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Long-term outcome of liver transplantation for autoimmune hepatitis: A French nationwide study over 30 years

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Abbreviations: ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; AKI, acute kidney injury; ANA, antinuclear antibodies; Anti-LKM1, liver/kidney microsomal antibody type 1; CDR, chronic ductopenic rejection; CI, confidence interval; CLD, chronic liver disease; CNJ, calcineurin inhibitor; DSA, donor-specific antibodies; FH, fulminant hepatitis; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HLA, human leucocyte antigen; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; LT, liver transplantation; MDRD, modification of diet in renal disease; mTOR-i, mTOR inhibitor; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PTLT, post-transplant lymphoproliferative disorders; SMA, smooth muscle antibodies; TCMR, T-cell-mediated rejection; UDCA, ursodeoxycholic acid.

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Abstract

Background & Aims: Autoimmune hepatitis (AIH) is a rare indication for liver transplantation (LT). The aims of this study were to evaluate long-term survival after LT for AIH and prognostic factors, especially the impact of recurrent AIH (rAIH).

Methods: A multicentre retrospective nationwide study including all patients aged ≥ 16 transplanted for AIH in France was conducted. Early deaths and retransplantations (≤ 6 months) were excluded.

Results: The study population consisted of 301 patients transplanted from 1987 to 2018. Median age at LT was 43 years (IQR, 29.4–53.8). Median follow-up was 87.0 months (IQR, 43.5–168.0). Seventy-four patients (24.6%) developed rAIH. Graft survival was 91%, 79%, 65% at 1, 10 and 20 years respectively. Patient survival was 94%, 84% and 74% at 1, 10 and 20 years respectively. From multivariate Cox regression, factors significantly associated with poorer patient survival were patient age ≥ 58 years (HR = 2.9; 95% CI, 1.4–6.2; $p = 0.005$) and occurrence of an infectious episode within the first year after LT (HR = 2.5; 95% CI, 1.2–5.1; $p = 0.018$). Risk factors for impaired graft survival were: occurrence of rAIH (HR = 2.7; 95% CI, 1.5–5.0; $p = 0.001$), chronic rejection (HR = 2.9; 95% CI, 1.4–6.1; $p = 0.005$), biliary (HR = 2.0; 95% CI, 1.2–3.4; $p = 0.009$), vascular (HR = 1.8; 95% CI, 1.0–3.1; $p = 0.044$) and early septic (HR = 2.1; 95% CI, 1.2–3.5; $p = 0.006$) complications.

Conclusion: Our results confirm that survival after LT for AIH is excellent. Disease recurrence and chronic rejection reduce graft survival. The occurrence of an infectious complication during the first year post-LT identifies at-risk patients for graft loss and death.

KEYWORDS

biliary complication, chronic rejection, recurrence, sepsis, survival

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is a rare liver disease characterized by immune-mediated injury to hepatocytes. The pattern of clinical presentations spans from asymptomatic forms discovered on elevated liver enzymes to acute/subacute liver failure or decompensated cirrhosis. In cases of decompensated autoimmune cirrhosis, or cortico-resistant acute or subacute liver failure, liver transplantation (LT) may be the only therapeutic option. It is estimated that around 10% of patients suffering from AIH will require LT during their life.¹ Nevertheless, AIH is a rare indication for LT. In Europe, autoimmune cirrhosis (excluding fulminant presentations of AIH) represented 2% of all LT indications during the period 1988–2016.² LT for AIH is challenging, because it raises several specific issues. First, a higher risk of both acute and chronic rejection has been reported in this population.^{3,4} Second, disease recurrence is frequent, with an incidence rising to more than 40%, 5–10 years after LT.^{5,6} In some cases, patients may require retransplantation because of recurrent AIH (rAIH), whose impact on graft or patient

Key Points

- Autoimmune hepatitis (AIH) is a rare indication of liver transplantation (LT). Prognostic factors for graft and patient survival after LT for AIH are not yet fully characterized.
- The occurrence of an infectious complication during the first year after LT is the main prognostic factor for patient survival.
- Recurrence of AIH and development of chronic rejection significantly impair graft survival.

prognosis is still debated.^{7–9} Third, because of potential prolonged use in these patients (both before and after LT), short- and long-term complications of CST therapy are expected to be frequent, such as infections or metabolic disorders. The risk–benefit balance

of long-term CST therapy after LT is therefore unclear. Despite all these specificities, probably because of the young age of this population, overall prognosis of LT for AIH is considered good, with a 58%–65% graft survival and a 65%–77% patient survival at 10 years.^{2,8–12} The aim of the present retrospective multicentre study was, from a large French nationwide cohort with long follow-up, to evaluate the overall graft and patient survivals after LT for AIH and the factors influencing it, especially the impact of disease recurrence and immunosuppressive regimen, including long-term CST therapy.

2 | PATIENTS AND METHODS

2.1 | Study design

All patients, aged 16 and older, who were transplanted for AIH from July 1987 to April 2018 in 20 French LT centres were selected (Figure 1). We then excluded early deaths and retransplantations (≤ 6 months) to analyse more accurately risk factors for long-term prognosis and not those related to early post-operative complications. Initial diagnosis of AIH was established according to the European Association for the Study of the Liver guidelines,¹³ and was subsequently corroborated by a compatible histopathological examination of the explanted native liver. Patients with evidence of other competing aetiology (excess alcohol consumption, chronic viral hepatitis, advanced steatohepatitis) were excluded. Cases of overlap syndromes (association of AIH and PBC or primary sclerosing cholangitis [PSC]) were included. This study was conducted in accordance with the Declaration of Helsinki, and no donor organs were obtained from executed prisoners or other

institutionalized persons. According to French law (Loi Jardé), retrospective studies do not require Institutional Review Board (IRB) approval.

2.2 | Clinical and Laboratory data

Data collected from medical records included age at diagnosis, presence of other autoimmune disorders, AIH treatment before LT, immunoglobulin G (IgG) levels and presence of circulating antibodies. Type I AIH was defined by the presence of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA), and type II by the presence of anti-liver/kidney microsomal antibody type 1 (LKM1) and/or anti-liver cytosol type 1. Presence of pre-transplant anti-HLA antibodies was recorded. Indication for LT, Child–Pugh and MELD scores were assessed. Donor characteristics and technical aspects of LT were reported. Donor/recipient HLA mismatches were determined for the main loci A, B and DR.

2.3 | Follow-up after liver transplantation

All patients received grafts from cadaveric or living donors. Initial immunosuppressive regimen was based on a calcineurin inhibitor: cyclosporine (CYA) or tacrolimus (TAC). Starting on postoperative Day 1, methylprednisolone was tapered to reach a maintenance dose of 0–5 mg/day at 6 months post-transplantation. Azathioprine (AZA) or mycophenolate mofetil (MMF) or sirolimus/everolimus was either administered as part of an initial triple immunosuppressive regimen, or introduced during follow-up as a maintenance immunosuppressive agent. Long-term CST was defined as

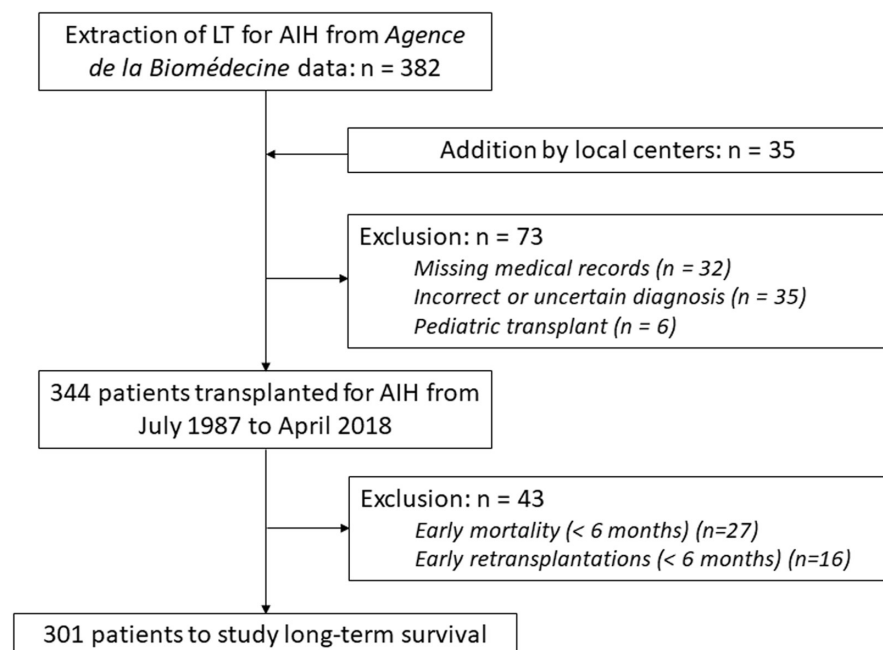


FIGURE 1 Flow chart of the study population selection. From the 344 patients' original cohort, only 301 patients were included after exclusion of early deaths and retransplantations (< 6 months).

a treatment during more than 75% of the time between LT and last follow-up. Outpatient follow-up visits were usually ensured monthly during the first year after transplantation, and every 3–12 months thereafter.

Depending on the local centre, patients underwent protocol biopsies ($n = 123$, 40.9%) or only when clinically indicated. Liver biopsies were performed in 235 patients with a mean number of 3.3 ± 2.6 per patient. Occurrence of biliary and vascular complications, anti-HLA antibodies, infections, diabetes, arterial hypertension, osteoporosis, cancer, autoimmune-associated diseases, pregnancies and miscarriages were systematically reported. Infectious episodes were defined by a sepsis that required hospitalization or resulted in significant morbidity or mortality. Osteoporosis was defined by a densitometry T-score equal or less than -2.5 standard deviation at either the femoral neck or the lumbar spine, or occurrence of osteoporosis-related fractures. Protocol screening of osteoporosis with realization of dual energy X-ray absorptiometry scans differed among local practices.

The end of follow-up corresponded to death, date of loss to follow-up or last medical examination. At that time, renal function was determined. Renal insufficiency was defined by an estimated glomerular filtration rate (GFR) less than $60 \text{ mL/min/1.73 m}^2$ using the Modification of Diet in Renal Disease equation.

2.4 | Diagnosis of rejection and recurrent autoimmune hepatitis

Diagnosis of recurrence and rejection was made following histological examination and exclusion of other aetiologies of liver damages, especially viral infections and drug toxicity. Histological lesions considered to be suggestive of rAIH were features of interface hepatitis, portal lymphoplasmocytic infiltration and lobular activity.¹³ Histological diagnosis of rejection was made and classified according to the Banff grading system in use at the date of the liver biopsy.¹⁴ Diagnosis of acute or chronic ductopenic rejection (CDR) was recorded separately.

2.5 | Statistical analysis

Data were described in their totality and according to recurrence status using median with interquartile range (IQR) or mean with standard deviation (SD) for continuous variables and number (percentage) for categorical variables. Different relevant cut-offs were tested to assess the impact of age. LT centres were dichotomized at the median according to the number of patients included in the study, to define high-volume versus low-volume centres. Categorical variables were compared with the Chi-square or Fischer's exact tests and quantitative variables were compared using the Student's *t*-test or non-parametric tests (Mann–Whitney or Kruskal–Wallis tests) when appropriate.

To analyse the risk factors for CDR, only a univariate Cox regression analysis was performed as a result of the low number of events. Rejection-free survival was defined as the time between LT and the first histological diagnosis of CDR, or to graft loss/death/last follow-up visit for patients who did not develop CDR.

Patient survival was calculated from the date of LT to that of death or the final clinical visit. Graft survival was calculated from the date of LT to that of retransplantation, death or last visit if no retransplantation.

Survival curves were constructed with the Kaplan–Meier method and compared with the Cox test in univariate analysis. Recurrence was introduced as a time-dependent covariate since this event occurs late after LT and competes with early deaths. Thus, the cumulative incidence function allows a more accurate evaluation of the recurrence on mortality or graft loss. The Cox proportional hazards regression model was also used in multivariate models. All significant variables in the univariate analysis with a level set at $p < 0.1$ were incorporated into multivariate models. Two sensitivity analyses were then performed, a Cox regression with clusters, a marginal approach that takes into account the correlation between each line of the same patient, and a frailty model, which allows the unexplained variability to be represented by a random variable. These last two models gave almost the same results. Only the model with clusters is presented here. Statistical significance was arbitrarily set at 5%. Analysis were performed by using SPSS software, version 23.0 (IBM) and R software (v 4.1.0) with the package survival.

3 | RESULTS

3.1 | Baseline characteristics and immunosuppression regimen

From the original cohort of 344 patients, the overall patient survival was 88.0%, 81.7%, 75.7%, 66.5%, 61.9% at 1, 5, 10, 20 and 25 years respectively. Graft survival was 84.2%, 76.7%, 69.3%, 56.4%, 51.7% at 1, 5, 10, 20 and 25 years respectively.

After exclusion of early deaths and graft losses, 301 patients were selected (Figure 1). The study population consisted mainly of women (79.7%), with a median age at LT of 43.0 years (IQR, 29.4–53.8; range, 16.4–70.7). The median duration of the disease before LT was 5.8 years (IQR, 0.9–12.1; range, 8 days to 44.0 years).

The indication for LT was fulminant or subfulminant liver failure in 16.3% of the cases.

Following LT, the majority of patients received a triple immunosuppressive therapy based on TAC (79.3%) and MMF (68.1%). At the end of the follow-up, 43.4% of the patients had triple or quadruple immunosuppression while 42.4% received double-therapy immunosuppression. Approximately, two-thirds of the patients (64.6%) were maintained on long-term CST therapy. The median time of follow-up was 87.0 months (IQR, 43.5–168.0). The main characteristics of the study population are shown in Table 1.

TABLE 1 Clinical and biological characteristics of the study population ($n = 301$).

| | |
|--|--------------------------|
| Gender (F/M) | 240/61 |
| Type of AIH | |
| Type I | 78.6% (206/262) |
| Type II | 10.3% (27/262) |
| Seronegative | 11.1% (29/262) |
| Overlap syndrome | 15.3% (46/301) |
| PSC | 23 |
| PBC | 23 |
| Associated autoimmune disorders before LT | 27.6% (83/301) |
| Median time from first symptoms of AIH to LT | 69.1 months (10.7–144.6) |
| Treatment of AIH before LT | |
| Subfulminant/fulminant hepatitis | |
| CST before LT | 66.0% (31/47) |
| CST at LT | 47.8% (22/46) |
| Duration of CST | 15 days (7–25) |
| Dose of CST | 60mg/d (40–60) |
| AZA | 27.1% (13/48) |
| Chronic liver disease | |
| CST before LT | 82.4% (197/239) |
| CST at LT | 54.4% (130/239) |
| Duration of CST | 48 months (12–108) |
| Dose of CST | 19.5 mg/d (10–30) |
| AZA | 60.8% (146/240) |
| CYA or TAC | 16.6% (40/241) |
| MMF | 10.4% (25/241) |
| Age at LT | 43.0 years (29.4–53.8) |
| Clinical features at LT | |
| Jaundice | 79.2% (232/293) |
| Coagulation disorder | 69.3% (203/293) |
| Ascites | 73.4% (215/293) |
| Hepatic encephalopathy | 47.3% (139/294) |
| Acute kidney injury | 13.8% (40/289) |
| Oesophageal varices | 56.9% (165/290) |
| Arterial hypertension | 11.1% (33/298) |
| Diabetes | 12.8% (38/298) |
| BMI (kg/m^2) | 23.7 (20.9–26.5) |
| Indication for LT | |
| Fulminant/subfulminant hepatitis | 16.3% (49/300) |
| Liver cirrhosis | 83.6% (251/300) |
| End-stage cirrhosis | $n = 193$ |
| Acute-on-chronic liver failure | $n = 43$ |
| Hepatocellular carcinoma | $n = 15$ |
| MELD score at LT | |
| Liver cirrhosis | 18 (14–27) |
| Fulminant/subfulminant hepatitis | 38 (34–40) |

TABLE 1 (Continued)

| | |
|---|-------------------|
| Child-Pugh score at LT* | C10 (B8–C12) |
| IgG level (g/L) at LT | 18.7 (14.4–25.8) |
| Auto-antibodies at LT | |
| ANA $\geq 1:40$ | 69.1% (177/256) |
| SMA $\geq 1:40$ | 56.3% (147/261) |
| LKM1 $\geq 1:40$ | 9.7% (24/247) |
| HLA antigens | |
| DR3 and/or DR4 | 65.8% (152/231) |
| A1B8DR3 | 18.9% (45/238) |
| Cold ischaemia time | 493 min (375–600) |
| Type of graft | |
| Partial graft | 24 |
| Split LT (brain death donor) | 15 |
| Living donor LT | 9 |
| Combined transplantation | 4 |
| Liver-kidney transplantation | 3 |
| Liver-lung transplantation | 1 |
| Heterotopic LT | 1 |
| Initial immunosuppressive treatment | |
| TAC | 79.3% (234/295) |
| CYA | 20.3% (60/295) |
| MMF | 68.1% (201/295) |
| AZA | 19.4% (57/294) |
| CST | 99.0% (292/295) |
| Maintenance immunosuppressive regimen at the last follow-up visit | |
| Number of immunosuppressive drugs | |
| 4 | 0.7% (2/297) |
| 3 | 42.8% (127/297) |
| 2 | 42.4% (126/297) |
| 1 | 13.5% (40/297) |
| 0 | 0.7% (2/297) |
| Immunosuppressive drugs | |
| TAC | 76.8% (228/297) |
| CYA | 12.5% (37/297) |
| mTOR-i | 11.4% (34/297) |
| MMF | 53.2% (158/297) |
| AZA | 10.8% (32/297) |
| Long-term CST therapy | 64.6% (192/297) |

Note: Data shown as either n (%) or median (interquartile range) for continuous variables. As a result of missing data, results are sometimes presented on a fraction of the population and not on all 301 patients. Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; AZA, azathioprine; BMI, body mass index; CLD, chronic liver disease; CST, corticosteroids; CYA, cyclosporine A; FH, fulminant hepatitis; IS, immunosuppression; LT, liver transplantation; MMF, mycophenolate mofetil; mTOR-i, mTOR inhibitor; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; TAC, tacrolimus.

*Child-Pugh score was determined only in cirrhotic patients.

3.2 | Rejection

T-cell-mediated rejection (TCMR) was diagnosed in 102 patients, in a median time of 1.4 month (IQR, 0.4–12.6). The cumulative incidence rate of TCMR was 25%, 33%, 37% and 43% at respectively 1, 5, 10 and 20 years.

Regarding CDR, the cumulative incidence rate was 1.4%, 5.2%, 6.5% and 9.9% at respectively 1, 5, 10 and 20 years. Median time to diagnosis was 23.4 months (IQR, 13.4–79.2). In univariate Cox regression, risk factors for CDR were period of LT (increased risk ≤ 1995 , HR = 3.1; 95% CI, 1.2–7.8; $p = 0.019$), presence of donor-specific antibodies at the time of LT (HR = 6.4; 95% CI, 2.4–17.1; $p < 0.001$), number of HLA mismatches (HR = 2.7; 95% CI, 2.0–3.6; $p < 0.001$), moderate-to-severe inflammatory activity in the liver explant (HR = 4.4; 95% CI, 1.0–19.6; $p = 0.048$), CYA-based initial immunosuppression (HR = 3.4; 95% CI, 1.4–8.6; $p = 0.008$) and occurrence of a previous TCMR episode (HR = 2.9; 95% CI, 1.1–7.3; $p = 0.024$). Older recipient age (HR = 0.95; 95% CI, 0.92–0.99; $p = 0.007$) and a long time between symptom onset and LT (HR = 0.96; 95% CI, 0.94–0.99; $p = 0.003$) significantly protected from CDR. Long-term UCDA therapy tended to be a protective factor (HR = 0.3; 95% CI, 0.1–1.1; $p = 0.078$), while rAIH was not associated with CDR.

3.3 | Extra-hepatic complications

Septic complications leading to hospitalization or resulting in severe morbi-mortality occurred in 60.8% of patients. Type of infection, dominated by cholangitis and pulmonary infections, is shown in Table S1. No statistical association was highlighted between the occurrence of a septic complication or sepsis-related death and long-term CST therapy. Equally, development of diabetes, arterial hypertension, obesity and osteoporosis after LT were not associated with

long-term CST therapy. Neoplastic complications, affecting 19.3% of the patients and including mainly non-melanoma skin cancer and post-transplant lymphoproliferative disorder (PTLD), were not associated with long-term CST therapy (Table S1).

3.4 | Graft survival

After exclusion of early deaths and retransplantations, graft survival was 91%, 84%, 79%, 65%, 54% at 1, 5, 10, 20 and 30 years respectively (Figure 2A). Thirty patients underwent a retransplantation after a median time of 34.2 months (IQR, 15.5–107.8). The main cause of retransplantation was rAIH and ischaemic cholangiopathy ($n = 9$ for each), followed by CDR (Table 2). Disease recurrence mainly accounted for late retransplantations (median time to retransplantation, 78.3 months). Patients undergoing retransplantation had a significant worse survival compared with others (HR = 2.7; 95% CI, 1.4–5.1; $p = 0.003$). Main risk factors for graft loss identified in univariate analysis were development of CDR, biliary

TABLE 2 Causes of retransplantation ($n = 30$).

| Indication | <i>n</i> | Median time to retransplantation (months) (IQR) |
|---|----------|---|
| rAIH | 9 | 78.3 (51.3–170.6) |
| Ischaemic cholangiopathy and/or HAT | 9 | 17.1 (14.2–38.4) |
| CDR | 8 | 20.5 (14.3–76.7) |
| Budd-Chiari syndrome | 1 | 7.4 |
| Haemorrhagic shock secondary to arterio-biliary fistula | 1 | 15.7 |
| HCV infection post-LT | 1 | 136.2 |
| Unknown | 1 | 16.2 |

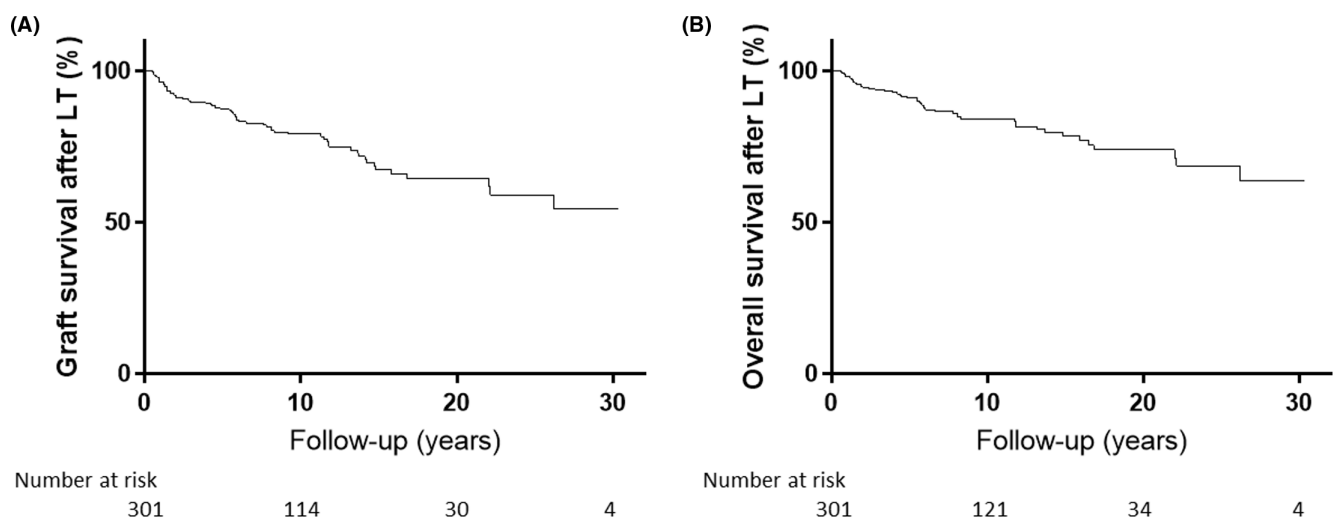


FIGURE 2 (A) Graft and (B) Patient actuarial survival according to Kaplan-Meier estimates. Overall graft survival after LT was 91%, 84%, 79%, 65%, 54% at 1, 5, 10, 20 and 30 years respectively. Overall patient survival after LT was 94%, 88%, 84%, 74%, 63% at 1, 5, 10, 20 and 30 years respectively.

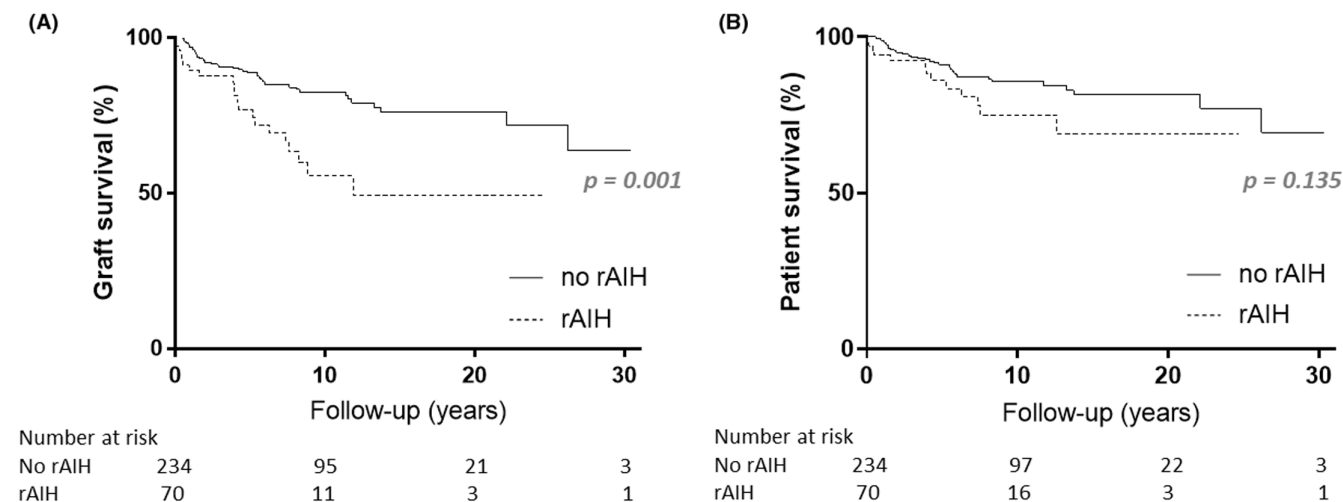


FIGURE 3 Impact of recurrence on global mortality and graft loss. (A) Probability of graft survival following recurrence or not. A significant effect of rAIH on graft loss was observed (HR = 3.2; 95% CI, 1.7–6.2; $p < 0.001$). Graft survival was 97%, 89%, 83%, 76% and 64% at 1, 5, 10, 20 and 30 years respectively for patients without rAIH, compared with 90%, 77%, 56%, 49% and 49% at 1, 5, 10, 20 and 30 years respectively for patients with rAIH. (B) Probability of survival following recurrence or not, with recurrence introduced as a time-dependent covariate. Occurrence of rAIH significantly impaired patient survival in univariate analysis (HR = 2.3; 95% CI, 1.2–4.5; $p = 0.014$) but no longer after adjustment for other risk factors. Patient survival was 99%, 91%, 86%, 81% and 69% at 1, 5, 10, 20 and 30 years respectively for patients without rAIH, compared with 94%, 86%, 75%, 69% and 69% at 1, 5, 10, 20 and 30 years respectively for patients with rAIH.

or early septic complications after LT and occurrence of rAIH (when introduced as a time-dependent covariate, Figure 3A). Long-term CST therapy and vascular complications also tended to negatively impact graft prognosis and were therefore introduced in multivariate analysis. With the exception of long-term CST maintenance, all factors were independent predictors for graft survival in multivariate analysis (Table 4).

3.5 | Patient survival

After exclusion of early deaths, overall patient survival was 94%, 88%, 84%, 74%, 63% at 1, 5, 10, 20 and 30 years respectively (Figure 2A). After the first LT, the leading causes of deaths were equally liver failure (including 3 rAIH-related graft failure) and extra-hepatic malignancies (Table 3). Among the 30 retransplanted patients, 12 patients died after a median time of 1.0 month after the second LT (IQR, 0.3–9.8). Main cause of mortality was liver failure (including 2 patients with a septic trigger), followed by sepsis (Table 3).

Significant risk factors for death in univariate analysis were patient age ≥ 58 years at LT, presence of the A1B8DR3 HLA haplotype, development of biliary complications, occurrence of a septic episode during the first year after LT and rAIH as a time-dependent variable (Figure 3B). Distribution during follow-up of patients according to the occurrence of rAIH and/or death is shown in Figure 4.

Multivariate analysis disclosed only two significant pejorative prognostic factors: patient age ≥ 58 years (HR = 2.9; 95% CI, 1.4–6.2; $p = 0.005$) and the occurrence of an infectious complication during the first year after LT (HR = 2.5; 95% CI, 1.2–5.1; $p = 0.018$).

Occurrence of rAIH did not reach statistical significance (HR = 1.9; 95% CI, 0.8–4.4; $p = 0.135$). Sex, type of AIH, overlap syndrome, MELD score, Child–Pugh score, period of LT, indication for LT, initial immunosuppressive regimen after LT, rejection episodes and long-term maintenance of CST therapy were not associated with poorer survival (Table 4).

We investigated then the cause of death among patients who developed an early infectious episode during the first year after LT. Of these 29 patients, only 4 died from sepsis, all of which occurred long after the initial episode (median time to death, 153 months; IQR, 119–202). Main cause of death in these patients was cancer ($n = 8$), followed by liver-related deaths ($n = 7$), with a median time to death of respectively 76 months (IQR, 53–108) and 25 months (IQR, 18–108). The other remaining patients died from post-operative complications ($n = 3$), cardio-cerebrovascular diseases ($n = 3$), haemoptysis ($n = 1$) and unknown aetiology ($n = 3$).

4 | DISCUSSION

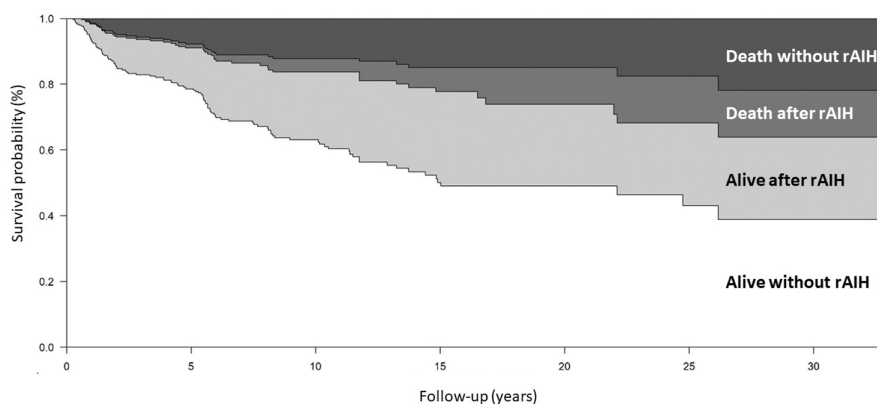
Since AIH is a rare indication for LT, little is known about the specific outcomes of these patients. A key question is the impact of rAIH on graft and patient survival. We report here comprehensive data from a large nationwide cohort with long-term follow-up (up to 30 years), allowing a detailed and robust analysis of patient outcome. Our study confirms a very good patient and graft survival rate after LT in this indication, consistent with previous studies. This is undoubtedly related to the specific population, of young women, concerned. Taken together, our current findings suggest a significant pejorative impact of rAIH on graft survival and highlight the impact of early

TABLE 3 Causes of deaths (n = 49) after the first (LT1) and second transplantation (LT2).

| | Causes of deaths | n | Median time LT1-death (months) (IQR) | Median time LT2-death (months) (IQR) |
|-----------------------|--|------------------|--------------------------------------|--------------------------------------|
| After LT1 (n = 37) | Liver failure | 8 | | |
| | <i>rAIH</i> | 3 | 97.0 (83.9–137.4) | |
| | <i>Chronic HEV</i> | 1 | 68.5 | |
| | <i>Acute rejection</i> | 1 | 18.8 | |
| | <i>Portopulmonary hypertension post-LT</i> | 1 | 24.5 | |
| | <i>Ischaemic cholangiopathy</i> | 1 | 14.0 | |
| | <i>Acute HBV infection post-LT</i> | 1 | 22.2 | |
| | Extra-hepatic malignancy | 8 | 76.7 (67.4–145.4) | |
| | Sepsis | 6 | 141.1 (105.1–159.1) | |
| | Cardio-cerebrovascular diseases | 3 | 16.8 (14.0–22.8) | |
| | HCC or hepatocholangiocarcinoma | 3 | 22.8 (17.1–59.9) | |
| | Haemoptysis | 1 | 7.2 | |
| | Postoperative (pancreatectomy) | 1 | 263.4 | |
| Unknown | 7 | 68.1 (34.2–85.0) | | |
| After LT2 (n = 12) | Liver failure | 5 | | |
| | <i>rAIH</i> | 1 | 79.5 | 1.2 |
| | <i>CDR</i> | 1 | 40.3 | 21.6 |
| | <i>Acute rejection</i> | 1 | 15.6 | 0.2 |
| | <i>Primary graft failure</i> | 2 | 17.1 (17.0–17.1) | 0.4 (0.2–0.5) |
| | Sepsis | 3 | 66.6 (59.3–128.6) | 1.2 (1.0–78.9) |
| | Postoperative complications | 2 | 57.0 (35.8–78.2) | 0.2 (0.1–0.2) |
| | Extra-hepatic malignancy | 1 | 198.0 | 8.9 |
| Unknown | 1 | 18.4 | 12.4 | |

Note: Italic values correspond to the different subcategories of the variable above (liver failure).

FIGURE 4 Patient actuarial survival with or without recurrence according to Kaplan–Meier estimates. Patients are distributed in four categories (dark grey: no rAIH and death; grey: rAIH and death; light grey: rAIH and alive at the last follow-up visit; white: no rAIH and alive at the last follow-up visit). Thirty years after LT, 63% of patients are still alive, of whom 61% did not develop rAIH. From the 40% of patients who developed rAIH, 36% died.



post-LT events as biliary, vascular and septic complications on long-term survival.

In our study population, main causes of retransplantation were disease recurrence, biliary complications and CDR. The impact of rAIH on graft survival was reported for the first time very recently in a large international cohort,⁹ while all previous studies did not manage to demonstrate.^{3,6,7,15,16} Since this event occurs late after LT, with a median time of 4.6 years in our cohort, sufficient length of

follow-up and time-dependent analysis are mandatory to point out its actual effect. Even if we did not find a significant impact of rAIH on patient survival in multivariate analysis, lack of statistical power could explain it, as it was recently demonstrated in the latter international cohort of 736 AIH-LT patients.⁹

Retransplantations for CDR were almost as frequent as for rAIH. This high rate of rejection, already reported several times for both acute and chronic rejection^{4,15,17–20} could be explained by inflation

TABLE 4 Analysis of risk factors for graft loss or death.

| Factor | Patient survival | | | | Graft survival | | | |
|---|-----------------------|------------------|-----------------------|------------------|---------------------|----------------|-----------------------|----------------|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | <i>p</i> value | HR (95% CI) | <i>p</i> value | HR (95% CI) | <i>p</i> value | HR (95% CI) | <i>p</i> value |
| Gender | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Type of AIH | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Overlap syndrome | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Autoimmune-associated disease pre-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Pre-LT arterial hypertension | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Pre-LT diabetes | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Duration of CST therapy > median (1 year) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Dose of CST > median (60mg) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| AZA at LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Any IS at LT (excepted CST) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| IgG level before LT ≥20g/L | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| ANA pre-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| SMA pre-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Anti-LKM1 pre-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Time from first symptoms to LT (per month) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| BMI at LT (per kg/m ²) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| BMI > 30 | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Age at LT (per year) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Age > median (43y) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Age > 2nd tertile (50y) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Age > 58y | HR = 2.5 (1.3–4.8) | <i>p</i> = 0.007 | HR = 2.9 (1.4–6.2) | <i>p</i> = 0.005 | | <i>p</i> = ns | | |
| Period of LT (before vs. after 2000) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Low-volume centre (high-volume centre as the reference) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Child–Pugh C | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| MELD score | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| FH (vs. CLD as the reference) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| ACLF and FH vs. other types of CLD | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| HLA DR3 and/or DR4 | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| HLA A1B8DR3 | HR = 2.0 (1.0–4.1) | <i>p</i> = 0.052 | HR = 1.5 (0.7–3.1) | <i>p</i> = 0.303 | | <i>p</i> = ns | | |
| Mismatch in the DR3/4 loci | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| High number of mismatches (>4) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Sex mismatch | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| CMV D+/R- status+ | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Donor age (per year) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Time of cold ischaemia (per minute) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Split LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |

TABLE 4 (Continued)

| Factor | Patient survival | | | | Graft survival | | | |
|--|-----------------------|-------------------------|-----------------------|-------------------------|-----------------------|----------------------------|-----------------------|-------------------------|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | <i>p</i> value | HR (95% CI) | <i>p</i> value | HR (95% CI) | <i>p</i> value | HR (95% CI) | <i>p</i> value |
| Moderate-to-severe inflammatory activity in the liver explant (vs. absent-to-mild) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Induction treatment | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| CYA initial treatment post-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| TAC initial treatment post-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| AZA initial treatment post-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| MMF initial treatment post-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Any antimetabolite post-LT | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Acute rejection | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| CDR | | <i>p</i> = ns | | | HR = 3.0 (1.3–6.5) | <i>p</i> = 0.007 | HR = 2.9 (1.4–6.1) | <i>p</i> = 0.005 |
| rAIH | HR = 2.3 (1.2–4.5) | <i>p</i> = 0.014 | HR = 1.9 (0.8–4.4) | <i>p</i> = 0.135 | HR = 3.2 (1.7–6.2) | <i>p</i> < 0.001 | HR = 2.7 (1.5–5.0) | <i>p</i> = 0.001 |
| Use of protocol biopsy | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Pre-LT anti-HLA antibodies* | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Post-LT anti-HLA antibodies* | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Biliary complications | HR = 1.9 (1.0–3.3) | <i>p</i> = 0.037 | HR = 1.6 (0.8–3.3) | <i>p</i> = 0.174 | HR = 2.5 (1.5–4.1) | <i>p</i> = 0.001 | HR = 2.0 (1.2–3.4) | <i>p</i> = 0.009 |
| Vascular complications | | <i>p</i> = ns | | | HR = 1.8 (1.0–3.2) | <i>p</i> = 0.064 | HR = 1.8 (1.0–3.1) | <i>p</i> = 0.044 |
| Early sepsis (<1 year) | HR = 2.2 (1.2–3.9) | <i>p</i> = 0.007 | HR = 2.5 (1.2–5.1) | <i>p</i> = 0.018 | HR = 2.2 (1.3–3.8) | <i>p</i> = 0.004 | HR = 2.1 (1.2–3.5) | <i>p</i> = 0.006 |
| Late sepsis (>1 year) | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| CMV infection or disease | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Long-term UDCA therapy | | <i>p</i> = ns | | | | <i>p</i> = ns | | |
| Long-term CST therapy | | <i>p</i> = ns | | | HR = 1.8 (1.0–3.5) | <i>p</i> = 0.068 | HR = 1.5 (0.8–2.8) | <i>p</i> = 0.176 |

Note: Data shown as either *n* (%) or median (interquartile range) for continuous variables. Each factor was tested in univariate analysis by Cox regression. Recurrence was considered as a time-dependent variable in univariate and multivariate analyses. Two multivariate models were tested: with or without a cluster variance to account for the intra-class correlation (since each subject have multiple events). We present here the model with clusters. Significant variables (*p* < 0.05) are highlighted in bold.

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; CLD, chronic liver disease; FH, fulminant hepatitis; IS, immunosuppression; LT, liver transplantation; ns, not significant.

*Anti-HLA antibody testing was performed in 189 patients before LT, 50 of whom were positive. Monitoring of HLA antibodies was performed in 122 patients after LT. Among them, 51 patients had anti-HLA antibodies, which were DSA in 24 patients.

of immune responses in patients with AIH, thus increasing the risk to detect mismatched donor antigens. In agreement with existing literature,^{5,10} TCMR did not influence graft survival, while development of CDR severely impaired graft survival. In a large European registry-based study, including 2515 patients transplanted for AIH, patients had an increased risk of graft loss and death owing to rejection compared with PBC, PSC and alcohol-related cirrhosis.⁸ High number of HLA mismatches and presence of DSA at the time of LT particularly increased this risk. However, the impact of CDR on graft prognosis must be updated in light of our current immunosuppressive protocols, since TAC and MMF were significantly reducing the

risk of CDR. Indeed, the incidence of CDR greatly decreased before year 1995 (20.5%) and after year 2005 (4.1%).

Regarding the impact of long-term maintenance of CST, we did not find an increased risk of metabolic, neoplastic or septic complications. However, it tended to be associated with poorer graft survival in univariate analysis. This unexpected result may be owing to a selection bias, with CST therapy being withdrawn more frequently in patients with uneventful post-LT course. Indeed, while 12 patients under long-term CST treatment underwent retransplantation or died because of rAIH, none did in the group without CST. However, the effectiveness and the safety of long-term CST therapy still appears

uncertain. Indeed, no previous study has ever managed to demonstrate the efficacy of such strategy to prevent rAIH. We recently did not find any statistical association between CST maintenance and rAIH occurrence in a cohort of 180 patients with histological follow-up (personal data). Some authors even reported decreased cholesterol and fasting glucose levels, reduced insulin need, reduced osteopenia, lesser need for anti-hypertensive medication, and the potential reduction in the risk of infections following CST discontinuation.^{21,22} Satapathy et al. also found that CST use for acute rejection in autoimmune liver diseases (while patients were maintained under a dual immunosuppression with TAC or mTOR-i and MMF) hampered significantly graft and patient survivals.²³ AASLD guidelines recommendation is thus to perform a gradual withdrawal of CST after LT.²⁴

In our cohort, the first cause of death was liver failure, including about one-third of rAIH. The usual causes of death in LT recipients, that is, cardiovascular events and cancer, were under-represented in this specific population. Tumours were mainly non-melanoma skin and HPV-induced cancers, reminding the importance of a regular screening in this population of young women. We also found a significant number of PTLD, which was the second cause of neoplasia and the first cause of cancer-related deaths ($n = 4/9$). An over-representation of autoimmune liver diseases among PTLD following LT has already been observed.²⁵ In line, haematological cancers have been previously determined as more frequent in AIH patients than in general population, as non-melanoma skin cancers.²⁶

Sepsis, reported as the leading cause of mortality following LT for AIH in a previous study,⁸ remained the second cause in our population even after excluding early deaths. Intriguingly, the strongest mortality predictor was the occurrence of early severe infectious events during the first year following LT. The latter patients died mainly of cancer or non-septic-related deaths. This observation generates different hypotheses. First, it could reflect an overall frailty underpinned by other factors not analysed here, such as malnutrition. Second, it may traduce a too strong immunosuppression pressure. Indeed, some authors reported that the level of TAC exposure during the first year following LT predicted the risk of solid organ cancers, cardiovascular events or non-melanoma skin cancers.^{27,28} Further additional data are needed in this area, but intensified immunosuppression following LT for AIH must be questioned.

The presence of the ancestral HLA A1B8DR3 haplotype, predictive of rAIH occurrence (personal data and⁶) and severe forms of AIH,²⁹ was associated with poorer survival after rAIH in univariate analysis. The loss of significance in multivariate analysis can be explained by the lack of power linked to the missing data on the HLA typing (available for 238 patients only). In general population, a previous study suggested that immune dysfunctions characteristics of A1B8DR3 haplotype may contribute to early mortality in women, since its frequency is lower than expected in elderly women.³⁰ HLA typing, often forgotten, seems to be of interest in these patients, both to monitor the risk of rAIH and CDR.

As a result of those two complications, principally concerning young patients, older age may have less impact on overall survival in patients transplanted for AIH. Indeed, only the choice of a very

high cut-off allowed to make age a significant risk factor for patient survival (>58 years, representing only 16% of the study population). In another registry-based study, the increased risk of dying for older patients after AIH-LT was mainly attributable to septic complications,³¹ which are earlier events than CDR or rAIH. Therefore, by excluding deaths and graft losses within the first 6 months following LT, we may have reduced the burden of age.

In conclusion, our nationwide study on long-term results of LT for AIH confirms a good patient and graft survival. It also substantiates the significant impact of rAIH on graft survival. Management of immunosuppressive pressure must be rethought in light of new studies, notably questioning the efficiency and safety of triple immunosuppressive maintenance therapy. Immunosuppression should probably be minimal as in all LT indications and in non-transplanted AIH patients, to avoid the occurrence of infectious and neoplastic complications, but sufficient to avoid the occurrence of rejection and rAIH in at-risk patients. Age, HLA typing, explant analysis, and early post-transplant events must be taken into account to determine personalized monitoring and treatment in this specific population.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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