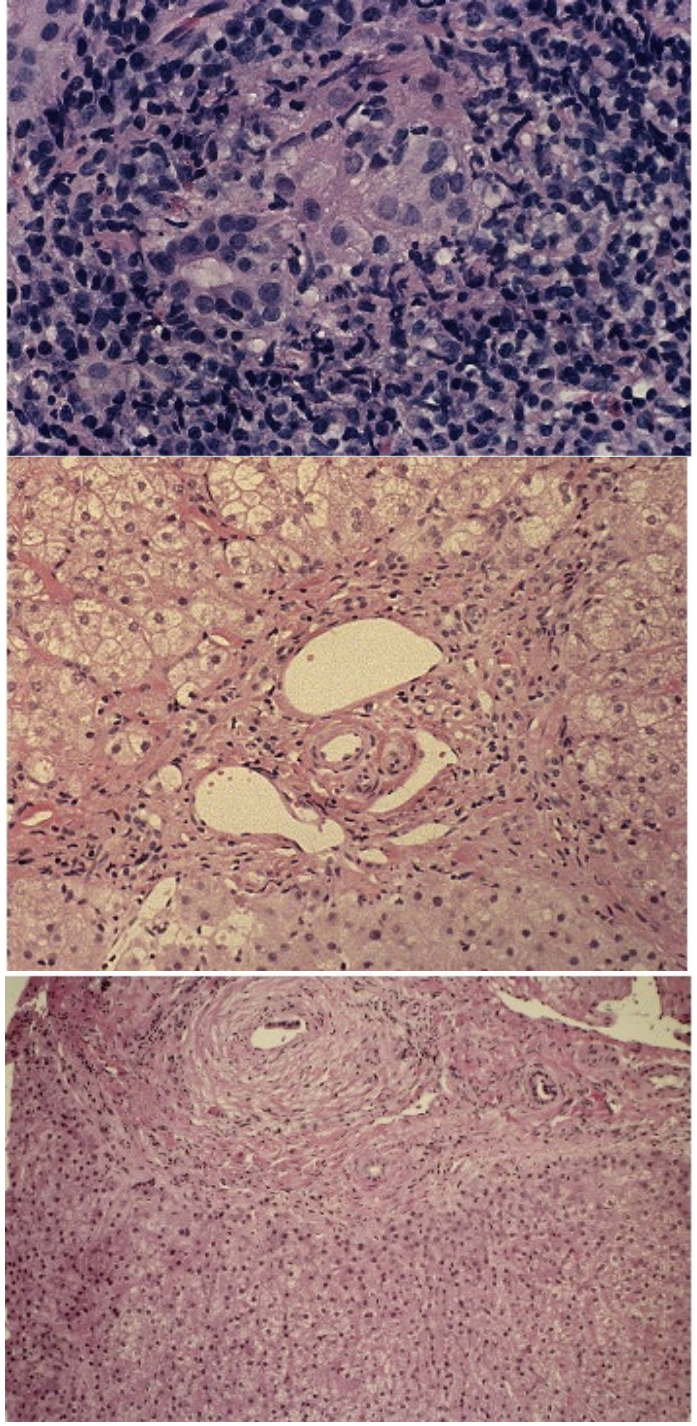

Table 3
Caveats regarding diagnosis of overlap syndromes

Caveat	Features	Implications
ERC or MRC findings falsely suggest PSC	Hepatic fibrosis distorts biliary tree[43] No focal biliary strictures and dilations[43]	PSC wrongly diagnosed[43,44] MRC abnormal in 10% AIH[44] PSC in only 1.7% AIH[43]
AMA without cholestatic phenotype or progressive bile duct injury or loss	AMA in 6%–18% with AIH[24,27,28,46] AMA can persist, appear, or disappear[27] Persistent AMA for 12–27 y[28,46] Histologic findings Typical AIH not PBC[28] Focal cholangitis as frequently in AMA^+ and AMA^- AIH[27,46] Does not progress to typical PBC[28,46]	AMA without cholestatic phenotype or bile duct injury insufficient for overlap[27,28] AMA alone does not alter diagnosis or treatment of AIH[27] Responds to steroid therapy[11,27]
Lymphocytic nondestructive cholangitis insufficient for overlap diagnosis	Dense lymphocytic aggregation around interlobular and septal bile ducts[19] Unassociated with decreased or damaged bile ducts[19]	Insufficient for overlap[19] Similar frequencies in classical PBC, PSC, and AIH[19]
Misuse of diagnostic scoring systems of IAIHG	Diagnostic scoring systems of IAIHG not discriminative indices[12] Lack prospective validation for AIH[47] Not designed for overlap detection[6,7,12] Low sensitivity for AIH in overlaps[48]	Diagnostic scoring systems of IAIHG should not be used for overlap diagnosis[12,48] Histologic examination is a major independent diagnostic factor[48,49] Clinical judgment is diagnostic gold standard[13,14,48,49]

Gastroenterol Clin N Am 46 (2017) 345–364

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TABLE 4. Proposed scoring criteria for the diagnosis of juvenile autoimmune liver disease

Variable	Cut-off	Points	
		AIH	ASC
ANA and/or SMA*	≥1:20†	1	1
	≥1:80	2	2
Anti-LKM-1* or	≥1:10†	1	1
	≥1:80	2	1
Anti-LC-1	Positive†	2	1
Anti-SLA	Positive†	2	2
pANNA	Positive	1	2
IgG	>ULN	1	1
	>1:20 ULN	2	2
Liver histology	Compatible with AIH	1	1
	Typical of AIH	2	2
Absence of viral hepatitis (A, B, E, EBV), NASH, Wilson disease, and drug exposure	Yes	2	2
Presence of extrahepatic autoimmunity	Yes	1	1
Family history of autoimmune disease	Yes	1	1
Cholangiography	Normal	2	−2
	Abnormal	−2	2

Score ≥7: probable AIH; ≥8: definite AIH. Score ≥7: probable ASC; ≥8: definite ASC. AIH = autoimmune hepatitis; ANA = anti-nuclear antibody; anti-LC-1 = anti-liver cytosol type 1; anti-LKM-1 = anti-liver kidney microsomal antibody type 1; anti-SLA = anti-soluble liver antigen; ASC = autoimmune sclerosing cholangitis; EBV = Epstein–Barr virus; IgG = immunoglobulin G; NASH = nonalcoholic steatohepatitis; pANNA = peripheral anti-nuclear neutrophil antibodies; SMA = anti-smooth muscle antibody; ULN = upper limit of normal.

*Antibodies measured by indirect immunofluorescence on a composite rodent substrate (kidney, liver, stomach).

†Addition of points achieved for ANA, SMA, anti-LKM-1, anti-LC-1, and anti-SLA autoantibodies cannot exceed a maximum of 2 points.

JPGN 2018;66: 345–360)

HEPATOLOGY COMMUNICATIONS, VOL. 2, NO. 3, 2018

New Scoring Classification for Primary Biliary Cholangitis–Autoimmune Hepatitis Overlap Syndrome

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Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are two major immune-mediated chronic liver diseases. Overlap syndrome (OS) is diagnosed if patients have features of both AIH and PBC; however, there is no consensus on the definition or diagnostic criteria for OS. Here, we report a new scoring classification for OS and evaluate its usefulness. This new scoring classification was developed by modifying the International Autoimmune Hepatitis Group classification by selecting histologic features of AIH and PBC along with modifications of biochemical and immunologic characteristics. We evaluated 272 patients with chronic liver disease, including 105 with AIH, 102 with PBC, and 65 with OS. The best performance for the diagnosis of OS was noted among patients with an overlap score of ≥21 who had a sensitivity of 98.5%, a specificity of 92.8%, a positive predictive value of 81.0%, and a negative predictive value of 99.5%. By using a cut-off score of 21, 64 (98.5%) patients were diagnosed with OS as opposed to 9 (8.8%) and 6 (5.7%) with PBC and AIH, respectively. All patients with OS had an aggregate score of >19, whereas most patients with PBC or AIH scored <19, making this a safe discriminatory cut-off point against OS. *Conclusion:* The new scoring system for the diagnosis of OS has a high sensitivity and specificity for scores ≥21, while a score <19 suggests a diagnosis other than OS. This classification can identify patients and diagnose OS with a reasonable amount of accuracy and may be superior to current OS scoring systems in detecting mild forms of OS. (*Hepatology Communications* 2018;2:245-253)

TABLE 1. PROPOSED SCORING CLASSIFICATION FOR OVERLAP SYNDROME

Component	Result	Score
Biochemical category		
AST or ALT above ULN	>2	+3
	1.5-2	+2
	1-1.5	+1
	<1	0
ALP above ULN	>1	+2
	0.75-1	+1
	<0.75	0
Serum globulin above ULN	>1.5	+2
	1-1.5	+1
	<1	0
Immunologic category		
ANA, ASMA, or LKM1	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
or		
Anti-SLA, pANCA	Positive	+2
AMA	Positive	+3
Histologic category		
	Interface hepatitis	+3
	Lymphoplasmacytic	+1
	Hepatic rosettes	+1
	Biliarydamage	
	Granulomas	+3
	Florid ductal lesion	+1
	Ductular proliferation	+1
	Bile duct loss	+1
Others category		
Viral markers	Positive	–3
	Negative	+3
Drugs	Yes	–4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	–2
Interpretation of scores	Definitive	≥21
	Probable	19 or 20
	Rejected	<19

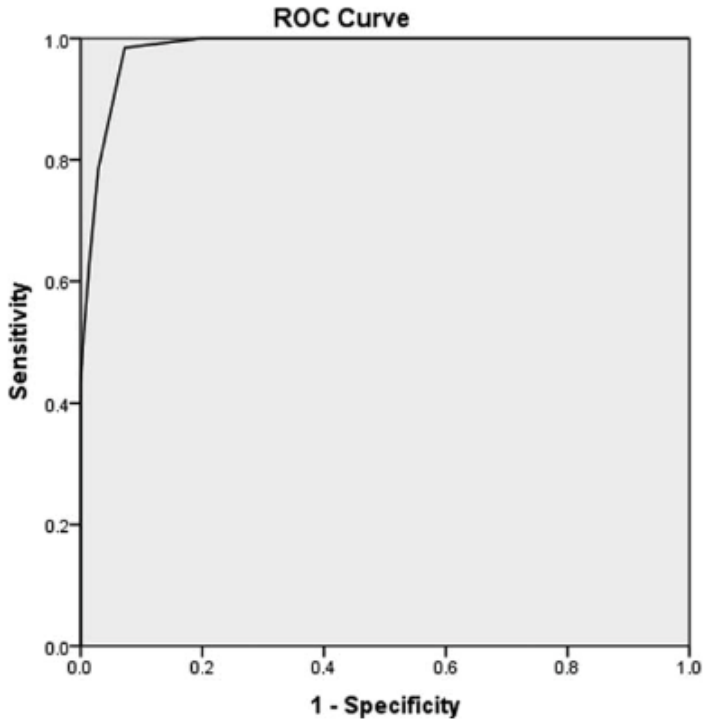

FIG. 2. ROC curve for overlap score predicting the overlap patients. A cut-off value of 21 provided the best balance of sensitivity (98.5%) and specificity (92.8%). Area under the ROC curve, 0.98 ($P < 0.0001$). Abbreviation: ROC, receiver operating characteristic.

Tedavi

- Steroid + AZA/MMF+ UDCA

UDCA dozu <20 mg/kg/g

- Vankomisin 50 mg/kg
- KC nakli

  nüks sık

  kontrollü IBD nüksü azaltır

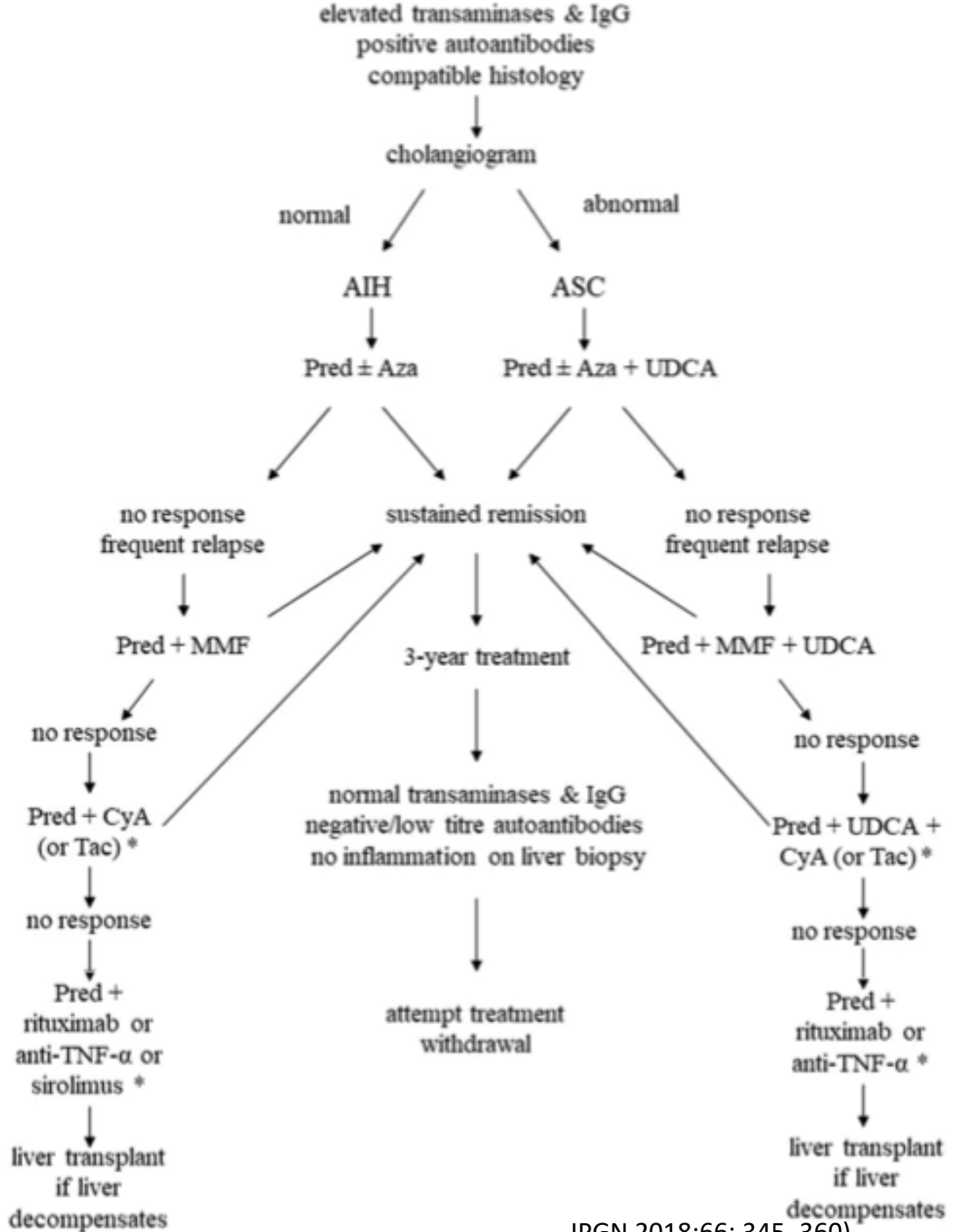

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TABLE 2. Alternative treatments for juvenile autoimmune liver disease

Agent	Pros	Cons
Mycophenolate mofetil	Favorable toxicity profile Experience in the transplant setting	Contradictory reports regarding its efficacy Teratogenicity
Tacrolimus	Potent immunosuppressant Experience in the transplant setting	Anecdotal experience Unclear efficacy Renal toxicity
Cyclosporine	Potent immunosuppressant Experience in the transplant setting	Unclear benefit over standard treatment Cosmetic effects Renal toxicity
Budesonide	High first pass metabolism in the liver	Ineffective in cirrhotic patients Less effective as first line treatment compared to standard treatment
Rituximab	Relatively favorable toxicity profile	Infectious complications Anecdotal experience Unclear efficacy
Infliximab	Potent immunomodulatory properties Effective in inflammatory bowel disease	Unclear efficacy in liver disease Infectious complications Paradoxical development of AIH
Ursodeoxycholic acid	Putative immunomodulatory capacities Choleretic	Efficacy yet to be demonstrated

Retrospective Study

Use of oral vancomycin in children with autoimmune liver disease: A single centre experience

Core Tip: Experience with oral vancomycin in children with autoimmune liver disease (AILD) is limited. We enrolled 75 children [median age 10.5 years (5.6-13.4)], 54 with autoimmune hepatitis and 21 with autoimmune sclerosing cholangitis; 63/75 achieved remission by standard immunosuppressive therapy (IS), whereas 12/75 (16%) required oral vancomycin treatment (OVT). In 6/12 patients (50%) the response was complete, whereas it was partial in 2/12 (17%), and absent in 4/12 (33%). Overall OVT increased the remission rate of the whole group of AILD patients from 81% to 92%. OVT may represent a valuable treatment option in children with AILD who do not respond to standard IS.

World J Hepatol 2021 December 27; 13(12): 2113-2127

The clinical characteristics, pre- and post–liver transplantation outcomes in patients having autoimmune overlap syndromes

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Funding information
This work was supported by the Grants for Development of New Faculty Staff, Ratchadaphiseksomphot Endowment Fund, Chulalongkorn University, Grant number: DNS_62_002_30_001_1.

Abstract

Background: There are little data on the pre- and post–liver transplantation (LT) outcomes of patients having autoimmune hepatitis-primary biliary cholangitis (AIH-PBC), AIH-primary sclerosing cholangitis (AIH-PSC), and AIH-small-duct PSC (AIH-SDPSC). The aim of this study was to analyze pre- and post-LT outcomes and survival of patients having different overlap syndromes (OS) undergoing LT.

Methods: Patients with compatible clinical and pathologic features of AIH-PBC (n = 86), AIH-PSC (n = 22), and AIH-SDPSC (n = 9) were included in the study. Demographic, laboratory, clinical, and survival data were analyzed. Multivariable analyses were performed to determine factors predicting transplant-free survival.

Results: AIH-primary sclerosing cholangitis patients were less treatment-responsive and were more likely to undergo LT than other OS. No survival difference was noted among the 3 groups. Liver decompensation was independently associated with higher mortality (HR 21.78; 95% CI 2.50-190.01). Thirteen patients with OS underwent LT. One-year survival post-LT was 91.7%. Overall recurrence rate for OS post-LT was 8%.

Conclusions: AIH-primary sclerosing cholangitis patients were more likely to require LT compared with patients having AIH-PBC. Transplant-free survival was similar among the three AIH-overlap syndromes. Allograft recurrence of OS occurred in about 10% of cases. Patients with OS appear to have good short- and medium-term post-LT outcomes in terms of graft function and overall survival.

KEYWORDS
clinical characteristics, liver transplantation, outcomes, overlap syndromes

	HR univariate (95% CI)	*P* value	HR multivariate (95% CI)	*P* value
Diagnosis				
AIH-PBC	1	.93		
AIH-PSC	0.75 (0.16-3.42)			
AIH-SDPSC	0 (no mortality)			
Age at diagnosis	1.04 (0.99-1.09)	.08		
Gender	0.88 (0.19-4.01)	.87		
ALT at diagnosis	1.00 (0.99-1.00)	.47		
AST at diagnosis	1.00 (1.00-1.01)	.04	1.00 (0.99-1.00)	.24
ALP at diagnosis	1.00 (0.99-1.01)	.21		
TB at diagnosis	1.21 (1.09-1.35)	<.001	1.03 (0.99-1.06)	.14
Immunosuppression	0.59 (0.18-1.92)	.38		
UDCA	0.73 (0.16-3.32)	.68		
Treatment response	0.26 (0.07-1.04)	.06		
Cirrhosis at diagnosis	4.33 (1.41-13.32)	.01	1.46 (0.45-4.77)	.53
Decompensation	40.13 (5.18-311.17)	<.001	21.78 (2.50-190.01)	.005

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; TB, total bilirubin.

Long-term results of pediatric liver transplantation for autoimmune liver disease

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Methods: Retrospective data from 30 children who underwent a first LT from 1988 to 2018 were collected.

Results: The study population consisted of 18 girls and 12 boys, transplanted for AIH type 1 ($n = 14$), AIH type 2 ($n = 7$) or PSC ($n = 9$). Mean age at LT was 11.8 ± 5.2 years. The main indications for LT were acute (36.7%) or chronic end-stage liver failure (63.3%). Graft rejection occurred in 19 patients (63.3%); 6 pts required retransplantation for chronic rejection. Recurrence of initial disease was observed in 6 patients (20.0%), all of them with type 1 AIH, after a median time of 42 months, requiring retransplantation in 2 cases. Overall patient survival rates were 96.4%, 84.6%, 74.8%, 68.0%, 68.0%, 68.0% and 68.0% at 1, 5, 10, 15, 20, 25 and 30 years, respectively. Age at LT < 1year ($p < 0.0001$), LT for fulminant failure ($p = 0.023$) and LT for type 2 AIH ($p = 0.049$) were significant predictive factors of death.

Conclusion: Long-term outcome after LT for pediatric autoimmune liver disease is impaired in patients with AIH because of consistent complications such as rejection and disease recurrence.

Clinics and Research in Hepatology and Gastroenterology 45 (2021) 101537

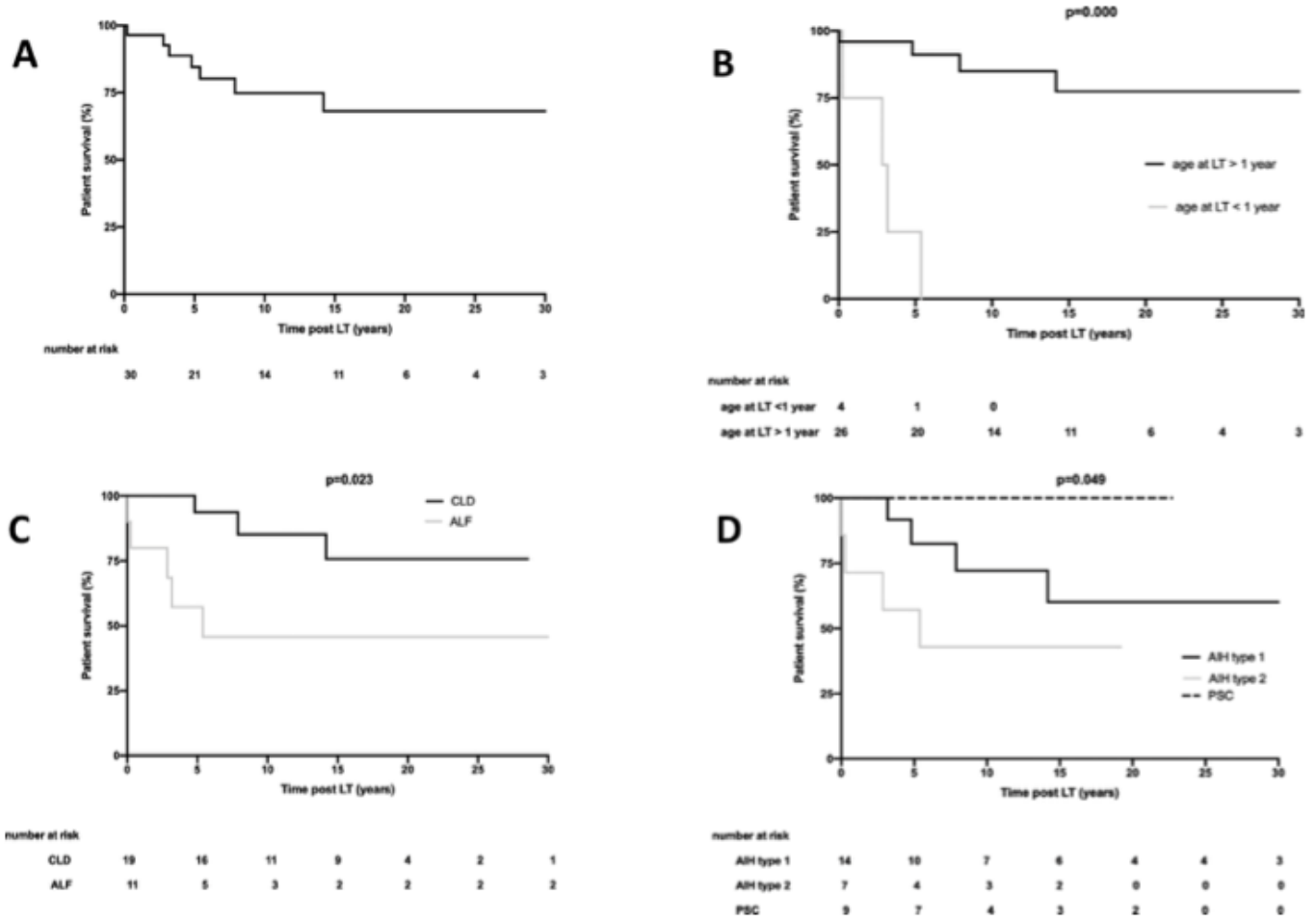

Figure 1 Patient survival after pediatric LT for AILD.
A: Overall patient survival was 96.4%, 84.6%, 74.8%, 68.0%, 68.0%, 68.0%, 68.0% at 1, 5, 10, 15, 20, 25 and 30 years, respectively.
B: Patient survival was 75.0%, 25.0% and 0.0% at 1, 5, 10, years, respectively for children transplanted before 1 year of age *vs.* 96.0%, 91.2%, 85.1%, 77.4%, 77.4%, 77.4% and 77.4% at 1, 5, 10, 15, 20, 25 and 30 years, respectively for children transplanted after 1 year of age (log-rank, $p < 0.001$).
C: Patient survival was 100.0% until 20 years of follow-up for children transplanted with PSC as initial diagnosis, *vs.* 100.0%, 82.5%, 61.9%, 49.5%, 49.5%, 49.5% and 49.5% at 1, 5, 10, 15, 20, 25 and 30 years, respectively for those transplanted with type 1 AIH *vs.* 71.4%, 57.1%, 42.9%, 42.9% at 1, 5, 10 and 15 years, respectively for those transplanted with type 2 AIH (log-rank, $p = 0.049$).
D: Patient survival was 80.0%, 57.1%, 45.7%, 45.7%, 45.7%, 45.7% and 45.7% at 1, 5, 10, 15, 20, 25 and 30 years, respectively for children transplanted with fulminant hepatitis *vs.* 100.0%, 93.8%, 85.2%, 75.8%, 75.8% and 75.8% at 1, 5, 10, 15, 20 and 25 years, respectively for children transplanted with chronic liver disease (CLD) (log-rank, $p = 0.023$).

J Pediatr Gastroenterol Nutr. 2022 Feb 1;74(2):200-207. doi: 10.1097/MPG.0000000000003353.

Examining the Hepatic Immune System in Children With Liver Disease With Fine Needle Aspiration

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Affiliations + expand

PMID: 34732645 DOI: 10.1097/MPG.0000000000003353

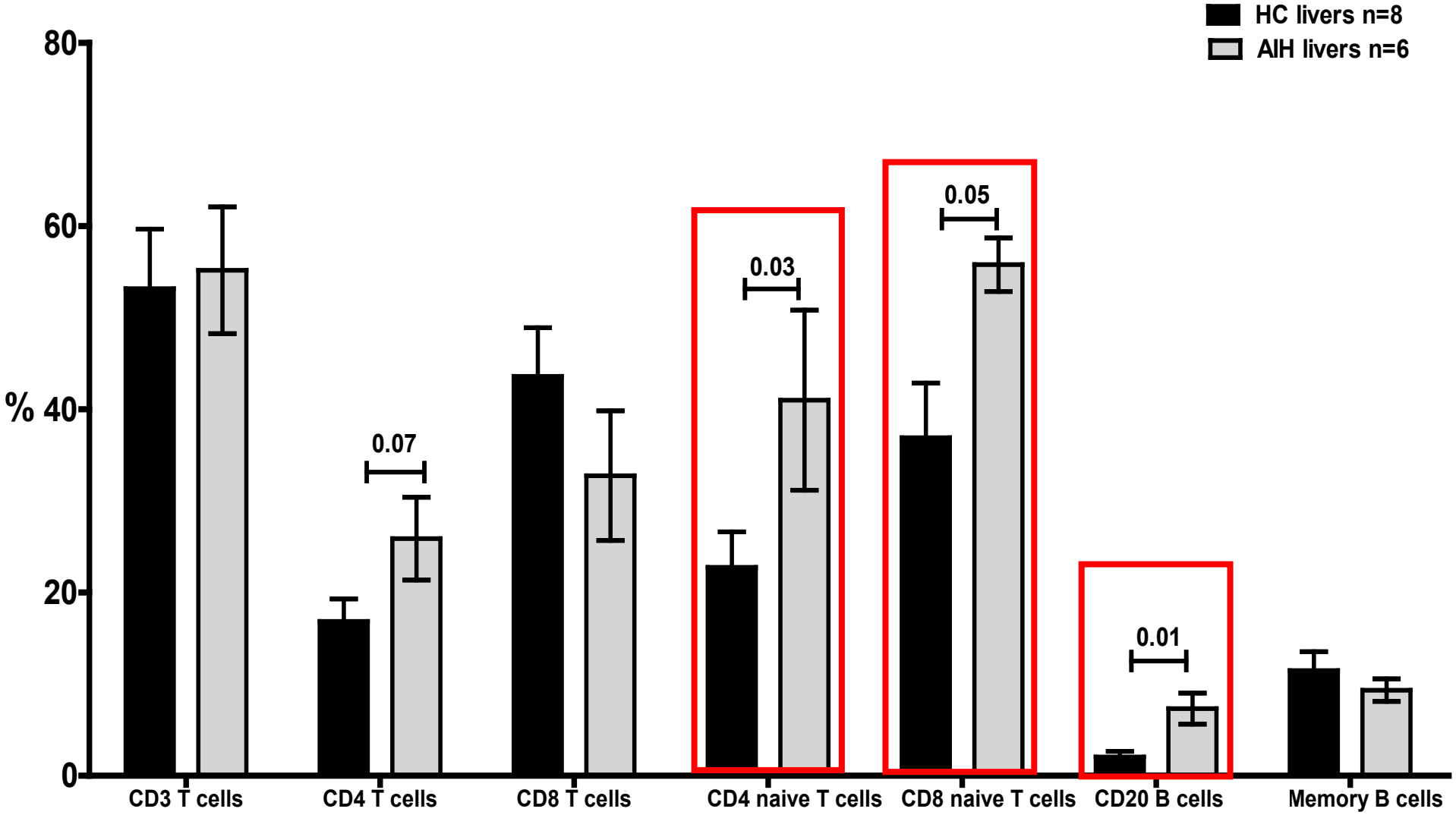
Abstract

Objectives: Liver biopsy is the standard in diagnosing liver diseases. Yet, it provides little space to perform comprehensive immune profiling of the liver. Hence, we explored whether fine needle aspirates (FNAs) could be used to elucidate the hepatic immunity in children.

Methods: We enrolled 74 children undergoing diagnostic (n = 17) or protocol biopsy (n = 57) following liver transplantation (LT). Matched blood and FNAs were obtained. Additionally, explant liver tissue was collected from children (n = 14) undergoing LT. Immune cells were isolated from peripheral blood, FNAs and explanted livers. Immune-phenotypical profiling was done by flow cytometry.

Results: Biopsied patients (58% female) were at a median age of 46 months (interquartile range [IQR]: 12-118) and LT patients (71% female) were 48 months (IQR: 21-134, P = 0.78) old. CD69+, a hallmark of tissue-resident immune cells was expressed in 1.3% of CD3+ T cells from blood being higher in FNA (20%) and tissue (49%, P < 0.001). CD4+ T-cell frequencies in tissue (13%) and FNAs (20%) were lower compared to blood (35%, P < 0.001) whereas CD8+ T cells in tissue (33.5%) and FNA (32%) were higher than in blood (25%, P < 0.01). Mucosal associated invariant T cells were enriched in liver tissue (8.8%) and in the FNA (4.4%) compared to blood (1.7%, P < 0.001). Whereas the percentage of total Tregs (CD4+CD25+FOXP3+CD127low/-) decreased, the proportion of activated Tregs (CD4+CD45RA-FOXP3high) increased in FNA and explant. Breg (CD19+CD20+CD24highCD38high) frequencies were similar in all groups.

HC liver vs AIH liver



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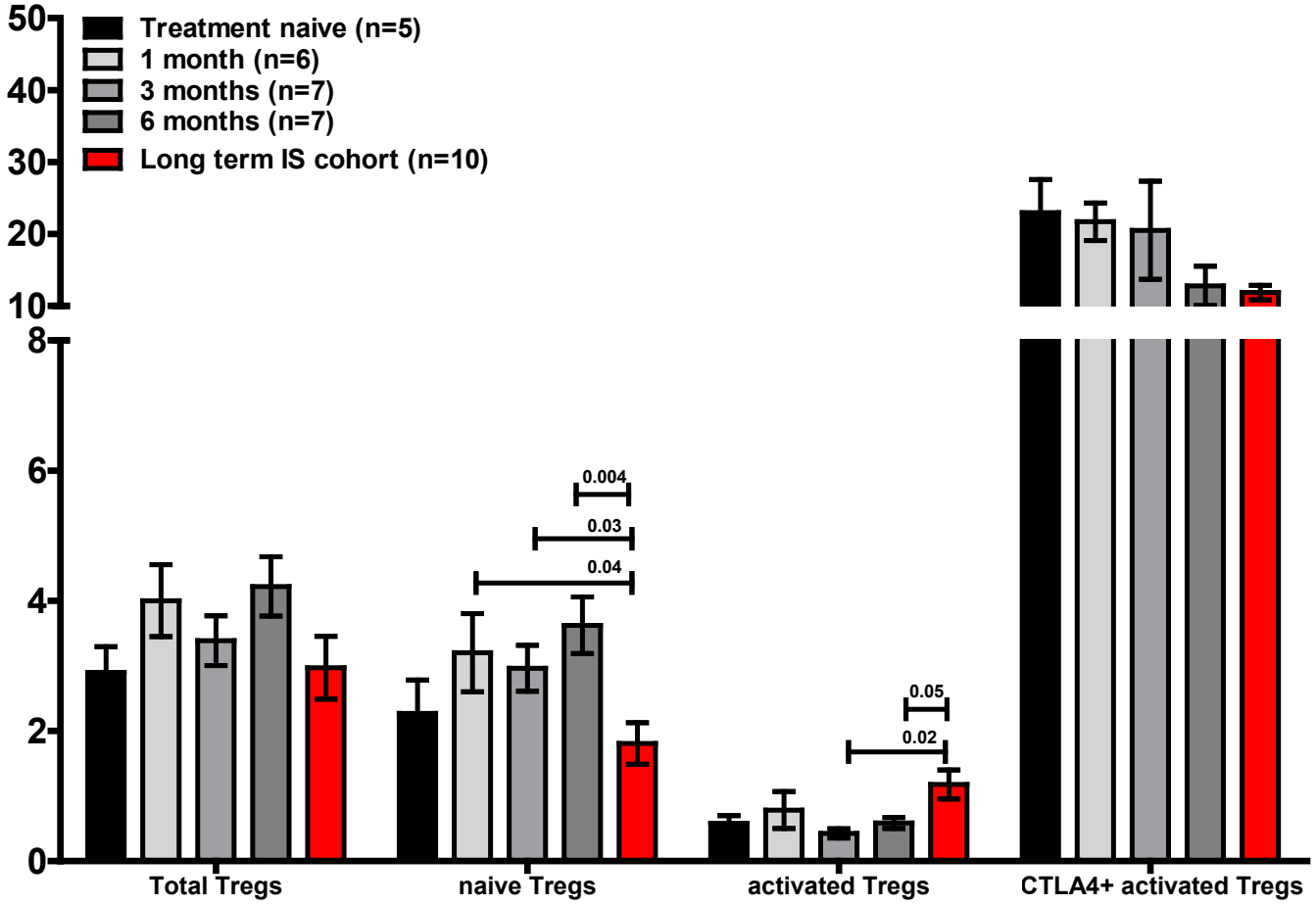
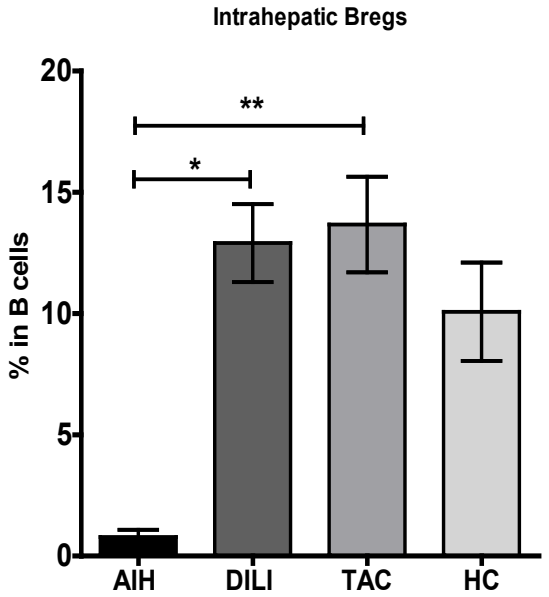
HC liver vs AIH liver vs DC liver





overall p < 0,05

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Özet

- AIKH ve OS bir spektrum
- AIH tanısı konulan her hastanın sistemik değerlendirilmesi gerekli
- Karaciğer testleri ve MRCP tek başına gösterge değil.
- Hastaların daha iyi tanımlanması için klinokopatolojik ve moleküler çalışmalar gerekiyor