Risk factors and outcomes associated with recurrent autoimmune hepatitis following liver transplantation

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Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

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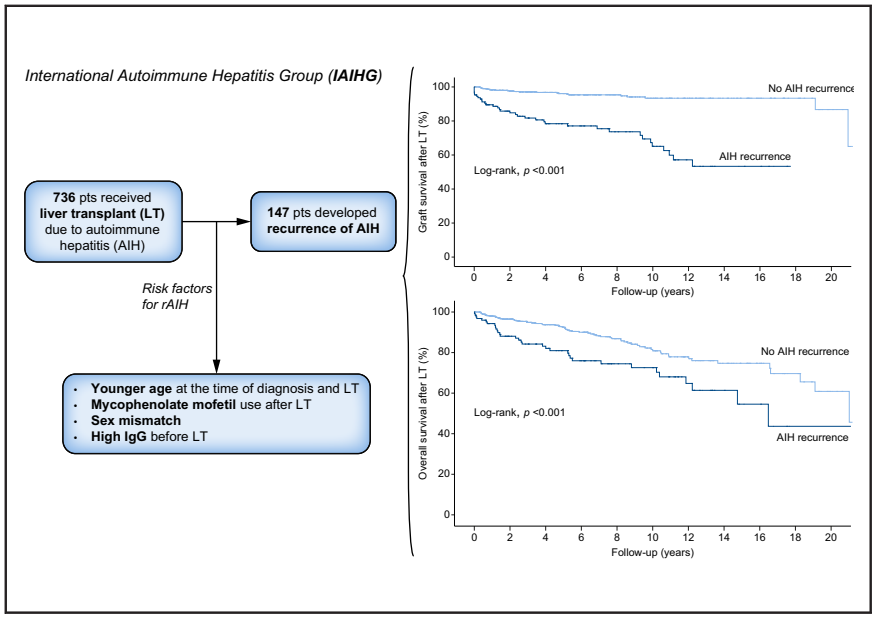
Graphical abstract



Highlights

- Recurrent AIH frequently occurs following LT.
- Recurrent AIH is associated with younger age at LT, use of mycophenolate mofetil post-LT, sex mismatch and higher IgG pre-LT.
- Recurrent AIH impacts on graft and overall survival after LT.
- Recurrent AIH following LT is clinically meaningful and requires improved management strategies.

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Lay summary

Recurrent autoimmune hepatitis following liver transplant is frequent and is associated with some recipient features and the type of immunosuppressive medications use. Recurrent autoimmune hepatitis negatively affects outcomes after liver transplantation. Thus, improved measures are required to prevent and treat this condition.

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Risk factors and outcomes associated with recurrent autoimmune hepatitis following liver transplantation

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Background & Aims: Autoimmune hepatitis can recur after liver transplantation (LT), though the impact of recurrence on patient and graft survival has not been well characterized. We evaluated a large, international, multicenter cohort to identify the probability and risk factors associated with recurrent AIH and the association between recurrent disease and patient and graft survival.

Methods: We included 736 patients (77% female, mean age 42±1 years) with AIH who underwent LT from January 1987 through June 2020, among 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 at higher risk of AIH recurrence based on histological diagnosis.

Results: AIH recurred in 20% of patients after 5 years and 31% after 10 years. Age at LT ≤42 years (hazard ratio [HR] 3.15; 95% CI 1.22-8.16; p = 0.02), use of mycophenolate mofetil post-LT (HR 3.06; 95% CI 1.39-6.73; p = 0.005), donor and recipient sex mismatch (HR 2.57; 95% CI 1.39-4.76; p = 0.003) and high IgG pre-LT (HR 1.04; 95% CI 1.01-1.06; p = 0.004) were associated with higher risk of AIH recurrence after adjusting for other confounders. In multivariate Cox regression, recurrent AIH (as a time-dependent covariate) was significantly associated with graft loss (HR 10.79, 95% CI 5.37-21.66, p <0.001) and death (HR 2.53, 95% CI 1.48-4.33, p = 0.001).

Conclusion: Recurrence of AIH following transplant is frequent and is associated with younger age at LT, use of mycophenolate mofetil post-LT, sex mismatch and high IgG pre-LT. We demonstrate an association between disease recurrence and impaired graft and overall survival in patients with AIH, highlighting the importance of ongoing efforts to better characterize, prevent and treat recurrent AIH.

Lay summary: Recurrent autoimmune hepatitis following liver transplant is frequent and is associated with some recipient features and the type of immunosuppressive medications use. Recurrent autoimmune hepatitis negatively affects outcomes after liver transplantation. Thus, improved measures are required to prevent and treat this condition.

Introduction

Autoimmune hepatitis (AIH) is a multifaceted liver disease, characterized by high IgG, autoantibodies, interface hepatitis on histological examination, and in most cases, an appropriate response to immunosuppression.[1,2]

Liver transplantation (LT) is a lifesaving intervention for patients with advanced disease, and 1- and 5-year survival rates are approximately 90% and 70%, respectively.[3–5] Recurrent AIH (*r*AIH) is a major cause of allograft dysfunction, reduced graft and patient survival, and need for re-transplantation. The prevalence of *r*AIH ranges from 17-42%, and this divergence seems to be related to differences in studies with respect to the use of protocol *vs.* clinically indicated liver biopsies, the small number of patients in each series, and variable follow-up times.[6–8]

Previous studies have also suggested that the development of *r*AIH has no significant impact on long-term patient survival or the need for a second LT[6,9] and thus its clinical significance has been questioned. However, these observations may be related to inadequate follow-up and limited numbers of patients. In fact, recent studies from the United Network for Organ Sharing (UNOS) and the European Liver Transplant Registry (ELTR) have demonstrated that overall survival after LT is inferior in AIH compared to patients receiving LT for the other chronic autoimmune liver diseases.[10]

The impact of immunosuppression after LT on *r*AIH risk is still controversial. Longstanding low-dose corticosteroid (prednisolone 5-10 mg) in combination with other immunosuppressive agents seems to reduce *r*AIH without risking patient and graft survival[9]; however, the most recent guidance from the American Association for the Study of Liver Diseases (AASLD) recommends glucocorticoids can be discontinued after LT and patients monitored for *r*AIH.[11]

In addition, the importance of alterations in serum liver tests shortly after LT, remains unknown in AIH, whereas early serum liver test abnormalities have been associated with recurrent disease and worse outcomes in patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).[12]

Accordingly, we conducted a multicenter study in 33 LT centers to evaluate the probability and risk factors associated with *r*AIH and the association between *r*AIH and patient and graft survival. In addition, we evaluated whether serum liver tests within the first year after LT were associated with subsequent recurrent disease. We hypothesized that serum liver test abnormalities during the first year after LT increase the risk for *r*AIH which, in turn, negatively impacts graft and patient survival.

Patients and methods

Study population

Eight hundred and fifty-five patients who received a LT from 1987 until 2020 with a diagnosis of AIH from 33 centers across Asia, Europe, North and South America, were evaluated (Supplementary Document 1 and Fig. S1). We excluded 119 patients who had features of overlap syndrome with PBC or PSC. All patients included were considered to have probable or definitive AIH according to simplified criteria,[13] and to the AASLD[14] and European Association for the Study of the Liver (EASL) guidelines.[2] Based on the median number of LTs performed by all centers, those contributing more than 16 LTs for AIH were designated as high-volume centers.

Clinical and laboratory assessments

The data extracted from the medical records included sex, ethnicity, age at diagnosis of AIH and LT, time between diagnosis of AIH and LT, blood group, concomitant autoimmune disease, antinuclear antibodies, smooth muscle antibodies, anti-liver kidney microsome type 1 antibodies, IgG concentrations before LT, treatment for AIH, LT indication (acute liver or decompensated cirrhosis), type of LT and biliary anastomosis, and model for end-stage liver disease

score.[15] We also recorded initial immunosuppression post-LT, long-term prednisone or prednisolone use (more than 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), year of LT, and number of LTs per center. In addition, we recorded donor age and sex, donor/recipient sex mismatch, donor's blood group, explant necroinflammatory activity and fibrosis score and rejection episodes.

In order to minimize the risk of variation in data collection, we discussed this project in our bi-annual meetings of the International AIH study group and developed instructions to standardize the collection of data. Serum liver function tests and immunosuppression levels were assessed every 1 to 3 months in all centers.

Liver serum tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin were collected at the time of LT, and 3-, 6-, and 12-months after LT. Values, both raw and divided by the upper limit of normal (ULN), based on center-specific values were taken into account for the analyses. The ULN for ALT ranged from 31 to 56 U/L, AST from 30 to 52 U/L, IgG from 16 to 18 g/L, and bilirubin from 18 to 22 μmol/L between the different LT centers.

Histological assessment of liver explants and liver biopsies after liver transplantation

Histological assessment of the liver explant and liver biopsies for *r*AIH diagnosis was graded according to the Batts–Ludwig scoring system.[16] On the basis of the Batts–Ludwig scoring system, grade 1 denotes necroinflammatory activities largely confined to the portal areas, with grades 2–3 representing extension beyond the portal areas and grade 4 signifying confluent necrosis in the form of bridging necrosis. Grade 0 represents no fibrosis, grade 1 conveys portal fibrosis, grade 2 signifies periportal fibrosis, grade 3 denotes septal fibrosis, and grade 4 indicates cirrhosis.

Diagnosis of recurrent autoimmune hepatitis

The diagnosis of *r*AIH was made histologically and defined by the presence of liver histology typical of AIH, positive autoantibodies, high IgG and negative viral hepatitis tests. Histologic features of *r*AIH were the presence of lymphoplasmacytic portal inflammation with interface hepatitis, with or without the presence of rosettes of regenerating hepatocytes, and hepatocyte emperipolesis in the absence of allograft rejection findings, such as endothelialitis, lymphocytic cholangitis or perivenular hepatocyte necrosis.[1] The simplified AIH score[13] was calculated in patients with a histological diagnosis of *r*AIH. In addition, the presence of other infections and concomitant use of potentially hepatotoxic drugs were ruled out.

Immunosuppressive regimens

The type of immunosuppression administered during the first year was recorded. The predominant calcineurin inhibitor (either cyclosporine or tacrolimus) and other immunosuppressive medications (including azathioprine, mycophenolate mofetil, and prednisone or prednisolone) were all recorded. Changes in the main immunosuppression after the first year of LT were also recorded.

Statistical analyses

The Fisher exact probability test was used to compare categorical variables, and the unpaired *t* test was used to compare differences in means of continuous variables. Prognostic factors for *r*AIH were analyzed by Cox regression univariate analysis.[17] Variables with p value ≤0.05 in the univariate analysis were included in the Cox regression multivariate analysis to avoid model overfitting. IgG and age cut-offs at diagnosis and at the time of LT were established based on median to reduce the risk of optimist bias. Cumulative incidences of *r*AIH after LT were calculated using the Kaplan-Meier method, and they were compared using the Log-Rank (Mantel-Cox) test.[18]

To determine whether *r*AIH was significantly associated with graft loss and overall survival, the impact of *r*AIH on the hazard ratio of graft loss and survival was assessed using univariate and multivariate Cox regression analyses. In these analyses, the time until patients had *r*AIH was modelled as a time-dependent covariate. The association of *r*AIH with graft loss and overall survival was also analyzed as a time-dependent covariate. Variables with $p \leq 0.05$ in the univariate analysis and other relevant variables were included in the Cox proportional hazard regression multivariate analysis. Patients that did not develop *r*AIH and died and those who were lost during follow-up were censored at the time of death or at the time of their last visit. In order to analyze the clinical impact of *r*AIH, patients who died or lost the graft within the first 3 months after LT were excluded from the survival analysis, as these outcomes were deemed related to surgical complications. Graft loss was defined using a death-censored definition of graft failure and therefore, graft loss did not include patients who died with a functioning graft. Graft loss only included deaths secondary to or associated with graft failure (*i.e.* recurrent disease, *de novo* disease, chronic ductopenic rejection, sepsis in patients with biliary or vascular complications, or cirrhosis development on the graft) or re-transplantation.

Cumulative probabilities of graft and overall survival after LT were calculated using semi-Markov models (so-called "clock reset" models) because each time the patient enters a new state, time is reset to 0 (in this case *r*AIH).[19] As the median survival time for our patient population was not reached, the mean 5-year, 10-year, 15-year and 20-year survival probabilities were reported.

In order to evaluate potential limitations of estimation of probabilities and impact of *r*AIH related to lack of liver biopsies in all patients, we performed subanalysis including only patients with liver biopsies after LT (n = 529). Data are presented as the mean ± standard error in tables and text, and median with interquartile ranges (IQR) in case data was not normally distributed. Statistical analyses were conducted using SPSS 26.0. (supplementary CTAT table). To handle the missing variables in the analysis, we used mean imputation for continuous variables and allocated a fixed number (99) for categorical variables.

Results

Characteristics, frequency and probability of autoimmune hepatitis recurrence

The mean age of the study population at LT was 42±1 years (median, 43 years; IQR: 41-45 years), and 563 patients (77%) were women. The 736 patients analyzed were transplanted because of acute liver failure secondary to AIH (n = 136, 19%), decompensated cirrhosis (n = 560, 76%) and hepatocellular carcinoma (n = 40, 5%). The main features of patients who received a LT for AIH are shown in Table 1. Recurrent AIH was diagnosed in 147 patients that represented 20% of the study population (n = 736) and 28% of those who had a liver biopsy after LT (n = 529). According to the simplified AIH score at the time of recurrence,[13] 38 patients (26%) were classified as likely AIH (≥7 points), 93

Table 1. Clinical features associated with recurrent AIH in univariable analyses.

Clinical features	All patients (n = 736)	*r*AIH (n = 147)	No *r*AIH (n = 589)	HR	95% CI	*p* value
Age at the time of diagnosis AIH (years)	34±1	27±1	36±1	0.98	0.97-0.99	<0.001
Age at diagnosis ≤34 (years), n (%)	306 (42)	82 (56)	224 (38)	1.76	1.20-2.58	0.004
Age at LT (years)	42±1	35±1	44±1	0.98	0.97-0.99	<0.001
Age at LT ≤42 (years), n (%)	350 (48)	99 (67)	251 (43)	1.91	1.34-2.72	<0.001
Men: women	173:563	28:119	145:444	0.75	0.49-1.15	0.18
Caucasian: non-Caucasian[¥]	391:345	76:71	315:274	0.83	0.59-1.16	0.26
Time AIH diagnosis and LT (years)	7.1±0.3	6.8±0.6	7.2±0.4	0.99	0.97-1.02	0.60
Blood group (recipient)						
AB	39 (5)	10 (7)	29 (5)			
A	262 (36)	46 (31)	216 (37)	0.80	0.39-1.64	0.55
B	94 (13)	10 (7)	84 (14)	0.45	0.18-1.11	0.08
O	341 (46)	81 (55)	260 (44)	0.95	0.47-1.89	0.88
Concomitant autoimmune disease, n (%)	153 (21)	40 (27)	113 (19)	1.56	1.07-2.26	0.02
Immunosuppression before LT, n (%):						
Prednisone	501 (68)	103 (70)	398 (68)	1.12	0.78-1.62	0.54
Budesonide	19 (3)	5 (4)	14 (2)	2.12	0.78-5.75	0.1
Azathioprine	341 (46)	74 (50)	267 (45)	1.35	0.97-1.89	0.08
Mycophenolate mofetil	60 (8)	11 (8)	49 (8)	1.04	0.54-1.98	0.92
LT indication, n (%)						
Acute liver failure	136 (18)	23 (16)	113 (19)			
Decompensated cirrhosis (including HCC)	600 (82)	124 (84)	476 (81)	1.19	0.74-1.89	0.48
Type of LT, n (%):						
Cadaveric	516 (70)	124 (84)	392 (67)			
Living related	143 (19)	11 (7)	132 (22)	0.35	0.18-0.68	0.002
Bile duct anastomosis, n (%):						
End-to-end	554 (75)	105 (71)	449 (76)			
Roux-en-Y	60 (8)	20 (14)	40 (7)	1.93	1.17-3.17	0.009
Initial immunosuppression post-LT, n (%):						
Tacrolimus	575 (78)	93 (63)	482 (82)	0.70	0.49-0.99	0.05
Cyclosporine	80 (11)	32 (22)	48 (8)	1.67	1.09-2.56	0.02
Prednisone or prednisolone	557 (76)	101 (69)	456 (78)	0.73	0.51-1.05	0.09
Mycophenolate Mofetil	404 (55)	73 (50)	331 (56)	1.59	1.11-2.27	0.01
Azathioprine	76 (10)	13 (9)	63 (11)	0.46	0.26-0.82	0.008
Sirolimus	15 (2)	1 (1)	14 (2)	0.47	0.66-3.37	0.45
Long-term prednisone-prednisolone, n (%)						
>1 year	362 (49)	87 (59)	275 (47)	1.15	0.82-1.62	0.41
>5 years	170 (23)	55 (37)	115 (20)	1.14	0.80-1.61	0.48
Tacrolimus (initial trough levels, ng/ml)	8.5±0.2	9.26±0.5	8.4±0.2	1.02	0.98-1.07	0.35
Cyclosporine levels (Initial trough levels, ng/ml)	327±42	299±62	344±56	0.99	0.99-1.001	0.32
Liver biopsies after LT, n (%):					1.50-3.50	<0.001
Protocol	204 (28)	27 (18)	177 (30)	2.29		
Clinically driven	325 (44)	113 (77)	212 (36)			
Changes in immunosuppression after the first year of LT	56 (8)	13 (9)	43 (7)	0.86	0.48-1.57	0.63
LT center volume (High[*]: Low), n	578:158	117:30	461:128	1.08	0.72-1.61	0.72
LT calendar year	2010±0.3	2006±0.6	2010±0.3	0.99	0.96-1.01	0.28
LT decade						
1987-1997	34 (5)	13 (9)	21 (4)			
1998-2008	215 (30)	74 (50)	141 (24)	1.25	0.69-2.30	0.46
2008-2020	460 (65)	52 (35)	408 (69)	0.86	0.45-1.66	0.66
Donor age (years)	42±1	39±2	42±1	0.996	0.99-1.01	0.50
Donor sex (Men: women), n	312:296	64:57	248:239	1.11	0.77-1.61	0.57
Donor/recipient sex mismatch, n (%)	295 (40)	70 (48)	225 (38)	1.48	1.02-2.15	0.04
Blood group (donor)						
AB	21 (3)	4 (3)	17 (3)			
A	220 (30)	37 (25)	183 (31)	0.83	0.29-2.32	0.72
B	73 (10)	9 (6)	64 (11)	0.55	0.17-1.79	0.32
O	422 (57)	97 (66)	325 (55)	0.97	0.36-2.65	0.96
Explant necroinflammatory activity score, n (%)						
Grade 0/1/2	392 (64)	63 (43)	329 (56)			
Grade 3/4	218 (36)	45 (31)	173 (29)	1.24	0.84-1.85	0.28
Explant fibrosis stage, n (%)						
Stage 1	34 (6)	3 (2)	31 (5)			
Stage 2	28 (5)	3 (2)	25 (4)	1.24	0.25-6.14	0.79
Stage 3	47 (8)	9 (6)	38 (6)	2.19	0.59-8.09	0.24
Stage 4	501 (82)	93 (63)	408 (69)	2.05	0.65-6.49	0.22

(*continued on next page*)

Table 1. (*continued*)

Clinical features	All patients (n = 736)	*r*AIH (n = 147)	No *r*AIH (n = 589)	HR	95% CI	*p* value
Explant infiltration with plasma cells, n (%)	297 (49)	58 (39)	239 (41)	1.12	0.75-1.66	0.58
Rejections, n (%)						
Acute	254 (35)	82 (56)	172 (29)	2.04	1.45-2.85	<0.001
Chronic	7 (1)	2 (1)	5 (1)	0.93	0.23-3.77	0.92

Hazard ratios were calculated using Cox proportional regression analyses. AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; LT, liver transplant; *r*AIH, recurrent AIH.
*>17 LT performed for AIH.
¥Non-Caucasian includes, 8.0% Asian, 1.1% Aboriginal, 0.3% Pacific Islander, 5.0% Middle Eastern/Arabian, 4.5% Black, 8.7% Turkish, 19.3% Other/Multiracial.

patients (63%) were classified as probable AIH (6 points), and 16 patients (11%) as possible AIH (≤5 points). Once *r*AIH was diagnosed, prednisone or prednisolone was added in 61 (42%) patients, azathioprine was added in 19 (13%), prednisone or prednisolone and azathioprine was added in 20 (14%), mycophenolate mofetil was added in 14 (10%), prednisone or prednisolone and mycophenolate mofetil was added in 17 (12%), and only the baseline immunosuppression (either with tacrolimus or cyclosporine) was increased in 16 (11%). The median time from LT to the recurrence of AIH was 2.6 years (IQR: 1.2-5.7). The probability of *r*AIH was 20%, 31%, 37%, and 49% at 5-, 10-, 15-, and 20-years, respectively (Fig. 1). In addition, the probability of *r*AIH in patients with liver biopsies after LT (n = 529) was 24%, 38%, 44%, and 55% at 5-, 10-, 15-, and 20-years, respectively. The frequency of *r*AIH varied between 0% to 69% among centers. The yearly recurrence rate ranged from 0% to 10.1%. The overall incidence rate of *r*AIH after LT was 3.27 cases per 100 patient-years (95% CI 3.05–3.49 cases per 100 patient-years over a total of 4,491 patient-years). In addition, the incidence rate of *r*AIH after LT, including only patients who had a liver biopsy after LT (n = 529) was 3.93 cases per 100 patient-years (95% CI 3.76–4.10 cases per 100 patient-years over a total of 3,564 patient-years).

The biochemical features after LT in patients with and without *r*AIH are presented in Table 2. The histological assessment of the liver explant was available for 610 patients (83%). Liver necroinflammatory activity was grade 0 in 47 patients (8%), grade 1 in 174 patients (29%), grade 2 in 171 patients (28%), grade 3 in 115 patients (19%) and grade 4 in 103 patients (17%). The fibrosis stage at the explant was stage 1 in 34 patients (6%), stage 2 in 28 patients (5%), stage 3 in 47 patients (8%), and stage 4 in 501 (82%). Two hundred and ninety-seven (49%) showed infiltration with plasma cells.

Biopsies after LT were performed in 529 patients (72%). Of those, 204 patients (39%) underwent protocol liver biopsies whereas 325 patients (61%) had clinically driven biopsies with abnormal serum liver tests. The histological necroinflammatory activity grade at *r*AIH diagnosis was grade 1 in 28 patients (19%), grade 2 in 100 patients (68%), grade 3 in 14 (10%), and grade 4 in 5 patients (3%); whereas the fibrosis stage at rAIH diagnosis was 0 in 20 patients (14%), stage 1 in 72 (49%), stage 2 in 40 (27%), 3 in 10 (7%) and stage 4 in 5 (3%).

Primary immunosuppression after LT included tacrolimus in 575 patients (78%), cyclosporine in 80 patients (11%), mycophenolate mofetil in 404 patients (55%), prednisone in 557 patients (76%), and azathioprine in 76 patients (10%) (Table 1).

The initial mean trough level of tacrolimus was 8.6 ng/ml (range, 1-40 ng/ml), and the initial mean trough level of cyclosporine was 327 ng/ml (range, 11-1,540 ng/ml). The mean initial dose of azathioprine was 100 mg daily (range, 50-250 mg/daily), mycophenolate mofetil was 1,523 mg daily (range, 360-1,200 mg/daily) and prednisone-prednisolone 21 mg/daily (range, 5-100 mg/daily).

Extended maintenance with prednisone or prednisolone was used in 362 patients (49%), for more than 1 year after LT, and in 170 patients (23%) more than 5 years after LT. Fifty-six patients had changes in their main immunosuppression after the first year that included switching from cyclosporine to tacrolimus (n = 13), tacrolimus to cyclosporine (n = 12), mycophenolate

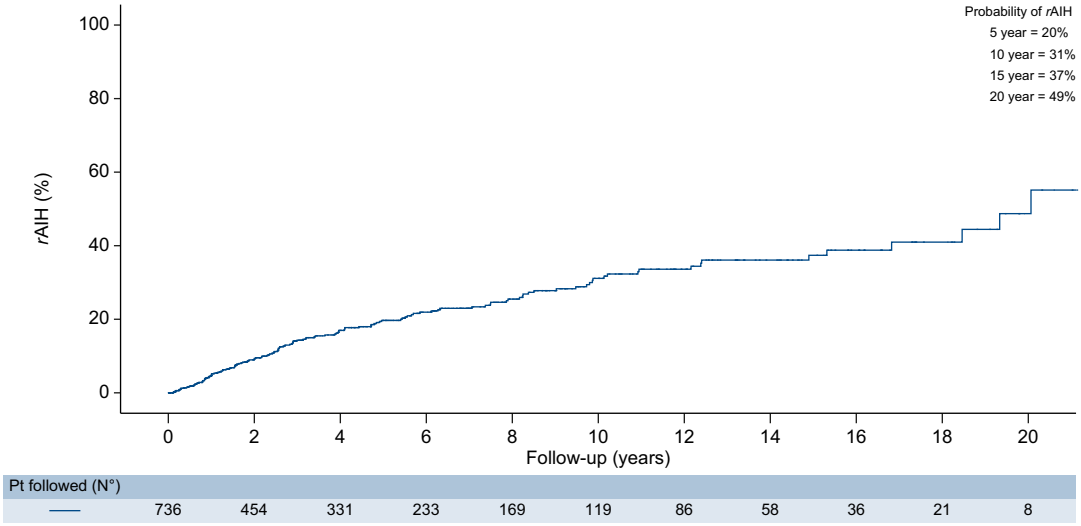

Fig. 1. Cumulative probability of *r*AIH. The probability of *r*AIH was 20%, 31%, 37%, and 49% at 5-, 10-, 15-, and 20-years, respectively. Cumulative probabilities were calculated using the Kaplan-Meier method. *r*AIH, recurrent autoimmune hepatitis.

Table 2. Biochemical features associated with recurrent AIH after liver transplantation in univariable analyses.

Biochemical features	All patients (n = 736)	*r*AIH (n = 147)	No *r*AIH (n = 589)	HR	95% CI	*p* value
Pre-LT						
ALT U/L	196±18	156±21	205±21	1.00	0.999-1.00	0.22
ALT times ULN	4.2±0.4	3.7±0.5	4.3±0.5	0.99	0.97-1.01	0.48
AST U/L	217±22	175±24	226±27	1.00	0.999-1.00	0.37
AST times ULN	5.5±0.5	5.1±0.8	5.6±0.7	0.997	0.98-1.01	0.70
Bilirubin μmol/L	189±13	216±44	183±12	1.00	1.00-1.001	0.56
Bilirubin times ULN	8.6±0.5	11.6±2.2	7.9±0.4	1.01	1.00-1.01	0.06
MELD Pre-LT	23±0.4	23±1	22±0.4	1.01	0.99-1.03	0.17
IgG g/L	23±0.5	27±2	22±0.5	1.03	1.01-1.04	0.006
IgG times ULN	1.4±0.03	1.7±0.1	1.4±0.03	1.47	1.10-1.95	0.008
3-month						
ALT U/L	53±4	64±12	50±4	1.001	1.00-1.002	0.19
ALT times ULN	1.2±0.08	1.4±0.2	1.1±0.1	1.04	0.97-1.12	0.27
AST U/L	37±2	46±7	35±2	1.002	1.00-1.01	0.05
AST times ULN	1.0±0.1	1.2±0.2	1.0±0.1	1.02	0.95-1.09	0.60
Bilirubin μmol/L	20±2	22±4	19±2	1.003	1.00-1.01	0.08
Bilirubin times ULN	0.9±0.1	1.0±0.2	0.9±0.1	1.01	0.95-1.08	0.74
6-month						
ALT U/L	55±4	63±10	52±5	1.001	1.00-1.002	0.07
ALT times ULN	1.2±0.1	1.4±0.2	1.1±0.1	1.06	1.01-1.11	0.03
AST U/L	39±3	44±6	38±3	1.003	1.00-1.01	0.04
AST times ULN	1.0±0.06	1.1±0.2	1.0±0.1	1.13	1.02-1.25	0.02
Bilirubin μmol/L	23±1	24±3	22±1	1.01	1.00-1.01	0.02
Bilirubin times ULN	1.1±0.1	1.2±0.1	1.1±0.1	1.19	1.05-1.34	0.006
12-month						
ALT U/L	46±4	63±8	41±4	1.001	1.00-1.003	0.01
ALT times ULN	1.0±0.07	1.4±0.2	0.9±0.1	1.08	1.03-1.14	0.004
AST U/L	37±2	48±6	34±2	1.003	1.001-1.01	0.003
AST times ULN	1.0±0.06	1.2±0.2	0.9±0.1	1.12	1.04-1.21	0.004
Bilirubin μmol/L	22±3	26±7	21±4	1.001	0.999-1.002	0.44
Bilirubin times ULN	1.1±0.2	1.3±0.4	1.0±0.2	1.01	0.98-1.05	0.50

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; LT, liver transplantation; MELD, model for end-stage liver disease; *r*AIH, recurrent AIH; ULN, upper limit of normal. Hazard ratios were calculated using Cox proportional regression analyses.

mofetil to azathioprine (n = 19), and azathioprine to mycophenolate (n = 12).

Clinical features associated with autoimmune hepatitis recurrence

By univariate Cox proportional hazard regression analysis, younger age at diagnosis of AIH (HR 0.98, 95% CI 0.97-0.99, p <0.001) and at the time of LT (HR 0.98, 95% CI 0.97-0.99, p <0.001) were associated with a higher risk of *r*AIH. Patients younger than 34 years-old at diagnosis of AIH and younger than 42 years-old at the time of LT had a higher risk for *r*AIH (HR 1.76, 95% CI 1.20-2.58, p = 0.004, and HR 1.91, 95% CI 1.34-2.72, p <0.001; respectively; Table 1). The year of LT (HR 0.99, 95% CI 0.96-1.01, p = 0.28) and the LT center volume (HR 1.08, 95% CI 0.72-1.61, p = 0.72) were not significantly associated with *r*AIH.

The use of mycophenolate mofetil after LT (HR 1.59; 95% CI 1.11-2.27; p = 0.01), concomitant autoimmune disease (HR 1.56; 95% CI 1.07-2.26; p = 0.02), living-related LT (HR 0.35, 95% CI 0.18-0.68, p = 0.002), Roux-en-Y bile duct anastomosis (HR 1.93;

Table 3. Features associated with AIH recurrence by multivariable analyses.

	HR	95% CI	*p* value
Age at diagnosis ≤34 (years)	0.60	0.23-1.57	0.30
Age at LT ≤42 (years)	3.15	1.22-8.16	0.02
Concomitant autoimmune disease	1.50	0.76-2.94	0.24
Tacrolimus post-LT	1.91	0.27-13.39	0.52
Cyclosporine post-LT	1.52	0.22-10.38	0.67
Prednisone or prednisolone post-LT	0.77	0.35-1.67	0.50
Mycophenolate mofetil post-LT	3.06	1.39-6.73	0.005
Azathioprine post-LT	1.56	0.46-5.27	0.48
Rejection (acute)	1.60	0.88-2.93	0.13
Type of LT, living related	0.39	0.14-1.11	0.08
Bile duct anastomosis, Roux-en-Y	1.73	0.70-4.25	0.23
Donor/recipient sex mismatch	2.57	1.39-4.76	0.003
Bilirubin μmol/L (6-mo)	1.00	0.999-1.001	0.61
IgG g/L (pre-LT)	1.04	1.01-1.06	0.004
ALT U/L (12-mo)	1.00	0.998-1.003	0.74

Hazard ratios were calculated using Cox proportional regression analyses. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; HR, hazard ratio; LT, liver transplantation.

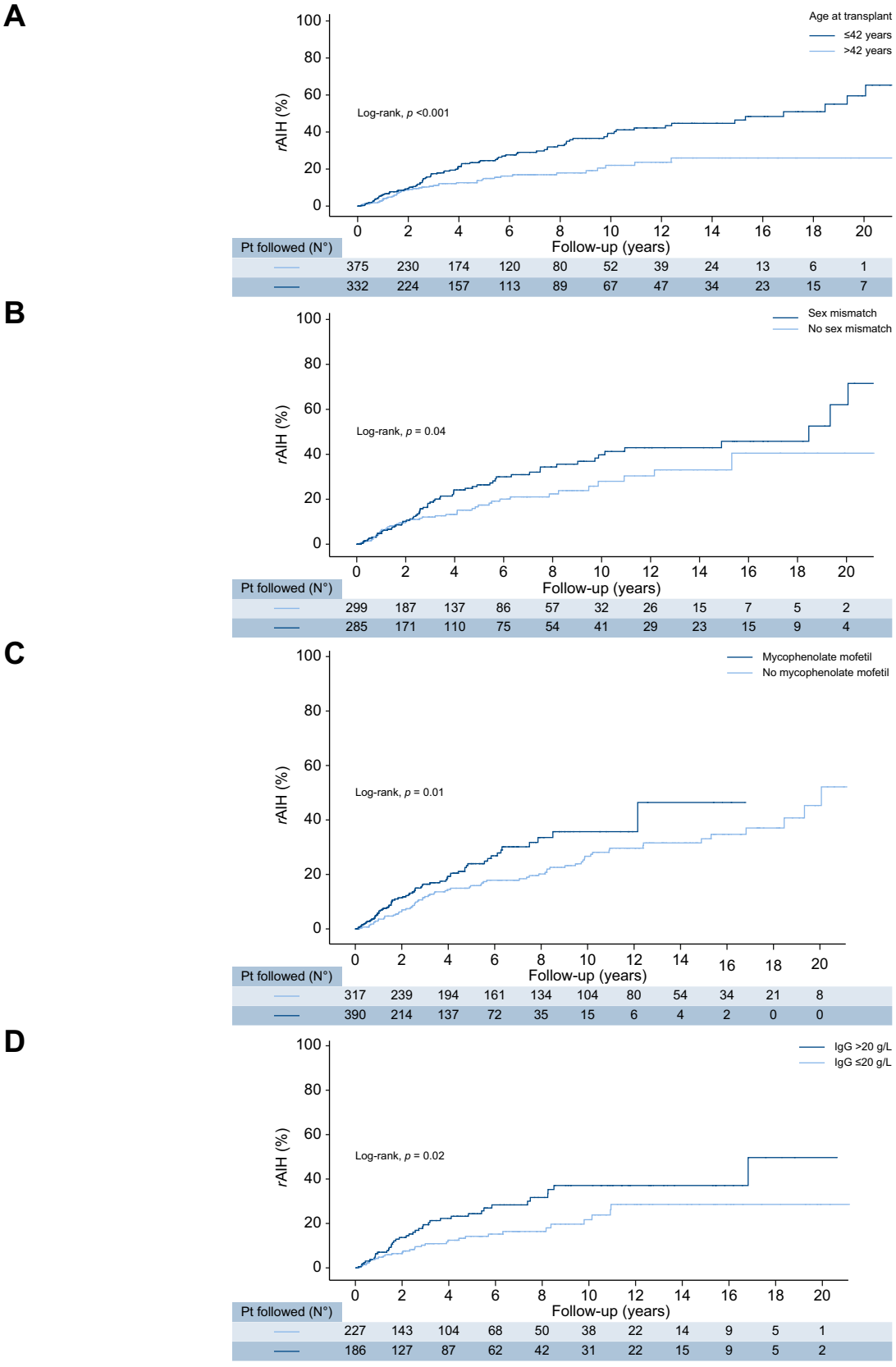

Fig. 2. Cumulative probability of *r*AIH. (A) In patients younger and older than 42 years at transplantation. The 5-year probability of *r*AIH was 25% and 15%, respectively (p <0.001, log-rank test). The 10-year probability of survival was 40% and 26% in these same groups. (B) In patients with and without donor/recipient sex mismatch. The 5-year probability of *r*AIH was 26% and 17%, respectively (p = 0.04, log-rank test). The 10-year probability of survival was 40% and 28% in these

95% CI 1.17-3.17; p = 0.009), donor/recipient sex mismatch (HR 1.48; 95% CI 1.02-2.15; p = 0.04), and acute rejection episodes (HR 2.04; 95% CI 1.45-2.85; p <0.001) were associated with *r*AIH (Table 1). There was no significant association with other clinical features such as recipient sex, ethnicity, age or sex of the donor, LT indication, changes in the main immunosuppression after the first year of LT, explant necroinflammatory activity, fibrosis, and infiltration with plasma cells and the risk of *r*AIH (Table 1).

In a sub-group analysis of sex mismatch, the frequency of male donor to female recipient mismatching was 78% (n = 230) and did not show a significant association with *r*AIH (HR 0.98, 95% CI 0.54-1.77, p = 0.95) when compared to female donor to male recipient mismatching.

Biochemical features associated with autoimmune hepatitis recurrence

By univariate Cox proportional hazard analysis, elevation of IgG pre-LT, bilirubin at 6 months, and both ALT and AST at 12 months after LT, were associated with a higher risk of *r*AIH (Table 2). Notably, a trend toward elevated ALT and AST levels from 3 months onwards, within the first year, was linked with increased risk of *r*AIH (Table 2), and more specifically, ALT above the ULN at 12 months after LT (HR 1.08, 95% CI 1.03-1.14, p = 0.004).

Multivariable analyses of features associated with autoimmune hepatitis recurrence

In the multivariable analysis, which included age at diagnosis ≤34 years, age at LT ≤42 years, concomitant autoimmune disease, post-LT use of tacrolimus, cyclosporine, mycophenolate mofetil and azathioprine, acute rejection, living-related LT, Roux-en-Y bile duct anastomosis, sex mismatch, bilirubin at 6 months, ALT at 12 months as well as IgG pre-LT, only age at LT ≤42 years (HR, 3.15; 95% CI, 1.22-8.16; p = 0.02), use of mycophenolate mofetil (HR, 3.06; 95% CI, 1.39-6.73; p = 0.005), sex mismatch (HR, 2.57; 95% CI, 1.39-4.76; p = 0.003) and IgG pre-LT (HR, 1.04; 95% CI, 1.01-1.06; p = 0.004) were independently associated with *r*AIH (Table 3, Fig. 2A-D).

In addition, we performed a multivariate subanalysis including only patients who had a liver biopsy after LT (n = 529), that showed that use of mycophenolate mofetil, sex mismatch and IgG pre-LT were associated with a higher risk of *r*AIH (Table S1).

Patient and graft survival associated with recurrent disease

Overall median survival after LT was 23 (IQR: 9-27) years. The overall 5-, 10-, 15- and 20-year probability of survival was 86%, 72%, 65%, and 58%, respectively (Fig. 3A). The graft 5-, 10-, 15-, and 20-year probability of graft survival was 88%, 81%, 75%, and 68%, respectively (Fig. 3B).

In a Cox proportional hazard regression analysis implementing recurrence as a time-dependent covariate, *r*AIH (HR 9.61, 95% CI 5.33-17.30, p <0.001) was associated with graft failure. Sex (HR 1.06, 95% CI 1.00-1.12, p = 0.045), use of mycophenolate mofetil (HR 1.10, 95% CI 1.04-1.17, p = 0.001), acute rejection (HR 1.11, 95% CI 1.05-1.17, p <0.001) and bilirubin at 12-months post-LT (HR 1.004, 95% CI 1.002-1.01, p <0.001) were also associated with graft failure in univariate analysis. However, only bilirubin at 12-months post-LT (HR 1.004, 95% CI 1.002-1.01, p <0.001) and *r*AIH (time-dependent HR 10.79, 95% CI 5.37-21.66, p <0.001, Table 4) were independently associated with graft failure in the multivariate analysis.

In the univariate Cox regression analysis, *r*AIH, as a time-dependent covariate (HR 1.95, 95% CI 1.24-3.06, p = 0.004), age at LT ≤42 years (HR 0.96, 95% CI 0.92-0.996, p = 0.03), bilirubin at 12-months post-LT (HR 1.003, 95% CI 1.001-1.01, p <0.001) and ALT at 12-months post-LT (HR 1.002, 95% CI 1.00-1.003, p = 0.002) were all associated with overall survival after LT. However, in the multivariable analysis, bilirubin at 12-months post-LT (HR 1.003, 95% CI 1.002-1.01, p <0.001), ALT at 12-months post-LT (HR 1.002, 95% CI 1.00-1.003, p = 0.004) and *r*AIH (HR 2.53, 95% CI 1.48-4.33, p = 0.001) were independently associated with overall survival after LT (Table 4).

In the multivariable Cox regression analysis, including only those patients who had liver biopsies after LT (n = 529), results were similar (Table S2).

Graft survival was significantly diminished to 12.2 years (95% CI 10.7-13.6) in patients with *r*AIH compared to 24.0 years (95% CI 21.4-26.6) in patients without *r*AIH (p <0.001, Fig. 4A).

The 5-, 10-, 15- and 20-year probability of graft survival was 78%, 65%, 53% and 53% in patients with *r*AIH and 96%, 93%, 93%, and 87% in patients without *r*AIH (Log-rank, p <0.001, Fig. 4A). The majority of patients with recurrence of AIH lost their graft as a result of cirrhosis related to rAIH (72%), and the remainder were attributed to either rejection (14%) or hepatic artery thrombosis-ischemic cholangiopathy (11%) and other etiologies (3%). In contrast, patients without recurrence of AIH lost their allograft as a result of rejection (23%), hepatic artery thrombosis-ischemic cholangiopathy (43%), or other causes (34%).

The overall survival was 15.1 years (95% CI 12.7-17.5) for patients with *r*AIH compared to 20.0 years (95% CI 17.8-22.2) for those without recurrent disease (p <0.001; Fig. 4B). The 5-, 10-, 15- and 20-year probability of overall survival was 81%, 73%, 55%, and 44% in patients with *r*AIH and 93%, 81%, 75%, and 61% in patients without *r*AIH (Log-rank, p <0.001, Fig. 4B).

The increased risk of death after LT in AIH was mainly attributable to infections, such as fungal sepsis occurring soon after LT. In addition, we found that the risk of septic complications after LT was higher in patients receiving mycophenolate mofetil (HR, 1.92, 95% CI 1.28-2.90, p = 0.002), whereas the use of azathioprine was associated with a lower risk (HR, 0.48, 95% CI 0.26-0.87, p = 0.02).

Discussion

In the largest comprehensive cohort of liver transplant patients with AIH to date, we demonstrate that recurrent disease affects more than one-third of patients at 10 years after LT. Furthermore, recurrence significantly increases the risk of graft loss and mortality, providing an impetus to evaluate potential interventions to prevent *r*AIH.[9] The type of immunosuppression after LT, specifically the use of mycophenolate mofetil, in

same groups. (C) In patients receiving mycophenolate mofetil after liver transplantation. The 5-year probability of *r*AIH was 24% and 16%, respectively (p = 0.01, log-rank test). The 10-year probability of survival was 36% and 27% in these same groups. (D) In patients with IgG >20 and ≤20 g/L before liver transplantation. The 5-year probability of *r*AIH was 24% and 14%, respectively (p = 0.05, log-rank test). The 10-year probability of survival was 37% and 22% in these same groups. Cumulative incidences were calculated using the Kaplan-Meier method, and they were compared using the Log-rank (Mantel-Cox) test. *r*AIH, recurrent autoimmune hepatitis.

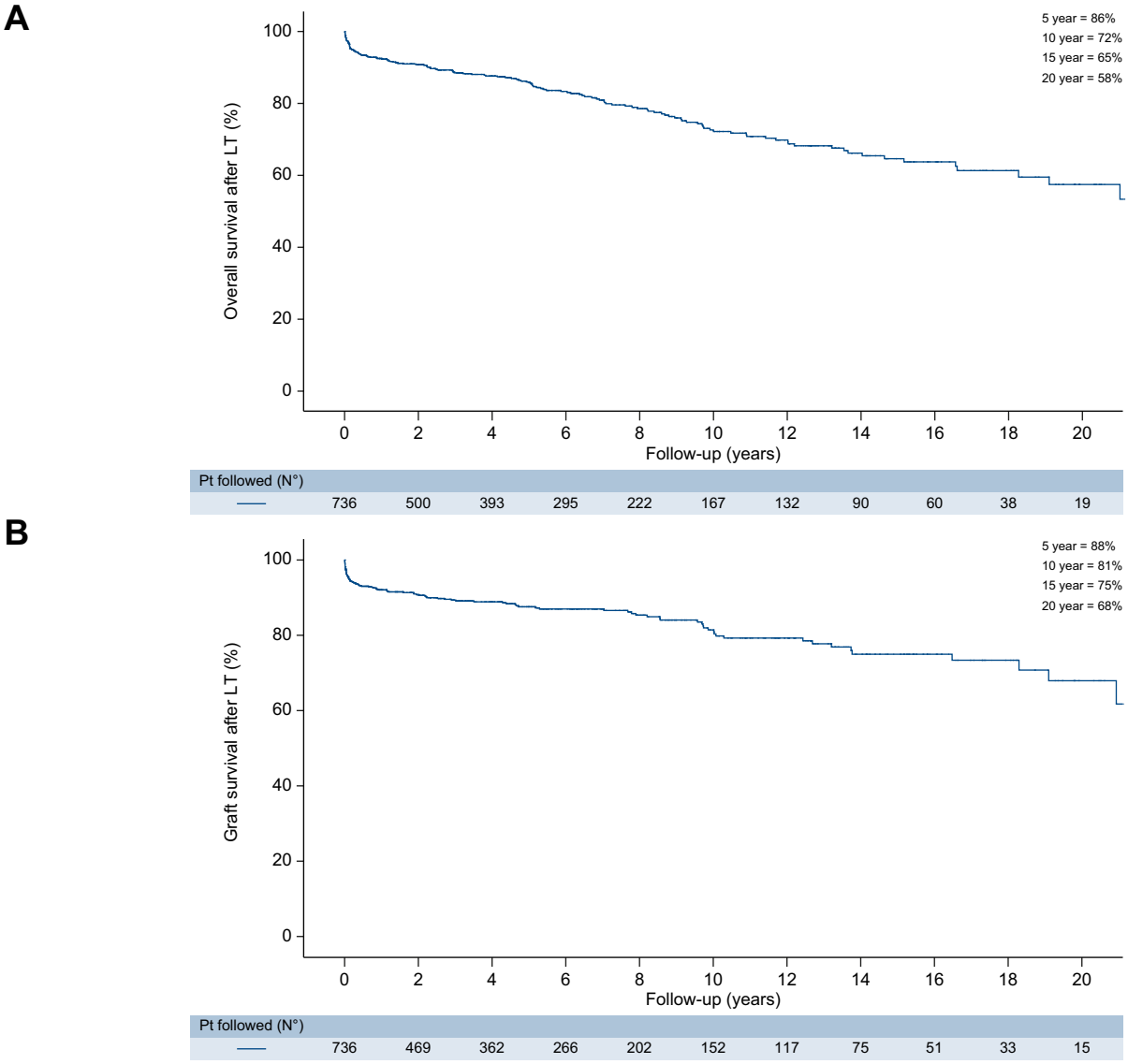

Fig. 3. Survival of patients with *r*AIH after liver transplantation. (A) Overall survival. The 5-, 10-, 15- and 20-year probability of survival was 86%, 72%, 65%, and 58%, respectively. (B) Graft Survival. The 5-, 10-, 15-, and 20-year graft survival probability was 88%, 81%, 75%, and 68%, respectively. Cumulative probabilities were calculated using the Kaplan-Meier method. LT, liver transplantation; *r*AIH, recurrent autoimmune hepatitis.

addition to younger age at LT, donor/recipient sex mismatch and high IgG level before LT were also found to be associated with the higher risk of *r*AIH. Prior single-center studies reported that *r*AIH had no significant impact on long-term survival or the need for re-transplantation.[6,9] However, the major limitations of these studies included the small size and their lack of long-term follow-up following LT, thereby limiting the probability of detecting differences in clinical outcomes. In addition, these case series were likely too small to demonstrate an increased risk of graft loss or mortality in recipients with *r*AIH compared to recipients with other liver diseases. Nevertheless, progression to cirrhosis, graft failure, and re-transplantation have previously been reported with *r*AIH[20,21] and these outcomes, estimated at a range of 13-23% in smaller series, have encouraged attempts to make an earlier diagnosis and find more effective treatment.

We also found that the probability of *r*AIH approaches 50% at 20 years. Indeed, we may have underestimated the incidence of recurrence in this study because not all patients underwent protocol liver biopsies necessary for confirmation of the diagnosis. In addition, younger age at LT was associated with a higher risk of *r*AIH, which is also a risk factor for graft loss and mortality. This finding is in agreement with other studies suggesting that age of onset and LT may be associated with a more aggressive AIH phenotype.[22,23]

This study provides further insight regarding the use of immunosuppression after LT with respect to both the incidence and accelerated onset of *r*AIH. We found that patients receiving mycophenolate had an increased risk of *r*AIH. Interestingly, there were no significant differences in the initial dose of mycophenolate mofetil (1,519±60 *vs.* 1,533±48 mg/daily, $p = 0.97$), nor the dose at 1 year after LT (1,335±76 *vs.* 1,314±41 mg/daily, $p = 0.82$) among

Table 4. Features associated with graft and patient survival after liver transplantation.

	Univariate			Multivariable		
Features	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Graft survival analysis						
Sex, male	1.06	1.00-1.12	0.045	1.56	0.80-3.05	0.20
Age at diagnosis ≤34 (years)	1.02	0.97-1.08	0.43			
Age at LT ≤42 (years)	1.05	0.997-1.11	0.06			
Mycophenolate mofetil post-LT	1.10	1.04-1.17	0.001	1.69	0.90-3.19	0.10
Rejection (acute)	1.11	1.05-1.17	<0.001	1.42	0.77-2.61	0.27
Recurrence of AIH**	9.61	5.33-17.30	<0.001	10.79	5.37-21.66	<0.001
ALT U/L (12-mo)	1.002	1.00-1.004	0.10			
Bilirubin μmol/L (12-mo)	1.004	1.002-1.01	<0.001	1.004	1.002-1.01	<0.001
Overall survival analysis						
Sex, male	1.02	0.97-1.06	0.47			
Age at diagnosis ≤34 (years)	0.96	0.92-1.01	0.09			
Age at LT ≤42 (years)	0.96	0.92-0.996	0.03	0.62	0.37-1.02	0.06
Mycophenolate mofetil post-LT	1.03	0.99-1.08	0.13			
Rejection (acute)	1.03	0.995-1.07	0.09			
Recurrence of AIH**	1.95	1.24-3.06	0.004	2.53	1.48-4.33	0.001
ALT U/L (12-mo)	1.002	1.00-1.003	0.002	1.002	1.00-1.003	0.004
Bilirubin μmol/L (12-mo)	1.003	1.001-1.01	<0.001	1.003	1.002-1.01	<0.001

Hazard ratios were calculated using Cox regression analyses with time-dependent covariate. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; HR, hazard ratio; LT, liver transplantation.
**These hazard ratios were obtained by considering recurrent AIH as a time-dependent covariate in univariable and multivariable analyses.

patients with and without *r*AIH. This finding suggests that we should consider the use of other agents such as azathioprine, mercaptopurine or long-term low dose of steroids in addition to calcineurin inhibitors. Indeed, prior studies have reported that patients receiving long-term prednisone have a lower risk of recurrence.[9] A previous study from the ELTR revealed inferior outcomes in patients transplanted for AIH compared to those transplanted for PBC or PSC.[10] The increased risk of death after LT in AIH was mainly attributable to infections, such as fungal sepsis occurring soon after LT. In fact, we found that the risk of septic complications after LT was higher in patients receiving mycophenolate mofetil, a potent immunosuppressive agent (HR 1.92, p = 0.002), whereas azathioprine was associated with a lower risk (HR 0.48, p = 0.02). However, there are alternative hypotheses to explain differences in the risk of *r*AIH related to the use of separate immunosuppressive regimens. Some have argued for an "era effect" as the use of azathioprine and prednisone was more prevalent in the 1980s and 1990s, when other factors such as cold ischemia times, shorter waiting periods and fewer sick patients might have impacted the development of *r*AIH. The role of mycophenolate mofetil on adaptive immune cells is also worth investigating in the future.

Another finding from our study is that donor and recipient sex mismatch was associated with a higher risk of *r*AIH. While prior studies have reported that recipients of sex-mismatched allografts had an 11% higher risk of graft loss,[24] none have linked this association with *r*AIH, possibly due to insufficient sample sizes in most reports.[6,21,25] Estrogen has a significant impact on immune cells and creating a tolerogenic environment; thus, this should be explored in future research.[26]

Similar to others,[6] we found that high IgG levels before LT were associated with a higher risk of *r*AIH. In fact, patients with IgG levels in excess of 20 g/L had an increased risk of *r*AIH (HR 1.76, 95% CI 1.11-2.79, p = 0.02) and this observation should prompt increased vigilance for *r*AIH because the disease may reoccur at any time after transplantation.

Another novel observation was that early elevation of ALT and the subsequent elevations in AST and bilirubin as well, within the first 12 months following LT (Tables 2 & 3), were helpful in risk stratification of *r*AIH. Although we lack biomarkers to distinguish whether the presence of high ALT at 6 and 12 months constitutes a risk factor for subsequent development of *r*AIH or indicates an early manifestation of *r*AIH, similar observations of early biochemical changes predicting subsequent recurrent disease in patients with PBC and PSC have also recently been reported.[12,27] Indeed, the use of more potent immunosuppression within the first year may mask the characteristic histological presentation of AIH, whereas non-specific inflammatory changes are a more common finding early on in the disease process.

Notably, 10% of patients had advanced fibrosis (F3-4) at the time of *r*AIH diagnosis. Even though there was no difference in the frequency of advanced fibrosis (F3-F4) among patients with protocol or clinically indicated biopsies (4% *vs.* 12%, p = 0.30), this could be related to the small number of patients (low power) and we recommend the implementation of protocol liver biopsies in patients transplanted for AIH, especially if they have factors associated with a higher risk of *r*AIH (younger age at LT, sex mismatch and high IgG pre-LT).

The pathogenic mechanisms for AIH before LT are probably similar to those that promote *r*AIH. However, the introduction of a donor allograft with different antigen-presenting and immune-reactive cells will likely modulate the immune response. Autoimmunity infers that there is a loss of tolerance for self-antigens and that an immune response is mounted against host antigens presented by host-derived antigen-presenting cells.[28,29] After LT, autoantigens may not only be presented by self-derived class I and II HLAs and recognized by self-derived CD4+ and CD8+ T cells, but they may also be presented by donor-derived HLAs and trigger an alloimmune response indistinguishable from autoimmunity. Accordingly, recipient memory T cells restricted to self-derived HLAs may also react with donor-derived HLAs, and trigger *r*AIH as a consequence.

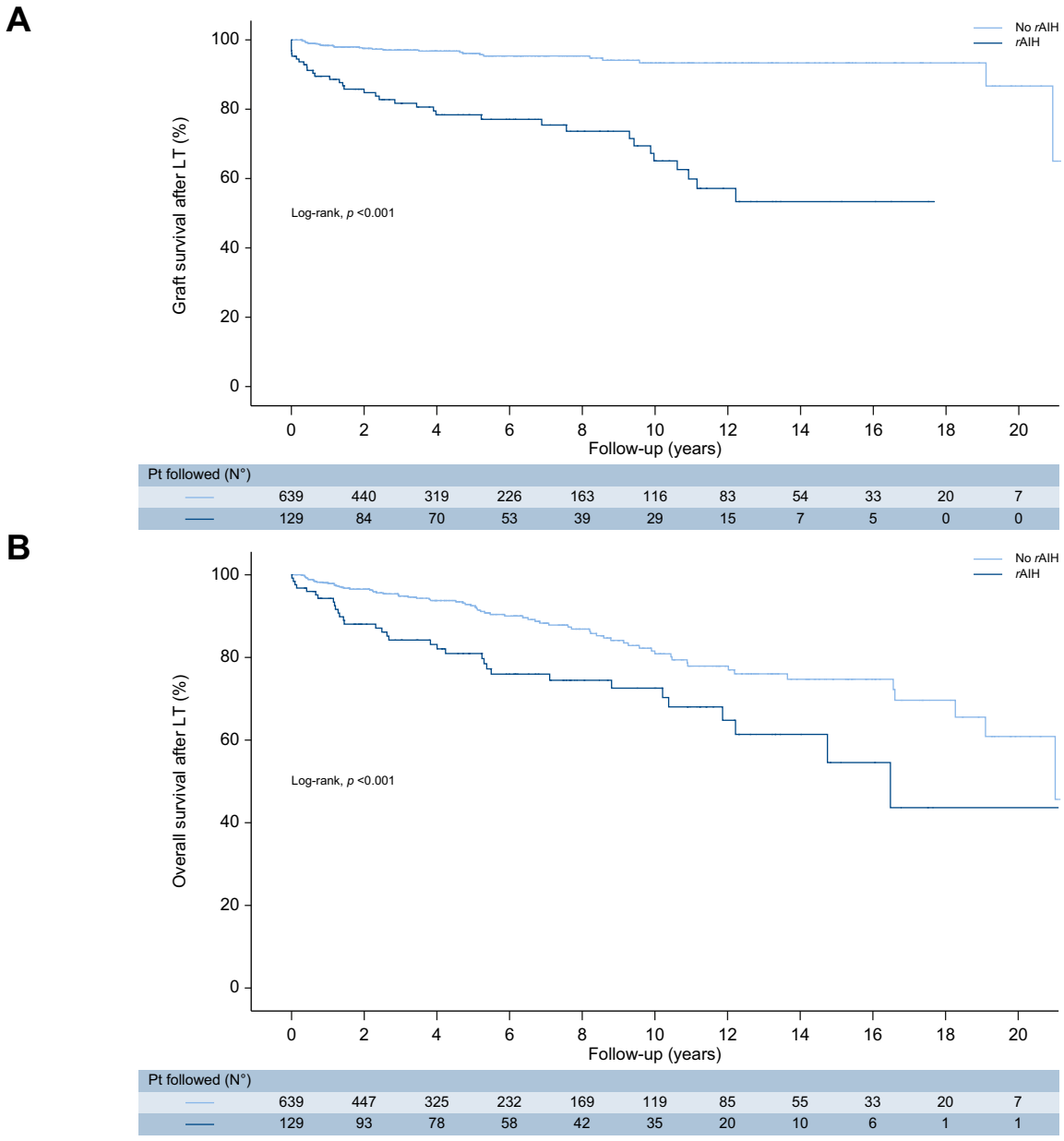

Fig. 4. Survival in patients with and without *r*AIH after liver transplantation. (A) Graft survival. (B) Overall survival. Patients who had no *r*AIH during their follow-up are in the blue line. Patients who developed *r*AIH are only represented in the blue line until they developed *r*AIH. These patients are censored and switched to a new survival curve (red line) once they have *r*AIH. The time is then reset as time 0 for their further follow-up. Levels of significance: p <0.001 [the semi-Markov models ("clock reset" model)]. LT, liver transplantation; *r*AIH, recurrent autoimmune hepatitis.

Most cases of *r*AIH in this cohort (93%) occurred in patients receiving calcineurin inhibitors, such as tacrolimus or cyclosporine. These drugs block T-cell activation through T-cell receptors, where interleukin-2 (IL-2) is required for the survival and proliferation of regulatory T cells (Tregs) which express the IL-2 receptor, CD25.[30] As these medications decrease the production of IL-2, Treg function may be altered. In animal models, autoimmune disease linked with the use of these immunosuppressive regimens has been related to the impairment of T cell-regulated suppressor function and subsequent development and activation of autoreactive T cells.[31,32] Thus, manipulation of Tregs following LT with IL-2-directed therapy may be relevant to prevent *r*AIH in the allograft.[33]

Our results suggest that patients at higher risk of *r*AIH should be considered for therapeutic strategies within the first year of LT to prevent the occurrence of *r*AIH. Treatment of *r*AIH is empiric and depends on the presentation, which can be variable. When patients present with asymptomatic disease and minimal changes in liver tests or histological features, minor increases in immunosuppression may be sufficient to suppress recurrent disease.[34,35]

Of note and similar to previous studies in patients with AIH, the level of bilirubin at diagnosis of *r*AIH was associated with a higher risk of graft loss (HR 1.004, 95% CI 1.002-1.006, p <0.001) and death (HR 1.003, 95% CI 1.001-1.005, p = 0.04).[36,37] In fact, patients with bilirubin >50 μmol/L at diagnosis of *r*AIH had a higher risk for graft loss (HR 4.21, 95% CI 2.13-8.34, p <0.001).

There was no difference in bilirubin levels at the time of *r*AIH between patients with advanced fibrosis (F3-4) compared to patients without advanced fibrosis (4.1±1.9 *vs.* 2.5±0.5 ULN, p = 0.31) suggesting that this finding was not related to missed cases of *r*AIH with advanced fibrosis.

A wide range in frequency of *r*AIH was observed, varying from 0.0% to 69% among centers, with a yearly recurrence rate ranging from 0% to 10%. This could be related to (i) different follow-up times between centers (mean total follow-up range 5-136 months, p <0.001), and (ii) difference in protocol liver biopsies that were not performed in 10 of the 33 LT centers.

We acknowledge there are limitations in this study. Due to the retrospective nature of the study, we were not able to accurately evaluate immunosuppression adherence and time era effect. In addition, liver biopsies were not re-evaluated to identify other important aspects, such as the presence of signs of acute or chronic rejection. As well, different follow-up strategies, and changes of immunosuppression over time that were not recorded might have influenced our results. Moreover, while the diagnosis of *r*AIH in our cohort was established according to liver biopsies,[38,39] biopsies were protocol-driven in some centers and clinically driven in others. This may have led to differences in time to diagnosis of *r*AIH between the different centers. Indeed, in the Cox regression analysis, clinically driven liver biopsies were associated with a higher risk of *r*AIH (Table 1), which may have been related to the higher frequency of abnormal serum liver function tests in patients with *r*AIH. Moreover, the mean time for *r*AIH was different between centers that perform protocol- and clinically driven liver biopsies (16.3 years, 95% CI 14.9-17.8 *vs.* 14.5 years, 95% CI 12.6-16.3 years, p <0.001). In addition, lack of biopsies after LT (especially protocol biopsies) might lead to overestimation of the prognosis after *r*AIH since mild cases may have been overseen or misclassified as not having *r*AIH. In order to minimize this, we performed a subanalysis in patients who had liver biopsies after LT (n = 529), and we found similar results; however, we recognized that the "true" *r*AIH prevalence and effect of the recurrence of the disease on prognosis would be better reflected in patients with protocol liver biopsies. Yet, we decided not to perform a subanalysis on patients with protocol biopsies, due to the small number of patients (n = 204), and the low number of events (*r*AIH: 27, graft failure: 4, and deaths: 25), which would not be representative of the whole cohort.

Although pre-screening of variables based on univariable p values is a commonly accepted approach and has been adopted in our large multicenter study, this strategy might lead to overestimation and risks for optimism bias.[40] Variables with p value equal or less than 0.05 in the univariate analysis were included in the Cox regression multivariate analysis to avoid model overfitting. In addition, we acknowledge that handling missing data using imputation by the mean or using a specific category for missing data is known to be suboptimal; however, as we had a relatively low frequency of missing data, we consider that the use of these strategies did not have a significant effect on our results.

Importantly, we found a high variation between centers regarding the frequency of *r*AIH (range, 0% to 69%) and yearly recurrence rate (range, 0 % to 10.1%). This broad variation seems to reflect differences in vigilance after LT, indication for liver biopsies, and different treatment strategies, emphasizing the need of standardized guidelines for follow-up and management strategies in patients transplanted for AIH.

In conclusion, we found that a younger age at the time of LT, use of mycophenolate mofetil, donor/recipient sex mismatch and IgG pre-LT were independently associated with an increased risk of *r*AIH in this large cohort of LT recipients with AIH. Recurrent AIH was associated with worse graft and overall survival after LT, suggesting that exploration of therapeutic interventions to prevent and treat *r*AIH are warranted.

Abbreviations

AIH, autoimmune hepatitis, ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELTR, European Liver Transplant Registry; HR, hazard ratio; INR, international normalized ratio; LT, liver transplantation; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; *r*AIH, recurrent AIH; Treg, regulatory T cell; ULN, upper limit of normal; UNOS, United Network for Organ Sharing.

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Conflicts of interest

These authors disclose the following: A.J. Montano-Loza has served on advisory boards for Intercept Pharmaceuticals. B.E. Hansen reports grants from Intercept Pharmaceuticals and Zambon Nederland B.V. and consulting work for Intercept Pharmaceuticals and Novartis. A.E. Kremer reports consulting work for CymaBay, GSK, Intercept Pharmaceuticals, and Mirum and grants from Intercept Pharmaceuticals. A. Parés consults for Intercept and Novartis. A. Floreani reports consulting activities for Intercept Pharmaceuticals. A. Mason consults for, is on the speakers' bureau of, and received grants from Intercept. He received grants from Merk. The remaining authors disclose no conflicts.

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

Authors' contributions

Aldo J. Montano-Loza, study design, analyses of the data, creation of the first draft of the manuscript and final version; Vincenzo Ronca, analyses of the data, creation of the first draft of the manuscript and final version; Maryam Ebadi, analyses of the data, creation of the first draft of the manuscript and final version and submitting manuscript for review; Bettina E. Hansen, analyses of the data, creation of the first draft of the manuscript and final version; Gideon Hirschfield, analyses of the data, creation of the first draft of the manuscript and final version; Saleh Elwir, analysis of the data and critical revision of the manuscript for important intellectual content; Mohamad Alsaed, analysis of the data and critical revision of the manuscript for important intellectual content; Piotr Milkiewicz,

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Data availability statement

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Supplementary data

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