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Recurrence of autoimmune hepatitis cholestatic variant syndromes after liver transplantation affects graft and patient survival

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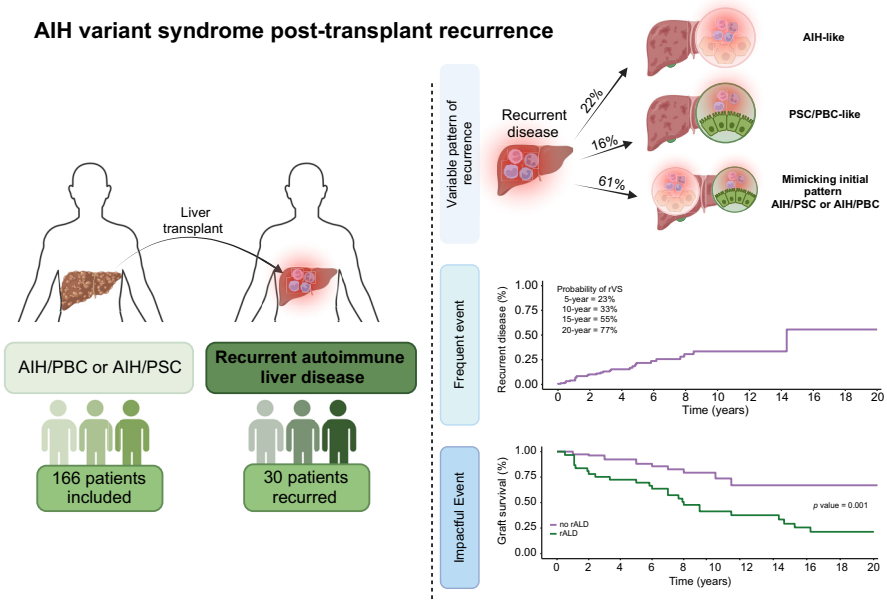
Graphical abstract



Highlights:

- Autoimmune liver diseases recur frequently on the graft of patients transplanted for AIH cholestatic variant syndromes.
- The pattern of disease recurrence often mimics the initial disease pattern.
- Recurrence of autoimmune liver disease on the graft is linked to poorer outcomes, including reduced graft and patient survival.
- Long-term patient outcomes emphasize the need for better strategies to prevent recurrence after liver transplantation.

Impact and implications:

This study investigated the recurrence of autoimmune liver diseases (rALD) in patients transplanted for variant syndromes (VSs) and its effect on graft and patient survival. The findings reveal a significant association between *r*ALD and poorer graft and overall survival, highlighting the need for preventive strategies. This research is crucial for transplant physicians and healthcare providers, as it underscores the impact of early liver enzyme monitoring and tailored immunosuppressive therapy on long-term outcomes. These insights can inform more effective post-LT management protocols, potentially improving patient prognosis.

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Research article

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Recurrence of autoimmune hepatitis cholestatic variant syndromes after liver transplantation affects graft and patient survival

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Background & Aims: A significant proportion of patients with variant syndromes (VSs), namely autoimmune hepatitis/primary biliary cholangitis or autoimmune hepatitis/primary sclerosing cholangitis, require liver transplantation (LT) despite treatment. The frequency of disease recurrence and the effect on graft survival are yet to be clarified. The aim of this international, multicentric, retrospective study is to evaluate the risk factors associated with recurrence and the impact of the disease recurrence after LT on graft and patient survival.

Methods: We evaluated 166 patients undergoing LT for VS in 33 centers in North America, South America, Europe, and Asia. Clinical data before and after LT, biochemical data within the first 12 months after LT, and immunosuppression after LT were analyzed to identify patients with a higher risk of recurrence of autoimmune disease based on a histological and radiological diagnosis. Cumulative probabilities of graft and overall survival after LT were calculated using a semi-Markov model.

Results: The autoimmune pattern of recurrence resembled the original VS in 19 cases (61%). Recurrence of autoimmune liver disease (*r*ALD) after LT was observed in 23% and 33% of patients after 5 and 10 years, respectively. Increased alkaline phosphatase (hazard ratio [HR] 1.60, 95% confidence interval [CI] 1.13–2.25, p <0.01) and alanine aminotransferase (HR 1.25, 95% CI 1.01–1.53, p = 0.03) at 12 months after LT and acute rejection (HR 3.58, 95% CI 1.60–7.73, p <0.01) were associated with a higher risk of VS recurrence, whereas the use of predniso(lo)ne was associated with a reduced risk (HR 0.30, 95% CI 0.14–0.64, p <0.01). After adjusting for alanine aminotransferase and alkaline phosphatase at 12 months, the use of predniso(lo)ne was found to be independently and negatively associated with recurrent disease. The *r*ALD was found to be significantly associated with graft loss and patient survival in the multivariate Cox regression analysis with a time-dependent covariate. The 5- and 10-year probabilities of graft survival were 68% and 41% in patients with recurrent VS compared with 83% and 60% in patients without recurrent disease, respectively (p = 0.01). The overall survival was significantly reduced in patients with recurrent disease (p = 0.01), with event probability at 5 and 10 years of 75% and 49% *vs*. 84% and 60% in patients without recurrence, respectively.

Conclusions: *r*ALD after LT is frequent and is associated with elevation in liver enzymes within the first year after LT and rejection episodes. According to our data, VS recurrence appears to be associated with poorer graft and patient survival. Further studies are needed to explore strategies that can prevent VS recurrence or mitigate its potential impact.

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^ The author passed away on August 1, 2023. This work is published posthumously in recognition of their contributions to this manuscript

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Introduction

Autoimmune hepatitis (AIH) is a clinically heterogeneous condition, characterized by the presence of autoantibodies, high levels of immunoglobulin G (IgG), and a typical histological pattern. Despite biochemical response to immunosuppression, specific subgroups of AIH exhibit a higher risk of progression toward end-stage liver disease.[1–4] Included in this subgroup are patients with cholestatic AIH variant syndrome (VS). The clinical presentation is typically with laboratory and histological features of either primary biliary cholangitis (PBC) in 10–20% of cases or primary sclerosing cholangitis (PSC) in 2–8%.[5–7] A diagnosis of cholestatic VS generally leads to worse clinical outcomes, particularly in the case of AIH/PSC, and liver transplantation (LT) remains the only life-saving treatment for patients who develop decompensated cirrhosis.[8–10]

We recently reported that the post-LT graft and overall outcomes in AIH are excellent, with a 5-year patient survival greater than 80%.[11] However, disease recurrence in the allograft is frequent, approaching 20% by 5 years, and this significantly impacts patient outcomes.[11]

Data on VS recurrence is scarce and generally comes from single-center experience describing a wide range of recurrence (0–50%).[12–14] Equally discrepant results have been reported on the effect of the recurrence on graft survival.[12–14]

One study using the United Network for Organ Sharing (UNOS) database reported a higher risk of graft failure in patients with AIH/PBC VS compared with those with AIH with recurrent disease.[15] Nevertheless, the frequency and risk factors associated with VS recurrence remain poorly studied because of the rarity of the condition.

Therefore, we evaluated a multicentric cohort of patients who underwent transplantation for AIH to analyze the cases of patients who underwent transplantation for VS and to evaluate the probability and risk factors associated with the recurrent disease and the impact of such occurrence on the graft and overall survival.

Patients and methods

Ethical approval

The research protocol was reviewed and approved by the institutional ethics review board of the University of Alberta Hospital (Pro00072855). All data were transferred to the University of Alberta Hospital according to the dedicated data transfer agreement.

Study population

Medical records from 911 patients who underwent transplantation for AIH from 1987 to 2020 in 33 tertiary centers across North and South America, Europe, and Asia were collected, as previously described.[10] We excluded patients with concomitant chronic liver disease and those younger than 18 years. We identified 166 patients diagnosed with cholestatic VS of AIH, either AIH/PBC (n = 78) or AIH/PSC (n = 94) (Fig. S1). The diagnosis of AIH/PBC was considered in patients with a diagnosis of AIH (based on histology, biochemical, and serological profiles), cholestatic laboratory/histological findings consistent with PBC, and antimitochondrial antibodies (AMA) using the Paris criteria.[6] Similarly, AIH/PSC was considered in patients with a diagnosis of AIH, histological features of bile duct injury or loss, and a magnetic resonance cholangiography (MRC) compatible with PSC.[1]

Clinical and biochemical profiles

The information retrieved from patient medical records included sex, ethnicity, blood group, concomitant autoimmune diseases, patient's age at VS diagnosis and LT, and the time between VS diagnosis and LT; serological profiles including antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and levels of IgG before LT. Relevant information on the LT, such as indication (end-stage liver disease/hepatocellular carcinoma [HCC] or acute liver failure), type of LT (cadaveric or live donor), biliary anastomosis, and model for end-stage liver disease (MELD) score were collected.[15] VS treatment and pre-LT ursodeoxycholic acid (UDCA) treatment were also recorded.

The initial immunosuppression regimens, long-term prednisolone use (beyond 1 and 5 years), initial trough levels of tacrolimus or cyclosporine, changes in immunosuppression after the first year of LT, liver biopsies after LT (protocol or clinically driven), and year of LT were also recorded.

We also collected the donor's age, blood group, and sex (including donor/recipient sex mismatch). Explant histology was recorded, particularly necroinflammatory activity and fibrosis score.

Evaluation of graft function included liver serum test, namely, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin, at the time of LT and 3, 6, and 12 months after LT. To account for the center variability, the values are shown as a factor of the upper limit of normal (ULN); the ULN ranged from 31 to 56 U/L for ALT, from 30 to 52 U/L for AST, from 16 to 18 g/L for IgG, and from 18 to 22 μmol/L for bilirubin across the different LT centers.

Given the multicentric nature of the project and to minimize the variability in VS diagnosis and data collection, the project was discussed during the biannual International Autoimmune Hepatitis Group (IAIHG) meetings to develop a protocol for diagnostic labeling of VS and consistent data collection across the participating centers.

Recurrent VS diagnosis

We define recurrent autoimmune liver disease (*r*ALD) as the appearance of any autoimmune condition on the graft (PBC, PSC, or AIH). The diagnosis of *r*ALD was based on histology and immunological profile in the case of AIH or PBC and magnetic resonance cholangiopancreatography (MRCP) assessment in the case of PSC. Recurrent AIH/PBC was defined by the simultaneous presence of histological features of AIH (lymphoplasmacytic portal inflammation with moderate to severe interface hepatitis) and biliary damage (significant portal infiltrate with destructive lymphocytic cholangitis and florid bile duct lesion), along with positive autoantibodies (AMA, ANA, SMA, anti-liver kidney microsome type 1 [anti-LKM-1]) and high IgG titer with confirmed negative viral hepatitis tests. Recurrent AIH/PSC was diagnosed based on the histological features of AIH and the histological (periductal fibrosis, obliterative ductular lesion, and bile duct loss) and radiological (intrahepatic and/or extrahepatic non-anastomotic biliary strictures) features of PSC in the absence of chronic rejection and the presence of normal hepatic arterial flow. Local histopathologists experienced in liver transplant pathology and

radiologists from all the tertiary centers involved performed the radiological and histological evaluation. In addition, the presence of other infections and concomitant use of potentially hepatotoxic drugs were ruled out.

Propensity score matching of the VS sub-cohort with the AIH population

As mentioned, the VS cases were extracted from a broader cohort of AIH cases. We took advantage of this setting to compare the two populations. We employed propensity score matching to assess the difference between the AIH cohort and the VS sub-cohort. The matching process was performed based on sex, age at transplantation, and transplantation date using the nearest-neighbor method at a 1:1 ratio.

Statistical analysis

The normal distribution of continuous variables was assessed graphically before the analysis. Those found approximately normally distributed were expressed as mean ± SD and compared across groups using an unpaired *t* test. Non-normally distributed continuous variables were expressed as median and IQRs and were compared using the Mann–Whitney *U* test. Fisher's exact probability assessment was used for the comparison of categorical variables.

Univariable Cox regression models were developed for demographic, clinical, and biochemical factors to identify potential predictors for *r*ALD. A multivariable model was then built using a backward stepwise approach (removal at $p > 0.1$) to identify independent predictors of recurrence. To ensure robustness and avoid overfitting, we adhered to the event-per-variable rule of thumb and included no more than five predictors.

The Kaplan–Meier method was used to compute the cumulative incidence of *r*ALD post LT, and the log-rank (Mantel–Cox) test was used for comparisons.

The effect of *r*ALD on the hazard rate of graft loss and overall patient survival was evaluated in both univariate and multivariate Cox regression analyses.

The model was fitted using *r*ALD as a time-dependent variable. The association of *r*ALD with graft loss and overall survival was also analyzed as a time-dependent covariate.

In the multivariable Cox proportional hazard regression model, variables with a p value of <0.1 in the univariate analysis and other pertinent variables were included. Patients who did not develop *rALD* and died or those who were lost during follow-up were censored at the time of death or their last follow-up visit. Patients who died or experienced graft loss within the first 3 months post LT were not included in the survival analysis, as it was assumed that these outcomes were linked to surgical complications rather than with *r*ALD. Graft loss did not include patients who died with a functioning graft but included only deaths related to or associated with graft failure or re-transplantation according to the death-censored definition of graft failure.

The cumulative probabilities of graft and overall survival post LT were computed using semi-Markov models ('clock reset' models), as the time resets to 0 every time a patient enters a new state (in this case, *r*ALD). Propensity score matching was performed to construct a cohort of patients with LT secondary to AIH to evaluate differences between patients who underwent transplantation for AIH and those for VS. The AIH cohort was well matched for age at LT ($p = 0.8$) and sex ($p = 1.0$), our matching parameters.

All the statistical analysis were done using R (Core Team [2024]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) and RStudio (RStudio: Integrated Development Environment for R. Posit PBC, Boston, MA, USA; https://posit.co/), as reported in the CTAT form.

Results

Characteristics, frequency, and probability of recurrent VS

The population of the study was predominantly female, with 111 individuals (65%) and a median age at LT of 46 years (IQR 30–56 years). The main features of the VS cohort are shown in Table 1. Recurrent VS was diagnosed in 30 patients, representing 18% of the entire study population (n = 166) and 26% of those who had at least one liver biopsy after LT (n = 117). Eight-two patients (49%) were diagnosed with AIH/PBC. Only 13 (8%) patients were started on UDCA prophylactically; 12 (38%) were treated with UDCA after the *r*ALD diagnosis was made. The other treatments offered for *r*ALD included predniso(lo)ne in 11 (35%) and mycophenolate (MMF) mofetil in 3 (10%). In 4 (13%) patients, the dose of the baseline immunosuppression with predniso(lo)ne, tacrolimus, or cyclosporine was increased. In one patient, predniso(lo)ne was added, and azathioprine was stopped and switched to MMF.

The median time from LT to the recurrence of VS was 2.8 years (IQR 1.2–5.7 years). The probability of *r*ALD was 23%, 33%, 55%, and 77% at 5, 10, 15, and 20 years, respectively (Fig. 1).

In addition, the probability of *r*ALD in patients with liver biopsies after LT (n = 117) was 26%, 41%, 61%, and 80% at 5, 10, 15, and 20 years, respectively (Fig. S2). The frequency of *r*ALD varied between 0% and 48% among centers. The yearly recurrence rate ranged from 2% to 6%. The overall incidence rate of *r*ALD after LT was 4.42 cases per 100 patient-years (95% confidence interval [CI] 4.39–4.43 cases per 100 patient-years). In addition, the incidence rate of *r*ALD after LT, including only patients who had liver biopsies after LT (n = 117), was 5.94 cases per 100 patient-years (95% CI 5.92–5.97 cases per 100 patient-years).

The biochemical features after LT in patients with and those without *r*ALD are presented in Table 2. Liver necroinflammatory activity was available in 118 patients (68%). It was grade 0 in two patients (2%), grade 1 in 28 patients (24%), grade 2 in 48 patients (41%), grade 3 in 30 patients (26%), and grade 4 in 10 patients (8%). The fibrosis assessment of the explant was available for 143 patients (83%). It was stage 1 in one patient (1%), stage 2 in three patients (2%), stage 3 in 15 patients (10%), and stage 4 in 124 patients (87%).

Biopsies after LT were performed in 117 patients (68%). Of these patients, 50 (29%) underwent protocol liver biopsies, whereas 67 (71%) had clinically driven biopsies because of abnormal serum liver tests.

Primary immunosuppression after LT included tacrolimus in 145 patients (91%), cyclosporine in 14 patients (9%), mycophenolate mofetil in 69 patients (45%), prednisone in 151 patients (75%), and azathioprine in 37 patients (26%) (Table 1).

The initial median tacrolimus trough level was 7.9 ng/ml (IQR 5–10.3 ng/ml), and the initial median cyclosporine trough level

Table 1. Clinical features associated with rALD in univariable analyses.

Clinical features	All patients (N = 166)	*r*ALD (n = 30)	No *r*ALD (n = 136)	HR	95% CI	*p* value
Age at the time of diagnosis (years), median (IQR)	36.5 (22–50)	38 (23–49)	36 (22–50)	0.99	0.97–1.02	0.55
Age at LT (years), median (IQR)	46 (30–56)	47 (25–56)	46 (31–56)	0.99	0.96–1.01	0.34
Male:female	57:109	8:22	51:85	1.02	0.46–2.13	0.94
Caucasian:non-Caucasian*	116:50	21:9	95:41	1.14	0.45–2.32	0.95
Time VS diagnosis and LT (years), median (IQR)	6.7 (1.3–10.0)	6.0 (1.0–10.0)	4.5 (2.0–9.8)	0.98	0.91–1.05	0.52
Variant syndrome, n (%)						
AIH/PBC**	82 (49)	16 (53)	66 (43)			
AIH/PSC	84 (51)	14 (47)	70 (56)	0.79	0.45–1.93	0.85
Blood group—recipient, n (%)						
0**	67 (38)	13 (46)	54 (42)			
A	68 (39)	13 (46)	55 (42)	0.85	0.32–1.59	0.42
B	16 (9)	2 (7)	14 (11)	0.63	0.16–3.21	0.67
AB†	7 (4)	0 (0)	7 (5)			
Concomitant autoimmune disease, n (%)	79 (48)	15 (50)	66 (48)	1.14	0.38–1.62	0.52
Immunosuppression before LT, n (%)						
Prednisone	120 (78)	25 (89)	95 (76)	2.76	0.80–9.00	0.10
Budesonide†	6 (4)	0 (0)	6 (5)			
Azathioprine	89 (61)	17 (65)	72 (60)	1.19	0.64–2.21	0.67
Mycophenolate mofetil	38 (15)	4 (20)	17 (15)	1.21	0.56–2.61	0.73
UDCA before LT, n (%)	27 (16)	6 (20)	21 (15)	1.37	0.55–3.38	0.50
Type of LT, n (%)						
Cadaveric**	128 (77)	25 (83)	103 (75)			
Living related	30 (23)	5 (17)	25 (25)	1.03	0.39–2.70	0.95
Bile duct anastomosis, n (%)						
Roux-en-Y	61 (48)	13 (47)	48 (40)			
End-to-end	86 (52)	15 (53)	71 (60)	0.86	0.42–1.60	0.65
Initial immunosuppression post LT, n (%)						
Tacrolimus	145 (91)	23 (79)	122 (94)	0.77	0.35-1.72	0.58
Cyclosporine	14 (9)	5 (17)	9 (7)	0.91	0.31-2.65	0.88
Prednisone or prednisolone	113 (75)	14 (52)	99 (80)	0.30	0.14-0.64	**<0.01**
Mycophenolate mofetil	69 (45)	6 (22)	63 (50)	0.46	0.19-1.42	0.11
Azathioprine	37 (26)	6 (22)	31 (25)	0.71	0.33-1.43	0.47
Tacrolimus (Initial trough levels, ng/ml), median (IQR)	7.9 (5.0–10.3)	7.5 (4.2–8.6)	8.1 (5.1–10.3)	1.05	0.89–1.12	0.93
Cyclosporine levels (initial trough levels, ng/ml), median (IQR)	250 (177–1,120)	322 (207–569)	225 (167–307)	0.99	0.99–1.03	0.87
UDCA after LT, n (%)	13 (7)	2 (6)	11 (8)	0.90	0.18–4.40	0.88
Long-term prednisone–prednisolone, n (%)						
>1 year	77 (44)	11 (35)	66 (46)	0.50	0.26–0.97	0.08
>5 years	34 (20)	13 (42)	21 (15)	1.75	0.92–3.30	0.22
Liver biopsies after LT, n (%)				0.32	0.63–3.03	0.42
Protocol**	50 (43)	10 (37)	40 (44)			
Clinically driven	67 (57)	17 (63)	50 (56)	0.32	0.63–3.03	0.42
LT center volume (high†:low)	147:19	27:3	120:16	1.64	0.60–5.55	0.42
LT decade						
1991–2000**	9 (5)	5 (17)	4 (3)			
2001–2010	40 (25)	13 (43)	26 (19)	1.22	0.35–4.26	0.75
2011–2020	117 (70)	12 (40)	106 (78)	0.51	0.14–1.83	0.30
Donor age (years), median (IQR)	40.5 (25-53)	38(34-47)	42(27-54)	0.98	0.95–1.00	0.12
Donor sex (male:female), median (IQR)	74:83	14:14	60:69	1.11	0.89–0.52	0.77
Donor–recipient sex mismatch, n (%)	55 (33)	13 (43)	42 (30)	1.72	0.58–0.82	0.15
Blood group—donor, n (%)						
0**	56 (45)	12 (60)	44 (48)			
A	41 (33)	7 (35)	34 (37)	0.81	0.22–1.59	0.30
B	10 (8)	1 (5)	9 (10)	1.33	0.06–3.57	0.46
AB†	5 (4)	0 (0)	5 (5)			
Explant necroinflammatory activity score, n (%)						
Grade 0/1/2**	78 (66)	17 (81)	61 (63)			
Grade 3/4	40 (34)	4 (19)	36 (37)	0.37	0.12–1.12	0.08
Explant fibrosis stage, n (%)						
Stage 1–2**	4 (2.6)	0 (0)	4(3.3)			
Stage 3–4	139 (97.4)	24 (100)	115 (96.7)	1.45	0.34–6.21	0.62
Acute rejections, n (%)	51 (30)	17 (57)	34 (25)	3.58	1.60–7.73	**<0.01**

HRs were calculated using Cox proportional regression analyses. AIH, autoimmune hepatitis; CI, confidence interval; HR, hazard ratio; LT, liver transplantation; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; *r*ALD, recurrent autoimmune liver disease; UDCA, ursodeoxycholic acid; VS, variant syndrome.

*Non-Caucasian includes, 13.4% Asian, 2.3% Turkish, 13.2% other/multiracial.

†Not displayed for lacking events in the no rALD group.

**Reference group. Bold means significant.

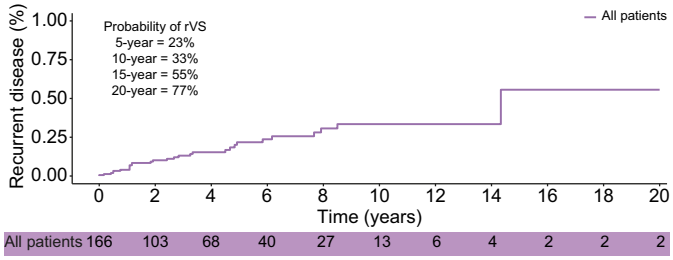

Fig. 1. Cumulative probability of *r*ALD. The probabilities of *r*ALD were 23%, 33%, 55%, and 77% at 5, 10, 15, and 20 years, respectively. The cumulative probabilities were calculated using the Kaplan–Meier method. *r*ALD, recurrent autoimmune liver disease.

was 250 ng/ml (IQR 177–1,120 ng/ml). The median initial doses were as follows: azathioprine, 100 mg daily (range 50–250 mg daily); mycophenolate mofetil, 1523 mg daily (range 360–1,200 mg daily); and predniso(lo)ne, 21 mg daily (range 5–100 mg daily).

Extended maintenance with predniso(lo)ne was used in 77 patients (44%) for >1 year after LT and in 34 patients (20%) for >5 years after LT.

Clinical and biochemical features associated with recurrent VS

Thirty patients developed recurrent diseases in our cohort. Of these patients, 15 underwent transplantation for AIH/PBC VS (55%). Among them, four had recurrent AIH (23.5%), four had recurrent PBC (23.5%), and nine exhibited features of both PBC and AIH (53%).

Among patients who underwent transplantation for AIH/PSC, three had recurrence with an AIH pattern (21%), one with a PSC pattern (7%), and 10 with features of both PSC and AIH (71%).

The use of predniso(lo)ne post LT (hazard ratio [HR] 0.30, 95% CI 0.14–0.64, p = 0.01) and T-cell-mediated rejection (TCMR) episodes (HR 3.58, 95% CI 1.60-7.73, p = 0.01) were significantly associated with the recurrent disease in the univariate analysis.

The era of LT (1991–2000 *vs*. 2001–2010, HR 1.22, 95% CI 0.35–4.26, p = 0.75; 1991–2000 *vs*. 2011–2020, HR 0.51, 95% CI 0.14–1.83, p = 0.30) did not show a significant association with rALD (Table 1).

There was no significant association with other clinical features, such as recipient sex, ethnicity, age or sex of the donor, LT indication, explant necroinflammatory activity and fibrosis, and the risk of *r*ALD (Table 1).

Higher levels of ALT (HR 1.25, 95% CI 1.01–1.53, p = 0.03), AST (HR 1.12, 95% CI 1.04–1.21, p <0.01), and ALP above the ULN (HR 1.60, 95% CI 1.13–2.25) at 12 months were associated with a higher risk of *r*ALD in the univariate Cox proportional hazard analysis (Table 2).

Multivariable analyses of features associated with VS recurrence

The multivariable analysis was modeled to include the use of predniso(lo)ne post LT, the type of VS, concomitant autoimmune diseases, and ALT and ALP at 12 months post LT. The use of steroids post LT, and ALT and ALP at 12 months were independently associated with the *r*ALD (Table 3).

In addition, we performed a multivariate sub-analysis including only patients who had a liver biopsy after LT (n = 117), showing that higher ALT (HR 1.83, 95% CI 1.0.6–3.16, p = 0.03) and ALP (HR 1.50, 95% CI 1.06–2.15, p = 0.02) at 12 months post LT were associated with a higher risk of recurrence. In contrast, AIH/PSC was associated with a lower risk compared with AIH/PBC VS (HR 0.27, 95% CI 0.10–0.90, p = 0.03) (Table S1).

Risk of recurrent disease and cohort comparison between VS and a matched cohort of AIH

We compared the VS cohort features with a propensity-matched cohort extracted from the AIH multicentric cohort we described in our previous study.[10] The population was well

Table 2. Biochemical features associated with recurrent autoimmune liver disease after liver transplantation in univariable Cox proportional hazard regression analyses.

Biochemical features	All patients (N = 166)	*r*ALD (n = 30)	No *r*ALD (n = 136)	HR	95% CI	*p* value
ALT × ULN (pre-LT)	1.24 (0.78–2.05)	1.20 (0.86–2.12)	1.26 (0.86–2.12)	1.00	0.96-1.04	0.96
AST × ULN (pre-LT)	2.37 (1.51–3.55)	2.23 (1.32–4.18)	2.41 (1.53–3.50)	0.99	0.96-1.03	0.78
Bilirubin × ULN (pre-LT)	9 (2.2–14.81)	4 (2–12)	5 (2–15)	1.04	0.92–1.01	0.09
ALP × ULN (pre-LT)	1.76 (1.15–2.44)	1.46 (1.02–2.73)	1.80 (1.22–2.98)	1.10	0.97–1.24	0.13
MELD (pre-LT)	18 (13–24)	18 (14–26)	18 (13–24)	1.00	0.97–1.05	0.65
IgG × ULN (pre-LT)	1.14 (0.71–1.61)	0.76 (0.59–1.29)	1.15 (0.75–1.68)	0.84	0.51–1.36	0.47
ALT × ULN (3 months)	0.58 (0.36–0.92)	0.58 (0.27–1.06)	0.60 (0.38–0.88)	1.08	0.86–1.35	0.50
AST × ULN (3 months)	0.55 (0.40–0.70)	0.53 (0.41–0.84)	0.55 (0.40–0.78)	1.47	0.88–2.44	0.13
Bilirubin × ULN (3 months)	0.48 (0.33–0.77)	0.45 (0.35–0.76)	0.50 (0.33–0.77)	0.51	0.18–1.47	0.21
ALP × ULN (3 months)	0.77 (0.56–1.28)	0.77 (0.54–1.47)	0.77 (0.57–1.26)	0.87	0.63–1.18	0.35
ALT × ULN (6 months)	0.56 (0.38–0.92)	0.76 (0.45–1.72)	0.54 (0.34–0.89)	1.04	0.91–1.18	0.53
AST × ULN (6 months)	0.58 (0.40–0.87)	0.75 (0.51–1.11)	0.58 (0.38–0.80)	1.17	0.97–1.42	0.09
Bilirubin × ULN (6 months)	0.60 (0.35–1.23)	0.67 (0.43–0.98)	0.60 (0.35–1.35)	0.98	0.91–1.05	0.62
ALP × ULN (6 months)	0.87 (0.65–1.60)	1.18 (0.68–1.83)	0.83 (0.63–1.54)	1.08	0.83–1.40	0.55
ALT × ULN (12 months)	0.57 (0.36–0.88)	0.62 (0.40–1.26)	0.57 (0.34–0.82)	1.25	1.01–1.53	0.03
AST × ULN (12 months)	0.54 (0.01–0.72)	0.55 (0.04–0.89)	0.43 (0.02–0.65)	1.12	1.04–1.21	<0.01
Bilirubin × ULN (12 months)	0.50 (0.34–0.75)	0.65 (0.35–1.03)	0.45 (0.33–0.70)	1.13	0.88–1.46	0.33
ALP × ULN (12 months)	0.91 (0.65–1.32)	1.05 (0.71–1.52)	0.90 (0.64–1.31)	1.60	1.13–2.25	<0.01

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; LT, liver transplantation; MELD, model for end-stage liver disease; *r*ALD, recurrent autoimmune liver disease; ULN, upper limit of normal.

Table 3. Features associated with autoimmune liver disease recurrence.

	HR	95% CI	*p* value
Prednisone or prednisolone post LT	0.34	0.14–0.76	**<0.01**
Variant syndrome (AIH/PSC)	0.40	0.13–1.17	0.09
Concomitant autoimmune disease	2.83	0.92–8.66	0.06
ALT × ULN (12 months)	2.10	1.32–3.34	**<0.01**
ALP × ULN (12 months)	1.49	1.06–2.09	**0.02**

Recurrence by multivariable Cox proportional hazard regression analyses. *p*-values in bold are significant. AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CI, confidence interval; HR, hazard ratio; PSC, primary sclerosing cholangitis; ULN, upper limit of normal.

matched for age at LT ($p = 0.8$) and sex ($p = 1.0$), our matching parameters (Table S2).

The population with VS had a higher frequency of concomitant autoimmune diseases compared with AIH alone (48% *vs*. 24%, $p < 0.01$) (Table S1). There was no difference in pre-LT immunosuppression, which was represented in both groups by predniso(lo)ne (AIH 79%, VS 78%) and azathioprine (AIH 55%, VS 61%) in most of the cases. Treatment with UDCA was started in 13% of patients with VS but in none of the patients with classical AIH (Table S2).

Liver function tests and IgG levels were similar in the two populations, except for ALP, which was higher in the VS group (249 *vs*. 151 U/L, $p < 0.01$). The MELD score differed between the two groups; it was higher in the AIH group than in the VS group (23 *vs*. 18, $p < 0.01$) (Table S2). Nineteen patients (32%) with AIH underwent transplantation for acute liver failure compared with 6 patients (4%) in the VS group ($p < 0.01$) (Table S2).

The choice of immunosuppression regimen after transplant differed significantly between the two groups, with azathioprine being used significantly more in the VS group (26% *vs*. 8%, $p < 0.01$) and mycophenolate mofetil more commonly in the AIH group (73% *vs*. 45%, $p < 0.01$) (Table S2).

The post-LT liver function tests were similar between the two populations, except for ALP, which was significantly higher in the VS group at 3 months (112 [77–206] *vs*. 95 [66–164], $p < 0.01$), 6 months (126 [85–222] *vs*. 99 [72–177], $p < 0.01$), and 12 months (130 [85–159] *vs*. 108 [72–180], $p = 0.05$).

The cumulative incidence of recurrent disease did not differ in the VS group compared with the AIH group (HR 1.19, 95% CI 0.68–2.10, $p = 0.53$) (Fig. S3).

Graft (HR 1.2, 95% CI 0.74–2.06, $p = 0.42$) and overall survival (HR 0.86, 95% CI 0.53–1.37, $p = 0.52$) were comparable between the two groups (Fig. S4A and B). The survival analysis demonstrated similar findings also in patients who had recurrent disease with no difference in the graft (HR 1.30, 95% CI 0.62–2.75, $p = 0.48$) and overall survival (HR 0.79, 95% CI

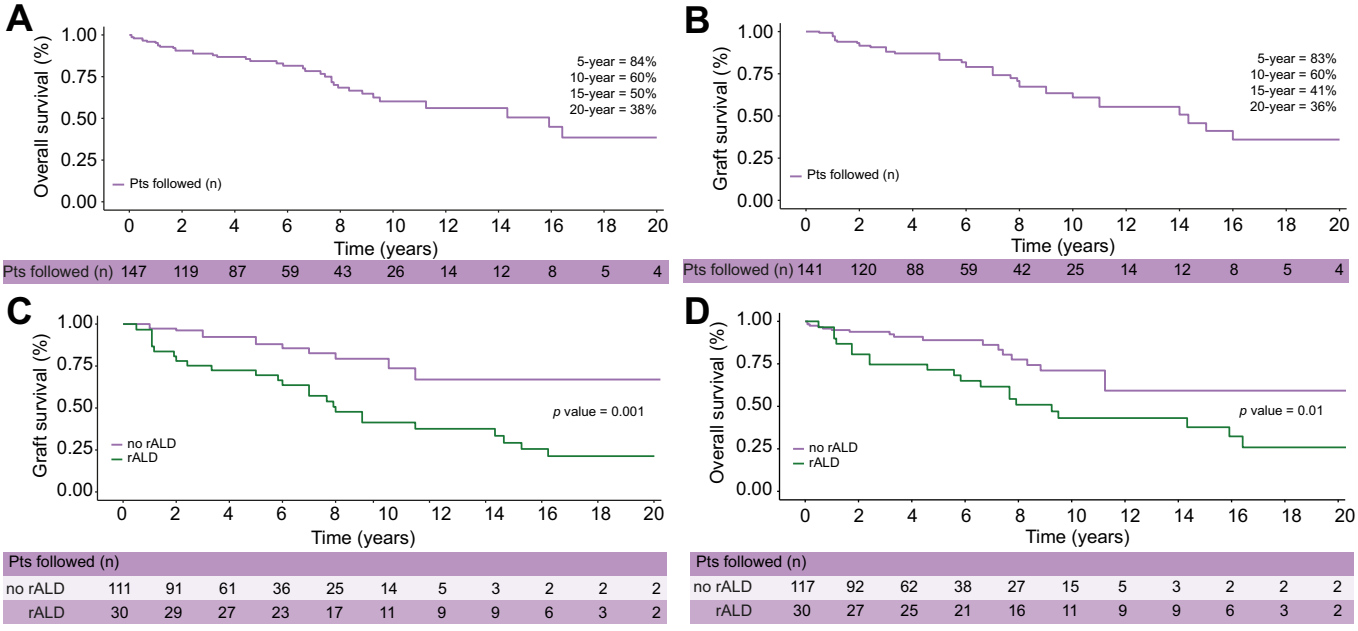

Fig. 2. Overall and graft survival. (A) Overall survival of VS patients after LT. The probabilities of survival at 5, 10, 15, and 20 years were 84%, 60%, 50%, and 38%, respectively. Cumulative probabilities were calculated using the Kaplan–Meier method. (B) Graft survival of VS patients after LT. The graft survival probabilities at 5, 10, 15, and 20 years were 83%, 60%, 41%, and 36%, respectively. Cumulative probabilities were calculated using the Kaplan–Meier method. (C) Graft survival in patients with and without recurrent VS after LT using the semi-Markov models ('clock reset' model) ($p = 0.01$). Cumulative probabilities were calculated using the Kaplan–Meier method. Patients who had no *r*ALD during their follow-up are represented by the pink line. Patients who developed *r*ALD are represented by the pink line only until they developed *r*ALD. These patients are then censored and switched to a new survival curve (green line) once they have *r*ALD. The time is then reset as time 0 for their further follow-up. (D) Overall survival in patients with and without recurrence of autoimmune liver disease after LT using the semi-Markov models ('clock reset' model) ($p = 0.001$). Cumulative probabilities were calculated using the Kaplan–Meier method. Patients who had no *r*ALD during their follow-up are represented by the pink line. Patients who developed *r*ALD are represented by the pink line only until they developed *r*ALD. These patients are then censored and switched to a new survival curve (green line) once they have *r*ALD. The time is then reset as time 0 for their further follow-up. LT, liver transplantation; rALD, recurrent autoimmune liver disease; VS, variant syndrome.

0.39–1.50, p = 0.50) in patients with recurrent AIH and *r*ALD (Fig. S5A and B).

Patient and graft survival associated with recurrent disease

Overall median survival after LT was 16.4 years (IQR 8.3–17 years). The probabilities of overall survival at 5, 10, 15, and 20 years were 84%, 60%, 50%, and 38%, respectively (Fig. 2A). The probabilities of graft survival at 5, 10, 15, and 20 years were 83%, 60%, 41%, and 36%, respectively (Fig. 2B).

In a Cox proportional hazard regression analysis implementing recurrence as a time-dependent covariate, *r*ALD (HR 3.12, 95% CI 1.57–6.19, p <0.01) was associated with graft failure. Age at LT (HR 1.05, 95% CI 1.00–1.11, p = 0.02) and ALT at 12 months post LT (HR 1.51, 95% CI 1.25–1.80, p <0.01) were also associated with graft failure in the univariate analysis. In the multivariate analysis, *r*ALD (HR 5.28, 95% CI 2.09–13.36, p <0.01), ALT at 12 months post LT (HR 2.03, 95% CI 1.16–3.82, p <0.01), and male sex (HR 2.63, 95% CI 1.03–6.65, p = 0.03) were independently associated with graft failure (Table 4).

In the univariate Cox regression analysis using time-dependent covariates, *r*ALD (HR 2.41, 95% CI 1.24–4.73, p = 0.01), TCMR episodes (HR 1.97, 95% CI 1.02–3.81, p = 0.04), donor/recipient sex mismatch (HR 1.97, 95% CI 1.02–3.78, p <0.001), and ALT at 12 months post LT (HR 1.29, 95% CI 1.09–1.52, p = 0.02) were all associated with overall survival after LT. In the multivariate analysis, only ALT at 12 months post LT (HR 1.27, 95% CI 1.03–1.56, p = 0.02) and *r*ALD (HR 2.06, 95% CI 1.00–4.24, p = 0.04) were independently associated with overall survival after LT (Table 4).

Of the 117 patients (68%) receiving biopsies post LT, 50 (42.7%) underwent protocol liver biopsies, whereas the remaining 67 (57.3%) had clinically driven biopsies resulting from abnormal serum liver tests. We performed a multivariable Cox regression analysis implementing recurrence as a time-dependent covariate only on those who had liver biopsies after LT (n = 117). The results were similar to those of the whole cohort (Table S3).

The impact of recurrent disease was clear on the mean graft survival, which was 18.8 years (95% CI 9.4–21.3) in patients who did not have *rALD* compared with 10.8 years (95% CI 3.6–13.8) in patients who were diagnosed with *r*ALD (p <0.01; Fig. 2C).

The probabilities of graft survival at 5, 10, 15, and 20 years were 68%, 41%, 26%, and 23% in patients with *r*ALD and 89%, 75%, 65%, and 61% in patients without *r*ALD, respectively (p <0.01; Fig. 2C). Most patients with *r*ALD lost their graft because of cirrhosis related to recurrent disease (81%), and the remainder were attributed to either ischemic-type biliary lesion (ITBL) (9%) or hepatic artery thrombosis–ischemic cholangiopathy (9%). In contrast, patients without *r*ALD lost their allograft because of ITBL (25%), hepatic artery thrombosis–ischemic cholangiopathy (18%), or other causes (56%).

Recurrent disease was also found to have an impact on the mean overall survival, which was 16.6 years (95% CI 2.7–29.7) for patients without *r*ALD compared with 8.8 years (95% CI 2.1–15.5) for those with *r*ALD (p <0.001; Fig. 2D). The probabilities of overall survival at 5, 10, 15, and 20 years were 74%, 44%, 36%, and 31% in patients with *r*ALD and 88%, 71%, 65%, and 62% in patients without *r*ALD, respectively (p <0.001; Fig. 2D). Most patients died because of infection episodes and sepsis, mainly bacterial (*r*ALD 50% *vs*. non-*r*ALD 47%) or malignancy (*r*ALD 30% *vs*. non *r*ALD 35%).

Discussion

In this multicentric study of 166 patients who underwent transplantation for cholestatic VS secondary to AIH, we explored the epidemiology of the recurrent disease and assessed its impact on graft and overall survival. Recurrence of VS on the graft was observed to be a common event, affecting nearly one-third of the patients within a decade post LT. Patients who experienced *r*ALD had a significant reduction in graft and overall survival, underscoring the need for preventive strategies in this patient population.

VS remains a rare clinical entity with no validated diagnostic criteria.[1] However, the presence of cholestatic features in patients with AIH is correlated with reduced response to immunosuppression and, in turn, with shorter transplant-free survival.[5,9,16] Data post LT for VS are scarce, particularly in studies assessing the risk of disease recurrence. In fact, there are only three small single-center case series in the literature showing an overall recurrence rate of disease ranging from 0 to 50%. The common definition of recurrent disease in these series was the presence of any autoimmune condition on the graft, consistent with the one adopted in our study.

Table 4. Features associated with graft and patient survival after LT.

	Univariate			Multivariable		
Features	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Graft survival analysis						
Age at LT	1.05	1.00–1.11	**0.02**	0.98	0.95–1.00	0.17
Sex (male)	1.08	0.98–1.17	0.06	2.63	1.03–6.65	**0.04**
Recurrence of VS*	3.12	1.57–6.19	**<0.01**	5.28	2.09–13.36	**<0.01**
Mycophenolate mofetil post LT	2.13	0.92–4.91	0.07	2.30	0.91–5.79	0.08
ALT × ULN (12 months)	1.51	1.25–1.80	**<0.01**	2.03	1.16–3.82	**<0.01**
Overall survival analysis						
Donor/recipient sex mismatch	1.97	1.02–3.78	**0.04**	1.84	0.92–3.66	0.08
TCMR episodes	1.97	1.02–3.81	**0.04**	1.26	0.61–2.59	0.53
Recurrence of VS*	2.41	1.24–4.73	**0.01**	2.06	1.00–4.24	**0.04**
ALT × ULN (12 months)	1.29	1.09–1.52	**0.02**	1.27	1.03–1	**0.02**

HRs were calculated using Cox proportional regression analyses. *p*-values in bold are significant. CI, confidence interval; HR, hazard ratio; LT, liver transplantation; *rALD*, recurrent autoimmune liver disease; TCMR, T-cell-mediated rejection; VS, variant syndrome.
*These HRs were obtained by considering *r*ALD as a time-dependent covariate in univariable and multivariable analyses.

Bhanji *et al.*[12] reported six cases of recurrent disease, four in patients with PBC/AIH and two in those with AIH/PSC. AIH/PBC recurred in two of the four cases with a PBC pattern, one as AIH and the other as AIH/PBC. In AIH/PSC, one of the two cases had a PSC pattern of recurrence on the graft, and the other recurred as AIH/PSC.[12] Chayanupatkul *et al.*[13] described three cases of recurrence (25%). Two of them had either an AIH/PBC or AIH/PSC pattern, whereas one recurred with an AIH pattern at first, developing PBC features during the follow-up.[13] In the third series, which included only patients with AIH/PBC, none experienced the recurrence of the graft.[15] The autoimmune pattern on the graft in our cohort resembled the original VS in 19 cases (63% [AIH/PBC 30% and AIH/PSC 33%]), whereas six patients recurred with an AIH pattern (20%), four with a PBC pattern (13%), and one as PSC (3%). However, the type of VS was not correlated to the risk of recurrence on the graft (AIH/PSC, HR 0.82, 95% CI 0.40–1.68, p = 0.60). Notably, not all the patients in our cohort underwent protocol biopsy, and this might have caused an underestimation of the incidence of the recurrent disease, as a biopsy is needed to confirm the diagnosis.

When we performed a multivariable Cox proportional hazard regression analysis on the sub-group of patients who received the liver biopsy, the AIH/PSC VS was found associated with a lower risk of developing recurrent disease compared with AIH/PBC (Table S1). Our cohort was derived from an international multicentric AIH cohort, which allowed us to compare our results in the VS cohort with a well-matched and characterized population of patients with AIH. Interestingly, the incidence rate of recurrent disease was not different in VS when compared with AIH. Such a comparison also revealed that patients with VS less frequently undergo transplantation for acute liver failure compared with patients with AIH. Furthermore, the AIH cohort was shown to be more frequently on mycophenolate mofetil compared with VS.

We previously demonstrated that the risk of recurrence was indeed increased by the use of mycophenolate mofetil in the first 12 months post LT.[11] The suggestion that a similar effect could be extended to VS comes from the study by Bhanji *et al.*,[12] which showed the use of mycophenolate mofetil was independently associated with recurrent disease on the graft of patients who underwent transplantation for VS.[12] Such evidence was not confirmed in our study, and we speculate that this might be a result of the under-representation of patients treated with MMF in our population. The cholestatic pattern of recurrence was reflected by an increased ALP at 3, 6, and 12 months in VS compared with AIH (Table S2). We found UDCA exposure to be surprisingly low. Only 16% of patients were started on UDCA before LT, and only 8% were started on UDCA right after LT. After the diagnosis of *r*ALD, 12 patients (38%) were started on UDCA. Of these patients, seven had a PBC or PBC/AIH pattern of recurrence (54% of the overall patients with either PBC or AIH/PBC), and five had a PSC or AIH/PSC pattern (45% of the overall patients with either PSC or AIH/PSC). None of the patients with an AIH pattern of recurrence was started on UDCA. Interestingly, the use of UDCA post LT did not reduce the risk of recurrence in our cohort at the univariate analysis (Table 1), and it did not have any impact on the overall or graft survival either.

Recently, Corpechot *et al.* demonstrated the effect of UDCA treatment post LT in preventing the recurrence of PBC on the graft (adjusted HR [aHR] 0.41,95% CI 0.28–0.61) and its benefit on the overall (aHR 0.69; 95% CI 0.49–0.96; p <0.05) and graft survival (aHR 0.33,95% CI 0.13–0.82). In their cohort, the use of preventive UDCA was more frequent (24%) than that in our cohort.[17] This discrepancy is likely attributable to the limited data and consensus on using UDCA in patients with VSs compared with those with PBC alone. Moreover, no preventive effect of UDCA has been demonstrated in patients with PSC; the UDCA effect in our cohort is likely mitigated by having pooled together patients with both forms of VS. However, we chose not to analyze the two cohorts separately in the interest of the sample size and number of events.

The low rate of UDCA used in patients with VSs post LT, especially those with AIH/PBC, may represent a missed opportunity for better management. Making UDCA use more routine for this subgroup could potentially improve outcomes, as suggested by its established benefits in reducing PBC recurrence and enhancing graft and overall survival.

Interestingly, we found that TCMR episodes were associated with a higher risk of *r*ALD and mortality in the univariate analysis. This finding is in line with a recent study that demonstrated that episodes of increased systematic inflammatory state, including TCRM episodes, increase the risk of recurrent PSC.[18] In addition, this could explain the increased risk of overall mortality associated with TRCM episodes in this cohort as a result of its association with rALD, as nowadays most episodes of TCMR are histologically mild, and alloimmune-mediated graft loss is infrequent.[19] It is possible that in some cases, differentiating TCMR from early AIH recurrence might have been challenging, which could have contributed to the observed associations.

We acknowledge that there are limitations in our study. The retrospective design of our study, with its fixed sample size, precluded a prospective power calculation. This could limit the interpretation of nonsignificant findings, as we cannot definitively rule out the possibility that some results may be underpowered to detect smaller effects. The lack of centralized reading of the liver biopsy might have caused heterogeneity in the diagnostic definition of the VS before the diagnosis and after the transplant. Furthermore, despite the diagnosis of *r*ALD relying significantly on liver biopsy,[11,19,20] only 10 centers had protocol biopsies in clinical practice, and in the other seven centers, they were clinically driven. This might have led to the difference in the timing of *r*ALD between the centers. However, in the Cox regression analysis, clinically driven biopsies were not associated with a higher risk of *r*ALD (Table 1). Furthermore, the mean time for *rALD* was not significantly different between centers that perform protocol-driven and clinically driven liver biopsies. The inclusion of patients who did not receive a liver biopsy might have led to overseeing or misclassifying some of the cases, underestimating the *r*ALD prevalence, and biasing the effect of *r*ALD on the prognosis. Therefore, we conducted a subgroup analysis including only the patients who received a liver biopsy to address this point and found similar results.

The main aim of the study was to investigate the epidemiology of the recurrent disease after transplant. Because we included in the study only patients who progressed to transplantation, it is possible that some of these patients had more aggressive disease phenotypes or were not started on UDCA, which contributed to their progression to end-stage liver disease and the need for LT.

Another possible limitation is the potential bias introduced by including "prednisolone at 12 months" in the Cox regression analysis, as some patients experienced recurrence earlier. To mitigate this risk, we conducted a sensitivity analysis excluding these patients, and the results remained consistent.

The heterogeneity in the frequency of *r*ALD in the different centers (0–44%) reflects the different approaches to these patients, for instance, in terms of vigilance and indication for liver biopsies.

Our data suggest that caution should be exercised when considering the strengthening of immunosuppression, as this may increase the risk of sepsis and other complications, highlighting the need for balanced management in this patient population.

This emphasizes the need for standardized guidelines to manage autoimmune liver diseases after transplant to improve the outcomes in this group of patients.

In conclusion, we presented data from the most extensive cohort of patients who underwent transplantation for VS, providing a clearer picture of the epidemiology of recurrence. Furthermore, our study suggests that the recurrence of autoimmune liver disease on the graft may be a clinically significant event, potentially impacting graft and overall survival. This highlights the importance of exploring therapeutic interventions to prevent *r*ALD or reduce its effects. A note of caution should be raised about increasing the dose of immunosuppression in patients experiencing *r*ALD, given the associated risk of infection. A careful, individualized risk-benefit evaluation is warranted.

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Abbreviations

aHR, adjusted HR; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; anti-LKM-1, anti-liver kidney microsome type 1; AST, aspartate aminotransferase; CI, confidence interval; ELTR, European Liver Transplant Registry; HCC, hepatocellular carcinoma; HR, hazard ratio; IgG, immunoglobulin G; ITBL, ischemic-type biliary lesion; LT, liver transplantation; MELD, model for end-stage liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; *r*ALD, recurrent autoimmune liver disease; SMA, smooth muscle antibodies; TCMR, T-cell-mediated rejection; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; UNOS, United Network for Organ Sharing; VS, variant syndrome.

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Conflicts of interest

There is no relevant conflict of interest to declare.

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

Authors' contributions

Study design: VR, MHe, YHO, AJM-L. Analyses of the data: VR, AParen, EL, BEH, GH, AB, ME, SE, MAI, PM, MJ, H-UM, MAB, CE, ARC, MHa, GK, DT, FdQO, AParés, LL, MAk, CA, MPM, RT, A-LW, TDS, BH, PC, PS, NO, NA, AT, CL, EFM, AG, MSe, IJ, TI, MR, MSt, CW-N, CS, MFD, AL, RJA, VRP, BvH, MB, AEK, YU, MD, MP, MJM, AF, PB, MFS, BTB-P, MS, GM, S-MJ, DD, MG, FL, MHe, ALM, YHO, AJM-L. Creation of the first draft and final version of the manuscript: VR, AParen, BEH, GH, ME, MHe, YHO, AJM-L. Submission of the manuscript for review: VR.

Collection of data across all centers: EL. Critical revision of the manuscript for important intellectual content: EL, AB, SE, MAI, PM, MJ, H-UM, MAB, CE, ARC, MHa, GK, DT, FdQO, AParés, LL, MAk, CA, MPM, RT, A-LW, TDS, BH, PC, PS, NO, NA, AT, CL, EFM, AG, MSe, IJ, TI, MR, MSt, CW-N, CS, MFD, AL, RJA, VRP, BvH, MB, AEK, YU, MD, MP, MJM, AF, PB, MFS, BTB-P, MS, GM, S-MJ, DD, MG, FL, ALM.

Data availability statement

The datasets generated and analyzed in this retrospective study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101332.

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