Title

Postinfantile Giant Cell Hepatitis in Native and Allograft Livers: A Multi-Institutional Clinicopathologic Study of 70 Cases

Journal

MODERN PATHOLOGY, 36(11)

ISSN

0893-3952

Authors

Jiao, Jingjing
Chezar, Ksenia
Zhang, Xuefeng
et al.

Publication Date

2023

DOI

10.1016/j.modpat.2023.100298

Peer reviewed

Mod Pathol 36 (2023) 100298

MODERN PATHOLOGY

USCAP UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY
Creating a Better Pathologist

Journal homepage: https://modernpathology.org/

Research Article

Postinfantile Giant Cell Hepatitis in Native and Allograft Livers: A Multi-Institutional Clinicopathologic Study of 70 Cases

Jingjing Jiao[a], Ksenia Chezar[b], Xuefeng Zhang[b], Donghai Wang[c], Wenqing Cao[c], Challa Bindu[d], Wei Chen[d], Antonio Galvao Neto[e], Patrick Henn[e], Irene Riahi[f], Hanlin L. Wang[f], David J. Papke Jr[g], Lei Zhao[g], Yue Xue[h], Xiaoyan Liao[i], Xuchen Zhang[a,*]

[a] *Department of Pathology, Yale University School of Medicine, New Haven, Connecticut;* [b] *Department of Pathology, Cleveland Clinic, Cleveland, Ohio;* [c] *Department of Pathology, New York University Langone Health, New York, New York;* [d] *Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, Ohio;* [e] *Department of Pathology, University of Colorado, Anschutz Medical Campus, Aurora, Colorado;* [f] *Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California;* [g] *Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts;* [h] *Department of Laboratory Medicine and Pathology, Northwestern University, Chicago, Illinois;* [i] *Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, New York*

ARTICLE INFO

Article history:
Received 26 March 2023
Revised 16 June 2023
Accepted 28 July 2023
Available online 6 August 2023

Keywords:
autoimmune liver disease
giant cell hepatitis
liver transplantation
postinfantile
syncytial giant cell hepatitis

ABSTRACT

Postinfantile giant cell hepatitis (PIGCH) is a rare hepatitis pattern in adults with variable etiologies and clinical outcomes. We conducted a multi-institutional retrospective study to define the clinicopathologic characteristics of patients with PIGCH. A total of 70 PIGCH cases were identified and reviewed for pathological features, including fibrosis, cholestasis, inflammation, steatosis, necrosis, and apoptosis, as well as the distribution of giant cells and the maximum number of giant cells per high-power field. Demographic and clinical data, including age, sex, laboratory results, etiologies, and follow-up results, were recorded. Among the 70 cases, 40% (28/70) were associated with autoimmune liver diseases, followed by 9 (13%) with unknown etiology, 8 (11%) with viral infection, 5 (7%) with medications, 5 with combined etiologies, and 4 (6%) with malignancies (mostly chronic lymphocytic leukemia). Notably, another 16% were de novo PIGCH in liver allografts, most of which occurred after a rejection event. During follow-up, 26 (37%) patients died of the disease and 44 (63%) were alive. Deceased patients were characterized by older age (mean age, 54.9 vs 45.5 years; $P = .02$), higher alkaline phosphatase level (mean value, 253.3U/L vs 166.3 U/L; $P = .03$), higher fibrosis stage (stage 3-4 vs stage 0-2, 57.7% vs 29.6%; $P = .03$), being more likely to have de novo PIGCH after transplantation (23.1% vs 11.4%; $P = .04$), and being less likely to have primary autoimmune liver disease etiology (26.9% vs 47.7%; $P = .04$). These results indicate that PIGCH is a rare pattern of liver injury associated with different etiologies and variable clinical outcomes. Autoimmune liver disease with PIGCH is associated with better survival, whereas de novo PIGCH in allografts is associated with poorer survival. Older age, higher alkaline phosphatase level, and advanced fibrosis are adverse prognostic factors.

Introduction

Giant cell hepatitis is a rare pattern of liver injury characterized histologically by the formation of syncytial hepatic giant cells (hepatocytes with abundant cytoplasm and more than 3 nuclei)[1] and hepatitis (lobular disarray, lobular inflammation, Kupffer cell hypertrophy, and spotty hepatocyte necrosis).[2,3] This pattern of liver

* Corresponding author.
E-mail address: Xuchen.Zhang@yale.edu (X. Zhang).

0893-3952/$ - see front matter © 2023 United States & Canadian Academy of Pathology. Published by Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.modpat.2023.100298

Table 1
Clinical, laboratory, and histologic parameters for all study subjects

Parameters	Values (N = 70)
Age (y) (n = 70)	49.0 (18.0-86.0)
Sex (n = 70)	
Male	31 (44.3%)
Female	39 (55.7%)
IgG (g/L) (n = 33)	2103.3 (577.0-4547.0)
AST (U/L) (n = 59)	604.3 (24.0-3270.0)
ALT (U/L) (n = 58)	591.3 (27.0-4060.0)
ALP (U/L) (n = 56)	197.3 (48.0-870.0)
GGT (U/L) (n = 21)	275.9 (29.0-2022.0)
TB (mg/dL) (n = 56)	10.0 (0.3-33.0)
Albumin (g/dL) (n = 52)	3.3 (1.8-4.7)
Etiology (n = 70)	
Autoimmune	28 (40%)
Infection	8 (11.4%)
Medicine/drug	5 (7.1%)
Malignancy	4 (5.7%)
Combined	5 (7.1%)
Unknown	9 (12.8%)
De novo posttransplantation	11 (15.7%)
Histology (n = 70)	
Giant cell score (number/40×)	
1: <5	23 (32.9%)
2: 5-10	28 (40.0%)
3:>10	19 (27.1%)
Distribution of giant cells	
>30% of lobule	31 (44.3%)
Scattered	39 (55.7%)
Giant cell location	
Zone 1	10 (14.3%)
Zone 2	4 (5.7%)
Zone 3	15 (21.4%)
Panlobular	38 (54.3%)
Others[a]	3 (4.3%)
Bile in giant cells	
No	44 (62.9%)
Yes	26 (37.1%)
Mallory-Denk bodies in giant cells	
No	58 (85.3%)
Yes	10 (14.7%)
Fibrosis	
Stage 0-2	42 (60%)
Stage 3 and 4	28 (40%)
Portal inflammation	
No	0 (0.0%)
Mild	25 (35.7%)
Moderate	35 (50.0%)
Severe	10 (14.3%)
Interface hepatitis	
No	22 (31.4%)
Mild	24 (34.3%)
Moderate	13 (18.6%)
Severe	11 (15.7%)
Portal plasma cell	
No	10 (14.3%)
Rare	36 (51.4%)
Moderate	17 (24.3%)
Severe	7 (10.0%)
Lobular inflammation	
No	2 (2.9%)
Mild	34 (48.6%)
Moderate	15 (21.4%)
Severe	19 (27.1%)
Lobular dropout	
No	24 (34.3%)
Scattered single-cell or spotty necrosis	26 (37.1%)
Bridging necrosis	14 (20.0%)
Zone 3 necrosis	4 (5.7%)
Submassive necrosis	2 (2.9%)
Apoptotic body	
No	23 (32.9%)
Yes	47 (67.1%)
Cholestasis	
No	28 (40.0%)
Canalicular	4 (5.7%)
Hepatocellular	14 (20.0%)
Mixed	24 (34.3%)
Steatosis	
No	59 (84.3%)
5%-33%	10 (14.3%)
34%-66%	1 (1.4%)
>67%	0 (0.0%)

Data are presented as mean (range) or n (%).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; TB, total bilirubin.
[a] Giant cells in zone 1 and zone 2 (n = 1), zone 1 and zone 3 (n = 1), and perifibrotic septa (n = 1).

injury is frequently seen in newborns with cholestasis[4] but can also occur rarely in adults, where it has a reported incidence of 0.14% and is termed postinfantile giant cell hepatitis (PIGCH) or syncytial giant cell hepatitis.[3] The clinical course of PIGCH varies broadly, ranging from minimal symptoms and complete recovery after treatment, to rapid progression to cirrhosis or fatal liver failure despite standard clinical care.[5-10] The clinicopathologic features are poorly understood. Here, we performed a multi-institutional retrospective study to characterize the clinical, histologic, and laboratory features that might predict the outcomes of PIGCH.

Materials and Methods

A multicenter, retrospective study (from 1988 to 2022) was conducted at the department of pathology of 9 institutions in the United States, including Yale-New Haven Hospital, Cleveland Clinic, New York University Langone Health, the Ohio State University Wexner Medical Center, University of Colorado, Ronald Reagan UCLA Medical Center, Brigham and Women's Hospital, Northwestern University, and University of Rochester Medical Center. Patient information (age, sex, laboratory results, etiologies, and follow-up results) was retrieved from the medical records. The slides were reviewed for pathological features, including fibrosis, cholestasis, inflammation, steatosis, necrosis, and apoptosis, as well as the distribution of giant cells and the maximum number of giant cells per high-power field (HPF).

Comparisons were made between deceased and living patients using 2-tailed Student *t* test for continuous variables and Fisher exact or χ^2 test for categorical variables as indicated. Multivariate logistic regression analysis was performed to estimate the adjusted odds ratio (AOR) and 95% CI for the association of clinical and pathological variables with the outcome. The differences in overall survival in patients with different etiologies and fibrosis stages were visualized using Kaplan-Meier survival curves (Prism). A *P* value of less than .05 was considered statistically significant.

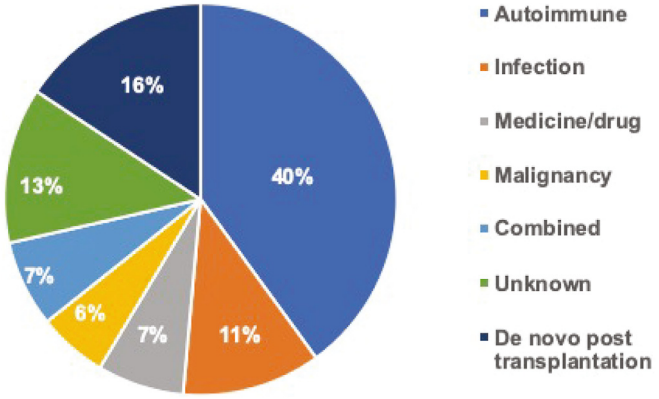

Figure 1.
Etiology distribution of postinfantile giant cell hepatitis.

Results

Clinical and Laboratory Characteristics of Study Subjects

Seventy patients with a descriptive pathologic diagnosis of PIGCH were identified (Table 1). The cohort included 31 men and 39 women with an mean age of 49 years (range, 18-86 years). The most common clinical symptoms/signs were jaundice (n = 23), abdominal pain/tenderness (n = 11), and nausea (n = 7). Abnormal liver function test results were the most common laboratory findings, including 57 patients (81.4%) with elevated alanine aminotransferase levels, 55 patients (78.6%) with elevated aspartate aminotransferase levels, 49 patients (70%) with elevated alkaline phosphatase (ALP) levels, and 44 patients (62.9%) with elevated total bilirubin levels. Etiology analysis revealed that the majority of cases (28/70, 40%) were associated with autoimmune liver diseases, including autoimmune hepatitis (AIH) (n = 25), primary sclerosing cholangitis (PSC) (n = 2), and overlapping AIH and PSC (n = 1). Viral infections accounted for 11% (8/70) of the cases, including hepatitis C virus (HCV) (n = 4), HIV (n = 1), HCV combined with HIV (n = 2), and HCV combined with hepatitis B virus (HBV) and hepatitis D virus (n = 1). Five cases (7%) were associated with medications (2 with dietary supplements, 2 with methamphetamine, and 1 with Trimethoprim/Sulfamethoxazole), and the other 5 (7%) had combined etiologies (AIH with alcoholic liver disease [ALD], n = 1; HCV with medication, n = 1; ALD with medication, n = 1; autoimmune liver disease with heterozygous *ABCB11* gene mutation, n = 1; and steatohepatitis with infection, n = 1). Four (6%) patients had underlying hematologic malignancies, including chronic lymphocytic lymphoma [CLL] (n = 3) and "small cleaved cell lymphoma" (n = 1). Notably, 16% (11/70) of the patients had de novo PIGCH in liver allografts. The remaining 9 cases (13%) had an unknown etiology after extensive workup (Fig. 1).

Recurrence of Postinfantile Giant Cell Hepatitis After Transplantation

Seventeen patients received liver transplantation as a treatment for PIGCH in this cohort, and 2 patients developed recurrent PIGCH after liver transplantation. One patient was a 36-year-old man with PIGCH of unknown etiology. He underwent liver transplantation, and the posttransplantation course was complicated by acute T cell–mediated rejection. PIGCH recurred 3 years after the first liver transplantation. The patient underwent a second liver transplantation, with a posttransplantation course again complicated by acute T cell–mediated rejection. His PIGCH recurred 13 months after the second liver transplant. The second patient was a 68-year-old woman with PIGCH associated with AIH who became HCV-positive after receiving an HCV-positive donor liver. The patient's PIGCH recurred 3 years after transplantation.

De Novo Postinfantile Giant Cell Hepatitis After Transplantation

As described in the previous section, 11 PIGCH cases developed de novo after liver transplantation (Table 2), with a time interval of 92 days to 18 years. Prior biopsies and explanted livers were reviewed, and no giant cells were observed. Native liver diseases included AIH (n = 3), end-stage ALD (n = 2), HCV cirrhosis (n = 1), cryptogenic cirrhosis (n = 1), PSC (n = 1), drug-induced liver injury (n = 1), congenital biliary atresia (n = 1), and acute hepatitis with submassive necrosis of unknown etiology (n = 1). Seven patients (64%) had a history of acute T cell–mediated rejection prior to the development of PIGCH. Two of these patients underwent a second liver transplantation without recurrence of PIGCH.

Table 2
Liver allografts with de novo postinfantile giant cell hepatitis

Case no.	Age (y)	Sex	Disease on native liver	Time interval between the first onset of PIGCH to the time of transplant	Outcome	History of rejection	Need another transplantation
Case 1	57	M	HCV	210 d	Deceased		
Case 2	56	M	PSC	92 d	Deceased	Yes	
Case 3	65	F	AIH	5 y	Deceased	Yes	
Case 4	38	F	AIH	6 y	Deceased	Yes	
Case 5	23	F	DILI	4 y	Alive	Yes	Yes
Case 6	35	M	ALD	1.7 y	Deceased	Yes	
Case 7	31	F	AIH	11 y	Deceased	Yes	
Case 8	24	F	Congenital biliary atresia	18 y	Alive		Yes
Case 9	50	F	Acute hepatitis with submassive necrosis	174 d	Alive	Yes	
Case 10	57	M	ALD	8 y	Alive		
Case 11	65	F	Cryptogenic cirrhosis	8 y	Alive		

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; DILI, drug-induced liver injury; F, female; HCV, hepatitis C virus; M, male; PIGCH, postinfantile giant cell hepatitis; PSC, primary sclerosing cholangitis.

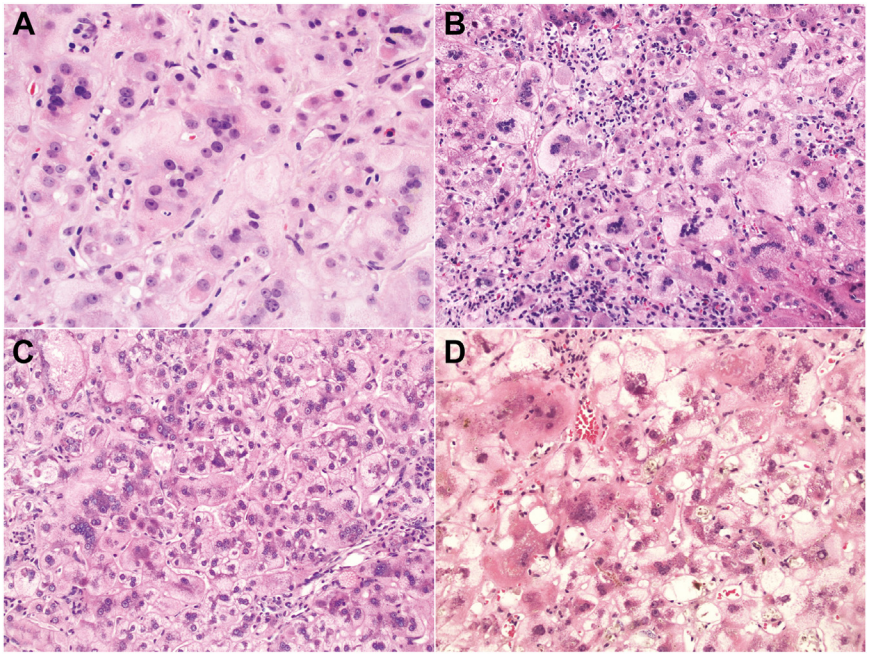

Figure 2.
Representative images of postinfantile giant cell hepatitis. (A) Giant cell hepatitis in a liver with autoimmune hepatitis. (B) Giant cells hepatitis in a liver with chronic lymphocytic leukemia. (C) Giant cells hepatitis in a liver with unknown etiology. (D) Recurrent giant cell hepatitis in an allograft liver. (A-D) Hematoxylin and eosin stain, original magnification 200×).

Histopathological Features of Postinfantile Giant Cell Hepatitis

Histopathological analysis revealed that 23 cases (32.9%) showed <5 giant cells per 40× HPF, 28 cases (40%) showed 5 to 10 giant cells per HPF, and 19 cases (27.1%) showed >10 giant cells per HPF (Fig. 2A-D). Thirty-one cases (44.3%) exhibited giant cell transformation involving more than 30% of the parenchyma, whereas 39 (55.7%) had scattered giant cells. Regarding the distribution pattern, 38 (54.3%) cases had giant cell transformation involving the liver parenchyma from zone 1 to zone 3 (panlobular), whereas 15 (21.4%) mainly involved zone 3, 10 (14.3%) mainly involved zone 1, and 4 (5.7%) mainly involved zone 2. Giant cells contained bile and Mallory-Denk bodies in 26 (37.1%) and 10 (14.7%) cases, respectively. Stage 3 or 4 fibrosis was present in 28 cases (40%). Varying degrees of portal inflammation appeared in all cases, whereas lobular inflammation was found in all but 2 cases. Lobular hepatocyte dropout, ranging from scattered single-cell or spotty necrosis to submassive necrosis, was identified in 46 cases (65.7%). Cholestatic features were found in 42 cases (60%), including canalicular cholestasis (4 cases, 5.7%), hepatocellular cholestasis (14 cases, 20%), and mixed cholestasis (24 cases, 34.3%). Steatosis was present in 11 cases (15.7%), of which 10 (14.3%) involved <33% of the parenchyma (Table 1).

The clinicopathological features of PIGCH were further analyzed among the 3 most commonly associated etiologies: AIH (n = 25), unknown etiology (n = 9), and de novo after liver transplantation. As expected, cases of PIGCH associated with AIH showed a higher level of immunoglobulin G (mean, 2376.1 g/L; P = .048), a higher degree of interface hepatitis (8/25, 32% with severe interface hepatitis; P = .04), lobular inflammation (12/25, 48% with severe lobular information; P = .01), and portal inflammation (7/25, 28% with severe portal inflammation; P = .10). In contrast, cases of PIGCH with unknown etiology were more likely to have bile in giant cells (6/9, 66.7%; P = .01). Finally, the majority of the de novo PIGCH cases after transplantation (7/11, 63.6%; P= .04) showed <5 giant cells per HPF with scattered distribution (9/11, 81.8%; P = .04), and both lobular inflammation (no to mild, 9/11, 81.8%; P = .01) and interface hepatitis (no to mild, 11/11, 100%; P = .04) appeared to be mild (Table 3).

Considering AIH is the most common etiology associated with PIGCH, these cases were further compared with 8 treatment-naive adult AIH cases without giant cell transformation identified in our archives in 2019. AIH with giant cell reactions appeared to be younger (mean age, 48.7 years vs 62.9 years; P = .039) and more likely to have any kind of cholestasis (canalicular or hepatocellular or mixed, 56% [14/25] vs 12.5% [1/8]; P = .046) compared with AIH without giant cells reactions (Supplementary Table S1).

Because viral etiologies, especially paramyxoviral infection, have been reported to be associated with PIGCH,[11,12] electron microscopy (EM) was performed to investigate whether viral particles were present in 10 cases, including PIGCH of unknown etiology (n = 5), chronic lymphocytic leukemia (n = 2), infection (HIV, n = 1), AIH (n = 1), and combined etiology (AIH and alcohol, n = 1). Except for 1 biopsy sample from a patient with a known HIV infection that showed HIV viral particles, all the remaining 9 biopsy samples were negative for viral particles. Instead, other abnormalities were identified, including smooth endoplasmic reticulum amplification (n = 7), mitochondrial changes (pleomorphic mitochondria with crystalline cristae in 3, bizarre mitochondria in 1, dilated mitochondria in 1, and abundant mitochondria in 1), and microvesicular steatosis (n = 5).

Clinical, Laboratory, and Pathological Features Associated With Worse Outcomes

During follow-up (3 days to 31 years; median, 4.1 years), 26 patients (37.1%) died and 44 (62.9%) were alive. The deceased

Table 3
Comparison of clinical, laboratory, and histologic parameters in postinfantile giant cell hepatitis patients due to autoimmune hepatitis, unknown etiology, and de novo posttransplantation

Parameters	AIH, n = 25	Unknown etiology, n = 9	De novo posttransplantation, n = 11	*P* value	AIH vs Unknown etiology	AIH vs de novo	Unknown etiology vs de novo
Age (y)	48.7 (18.0-71.0)	52.4 (24.0-86.0)	45.5 (23.0-65.0)	.71			
Sex				.97			
Male	8 (32.0%)	3 (33.3%)	4 (36.4%)				
Female	17 (68.0%)	6 (66.7%)	7 (63.6%)				
IgG (g/L)	2376.1 (717.0-4330.0), (n = 18)	1783.3 (1340.0-2710.0), (n = 4)	954.3 (577.0-1370.0), (n = 4)	.05	.54	.04	.48
AST (U/L)	595.2 (26.0-3000.0), (n = 24)	740.5 (30.0-2860.0), (n = 6)	274.9 (24.0-771.0), (n = 9)	.38			
ALT (U/L)	555.3 (46.0-2028.0), (n = 24)	491.5 (27.0-1434.0), (n = 6)	207.3 (38.0-510.0), (n = 8)	.24			
ALP (U/L)	192.3 (48.0-548.0), (n = 23)	183.2 (79.0-312.0), (n = 6)	252.0 (56.0-870.0), (n = 9)	.56			
GGT (U/L)	226.2 (29.0-828.0), (n = 12)	69.0 (63.0-75.0), (n = 2)	582.0 (33.0-2022.0), (n = 4)	.37			
TB (mg/dL)	7.6 (0.3-33.0), (n = 23)	11.2 (0.7-20.8), (n = 6)	11.9 (0.4-28.3), (n = 9)	.43			
Albumin (g/dL)	3.2 (1.8-4.7), (n = 22)	3.1 (2.2-4.0), (n = 5)	3.5 (2.3-4.6), (n = 7)	.68			
Histology	n = 25	n = 9	n = 11				
Giant cell score (number/40×)				.04			
1: <5	4 (16.0%)	3 (33.3%)	7 (63.6%)				
2: 5-10	13 (52.0%)	2 (22.2%)	3 (27.3%)				
3:>10	8 (32.0%)	4 (44.4%)	1 (9.1%)				
Distribution of giant cells				.04			
>30% of lobule	16 (64.0%)	4 (44.4%)	2 (18.2%)				
Scattered	9 (36.0%)	5 (55.6%)	9 (81.8%)				
Giant cell location				.42			
Zone 1	4 (16.0%)	2 (22.2%)	4 (36.4%)				
Zone 2	1 (4.0%)	0 (0.0%)	2 (18.2%)				
Zone 3	4 (16.0%)	1 (11.1%)	2 (18.2%)				
Zone 1 to zone 3	15 (60.0%)	5 (55.6%)	2 (18.2%)				
Others[a]	1 (4.0%)	1 (11.1%)	1 (9.1%)				
Bile in giant cell				.01			
No	14 (56.0%)	3 (33.3%)	11 (100.0%)				
Yes	11 (44.0%)	6 (66.7%)	0 (0.0%)				
Mallory-Denk body in giant cell				.11			
No	18 (72.0%)	8 (88.9%)	11 (100.0%)				
Yes	7 (28.0%)	1 (11.1%)	0 (0.0%)				
Fibrosis				.25			
Stage 0-2	16 (64.0%)	3 (33.3%)	7 (63.6%)				
Stage 3 and 4	9 (36.0%)	6 (66.7%)	4 (36.4%)				
Portal inflammation				.10			
No	0 (0.0%)	0 (0.0%)	0 (0.0%)				
Mild	7 (28.0%)	3 (33.3%)	6 (54.5%)				
Moderate	11 (44.0%)	6 (66.7%)	5 (45.5%)				
Severe	7 (28.0%)	0 (0.0%)	0 (0.0%)				
Interface hepatitis				.04			
No	6 (24.0%)	4 (44.4%)	6 (54.5%)				
Mild	6 (24.0%)	2 (22.2%)	5 (45.5%)				
Moderate	5 (20.0%)	3 (33.3%)	0 (0.0%)				
Severe	8 (32.0%)	0 (0.0%)	0 (0.0%)				
Portal plasma cell				.26			
No	2 (8.0%)	3 (33.3%)	3 (27.3%)				
Rare	10 (40.0%)	4 (44.4%)	4 (36.4%)				
Moderate	9 (36.0%)	2 (22.2%)	1 (9.1%)				
Severe	4 (16.0%)	0 (0.0%)	3 (27.3%)				
Lobular inflammation				.01			
No	0 (0.0%)	1 (11.1%)	0 (0.0%)				
Mild	7 (28.0%)	5 (55.6%)	9 (81.8%)				
Moderate	6 (24.0%)	0 (0.0%)	2 (18.2%)				
Severe	12 (48.0%)	3 (33.3%)	0 (0.0%)				
Lobular dropout				.19			
No	9 (36.0%)	6 (66.7%)	5 (45.5%)				
Scattered single-cell or spotty necrosis	7 (28.0%)	2 (22.2%)	6 (54.5%)				
Bridging necrosis	7 (28.0%)	1 (11.1%)	0 (0.0%)				

(*continued on next page*)

Table 3 (*continued*)

Parameters	AIH, n = 25	Unknown etiology, n = 9	De novo posttransplantation, n = 11	*P* value	AIH vs Unknown etiology	AIH vs de novo	Unknown etiology vs de novo
Zone 3 necrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)				
Submassive necrosis	2 (8.0%)	0 (0.0%)	0 (0.0%)				
Apoptotic body				.48			
No	6 (24.0%)	4 (44.4%)	4 (36.4%)				
Yes	19 (76.0%)	5 (55.6%)	7 (63.6%)				
Cholestasis				.53			
No	11 (44.0%)	1 (11.1%)	6 (54.5%)				
Canalicular	2 (8.0%)	1 (11.1%)	0 (0.0%)				
Hepatocellular	4 (16.0%)	3 (33.3%)	2 (18.2%)				
Mixed	8 (32.0%)	4 (44.4%)	3 (27.3%)				
Steatosis				.43			
No	22 (88.0%)	9 (100.0%)	9 (81.8%)				
5%-33%	3 (12.0%)	0 (0.0%)	2 (18.2%)				
34%-66%	0 (0.0%)	0 (0.0%)	0 (0.0%)				
>67%	0 (0.0%)	0 (0.0%)	0 (0.0%)				

Data are presented as mean (range) or n (%).
AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; TB, total bilirubin.
[a] Giant cells in zone 1 and zone 2 (n = 1), zone 1 and zone 3 (n = 1) and perifibrotic septa (n = 1).

patients were grouped as "PIGCH with poor outcome" and those still alive were grouped as "PIGCH with good outcome" with no restriction on the cause of death. Patients with a poor outcome were significantly older (mean age, 54.9 vs 45.5 years; $P = .02$), had significantly higher levels of ALP (mean value, 256.3 vs 166.3 U/L; $P = .03$), and were more likely to have higher stages of fibrosis (stage 3 or 4 fibrosis, 57.7% [15/26] vs 29.6% [13/44]; $P = .03$). Etiologically, those with a poor outcome were more likely to have de novo PIGCH after transplantation and less likely to have primary autoimmune liver disease etiology (23.1% [6/26] vs 11.4% [5/44] and 26.9% [7/26] vs 47.7% [21/44], respectively; $P = .04$). There were no differences in sex distribution, other laboratory results (aminotransferases, total bilirubin, gamma-glutamyl transferase, and albumin), number or localization of giant cells, and other pathological features including cholestasis, steatosis, portal inflammation, interface hepatitis, lobular inflammation, lobular dropout, and apoptosis. A detailed comparison is summarized in Table 4.

Among the 26 deceased patients, 16 patients died of liver-related etiology, whereas 10 patients died of other non–liver-related etiologies. Patients who died of liver-related etiology had the highest ALP level (mean value, 304.8 vs 157.6 U/L and 166.3 U/L, respectively, $P = 0.002$) and were more likely to have stage 3 or 4 fibrosis (68.8% [11/16] vs 40% [4/10] and 29.6% [13/44], respectively; $P = .023$) compared with patients who died of non–liver-related etiologies and alive patients. Among the 16 patients who died of liver-related etiology, 6 patients (37.5%) had de novo PIGCH after liver transplantation, compared with 0% (0/10) and 11.4% (5/44) of patients who died of non–liver-related etiologies and alive patients, respectively, whereas the percentages of autoimmune-related etiology were 31.3% (5/16), 20% (2/10), and 47.7% (21/44), respectively, in these 3 groups ($P = .005$). Patients who died of liver-related etiology (54.1 years) or non–liver-related etiology (56.1 years) tended to be older than alive patients (45.5 years), whereas the overall *P* value was of borderline significance ($P = .057$) (Table 5).

Moreover, when deceased patients (liver-associated and other etiologies) were compared with alive patients within 3 years, patients in this particularly poor outcome subgroup were more likely to have a higher stage of fibrosis (stage 3 or 4 fibrosis, 64.3% [9/14] vs 25% [4/16]; $P = .03$), more likely to have de novo PIGCH after transplantation, and less likely to have primary autoimmune liver disease etiology (35.7% [5/14] vs 6.3% [1/16] and 14.3% [2/14] vs 50% [8/16], respectively; $P = .048$), whereas no significant difference was identified in age (58.7 vs 48.9 years; $P = .13$) and ALP value (256.5 vs 171.9 U/L; $P = .23$) (Supplementary Table S2).

Among the 44 surviving patients, 13 survived liver transplantation after disease progression. We further combined deceased patients and patients who survived after transplantation as one group of "poorer outcome" (n = 39) and compared with patients who survived without transplantation (n = 31). There was a correlation between ALP and poorer outcome (mean value, 233.4 vs 152.7 U/L; $P = .01$). Moreover, patients in the poorer outcome group had lower levels of albumin (mean value, 3.1 vs 3.6 g/dL; $P = .04$) and were more likely to have cholestasis (71.8% [28/39] vs 45.2% [14/31]; $P = .04$). There was no statistically significant correlation between outcomes and etiology, although there was a trend toward worse outcomes in de novo PIGCH and better outcomes in autoimmune liver disease (20.5% [8/39] vs 9.7% [3/31] and 28.2% [11/39] vs 54.8% [17/31], respectively; $P = .19$). However, the prognostic implication of age (mean age, 49.4 vs 48.5 years; $P = .82$) and stage 3 and 4 fibrosis (46.2% [18/39] vs 32.3% [10/31]; $P = .65$) diminished (Supplementary Table S3). This is likely due to the fact that patients who needed liver transplantation were significantly younger (mean age, 38.4 vs 54.9 years; $P = .008$) and were less likely to have stage 3 or 4 fibrosis (23.1% [3/13] vs 57.7% [15/26]; $P = .0574$) (Supplementary Table S4).

Multivariate logistic regression analysis showed that increased age (odds ratio (OR), 1.04; 95% CI, 1.01-1.08; $P = .02$), stage 3 and 4 fibrosis (OR, 3.25; 95% CI, 1.20-9.19; $P = .02$), and increased ALP level (OR, 1.01; 95% CI, 1.00-1.02; $P = .04$) were associated with worse outcomes. Because ALP was significantly correlated with fibrosis stage (Spearman correlation $r = 0.29$; $P = .03$), it was excluded from analysis in the model. Age (AOR, 1.04; 95% CI, 1.01-1.09; $P = .02$) and fibrosis stage (AOR, 3.85; 95% CI, 1.29-12.56; $P = .02$) remained independent factors associated with worse outcomes (Table 6).

Table 4
Comparison of clinical, laboratory, and histologic parameters in postinfantile giant cell hepatitis patients who died of disease vs those who are alive

Parameters	Deceased (n = 26)	Alive (n = 44)	*P* value
Age (y) (n = 70)	54.9 (23.0-86.0)	45.5 (18.0-71.0)	.02
Sex (n = 70)			>.99
Male	12 (46.2%)	19 (43.2%)	
Female	14 (53.8%)	25 (56.8%)	
IgG (g/L) (n = 33)	1909.6 (577.0-3386.0)	2187.6 (717.0-4547.0)	.52
AST (U/L) (n = 59)	688.2 (28.0-3270.0)	561.3 (24.0-3000.0)	.55
ALT (U/L) (n = 58)	760.9 (57.0-4060.0)	508.6 (27.0-1531.0)	.32
ALP (U/L) (n = 56)	253.3 (80.0-870.0)	166.3 (48.0-324.0)	.03
GGT (U/L) (n = 21)	470.8 (75.0-2022.0)	156.0 (29.0-828.0)	.22
TB (mg/dL) (n = 56)	9.8 (0.3-28.3)	10.1 (0.3-33.0)	.93
Albumin (g/dL) (n = 52)	3.3 (1.8-4.6)	3.3 (1.8-4.7)	.90
Etiology (n = 70)			.04
Autoimmune	7 (26.9%)	21 (47.7%)	
Infection	4 (15.4%)	4 (9.1%)	
Medicine/drug	0 (0.0%)	5 (11.4%)	
Malignancy	4 (15.4%)	0 (0.0%)	
Combined	2 (7.7%)	3 (6.8%)	
Unknown	3 (11.5%)	6 (13.6%)	
De novo posttransplantation	6 (23.1%)	5 (11.4%)	
Histology (n = 70)			
Giant cell score (number/40×)			.97
1: <5	9 (34.6%)	14 (31.8%)	
2: 5-10	10 (38.5%)	18 (40.9%)	
3:>10	7 (26.9%)	12 (27.3%)	
Distribution of giant cells			>.99
>30% of lobule	11 (42.3%)	20 (45.5%)	
Scattered	15 (57.7%)	24 (54.5%)	
Giant cell location (n = 70)			.71
Zone 1	4 (15.4%)	6 (13.6%)	
Zone 2	2 (7.7%)	2 (4.5%)	
Zone 3	6 (23.1%)	9 (20.5%)	
Panlobular	14 (53.8%)	24 (54.5%)	
Others[a]	0 (0.0%)	3 (6.8%)	
Bile in giant cells			.61
No	15 (57.7%)	29 (65.9%)	
Yes	11 (42.3%)	15 (34.1%)	
Mallory-Denk bodies in giant cells			>.99
No	22 (84.6%)	38 (86.4%)	
Yes	4 (15.4%)	6 (13.6%)	
Fibrosis			.03
Stage 0-2	11 (42.3%)	31 (70.4%)	
Stage 3 and 4	15 (57.7%)	13 (29.6%)	
Portal inflammation			.27
No	0 (0.0%)	0 (0.0%)	
Mild	8 (30.8%)	17 (38.6%)	
Moderate	16 (61.5%)	19 (43.2%)	
Severe	2 (7.7%)	8 (18.2%)	
Interface hepatitis			.56
No	9 (34.6%)	13 (29.5%)	
Mild	10 (38.5%)	14 (31.8%)	
Moderate	5 (19.2%)	8 (18.2%)	
Severe	2 (7.7%)	9 (20.5%)	
Portal plasma cell			.62
No	4 (15.4%)	6 (13.6%)	
Rare	15 (57.7%)	21 (47.7%)	
Moderate	4 (15.4%)	13 (29.5%)	
Severe	3 (11.5%)	4 (9.1%)	
Lobular inflammation			.21
No	0 (0.0%)	2 (4.5%)	
Mild	15 (57.7%)	19 (43.2%)	
Moderate	7 (26.9%)	8 (18.2%)	
Severe	4 (15.4%)	15 (34.1%)	

(*continued on next page*)

Table 4 (*continued*)

Parameters	Deceased (n = 26)	Alive (n = 44)	*P* value
Lobular dropout			.07
No	8 (30.8%)	16 (36.4%)	
Scattered single-cell or spotty necrosis	13 (50.0%)	13 (29.5%)	
Bridging necrosis	2 (7.7%)	12 (27.3%)	
Zone 3 necrosis	3 (11.5%)	1 (2.3%)	
Submassive necrosis	0 (0.0%)	2 (4.5%)	
Apoptotic body			.60
No	10 (38.5%)	13 (29.5%)	
Yes	16 (61.5%)	31 (70.5%)	
Cholestasis			.30
No	9 (34.6%)	19 (43.2%)	
Canalicular	0 (0.0%)	4 (9.1%)	
Hepatocellular	6 (23.1%)	8 (18.2%)	
Mixed	11 (42.3%)	13 (29.5%)	
Steatosis			.22
No	23 (88.5%)	36 (81.8%)	
5%-33%	2 (7.7%)	8 (18.2%)	
34%-66%	1 (3.8%)	0 (0.0%)	
>67%	0 (0.0%)	0 (0.0%)	

Data are presented as mean (range) or n (%).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; TB, total bilirubin.
[a] Giant cells in zone 1 and zone 2 (n = 1), zone 1 and zone 3 (n = 1) and perifibrotic septa (n = 1).

We further evaluated whether etiology and fibrosis stage could have an impact on prognosis in patients with PIGCH by calculating and plotting Kaplan-Meier survival curves. Patients with non-autoimmune etiology (Fig. 3A), de novo PIGCH after transplantation (Fig. 3B), and stage 3 or 4 fibrosis (Fig. 3C) had significantly poorer survival. When the analysis was performed in patients with stage 3 or 4 fibrosis, the overall survival of patients with nonautoimmune etiology was significantly poorer ($P = .03$; Fig. 3D).

Discussion

Our multi-institutional study analyzed the largest reported cohort of PIGCH to date, with a focus on outcomes. Consistent with previous studies, there was a high prevalence of necroinflammatory changes (portal inflammation, 100%; lobular inflammation, 97%; and lobular dropout, 65.7%) and cholestasis (60%) in the livers with PIGCH.[10,13] Also consistent with previous reports, we confirmed that autoimmune liver disease, especially AIH, was the most common etiology associated with PIGCH, accounting for 40% of cases.[1,3,14] Among the 5 PIGCH cases associated with medication, both methamphetamine and Bactrim (trimethoprim-sulfamethoxazole) had known liver toxicity; methamphetamine has been previously reported to induce giant cell transformation in hepatocyte.[15,16]. Notably, 2 cases were associated with "dietary supplements," which have been associated with PIGCH in previous reports[17,18]; this association is likely underestimated because of underreporting of supplement consumption in medical histories. Lymphoproliferative disorders are the most common PIGCH-associated malignancies in the literature, especially CLL.[19-28] In our current study, all 4 patients with a history of malignancy had lymphoproliferative disorders, including 3 patients with CLL and 1 with "small cleaved cell lymphoma" (diagnosed in 1988, no further classification could be obtained). It has been hypothesized that the host immune environment in CLL promotes the development of PIGCH. Patients with CLL have a 5% to 10% risk of developing autoimmune complications,[28] the most common of which is autoimmune hemolytic anemia.[21] Autoimmune hemolytic anemia is associated with giant cell hepatitis in infants[29-31] via a humoral immune-driven mechanism.[32] Moreover, patients with CLL often have immunodeficiency, rendering them susceptible to infections (eg, Epstein-Barr virus or Paramyxoviridae-like virus). However, among the 3 patients with CLL in our study, none had viral infection or known autoimmune complications.

Although early studies reported involvement of paramyxoviral infection in PIGCH cases,[11,12] the observations were challenged by other subsequent studies.[33,34] The previously recognized viral/viral-like particles appeared to be microtubular aggregates[35] or abnormal responses of the endoplasmic reticulum in injured and/or stimulated cells.[36] In the current study, the 10 cases that underwent EM examination did not reveal paramyxoviral or viral-like particles, except for HIV viral particles present in a known HIV-positive patient. These findings indicate that paramyxoviral infection may not be the etiology in the development of PIGCH. Similar to our findings, one study reported the EM features in a PIGCH case by showing the presence of abundant endoplasmic reticulum and numerous mitochondria in multinucleated cells.[37] These EM morphologic features are nonspecific, which may indicate reactive or regenerative changes in the hepatocytes.[9,37]

The broad variation in the clinical course and outcome in PIGCH is already known,[8-10,38] but the majority of these studies were descriptive. Estradas et al[39] suggested that PIGCH associated with AIH usually has a severe clinical course, whereas Bihari et al[38] reported a better outcome in PIGCH associated with hepatitis virus (HCV, HBV, and hepatitis E virus), a moderate outcome in PIGCH associated with autoimmune diseases, and a poor outcome in PIGCH associated with paramyxovirus, Epstein-Barr virus, hepatitis A virus, and posttransplant human papillomavirus infections.[38] Previously, we performed a meta-analysis based on published articles on PIGCH and found that patients with poor outcomes were characterized by older age, lower levels of platelet and albumin, higher levels of total bilirubin, and a panlobular distribution of giant cells.[40] However, our previous meta-analysis was literature-based, which could have been influenced by the quality of each individual case report; detailed histologic description was not always provided, and cases with unknown

Table 5
Comparison of clinical, laboratory, and histologic parameters among patients with postinfantile giant cell hepatitis who are deceased due to liver-related etiology vs non−liver-related etiology vs alive

Parameters	Died of liver etiology (n = 16)	Died of nonliver etiology (n = 10)	Alive (n = 44)	*P*	*P* value (nonliver vs liver)	*P* value (liver vs alive)	*P* value (nonliver vs alive)
Age (n = 70)	54.1 (23.0-86.0)	56.1 (29.0-83.0)	45.5 (18.0-71.0)	.057			
Sex (n = 70)				.925			
Male	7 (43.8%)	5 (50.0%)	19 (43.2%)				
Female	9 (56.3%)	5 (50.0%)	25 (56.8%)				
IgG (g/L) (n = 33)	1921.9 (577.0-3386.0)	1881.0 (1080.0-2710.0)	2187.6 (717.0-4547.0)	.813			
AST (U/L) (n = 59)	682.5 (110.0-2360.0)	698.6 (28.0-3270.0)	561.3 (24.0-3000.0)	.833			
ALT (U/L) (n = 58)	709.7 (63.0-2290.0)	848.9 (57.0-4060.0)	508.6 (27.0-1531.0)	.413			
ALP (U/L) (n = 56)	304.8 (93.0-870.0)	157.6 (80.0-235.0)	166.3 (48.0-324.0)	.002	.024	.001	.982
GGT (U/L) (n = 21)	549.2 (92.0-2022.0)	235.5 (75.0-396.0)	156.0 (29.0-828.0)	.200			
TB (mg/dL) (n = 56)	12.3 (1.1-28.3)	5.3 (0.3-20.8)	10.1 (0.3-33.0)	.302			
Albumin (g/dL) (n = 52)	3.0 (1.8-4.0)	3.6 (2.6-4.6)	3.3 (1.8-4.7)	.396			
Etiology (n = 70)				.005			
Autoimmune	5 (31.3%)	2 (20.0%)	21 (47.7%)				
Infection	1 (6.3%)	3 (30.0%)	4 (9.1%)				
Medicine/drug	0 (0.0%)	0 (0.0%)	5 (11.4%)				
Malignancy	1 (6.3%)	3 (30.0%)	0 (0.0%)				
Combined	1 (6.3%)	1 (10.0%)	3 (6.8%)				
Unknown	2 (12.5%)	1 (10.0%)	6 (13.6%)				
De novo posttransplantation	6 (37.5%)	0 (0.0%)	5 (11.4%)				
Histology							
Giant cell score (number/40×) (n = 70)				.829			
1: <5	6 (37.5%)	3 (30.0%)	14 (31.8%)				
2: 5-10	7 (43.8%)	3 (30.0%)	18 (40.9%)				
3:>10	3 (18.8%)	4 (40.0%)	12 (27.3%)				
Distribution of giant cells (n = 70)				.588			
>30% of lobule	8 (50.0%)	3 (30.0%)	20 (45.5%)				
Scattered	8 (50.0%)	7 (70.0%)	24 (54.5%)				
Giant cell location (n = 70)				.359			
Zone 1	4 (25.0%)	0 (0.0%)	6 (13.6%)				
Zone 2	2 (12.5%)	0 (0.0%)	2 (4.5%)				
Zone 3	2 (12.5%)	4 (40.0%)	9 (20.5%)				
Zone 1 to zone 3	8 (50.0%)	6 (60.0%)	24 (54.5%)				
Others[a]	0 (0.0%)	0 (0.0%)	3 (6.8%)				
Bile in giant cell (n = 70)				.643			
No	10 (62.5%)	5 (50.0%)	29 (65.9%)				
Yes	6 (37.5%)	5 (50.0%)	15 (34.1%)				
Mallory-Denk body in giant cell (n = 70)				.851			
No	14 (87.5%)	8 (80.0%)	38 (86.4%)				
Yes	2 (12.5%)	2 (20.0%)	6 (13.6%)				
Fibrosis (n = 70)				.023			
Stage 0-2	5 (31.3%)	6 (60.0%)	31 (70.4%)				
Stage 3 and 4	11 (68.8%)	4 (40.0%)	13 (29.6%)				
Portal inflammation (n = 70)				.474			
No	0 (0.0%)	0 (0.0%)	0 (0.0%)				
Mild	4 (25.0%)	4 (40.0%)	17 (38.6%)				
Moderate	11 (68.8%)	5 (50.0%)	19 (43.2%)				
Severe	1 (6.3%)	1 (10.0%)	8 (18.2%)				
Interface hepatitis (n = 70)				.646			
No	4 (25.0%)	5 (50.0%)	13 (29.5%)				
Mild	7 (43.8%)	3 (30.0%)	14 (31.8%)				
Moderate	3 (18.8%)	2 (20.0%)	8 (18.2%)				
Severe	2 (12.5%)	0 (0.0%)	9 (20.5%)				
Portal plasma cell (n = 70)				.417			
No	3 (18.8%)	1 (10.0%)	6 (13.6%)				
Rare	7 (43.8%)	8 (80.0%)	21 (47.7%)				
Moderate	3 (18.8%)	1 (10.0%)	13 (29.5%)				
Severe	3 (18.8%)	0 (0.0%)	4 (9.1%)				

(*continued on next page*)

Table 5 (*continued*)

Parameters	Died of liver etiology (n = 16)	Died of nonliver etiology (n = 10)	Alive (n = 44)	*P*	*P* value (nonliver vs liver)	*P* value (liver vs alive)	*P* value (nonliver vs alive)
Lobular inflammation (n = 70)				.467			
No	0 (0.0%)	0 (0.0%)	2 (4.5%)				
Mild	8 (50.0%)	7 (70.0%)	19 (43.2%)				
Moderate	5 (31.3%)	2 (20.0%)	8 (18.2%)				
Severe	3 (18.8%)	1 (10.0%)	15 (34.1%)				
Lobular dropout (n = 70)				.186			
No	5 (31.3%)	3 (30.0%)	16 (36.4%)				
Scattered single-cell or spotty necrosis	9 (56.3%)	4 (40.0%)	13 (29.5%)				
Bridging necrosis	1 (6.3%)	1 (10.0%)	12 (27.3%)				
Zone 3 necrosis	1 (6.3%)	2 (20.0%)	1 (2.3%)				
Submassive necrosis	0 (0.0%)	0 (0.0%)	2 (4.5%)				
Apoptotic body (n = 70)				.456			
No	5 (31.3%)	5 (50.0%)	13 (29.5%)				
Yes	11 (68.8%)	5 (50.0%)	31 (70.5%)				
Cholestasis (n = 70)				.491			
No	5 (31.3%)	4 (40.0%)	19 (43.2%)				
Canalicular	0 (0.0%)	0 (0.0%)	4 (9.1%)				
Hepatocellular	5 (31.3%)	1 (10.0%)	8 (18.2%)				
Mixed	6 (37.5%)	5 (50.0%)	13 (29.5%)				
Steatosis (n = 70)				.110			
No	15 (93.8%)	8 (80.0%)	36 (81.8%)				
5%-33%	1 (6.3%)	1 (10.0%)	8 (18.2%)				
34%-66%	0 (0.0%)	1 (10.0%)	0 (0.0%)				
>67%	0 (0.0%)	0 (0.0%)	0 (0.0%)				

Data are presented as mean (range) or n (%).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; TB, total bilirubin.
[a] Giant cells in zone 1 and zone 2 (n = 1), zone 1 and zone 3 (n = 1) and perifibrotic septa (n = 1).

etiology might have been underestimated due to publication bias. In our current analysis, we systematically reviewed 70 PIGCH cases across multiple institutions and found that patients who died of disease were significantly older, had significantly higher levels of ALP, and were significantly more likely to have advanced stage fibrosis than patients who survived. Patients who died of the disease were more likely to have de novo PIGCH after transplantation, and were less likely to have primary autoimmune liver disease etiology. There were no differences in the sex distribution, other laboratory results, or histologic features. In addition, multivariate logistic regression analysis revealed that advanced liver fibrosis stage was an independent and strong predictor of poor outcome.

Eleven of the 70 patients developed de novo PIGCH in allograft livers, of whom 7 had a history of rejection. This phenomenon has been reported in the literature, including 2 patients with infections (human herpesvirus 6A and cytomegalovirus), 2 patients with chronic rejection, and 3 patients with unknown etiology.[3,41,42] In the reported cases of PIGCH associated with allograft rejection, giant cells were located at the interface between centrilobular necrosis and preserved parenchyma, and both patients had PSC in the native liver.[43] None of the patients in our cohort had an identified viral etiology, but the close association with rejection suggests a possible role of immune dysregulation in the development of de novo PIGCH.

Genetic defects in bile secretion may play a role in the development of giant cell hepatitis in adults. Progressive familial intrahepatic cholestasis (PFIC), a group of rare autosomal recessive disorders caused by defects in bile secretion, usually presents with cholestasis during infancy and childhood.[44] Giant cell transformation is a common histologic feature of PFIC,[45] especially PFIC type 2, which is caused by mutations in *ABCB11*, a gene encoding a bile salt export pump.[46-48] A 39-year-old woman in our cohort presented with incidental liver function test abnormalities and was managed with the presumption of having AIH for years, but was later diagnosed with PSC and was found to have a heterozygous mutation in *ABCB11*. Although PFIC is usually considered a disease in pediatric patients, variants in genes

Table 6
Factors associated with poor outcome

Factors	Univariate analysis		*P* value	Multivariate analysis		*P* value
	OR	95%CI		AOR	95%CI	
Age	1.04	1.01–1.08	.02	1.04	1.01-1.09	.02
Male sex	1.13	0.42-3.00	.81	1.96	0.65-6.39	.24
Fibrosis (stage 3 and 4)	3.25	1.20-9.19	.02	3.85	1.29-12.56	.02
Autoimmune liver disease	0.40	0.13-1.11	.09			
de novo PIGCH	2.34	0.63-9.04	.20			
Alkaline phosphatase	1.01	1.00-1.02	.04			

AOR, adjusted odds ratio; OR, odds ratio; PIGCH, postinfantile giant cell hepatitis.

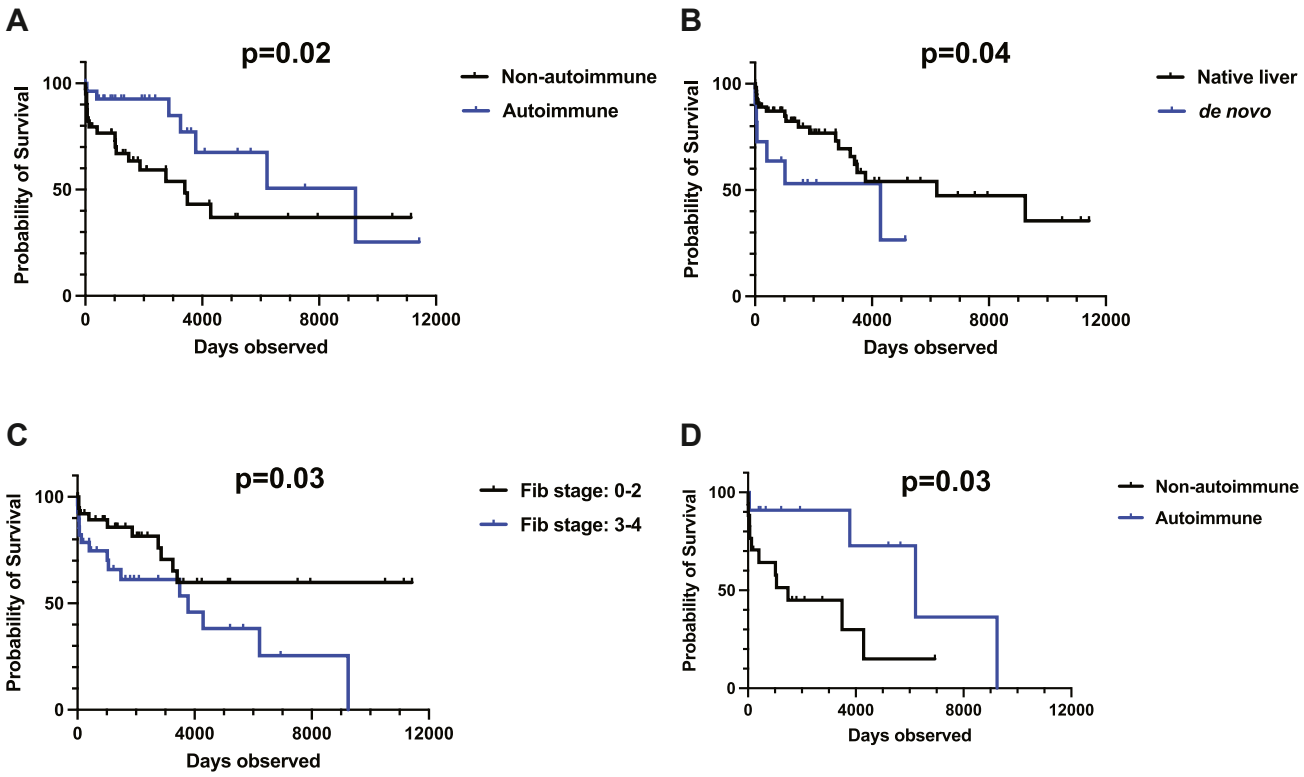

Figure 3.
Kaplan-Meier curve of overall survival for patients with postinfantile giant cell hepatitis stratified by etiology. (A) Autoimmune liver disease vs nonautoimmune liver disease. (B) De novo giant cell hepatitis on liver explant vs native liver. (C) Fibrosis stage (stage 0-2 vs stage 3 and 4). (D) Autoimmune liver disease vs nonautoimmune liver disease in patients with advanced fibrosis (stage 3-4).

associated with PFIC, including *ATP8B1*, *ABCB11*, *ABCB4*, and *TJP2* (associated with PFIC types 1, 2, 3, and 4, respectively), also contribute to adult-onset cholestasis.[49-53] Cholestasis was identified in 60% of our cohort, including 8 of 9 (89%) patients with unknown etiology after extensive workup. Genetic testing for PFIC may provide an insightful clue for patients with PIGCH of unknown etiology.

One enigmatic issue is the recurrence of PIGCH after liver transplantation.[54] Recurrent disease might be triggered by viral infection, as seen in 1 patient in our cohort who underwent transplantation for AIH-associated PIGCH and later developed PIGCH associated with HCV infection acquired from a donor liver with chronic hepatitis C. There is a similar literature report of a patient who underwent transplantation for cirrhosis with PIGCH (virus negative), and who redeveloped PIGCH in the allograft in association with acquired HBV infection and then again after a second transplantation.[55] However, recurrence of PIGCH cannot always be explained by a transmissible etiology (eg, virus),[56] as observed in the other patients with PIGCH in our cohort, whose disease recurred after 2 liver transplantations despite no identified etiology. It is known that giant cell hepatitis caused by PFIC type 2 in pediatric patients can reoccur in the allograft due to anti−bile salt export pump antibodies.[57,58] Additional studies are warranted to determine whether a similar autoimmune-mediated mechanism may be responsible for recurrent PIGCH in adults.

In summary, PIGCH is a rare histologic pattern of liver injury associated with different etiologies and highly variable clinical outcomes, rather than a specific pathology entity. The diagnosis of PIGCH should be followed by etiologic investigation to guide the clinician for proper patient management. Worse outcomes are associated with older age, cholestasis, and advanced fibrosis stage. Autoimmune liver diseases and cholestasis may be involved in hepatocyte giant cell transformation, and further studies are needed to better elucidate the pathogenesis of this rare liver disease.

Author Contributions

J.J. and X.Z. developed the study concept and design; performed data acquisition, analysis and interpretation of data, and statistical analysis; and wrote, reviewed, and revised the paper. K.C., X.Z., D.W., W.C., C.B., W.C., A.G.N., P.H., I.R., H.L.W., D.J.P., L.Z., Y.X., and X.L. acquired and reviewed the pathology material. All the authors read and approved the final manuscript.

Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Funding

The authors received no specific funding for this work.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Ethics Approval and Consent to Participate

The study was approved by the Yale University Human Investigation Committee. This study was conducted in accordance with the principles of Declaration of Helsinki. This was a retrospective research which received a waiver of informed consent from the IRB.

Supplementary Material

The online version contains supplementary material available at https://doi.org/10.1016/j.modpat.2023.100298

References

1. Devaney K, Goodman ZD, Ishak KG. Postinfantile giant-cell transformation in hepatitis. *Hepatology*. 1992;16(2):327–333. https://doi.org/10.1002/hep.1840160208
2. Celli R, Zhang X. Liver with non-specific/minimal histologic findings. In: Olave-Martinez M, ed. *Practical Interpretation of Liver Biopsy*. Cambridge Scholars Publishing; 2020:59–107.
3. Matta B, Cabello R, Rabinovitz M, Minervini M, Malik S. Post-infantile giant cell hepatitis: a single center's experience over 25 years. *World J Hepatol*. 2019;11(12):752–760. https://doi.org/10.4254/wjh.v11.i12.752
4. Torbenson M, Hart J, Westerhoff M, et al. Neonatal giant cell hepatitis: histological and etiological findings. *Am J Surg Pathol*. 2010;34(10):1498–1503. https://doi.org/10.1097/PAS.0b013e3181f069ab
5. Zenda T, Araki I, Sasaki M. Asymptomatic giant cell hepatitis: a subtype of post-infantile giant cell hepatitis? *Clin J Gastroenterol*. 2019;12(4):367–371. https://doi.org/10.1007/s12328-019-00950-6
6. Cairns A, McMahon RF. Giant cell hepatitis associated with systemic lupus erythematosus. *J Clin Pathol*. 1996;49(2):183–184. https://doi.org/10.1136/jcp.49.2.183
7. Moreno A, Moreno A, Pérez-Elías MJ, et al. Syncytial giant cell hepatitis in human immunodeficiency virus-infected patients with chronic hepatitis C: 2 cases and review of the literature. *Hum Pathol*. 2006;37(10):1344–1349. https://doi.org/10.1016/j.humpath.2006.05.003
8. Teles C, Santos R, Silva CD, Vaio T. Postinfantile giant cell hepatitis in the setting of autoimmune hepatitis: exclusively a histological pattern or a prognosis predictor? *BMJ Case Rep*. 2021;14(7):e243660. https://doi.org/10.1136/bcr-2021-243660
9. Richey J, Rogers S, Van Thiel DH, Lester R. Giant multinucleated hepatocytes in an adult with chronic active hepatitis. *Gastroenterology*. 1977;73(3):570–574. https://doi.org/10.1016/S0016-5085(19)32143-2
10. Johnson SJ, Mathew J, MacSween RN, Bennett MK, Burt AD. Post-infantile giant cell hepatitis: histological and immunohistochemical study. *J Clin Pathol*. 1994;47(11):1022–1027. https://doi.org/10.1136/jcp.47.11.1022
11. Fimmel CJ, Guo L, Compans RW, et al. A case of syncytial giant cell hepatitis with features of a paramyxoviral infection. *Am J Gastroenterol*. 1998;93(10):1931–1937. https://doi.org/10.1111/j.1572-0241.1998.00548.x
12. Phillips MJ, Blendis LM, Poucell S, et al. Syncytial giant-cell hepatitis. Sporadic hepatitis with distinctive pathological features, a severe clinical course, and paramyxoviral features. *N Engl J Med*. 1991;324(7):455–460. https://doi.org/10.1056/NEJM199102143240705
13. Lau JY, Koukoulis G, Mieli-Vergani G, Portmann BC, Williams R. Syncytial giant-cell hepatitis–a specific disease entity? *J Hepatol*. 1992;15(1-2):216–219. https://doi.org/10.1016/0168-8278(92)90039-r
14. Xiao Y, Gao ZH, Deschenes M. Autoimmune post-infantile giant cell hepatitis: a case report and review of the literature. *Can Liver J*. 2021;4(2):104–109. https://doi.org/10.3138/canlivj-2020-0024
15. Kouklakis G, Mpoumponaris A, Zezos P, et al. Cholestatic hepatitis with severe systemic reactions induced by trimethoprim-sulfamethoxazole. *Ann Hepatol*. 2007;6(1):63–65. https://doi.org/10.1016/S1665-2681(19)31956-8
16. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Amphetamines. Updated August 25, 2021. Accessed February 15, 2023. https://www.ncbi.nlm.nih.gov/books/NBK548941/
17. Fraquelli M, Colli A, Cocciolo M, Conte D. Adult syncytial giant cell chronic hepatitis due to herbal remedy. *J Hepatol*. 2000;33(3):505–508. https://doi.org/10.1016/s0168-8278(00)80289-5
18. Schoepfer AM, Engel A, Fattinger K, et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. *J Hepatol*. 2007;47(4):521–526. https://doi.org/10.1016/j.jhep.2007.06.014
19. Alexopoulou A, Deutsch M, Ageletopoulou J, et al. A fatal case of postinfantile giant cell hepatitis in a patient with chronic lymphocytic leukaemia. *Eur J Gastroenterol Hepatol*. 2003;15(5):551–555. https://doi.org/10.1097/01.meg.0000050026.34359.7c
20. Arvaniti P, Zachou K, Koukoulis GK, Dalekos GN. Postinfantile giant cell hepatitis with features of acute severe autoimmune hepatitis probably triggered by diclofenac in a patient with primary myelofibrosis. *Case Reports Hepatol*. 2018;2018, 9793868. https://doi.org/10.1155/2018/9793868
21. Autore F, Pasquale R, Innocenti I, Fresa A, Sora F, Laurenti L. Autoimmune hemolytic anemia in chronic lymphocytic leukemia: a comprehensive review. *Cancers (Basel)*. 2021;13(22):5804. https://doi.org/10.3390/cancers13225804
22. Colombo M, Donato MF. Images in hepatology. Adulthood giant-cell hepatitis. *J Hepatol*. 1997;27(3):587. https://doi.org/10.1016/s0168-8278(97)80366-2
23. Doria NA, Shaikh O, Tao SY, Frye RA. S2405 post-infantile giant cell hepatitis. *Am J Gastroenterol*. 2020;115(1):S1276–S1277. https://doi.org/10.14309/01.ajg.0000711668.07016.c8
24. Gupta E, Yacoub M, Higgins M, Al-Katib AM. Syncytial giant cell hepatitis associated with chronic lymphocytic leukemia: a case report. *BMC Blood Disord*. 2012;12:8. https://doi.org/10.1186/1471-2326-12-8
25. Gupta N, Njei B. Syncytial giant cell hepatitis in a patient with chronic lymphocytic leukemia. *J Dig Dis*. 2015;16(11):683–688. https://doi.org/10.1111/1751-2980.12273
26. Kethireddy N, Boyle E, Haley M, Reddy A, Forouhar F, Clement J. CLL associated giant cell hepatitis. *Leuk Res*. 2019;82:43–45. https://doi.org/10.1016/j.leukres.2019.05.011
27. Rhodes JM, Schuster SJ, Furth EE, et al. Management of giant cell hepatitis associated with chronic lymphocytic leukemia—a case series and review of the literature. *Cancer Biol Ther*. 2019;20(8):1136–1140. https://doi.org/10.1080/15384047.2019.1598763
28. Zent CS, Kay NE. Autoimmune complications in chronic lymphocytic leukaemia (CLL). *Best Pract Res Clin Haematol*. 2010;23(1):47–59. https://doi.org/10.1016/j.beha.2010.01.004
29. Nastasio S, Matarazzo L, Sciveres M, Maggiore G. Giant cell hepatitis associated with autoimmune hemolytic anemia: an update. *Transl Gastroenterol Hepatol*. 2021;6:25. https://doi.org/10.21037/tgh.2020.03.10
30. Poddighe D, Madiyeva A, Talipova D, Umirbekova B. Infantile giant cell hepatitis with autoimmune hemolytic anemia. *World J Hepatol*. 2021;13(4):411–420. https://doi.org/10.4254/wjh.v13.i4.411
31. Matarazzo L, Di Chio T, Nastasio S, Tommasini A, Ventura A, Maggiore G. B-cell depletion induces prolonged remission in patients with giant cell hepatitis and autoimmune hemolytic anemia. *Clin Res Hepatol Gastroenterol*. 2020;44(1):66–72. https://doi.org/10.1016/j.clinre.2019.03.010
32. Whitington PF, Vos MB, Bass LM, et al. Humoral immune mechanism of liver injury in giant cell hepatitis with autoimmune hemolytic anemia. *J Pediatr Gastroenterol Nutr*. 2014;58(1):74–80. https://doi.org/10.1097/MPG.0b013e3182a98dbe
33. Yunis E, Agostini R. Syncytial giant-cell hepatitis. *N Engl J Med*. 1992;327(2):130–131. https://doi.org/10.1056/NEJM199207093270218
34. Koff RS. Acute and chronic giant cell hepatitis: a paramyxovirus infection? *Gastroenterology*. 1991;101(3):863–864. https://doi.org/10.1016/0016-5085(91)90553-w
35. Spichtin HP, Gudat F, Schmid M, Pirovino M, Altorfer J, Bianchi L. Microtubular aggregates in human chronic non-A, non-B hepatitis with bridging hepatic necrosis and multinucleated hepatocytic giant cells. *Liver*. 1982;2(4):355–360. https://doi.org/10.1111/j.1600-0676.1982.tb00834.x
36. Yunis EJ, Agostini Jr RM, Glew RH. Fine structural observations of the liver in alpha-1-antitrypsin deficiency. *Am J Pathol*. 1976;82(2):265–286.
37. Pessayre D, Degos F, Feldmann G, Degott C, Bernuau J, Benhamou JP. Chronic active hepatitis and giant multinucleated hepatocytes in adults treated with clometacin. *Digestion*. 1981;22(2):66–72. https://doi.org/10.1159/000198597
38. Bihari C, Rastogi A, Sarin SK. Postinfantile giant cell hepatitis: an etiological and prognostic perspective. *Hepat Res Treat*. 2013;2013, 601290. https://doi.org/10.1155/2013/601290
39. Estradas J, Pascual-Ramos V, Martínez B, Uribe M, Torre A. Autoimmune hepatitis with giant-cell transformation. *Ann Hepatol*. 2009;8(1):68–70. https://doi.org/10.1016/S1665-2681(19)31815-0
40. Jiao J, Zhang X. Post-infantile giant cell hepatitis: a literature review and meta-analysis. *J Clin Transl Pathol*. 2022;2(3):100–107. https://doi.org/10.14218/jctp.2022.00016
41. Potenza L, Luppi M, Barozzi P, et al. HHV-6A in syncytial giant-cell hepatitis. *N Engl J Med*. 2008;359(6):593–602. https://doi.org/10.1056/NEJMoa074479
42. Pappo O, Yunis E, Jordan JA, et al. Recurrent and de novo giant cell hepatitis after orthotopic liver transplantation. *Am J Surg Pathol*. 1994;18(8):804–813. https://doi.org/10.1097/00000478-199408000-00007
43. Ludwig J, Gross Jr JB, Perkins JD, Moore SB. Persistent centrilobular necroses in hepatic allografts. *Hum Pathol*. 1990;21(6):656–661. https://doi.org/10.1016/s0046-8177(96)90013-1
44. Hassan S, Hertel P. Overview of progressive familial intrahepatic cholestasis. *Clin Liver Dis*. 2022;26(3):371–390. https://doi.org/10.1016/j.cld.2022.03.003
45. Alonso EM, Snover DC, Montag A, Freese DK, Whitington PF. Histologic pathology of the liver in progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 1994;18(2):128–133. https://doi.org/10.1097/00005176-199402000-00002
46. Morotti RA, Suchy FJ, Magid MS. Progressive familial intrahepatic cholestasis (PFIC) type 1, 2, and 3: a review of the liver pathology findings. *Semin Liver Dis*. 2011;31(1):3–10. https://doi.org/10.1055/s-0031-1272831

47. Pawlikowska L, Strautnieks S, Jankowska I, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. *J Hepatol*. 2010;53(1):170–178. https://doi.org/10.1016/j.jhep.2010.01.034
48. Davit-Spraul A, Fabre M, Branchereau S, et al. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. *Hepatology*. 2010;51(5):1645–1655. https://doi.org/10.1002/hep.23539
49. Nayagam JS, Foskett P, Strautnieks S, et al. Clinical phenotype of adult-onset liver disease in patients with variants in ABCB4, ABCB11, and ATP8B1. *Hepatol Commun*. 2022;6(10):2654–2664. https://doi.org/10.1002/hep4.2051
50. Dröge C, Bonus M, Baumann U, et al. Sequencing of FIC1, BSEP and MDR3 in a large cohort of patients with cholestasis revealed a high number of different genetic variants. *J Hepatol*. 2017;67(6):1253–1264. https://doi.org/10.1016/j.jhep.2017.07.004
51. Vitale G, Gitto S, Raimondi F, et al. Cryptogenic cholestasis in young and adults: ATP8B1, ABCB11, ABCB4, and TJP2 gene variants analysis by high-throughput sequencing. *J Gastroenterol*. 2018;53(8):945–958. https://doi.org/10.1007/s00535-017-1423-1
52. Hsu YC, Chen HL, Wu MZ, et al. Adult progressive intrahepatic cholestasis associated with genetic variations in ATP8B1 and ABCB11. *Hepatol Res*. 2009;39(6):625–631. https://doi.org/10.1111/j.1872-034X.2009.00499.x
53. Degiorgio D, Crosignani A, Colombo C, et al. ABCB4 mutations in adult patients with cholestatic liver disease: impact and phenotypic expression. *J Gastroenterol*. 2016;51(3):271–280. https://doi.org/10.1007/s00535-015-1110-z
54. Durand F, Degott C, Sauvanet A, et al. Subfulminant syncytial giant cell hepatitis: recurrence after liver transplantation treated with ribavirin. *J Hepatol*. 1997;26(3):722–726. https://doi.org/10.1016/s0168-8278(97)80440-0
55. Hassoun Z, N'Guyen B, Cote J, et al. A case of giant cell hepatitis recurring after liver transplantation and treated with ribavirin. *Can J Gastroenterol*. 2000;14(8):729–731. https://doi.org/10.1155/2000/807681
56. Nair S, Baisden B, Boitnott J, Klein A, Thuluvath PJ. Recurrent, progressive giant cell hepatitis in two consecutive liver allografts in a middle-aged woman. *J Clin Gastroenterol*. 2001;32(5):454–456. https://doi.org/10.1097/00004836-200105000-00024
57. Patel KR, Harpavat S, Finegold M, et al. Post-transplant recurrent bile salt export pump disease: a form of antibody-mediated graft dysfunction and utilization of C4d. *J Pediatr Gastroenterol Nutr*. 2017;65(4):364–369. https://doi.org/10.1097/MPG.0000000000001653
58. Kubitz R, Dröge C, Kluge S, et al. Autoimmune BSEP disease: disease recurrence after liver transplantation for progressive familial intrahepatic cholestasis. *Clin Rev Allergy Immunol*. 2015;48(2-3):273–284. https://doi.org/10.1007/s12016-014-8457-4