Received: 9 June 2022 | Revised: 6 December 2022 | Accepted: 19 December 2022

DOI: 10.1111/liv.15500

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Liver transplantation for autoimmune hepatitis: Pre-transplant does not predict the early post-transplant outcome

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Abbreviations: ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; AKI, acute kidney injury; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; Anti-LKM1, liver/kidney microsomal antibody type 1; AZA, azathioprine; BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; CNI, calcineurin inhibitor; HCC, hepatocellular carcinoma; HLA, human leukocyte antigen; HR, hazard ratio; ICU, intensive care unit; IL-2, interleukin-2; IQR, interquartile range; LT, liver transplantation; MMF, mycophenolate mofetil; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SD, standard deviation; SMA, smooth muscle antibodies.

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Funding information
Fondation Léon Bouchut

Handling Editor: Alejandro Forner

Abstract

Background and Aims: Autoimmune hepatitis (AIH) is a rare indication (<5%) for liver transplantation (LT). The aim of this study was to describe the early outcome after LT for AIH.

Methods: A multicenter retrospective nationwide study including all patients aged ≥16 transplanted for AIH in France was conducted. Occurrences of biliary and vascular complications, rejection, sepsis, retransplantation and death were collected during the first year after LT.

Results: A total of 344 patients (78.8% of women, 17.0% of (sub)fulminant hepatitis and 19.2% of chronic liver diseases transplanted in the context of acute-on-chronic liver failure [ACLF]) were included, with a median age at LT of 43.6 years. Acute rejection, sepsis, biliary and vascular complications occurred in respectively 23.5%, 44.2%, 25.3% and 17.4% of patients during the first year after LT. One-year graft and patient survivals were 84.3% and 88.0% respectively. The main cause of early death was sepsis. Pre-LT immunosuppression was not associated with an increased risk for early infections or surgical complications. Significant risk factors for septic events were LT in the context of (sub)fulminant hepatitis or ACLF, acute kidney injury at the time of LT (AKI) and occurrence of biliary complications after LT. AKI was the only independent factor associated with graft (HR = 2.5; 95% CI: 1.1–5.4; $p = .02$) and patient survivals (HR = 2.6; 95% CI: 1.0–6.5; $p = .04$).

Conclusion: Early prognosis is good after LT for AIH and is not impacted by pre-LT immunosuppression but by the presence of AKI at the time of LT.

KEYWORDS
early infection, fulminant hepatitis, immunosuppression, sepsis, survival

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that can lead to acute liver failure or cirrhosis. First-line medical therapy is based on corticosteroids (CST) and azathioprine (AZA)[1] and is efficient in the vast majority of patients. However, in the case of decompensated cirrhosis, hepatocellular carcinoma (HCC) or cortico-resistant acute or sub-acute liver failure, liver transplantation (LT) may be the only option; it is estimated that around 10% of patients suffering from AIH will require LT during their life.[2–4] LT for AIH (AIH-LT) raises several specific issues in the early postoperative period. Notably, this population includes a large part of patients transplanted in the context of fulminant liver failure, which is known to be associated with a higher risk of early mortality.[5,6] In this setting, infection is one of the leading causes of early mortality whatever the initial liver disease.[7,8] A higher risk of fatal infections in patients undergoing AIH-LT compared to primary biliary cholangitis (PBC) has been reported, especially within the first 3 months after LT.[9,10] The impact of current and previous immunosuppressive therapies at the time of LT on these early-onset infectious episodes remains poorly understood and explored. In addition to infectious complications, a higher risk of acute rejection has been reported in AIH-LT recipients,[11,12] as disease recurrence[13] or biliary and vascular complications, which are both major causes of graft loss following LT, especially hepatic artery thrombosis (HAT) and ischemic cholangiopathy.[14–17] Finally, AIH-LT recipients are younger, more frequently women, and have very different co-morbidities when

Key Points

- Management of autoimmune hepatitis (AIH) is based on immunosuppressive treatments and liver transplantation (LT) if needed.
- Patients undergoing LT for AIH frequently develop early septic complications after LT. The impact of pre-LT immunosuppression on septic complications and overall survival has not yet been elucidated.
- Here, we found that the main cause of early deaths after LT for AIH is sepsis, but pre-LT immunosuppression is not associated with an increased risk for early infections. Acute kidney injury at the time of LT is the main risk factor for both graft loss and death.

compared to frequent indications for LT, that is, alcohol-related liver disease, viral hepatitis and non-alcoholic steatohepatitis.

Since risk factors for early postoperative complications and mortality have not been extensively elucidated yet, the present multicenter retrospective study from a large French nationwide cohort focused on early postoperative outcomes after AIH-LT in adults. Our aims were (1) to identify the prognostic factors for both 1-year patient and graft survivals, (2) to identify predictive factors for early complications after LT (namely sepsis, acute rejection, biliary and vascular complications) with specific attention on pre-LT immunosuppressive therapy.

2 | PATIENTS AND METHODS

2.1 | Study population

From the databases of the French *Agence de la Biomédecine* (ABM) and all French LT centres, were selected all patients aged 16 and older, transplanted for AIH in France from January 1985 to April 2018. 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. Diagnosis of AIH was based on clinical and biological characteristics, histopathological examination of the explanted native liver, and if there was no evidence of other competing aetiology (excess alcohol consumption, chronic viral hepatitis, advanced steatohepatitis). Overlap syndromes (association of AIH and PBC or primary sclerosing cholangitis [PSC]) were included. PSC overlap diagnosis in AIH patients was established based on the presence of typical findings of sclerosing cholangitis on high-quality cholangiography, after the exclusion of secondary causes.[18] PBC variant was diagnosed with persistent cholestatic abnormalities, histological findings of chronic non-suppurative, granulomatous, lymphocytic small bile duct cholangitis and presence of autoantibodies (anti-mitochondrial antibodies [AMA]), anti-sp100, anti-gp210.[19] Indications for LT were a fulminant and subfulminant liver failure, end-stage autoimmune cirrhosis and/or HCC. (Sub)Fulminant liver failure was defined as a severe liver injury with the onset of hepatic encephalopathy within 12 weeks since the onset of jaundice in the absence of pre-existing liver disease. Acute-on-chronic liver failure (ACLF) was defined as an acute flare of pre-existing cirrhosis associated with organ failure(s) according to the Chronic Liver Failure-Sequential Organ Failure Assessment score.[20]

2.2 | Clinical and laboratory assessments

Baseline demographic characteristics including age at diagnosis, other autoimmune disorders, the occurrence of HCC and portal hypertension complications were collected from medical records. Prior treatment to LT was determined, including duration and dose of CST at the time of LT. Presence and titers of circulating antibodies (antinuclear antibodies [ANA], smooth muscle antibodies [SMA], and liver/kidney microsomal type 1 [anti-LKM1] and anti-liver cytosol type 1 [anti-LC1]) antibodies and levels of immunoglobulin G (IgG) were recorded. Type I AIH was defined by the presence of ANA and/or SMA, and type II by the presence of anti-LKM1 and/or anti-LC1. Acute kidney injury (AKI) at LT time was defined by serum creatinine following AKIN criteria (increase of ≥26.5 mmol/L or ≥1.5-fold from baseline).[21] Severity scores at the time of LT (Child-Pugh and MELD scores) were determined.

Donor characteristics included gender, age, body mass index (BMI) and serological human leukocyte antigen (HLA) typing. Donor/recipient mismatches in the HLA system were determined for the main loci A, B and DR. Presence of pre-transplant anti-HLA antibodies including donor-specific antibodies (DSA) was reported.

2.3 | Follow-up after liver transplantation

All patients received grafts (whole or partial) from cadaveric or living donors. The initial immunosuppressive regimen was defined as the treatment at the end of the hospitalization for LT, and was based on a calcineurin-inhibitor: cyclosporine (CYA) or tacrolimus (TAC), possibly combined with AZA or mycophenolate mofetil (MMF). Induction therapy by anti-interleukin-2 receptor antibodies was mainly administered in the case of AKI. Other types of induction therapies (antithymocyte globulins, OKT3, daclizumab, intravenous immunoglobulins) have been used infrequently. Starting on postoperative day 1, methylprednisolone was tapered to reach a maintenance dose of 0–5 mg/day at 6 months post-transplantation. Outpatient follow-up visits were usually ensured monthly during the first year after transplantation.

Incidences of infections, rejections, biliary and vascular complications after LT were reported. Infectious episodes were defined by sepsis that required hospitalization or resulted in significant morbidity or mortality. Diagnosis of rejection was based on histological examination and exclusion of other etiologies of liver damage, especially viral infections and drug toxicity. The rejection episode was classified according to the Banff grading system in use at the date of the liver biopsy.[22] The end of follow-up corresponded to death or 1-year post-transplant evaluation.

2.4 | Statistical analysis

Data were described using median with interquartile range (IQR) or mean with standard deviation (SD) for continuous variables and number (percentage) for categorical variables. Age at LT and diagnosis was dichotomized at the median. To analyse the effect of LT time, patients were divided into three groups: LT before the year 1996, LT from 1996 to 2005 included and LT after the year 2006. 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.

The following variables were analysed as risk factors for postoperative complications, early septic episodes and acute rejection: age (at diagnosis and LT), type of AIH, associated autoimmune diseases, pre-LT diabetes or arterial hypertension, pre-LT immunosuppression, Child-Pugh and MELD scores, the indication of LT, BMI, donor age and sex, donor-recipient age difference, cold ischemia time, type of LT, centre volume, initial immunosuppression after LT including induction treatment and occurrence of biliary or vascular complications after LT. Univariate and multivariate analyses of these variables were performed with binary logistic regression.

Patient survival was calculated from the date of LT to that of death or the 1-year clinical visit. Graft survival was calculated from the date of LT to that of retransplantation, death or 1-year visit if no retransplantation. Survival curves were constructed with the Kaplan–Meier method and compared with the log-rank test in univariate analysis. The Cox proportional hazards regression model was used in both univariate and multivariate models. All significant variables in the univariate analysis with a level set at $p < .10$ were incorporated into multivariate models. A p-value less than .05 was considered statistically significant. Statistical analyses were done using SPSS software, version 23.0 (IBM, Armonk, NY, USA).

3 | RESULTS

3.1 | Study population

The study population consisted of 344 patients; 78.8% were women with mainly type I AIH (Table 1). Forty-nine patients (14%) with overlap syndromes were included. The median age at LT was 43.6 years. The median duration of the disease before LT was 5.8 years. CST therapy was administered in the vast majority of patients with chronic liver diseases (83% of the cases) with a median duration of 4.0 years, and a mean dose of 21.7 mg/day at the time of LT. For fulminant and subfulminant liver failure, CST therapy was administered before LT in two-thirds of the cases, with a median duration of 15 days and a mean dose of 57.5 mg/day. Excluding (sub) fulminant liver presentations, 19.1% of patients with autoimmune cirrhosis required transplantation in the context of ACLF, with a median MELD score of 34 (IQR, 29–40). Initial immunosuppressive treatment after LT consisted of a combination of TAC, MMF and CST in the vast majority of the patients.

3.2 | Early surgical complications and infections

Biliary and vascular complications occurred in respectively 25.3% and 17.4% of the patients (Table 2). Pre-LT immunosuppression (type of immunosuppressive therapy, and dose and duration for CST therapy) and period of LT were not associated with the occurrence of early surgical complications (see Table S1).

TABLE 1 Clinical and biological characteristics of the study population ($n = 344$).

Gender (F/M)	271/73
Median age at LT (IQR)	43.6 years (30.3–54.8)
Type of AIH	
Type I	78.4% ($n = 236$)
Type II	10.3% ($n = 31$)
Seronegative	11.3% ($n = 34$)
Not available	$n = 43$
Overlap syndrome	14.2% ($n = 49$)
PSC	23
PBC	26
Other autoimmune disorders	27.6% ($n = 95$)
Treatment before LT	
Subfulminant/fulminant hepatitis	67.9% (38/56)
CST	15 days (7–30)
Median duration of CST (IQR)	29.8% (17/57)
AZA	1.8% (1/57)
CYA or TAC	1.8% (1/57)
MMF	82.6% (223/270)
Chronic liver diseases	4.0 years (1.0–10.0)
CST	61.6% (167/271)
Median duration of CST (IQR)	17.6% (48/272)
AZA	11.8% (32/272)
CYA or TAC	24.4% (66/271)
MMF	1.1% (3/272)
UDCA	0.7% (2/272)
Cyclophosphamide	1.5% (4/272)
Everolimus or sirolimus	
Methotrexate, rituximab, plasmapheresis, intravenous immunoglobulin	
Treatment at the time of LT	
Subfulminant/fulminant hepatitis	45.5% (25/55)
CST (prednisolone or budesonide)	57.5 mg/d (±23.3)
Mean dose of CST (±SD)	17.5% (10/57)
AZA	56,1% (147/262)
Chronic liver diseases	21.7 mg/d (±23.1)
CST	31.3% (84/268)
Mean dose of CST (±SD)	
AZA	
Median time from first symptoms to LT (IQR)	69.1 months (10.1–143.7)
Clinical features at the time of LT	
Jaundice	78.1% (261/334)
Coagulation disorder	69.8% (233/334)
Ascites	74.8% (250/334)
History of hepatic encephalopathy	49.3% (165/335)
AKI	16.1% (53/330)

(Continues)

TABLE 1 (Continued)

Portal vein thrombosis	10.8% (36/334)
Oesophageal varices	56.5% (186/329)
Portocaval anastomosis	7.5% (25/334)
Albumin dialysis	6.0% (20/331)
Mean BMI (kg/m^2) (±SD)	24.1 (±8.8)
Indication for LT	
Fulminant/subfulminant hepatitis	17.0% (58/341)
Liver cirrhosis	83.0% (283/341)
Acute-on-chronic liver failure	19.1% (54/283)
Hepatocellular carcinoma/ hepatocholangiocarcinoma	6.0% (17/283)
Not available	0.9% (3/344)
Median MELD score at LT (IQR)	22 (15–33)
Median Child-Pugh score at LT (IQR)	C11 (B8-C12)
Median IgG level (g/L) at LT (IQR)	18.9 (14.5–25.3)
Autoantibodies at LT	
ANA ≥ 1:40	69.7% (205/294)
SMA ≥ 1:40	53.7% (159/296)
LKM1 ≥ 1:40	9.2% (26/282)
LC1 ≥ 1:40	4.6% (13/282)
AMA ≥ 1:40	6.7% (19/292)
ANCA ≥ 1:20	49.1% (28/57)
HLA	
DR3 and/or DR4	66.9% (172/257)
B8	33.2% (88/265)
A1B8DR3	20.4% (54/265)
Median cold ischemia time (IQR)	494 min (380–601)
Donor characteristics	
Gender (F/M)	157/169
Median age (IQR)	45 (29–60)
Mean BMI (kg/m^2) (±SD)	23.9 (±3.9)
Type of graft	
Mean graft weight (g) (±SD)	1395 (±345)
Partial graft	25
Split LT (brain death donor)	16
Living donor LT	9
Combined transplantations	6
Liver-kidney transplantation	5
Liver-lung transplantation	1
Heterotopic LT	1
Induction therapy	
Lympho-depleting therapy (antithymocyte globulin or antilymphocyte serum)	8.7% (26/298)
IL-2 receptor antagonist	18.1% (54/298)
Other (OKT3, intravenous immunoglobulins…)	3.7% (11/298)

TABLE 1 (Continued)

Initial immunosuppressive treatment	
TAC	79.6% (265/333)
CYA	19.5% (65/333)
MMF	69.1% (230/333)
AZA	17.8% (59/332)
CST	99.1% (330/333)

Note: Data are shown as either *n* (%) or median (interquartile range) for continuous variables.

Abbreviations: AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; AZA, azathioprine; BMI, body mass index; CYA, cyclosporine A; CST, corticosteroids; IgG, immunoglobulin G; IQR, interquartile range; IL-2, interleukin-2; LT, liver transplantation; MMF, mycophenolate mofetil; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SD, standard deviation; SMA, smooth muscle antibodies; TAC, tacrolimus.

TABLE 2 Infectious, biliary and vascular complications during the first year after AIH-LT

	Number of patients (%) Number of events
Infectious episodes	153 (44.2%)
CMV infection or disease	49
Pneumonia	35
Cholangitis/liver abscess	27
Skin and soft tissue infection	13
Isolated septicemia	13
Urinary tract infection	13
VZV infection	9
Spontaneous bacterial peritonitis	8
Gastrointestinal infection	7
Systemic opportunistic infection	6
Secondary peritonitis	2
Septic arthritis or osteomyelitis	2
Other	4
Biliary complications	87 (25.3%)
Anastomotic stricture	54
Biliary leak	24
Ischemic cholangiopathy	16
Other	3
Vascular complications	60 (17.4%)
Hepatic artery thrombosis	22
Hepatic artery stenosis	17
Portal vein thrombosis or stenosis	13
Hepatic vein thrombosis or stenosis	6
Hepatic artery pseudoaneurysm	3

Almost half of the patients (44.2%) developed sepsis during the first year after LT. CMV was the main cause of infection, including a high percentage (30.6%) of CMV disease. Severe forms of VZV

primary infection or reactivation were equally reported in 9 patients. The second leading cause of sepsis was pulmonary infection (including 5 invasive aspergilloses, 2 pneumocystoses and 1 nocardiosis), followed by biliary tract-related infections. Systemic opportunistic infections included systemic candidiasis, cryptococcosis, disseminated trichosporonosis, toxoplasmosis and mucormycosis.

Multivariate analysis disclosed as significant risk factors for early septic events occurrence of biliary complications after LT (odds ratio [OR] = 1.8; 95% CI: 1.1–3.0; p = .025) and LT in the context of (sub) fulminant hepatitis or ACLF (OR = 1.7; 95% CI: 1.1–2.9; p = .030). AKI was also a significant risk factor for early sepsis in a multivariate model excluding LT (OR = 2.0; 95% CI: 1.0–3.8; p = .035) (see Table S2).

We also investigated the impact of previous immunosuppression on the occurrence of bacterial and/or fungal infections after LT. These two types of infections, whether tested separately or together, were not associated with the administration of CST therapy at the time of LT (or its dose or duration) nor by the administration of any other immunosuppressive drug. In the same way, when analysing the subgroups of ACLF and fulminant hepatitis, no impact of previous immunosuppression on early infections was highlighted.

3.3 | Rejection

Eighty-one patients (23.5%) presented one or several episodes of acute rejection during the first year post-LT. The incidence of acute rejection decreased with the time of LT (Figure 1). The first episode of rejection occurred after a median time of 14 days post-LT (IQR, 9–86). Over the 54 episodes with available Banff grading, 37.0%, 51.9% and 11.1% were classified as mild, moderate and severe respectively. No acute rejection-related graft loss occurred, but one of the patients developed rapid chronic ductopenic rejection after 2 documented previous acute rejections, requiring retransplantation 6.1 months after the initial LT.

In multivariate analysis, 3 independent protective factors were identified: age at LT (per year; OR = 0.971; 95% CI: 0.949–0.993; p = .012), use of an induction treatment (OR = 0.3; 95% CI: 0.2–0.8; p = .009) and triple immunosuppressive regimen with any antimetabolite (OR = 0.4; 95% CI: 0.2–0.99; p = .047) (see Table S3).

3.4 | Patient survival

Patient survival was 88.0% at 1 year. Of the 40 deaths, half occurred during the first month. The leading cause of early death was sepsis (n = 18) (Table 3), with a median time for fatal infectious episodes of 0.8 months. Liver-related deaths represented the second-leading cause of mortality. Identified risk factors in univariate analysis were Child-Pugh score (p = .008), AKI (p < .001), LT indication (with a poorer prognosis for patients transplanted in the context of ACLF, p = .004), anti-IL2 induction therapy (p = .006), MELD score (p = .038), age at LT (p = .002) and donor age (p = .011) (Table 4). Whatever the multivariate analysis model (including or not the presence of anti-HLA antibodies [significant proportion of missing data], MELD and/or Child-Pugh scores [collinearity]), only AKI at LT was independently associated with patient survival (HR = 2.6; 95% CI: 1.0–6.5; p = .04) (Figure 2A). The period of LT did not impact survival probability. One-year survival was 93.8%, 92.6% and 84.7% for patients transplanted before 1996, from 1996 to 2005 and after 2006 respectively (Figure 2D).

3.5 | Graft survival

Twenty-one patients required retransplantation within the first year following LT (Table 3) after a median time of 10 days (IQR, 3–185).

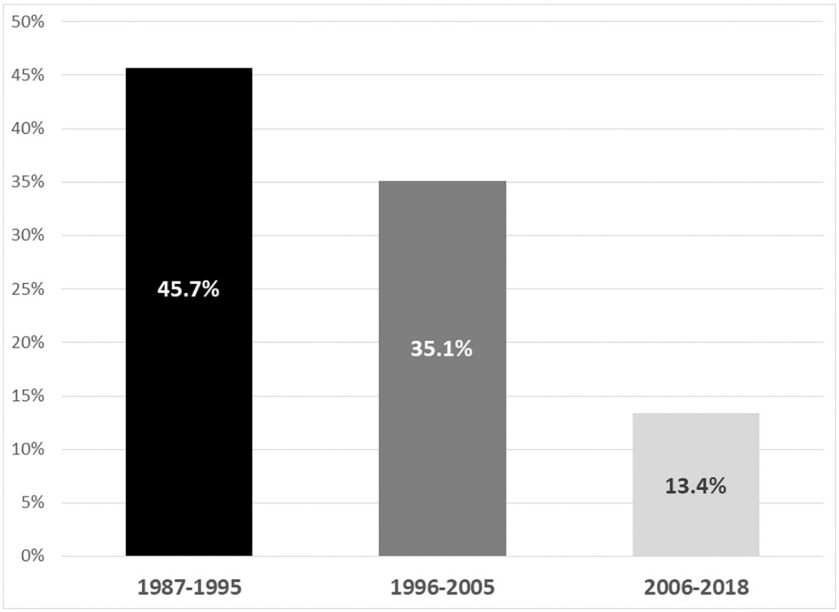

FIGURE 1 Risk of acute rejection during the first year after liver transplantation (LT) depending on the time period of LT. Incidence of acute rejection progressively decreased with time period, from 45.7% for LT before the year 1996 to 13.4% for LT after the year 2006.

TABLE 3 Causes of death and retransplantation (re-LT) during the first year after AIH-LT

		Causes	*n*	Median time from first LT (months)
Retransplantation (*n* = 21)		Primary graft nonfunction	9	2 days (2–5)
		Ischemic cholangiopathy	4	5.4 months (3.1–7.9)
		Chronic ductopenic rejection	3	4.9 months (4.4–5.5)
		Recurrent AIH	1	11.4 months
		Hemorrhagic shock	1	6 days
		Small-for-size syndrome	1	6 days
		Acute liver failure after TIPS placement for refractory ascites	1	2.6 months
		Budd-Chiari syndrome	1	7.4 months
Deaths (*n* = 40)	No re-LT	Sepsis	15	0.8 (0.2–1.6)
		Cerebro- or cardio-vascular related	4	0.4 (0.3–3.1)
		Unexplained multiorgan failure	3	0.1 (0.1–0.1)
		Primary graft nonfunction	3	0.1 (0.1–1.1)
		Hemorrhagic shock	2	4.3 (2.8–5.7)
		Hepatocholangiocarcinoma recurrence	1	11.4
		N/a	4	5.4 (1.8–8.9)
	Re-LT	Sepsis	3	3.5 (2.1–5.3)
		Graft failure following retransplantation	3	1.2 (0.8–1.7)
		Cardiovascular	1	0.2
		N/a	1	10.7

The first cause of retransplantation was primary graft nonfunction (*n* = 9). Four patients developed chronic ductopenic rejection within the first year, leading 3 of them to early retransplantation after a median time of 4.9 months.

In univariate analysis, significant risk factors for graft loss were MELD score ($p = .015$), AKI at LT ($p < .001$), donor age ($p = .009$), anti-IL2 induction therapy ($p = .007$) and occurrence of acute rejection ($p = .041$) (Table 4). The risk of graft loss differed significantly according to the LT period ($p = .008$, Figure 2C) and to the indication ($p = .016$), with a poorer prognosis for ACLF followed by fulminant hepatitis. Age at LT was also weakly associated with graft loss ($p = .058$). Only AKI at LT was an independent significant factor associated with graft survival (HR = 2.5; 95% CI: 1.1–5.4; $p = .022$) (Figure 2B).

4 | DISCUSSION

Our study is one of the largest available, based on individual data, and confirms an overall early good prognosis of AIH-LT: 1-year graft and patient survivals were respectively 84.3% and 88.0%, in agreement with previous studies.[10,23] We confirm the need to manage septic risk in the early post-transplant period, as it represents the leading cause of early deaths. Other types of usual early complications after LT, namely acute rejection, biliary and vascular complications, have also to be managed during this period, with an incidence that appears to be high. However, these results need to be weighted by a possible effect of time, since our cohort was included in a large time frame. Our most relevant result is the demonstration of renal failure as the main factor impacting early outcome, rather than factors associated with liver function or the pre-LT immunosuppressive treatment.

As previously described, infectious episodes requiring hospitalization or resulting in significant morbidity or mortality were frequent after AIH-LT in the first year, affecting almost half of the recipients.[10] An unresolved issue regarding this high risk of sepsis was the role of previous immunosuppressive therapies in these patients. To our knowledge, no study investigated this question before. Here, we tested each type of immunosuppressive therapy separately and in combination, including the dose and duration of treatment for CST. We did not find any detrimental impact of previous immunosuppression on the occurrence of sepsis after AIH-LT, even considering all types of infection or only bacterial or fungal ones. Unexpectedly, we observed that AZA treatment at the time of LT was associated with a lower risk of infection during the first year in the univariate analysis. However, this observation may only reflect the increased risk of sepsis in the case of ACLF or (sub)fulminant hepatitis, since the treatment is frequently withdrawn in these 2 conditions, and concordantly with the absence of statistical significance found in multivariate analysis. Importantly, the administration of steroids at the time of LT was not associated with an increased risk of sepsis in the early postoperative period.

After AIH-LT, infectious complications were frequent in our cohort and were the main cause of 1-year mortality. A large recent

TABLE 4 Risk factors associated with graft loss and death (univariate and multivariate analysis)

	Graft loss			Death		
		Multivariate analysis			Multivariate analysis	
Factor	Univariate analysis	HR (95% CI)	*p*-value	Univariate analysis	HR (95% CI)	*p*-value
Gender	$p = .184$			$p = .571$		
Age at LT	$p = .058$	1.007 (0.986–1.028)	$p = .531$	**$p = .002$**	1.024 (0.998–1.052)	$p = .074$
Type of AIH	$p = .629$			$p = .843$		
Overlap syndrome	$p = .266$			$p = .188$		
Autoimmune associated disease	$p = .318$			$p = .953$		
Pre-LT diabetes	$p = .971$			$p = .602$		
Pre-LT arterial hypertension	$p = .659$			$p = .148$		
CST therapy at LT	$p = .760$			$p = .972$		
Length of CST therapy	$p = .611$			$p = .422$		
Dose of CST at LT	$p = .865$			$p = .981$		
AZA at LT	$p = .829$			$p = .967$		
Any immunosuppression at LT	$p = .671$			$p = .600$		
IgG level at LT	$p = .428$			$p = .368$		
Time from first symptoms to LT	$p = .631$			$p = .298$		
BMI at LT	$p = .660$			$p = .342$		
Split LT	$p = .346$			$p = .606$		
Period of LT	**$p = .008$**			$p = .067$		
1987–1995		1.0 (reference)	$p = .997$		1.0 (reference)	$p = .913$
1996–2005		0.997 (0.2–5.2)	$p = .161$		1.1 (0.1–10.4)	$p = .360$
2006–2018		3.0 (0.7–13-5)			2.7 (0.3–22.5)	
LT in high-volume centres	$p = .381$			$p = .138$		
Child-Pugh class	$p = .201$			**$p = .008$**		
A		1.0 (reference)	$p = .813$		1.0 (reference)	$p = .850$
B		1.2 (0.3–5.4)	$p = .807$		0.9 (0.2–4.1)	$p = .198$
C		0.8 (0.2–3.8)			0.3 (0.1–1.8)	
MELD score	**$p = .015$**			**$p = .038$**	*0.9 (0.9–1.0)* [a]	*$p = .086$* [a]
AKI at LT	**$p < .001$**	2.5 (1.1–5.4)	**$p = .022$**	**$p < .001$**	2.6 (1.0–6.5)	**$p = .040$**
FH versus CLD	$p = .855$			$p = .832$		
Indication of LT	**$p = .016$**			**$p = .004$**		
CLD without ACLF		1.0 (reference)	$p = .743$		1.0 (reference)	$p = .489$
Fulminant hepatitis		0.9 (0.3–2.2)	$p = .302$		1.5 (0.5–4.9)	$p = .057$
ACLF		1.5 (0.7–3.5)			2.7 (0.97–7.5)	
HLA DR3 and/or DR4	$p = .689$			$p = .781$		
HLA A1B8DR3	$p = .108$			$p = .193$		
CMV D+/R− status	$p = .649$			$p = .327$		
High number of mismatches (>4)	$p = .271$			$p = .583$		
Pre-LT anti-HLA antibodies	$p = .118$			$p = .059$	na[b]	na[b]
Donor age	**$p = .009$**	1.005 (0.988–1.021)	$p = .584$	**$p = .011$**	1.006 (0.986–1.026)	$p = .579$

(Continues)

TABLE 4 (Continued)

Factor	Graft loss			Death		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
		HR (95% CI)	*p*-value		HR (95% CI)	*p*-value
Donor-recipient age difference	$p = .272$			$p = .860$		
Gender mismatch	$p = .993$			$p = .764$		
Cold ischemia time	$p = .258$			$p = .105$		
Anti-IL2 induction therapy	**$p = .009$**	1.2 (0.6–2.4)	$p = .615$	**$p = .008$**	1.212 (0.549–2.677)	$p = .634$

Note: Data are shown as either *n* (%) or median (interquartile range) for continuous variables. Each factor was tested in univariate analysis by Cox regression. Variables with a *p*-value < .010 were introduced in the multivariate models. Variables with $p < .05$ were considered as statistically significant and labelled in bold.

Abbreviations: ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; AKI, acute kidney injury; AZA, azathioprine; BMI, body mass index; CLD, chronic liver disease; CST, corticosteroids; HLA, human leukocyte antigen; LT, liver transplantation; na, not analysed.

[a]The MELD score was introduced into another multivariate analysis model, in place of the Child-Pugh score. In the same way, only AKI was a significant risk factor in this model (HR = 3.5; 95% CI: 1.2–9.8; $p = .017$).

[b]Pre-LT anti-HLA antibodies (whether or not corresponding to donor-specific antibodies) were not introduced into multivariate analysis because of a large number of missing data (data obtained from 208 of 344 patients).

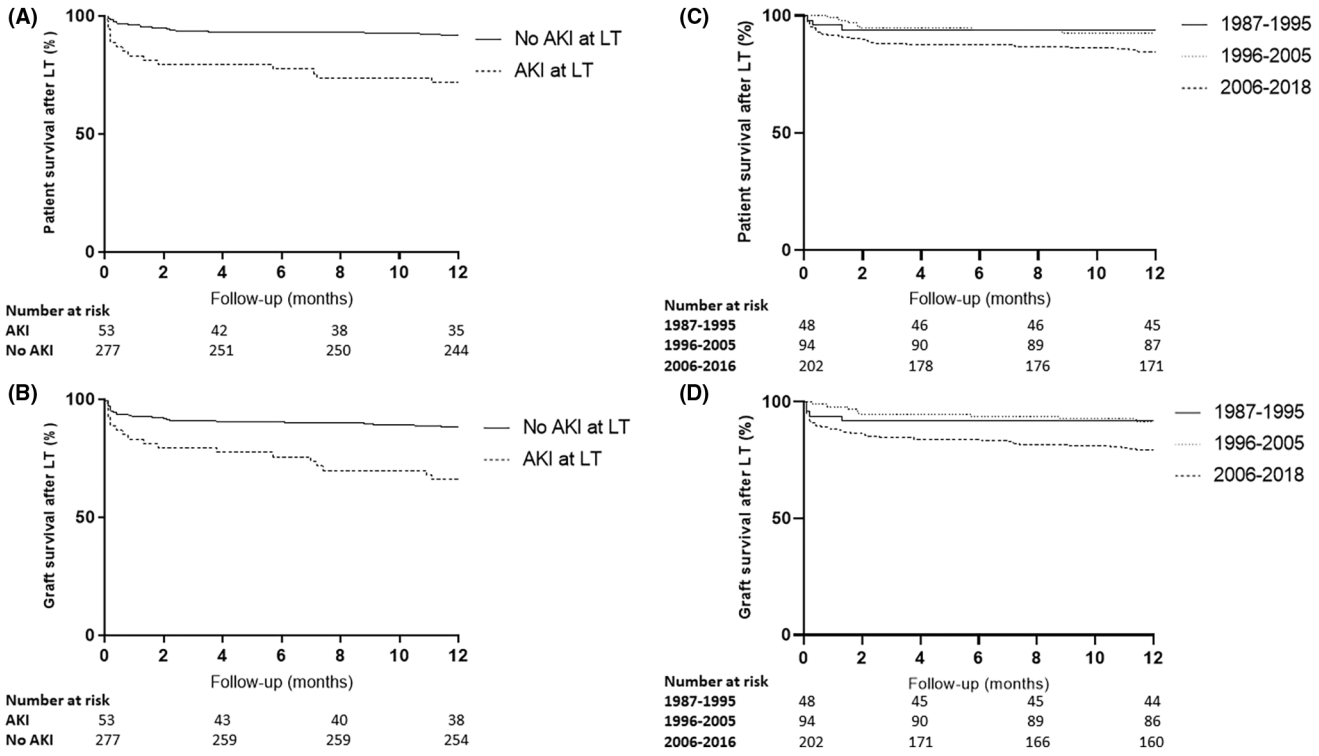

FIGURE 2 Survival functions of grafts and patients, with or without the presence of acute kidney injury at the time of liver transplantation (LT) and according to time periods. (A) Presence of acute kidney injury (AKI) significantly and independently impaired graft (HR = 2.5; 95% CI: 1.1–5.4; $p = .022$) and (B) patient survival (HR = 2.6; 95% CI: 1.0–6.5; $p = .04$). One-year graft and patient survivals were, respectively, 64.2% and 71.7% in the case of AKI at LT and 87.0% and 91.7% in its absence. For 15 patients, no information was available on renal function at the time of LT. (C) Graft and (D) patient survival according to different time periods: 1987–1995, 1996–2005 and 2006–2018. The probability of graft loss was significantly higher in more recent years ($p = .008$ using the Cox test), whilst patient survival tended to be poorer in 2006–2018 without reaching statistical significance ($p = .067$).

multicenter study based on the European Liver Transplantation Registry (ELTR) compared the prognosis of 2515 AIH-LT patients (excluding fulminant hepatitis and overlap syndromes) with LT for PBC, PSC and alcoholic-related cirrhosis.[10] These authors found a reduced graft and patient survival after LT for AIH compared with PBC and PSC, and an increased risk of early fatal infections

(especially, fungal infections) compared to all other groups. Almost half of these fatal infectious episodes occurred during the first 90 days after LT, and 69.7% occurred during the first year. All of the lethal fungal infections occurred during the first year. In our cohort, 4 patients (10% of all deaths, and 22.2% of sepsis-related deaths) died of a fungal infection, always in the context of multiple organ damages (acute respiratory distress syndrome, ischemic colitis, colon perforation, acute coronary syndrome, pulmonary embolism…). All of them died during the first year after the first (n = 2) or second LT (n = 2). The identified fungi were candida (n = 2), trichosporon and mucormycosis and the median delay to death was 16 days (IQR, 8–45) after the last LT. These observations strongly question the need for systematic antifungal prophylaxis after AIH-LT. If data are still insufficient, systematic administration in selected patients (with AKI, fulminant hepatitis or ACLF and retransplantation) seems mandatory. In the ELTR study, patient aged ≥ 53 years was a risk factor for sepsis-related deaths[10] and tended to be statistically significant for all causes of death in our study. Therefore, the administration of antifungal and/or antibiotic prophylaxis in this population is also questionable.

The only independent risk factor for both graft and patient 1-year survival in our cohort was AKI at the time of LT. The huge impact of kidney failure on prognosis has not been extensively studied in AIH-LT. In a retrospective study based on the United Network for Organ Sharing data (64 977 patients transplanted from 2002 to 2016, all causes of liver disease), 1-year mortality was associated with AKI,[8] together with donor and recipient ages. This condition may reflect hemodynamic instability at the time of LT or may account for increased susceptibility to infections, as it is already described for fungal infection, whether for pre-operative or post-operative kidney injury.[24] Concordantly, the presence of AKI at LT was associated with a higher risk of early septic events in our cohort. Induction treatment with an anti-IL2 antibody, which protected from the occurrence of acute rejection, was associated with an increased risk of death in univariate analysis. However, since this therapy is mainly administered in the case of acute renal injury to delay or reduce TAC introduction, we assume that it has no damaging effect in itself, corroborated by the absence of effect observed in the multivariate analysis. Interestingly, LT in the context of fulminant hepatitis, in our cohort, did not impair patient or graft survival. However, LT in the setting of ACLF tended to be an independent pejorative risk factor for patient survival, and early septic events were significantly more frequent in these two subgroups, suggesting the need to carefully monitor these patients.

Arterial complications and especially HAT incidence seem higher in AIH-LT compared to other indications of LT. Indeed, we found 12.2% of arterial complications and 6.4% of HAT, which is about double the rates reported in the literature.[25,26] In a register-based study on UNOS data over 65 646 LT, the risk of postoperative vascular thrombosis (the type of complication being unspecified) was significantly increased in AIH-LT (OR = 1.64). One hypothesis would be the existence of a hypercoagulable state in AIH-LT, as it has already been described in autoimmune conditions.[27] In addition to vascular complications, biliary complications were also frequent. The incidence of biliary strictures is usually from 5% to 15% after deceased donor LT,[28] compared to 20.6% in our cohort (excluding the 9 LT with living donor). Biliary tract complications represented the second cause of retransplantation and the third cause of infectious complications. AIH has previously been described as an independent risk factor for non-anastomotic biliary strictures, with a 3-fold increased risk.[14,16] This higher risk of biliary complications is obviously linked with the increase in arterial complications, but it could also be secondary to immunological events.[28] Of note, pre-LT immunosuppression had no impact on the occurrence of biliary and vascular complications in our population, and patients with overlap syndromes had the same prognosis as others.

Both chronic and acute rejection is usually reported as more frequent in AIH-LT.[12,29–34] Indeed, we observed a high rate of acute rejection at 1 year (23.5%) and 3 early graft losses related to chronic ductopenic rejection. However, a strong time-period bias should be taken into account, since the incidence of acute rejection markedly decreased with a period of LT. Considering our current immunosuppressive regimen, this issue is less of a problem nowadays.

In conclusion, our results from a large national multicenter study, with uniformly compiled and precise data, confirm the huge impact of septic complications on early mortality after AIH-LT, but the absence of deleterious effect of previous immunosuppression on both septic risk and patient and graft 1-year survival. We also identified patients at risk of poor outcomes, with kidney failure being the most robust factor related to early mortality. Close monitoring of the septic risk seems mandatory, and the benefits of antifungal prophylaxis should be considered.

ACKNOWLEDGEMENTS

To all the participating centres, Fondation Léon Bouchut and the Agence de la Biomédecine.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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SUPPORTING INFORMATION

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How to cite this article: Chouik Y, Francoz C, De Martin E, et al. Liver transplantation for autoimmune hepatitis: Pre-transplant does not predict the early post-transplant outcome. *Liver Int*. 2023;43:906-916. doi:10.1111/liv.15500