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ORIGINAL ARTICLE

Liver transplantation for NAFLD cirrhosis: Age and recent coronary angioplasty are major determinants of survival

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Abbreviations: CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; CNI, calcineurin inhibitor; COPD, Chronic Obstructive Pulmonary Disease; CST, corticosteroid; CV, cardiovascular; DRI, donor risk index; DSE, dobutamine stress echocardiography; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-c, High-Density Lipoproteins Cholesterol; ICA, invasive coronary angiography; IQR, interquartile range; LDL-c, Low-Density Lipoproteins; LT, liver transplantation; MELD, model for end-stage liver disease; MDRD, Modification of Diet in Renal Disease; MS, metabolic syndrome; mTOR-i, m-TOR inhibitor; NAFLD, non-alcoholic fatty Liver disease; NASH, non-alcoholic steatohepatitis; OSAS, Obstructive Sleep Apnoea syndrome; TACE, Trans-Arterial Chemo-Embolization; TTE, Transthoracic Echocardiography.

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Abstract

Background and Aims: Liver transplantation (LT) is the treatment of end-stage non-alcoholic liver disease (NAFLD), that is decompensated cirrhosis and/or complicated by hepatocellular carcinoma (HCC). Few data on long-term outcome are available. The aim of this study was to evaluate overall patient and graft survivals and associated predictive factors.

Method: This retrospective multicentre study included adult transplant patients for NAFLD cirrhosis between 2000 and 2019 in participating French-speaking centres.

Results: A total of 361 patients (69.8% of male) were included in 20 centres. The median age at LT was 62.3 years [57.4–65.9] and the median MELD score was 13.9 [9.1–21.3]; 51.8% of patients had HCC on liver explant. Between 2004 and 2018, the number of LT for NAFLD cirrhosis increased by 720%. A quarter of the patients had cardiovascular history before LT. Median follow-up after LT was 39.1 months [15.8–72.3]. Patient survival at 1, 5 and 10 years after LT was 89.3%, 79.8% and 68.1% respectively. The main causes of death were sepsis (37.5%), malignancies (29.2%) and cardiovascular events (22.2%). In multivariate analysis, three risk factors for overall mortality after LT were recipient pre-LT BMI < 32 kg/m^2 at LT time (OR: 2.272; $p = .012$), pre-LT angioplasty during CV check-up (OR: 2.916; $p = .016$), a combined donor and recipient age over 135 years (OR: 2.020; 95%CI: $p = .035$).

Conclusion: Survival after LT for NAFLD cirrhosis is good at 5 years. Donor and recipient age, and cardiovascular history, are major prognostic factors to consider.

KEYWORDS
liver transplantation, metabolic syndrome, NAFLD, survival

1 | BACKGROUND AND AIMS

Chronic liver diseases are a frequent cause of mortality and morbidity worldwide. Over the last two decades, the epidemiology of liver diseases changed and non-alcoholic fatty liver disease (NAFLD) became the most common.[1] NAFLD is a spectrum of disease that ranges from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), characterized by steatosis, inflammation, hepatocyte ballooning and varying degrees of hepatic fibrosis which may progress to cirrhosis and end-stage liver disease.[2] The prevalence of NAFLD has dramatically increased along with obesity and diabetes: currently, 23.7% of the population in Europe has NAFLD and 24.1% in North America.[3] Liver transplantation (LT) may therefore be indicated in case of decompensated NAFLD-related cirrhosis and/or development of hepatocellular carcinoma (HCC).

Although rare before 2000, NAFLD recently became a growing and frequent indication for LT, with significant geographical disparities. During the past decade, because of the highly effective direct-acting antivirals drugs, the number of LT for hepatitis C virus (HCV) infection drastically decreased and NAFLD became the second most common indication for LT in the USA (after alcohol-related liver disease) with a 170% increase in 10 years (2004–2013).[4] In 2019 in USA, NAFLD-related cirrhosis represented 28% of patients on the LT waiting list.[5] In Europe, NAFLD is also a rapidly emergent indication, representing 8.4% of all LT in 2016 with many disparities depending on the country: NAFLD represented 12% of all LT in UK in 2019 and 7.9% in France.[6,7] In a recent Spanish study, NAFLD represented 18% of LT in 2021 with

Lay Summary

- NAFLD became a growing and frequent indication for LT.
- Small and few studies have reported satisfactory outcome after LT. First European cohort study and the largest worldwide cohort with 361 patients.
- Patient and graft survival were good. Identified significant pejorative prognostic factors were: recipient BMI < 32 kg/m^2 at time of LT, pre-LT angioplasty, a combined donor and recipient age over 135 years and an early post-operative dialysis.

TABLE 1 Characteristics of the study population at LT listing

A- General characteristics	
Sex (M/F)	**252 (69.8%)/109 (30.2%)**
Median age at LT (years) [IQR]	62.3 [57.4–65.9]
HCC	*n* = 186 (51.5%)
Patients with neoadjuvant treatment (single or combined)	*n* = 121 (33.5%)
TACE	*n* = 83 (23.0%)
Radiofrequency ablation	*n* = 50 (13.9%)
Surgical resection	*n* = 32 (8.9%)
Others	*n* = 21 (5.8%)
Primary indication of LT	
End-stage liver disease	*n* = 136 (37.7%)
HCC	*n* = 149 (41.3%)
Refractory ascites	*n* = 40 (11.1%)
Hepatic encephalopathy	*n* = 21 (5.8%)
Hepatopulmonary syndrome	*n* = 8 (2.2%)
Hydrothorax	*n* = 5 (1.4%)
Recurrent gastro-intestinal bleeding	*n* = 1 (0.3%)
Porto-pulmonary syndrome	*n* = 1 (0.3%)
Median MELD score at LT listing [IQR]	13.9 [9.1–21.3]
Median CHILD-PUGH score at LT listing [IQR]	B9 [B7-C12]
Class A	*n* = 84 (23.3%)
Class B	*n* = 98 (27.2%)
Class C	*n* = 178 (49.4%)
ICU at LT time	*n* = 16 (4.4%)
Kidney function	
Median serum creatinine level (μmol/L) [IQR]	84.0 [68–107.3]
Medium glomerular filtration rate (μmol/L) (MDRD) [IQR]	79.9 [57.9–103.6]
Stade 3 CKD	*n* = 81 (22.4%)
Stade 4 CKD	*n* = 17 (4.7%)
Renal dialysis before LT	*n* = 11 (3.1%)
Metabolic characteristics	
Metabolic syndrome	*n* = 205 (56.8%)
Diabetes mellitus	*n* = 279 (77.3%)
Arterial hypertension	*n* = 301 (83.4%)
Fibrate or statins therapy	*n* = 53 (14.7%)
B- Medical history	
CV history (Patients)	*n* = 92 (25.5%)
Patients with ≥2 CV history	*n* = 18 (5.0%)
Acute Myocardial Infarction	n = 28 (7.8%)
Atrial fibrillation	*n* = 20 (5.5%)
Stroke	*n* = 17 (4.7%)
CAD	*n* = 13 (3.6%)
Peripheral and Aorta arterial disease	*n* = 11 (3.0%)
Cardiac arrest	*n* = 2 (0.6%)
Others	*n* = 21 (5.8%)
Pulmonary history (patients)	*n* = 44 (12.2%)
Patients with ≥2 pulmonary diseases	*n* = 16 (4.4%)
OSAS	*n* = 40 (11.1%)
COPD	*n* = 10 (2.8%)
Hepatopulmonary syndrome	*n* = 9 (2.5%)
Porto-pulmonary syndrome	*n* = 1 (0.3%)
Malignancies history	*n* = 9 (2.5%)
C- Liver Transplantation characteristics	
Median waiting-time on the LT list (months) [IQR]	4.4 [1.6–9.8]
Donors characteristics	
Median age (years) [IQR]	60 [47–70]
Sex (M/F)	171 (62.0%)/105 (38.0%)
Median BMI (Kg/m^2) [IQR]	24.8 [22.5–28.1]
Obesity (all stages)	38 (13.8%)
Graft characteristics	
Steatosis ≥5% (all stages)	49.3% (132/268)
Grade 1	39.6% (106/268)
Grade 2	9.3% (25/268)
Grade 3	1.9% (5/268)
Fibrosis	27.2% (73/268)
F1	22.8% (61/268)
F2	4.5% (12/268)

Abbreviations: BMI, Body Mass Index; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; CV, Cardiovascular; HCC, Hepatocellular Carcinoma; Intensive Care Unit; IQR, Interquartile Range; LT, Liver Transplantation; MELD, Model for End-Stage Liver Disease; OSAS, Obstructive Sleep Apnoea syndrome; TACE, Trans-Arterial Chemo-Embolization.

a 6.4-fold increase between 2010 and 2021.[8] Due to the 'young age' of this indication, available data on outcome after LT are scarce and from small cohorts, almost exclusively from the USA. Prognosis after LT in this indication probably has some specificities, because of associated metabolic comorbidities, which may have a significant impact on both survival and recurrence of the initial disease on the graft.

The aim of the present nationwide retrospective study was to evaluate from a large cohort of patients the overall survival after LT for NAFLD and identify the factors influencing it.

2 | PATIENTS AND METHODS

2.1 | Study population

Were included all adult patients from all French LT centres and in Geneva (Switzerland), based on the national database of the French *Agence de la Biomédecine* (ABM) and local databases (the

'NASH/NAFLD' item did not exist in the ABM thesaurus before 1 January 2018). We first selected all patients transplanted between 1 January 2000 to 31 December 2019 for 'other causes of cirrhosis', 'cirrhosis of unknown cause', 'metabolic disease' or 'HCC' and 'NASH/NAFLD' disease after January 2018 in the ABM database. All medical records were reviewed in each LT centres and patients were finally included based on histopathological examination of available liver biopsies before LT or the native liver compatible with a NAFLD cirrhosis, history of metabolic risks factors (diabetes, obesity or overweight, arterial hypertension) and the absence of other aetiology (alcohol consumption, autoimmune disease, viral hepatitis, Wilson's disease or haemochromatosis).

This study was conducted in accordance with the Declaration of Helsinki. According to French law (Loi Jardé), retrospective studies do not require Institutional Review Board (IRB) approval.

2.2 | Clinical and biological characteristics at the time of listing

Liver disease characteristics at time of listing were specified with the MELD score and CHILD-PUGH score and complications. Metabolic characteristics were recorded: weight, height and maximum lifetime weight were collected. Body mass index (BMI, kg/m^2) was calculated from these values. Lipid profile, glycated haemoglobin (HbA1c) was collected. Metabolic syndrome (MS) was defined according to the American Heart Association, replacing waist circumference with BMI over than $30 kg/m^2$.[9] Cardiovascular (CV) comorbidities were collected (coronary artery diseases [CAD], stroke, atrial fibrillation, cardiac arrest, valvular heart disease) and pre-LT CV check-up was specified. All patients received grafts from cadaveric or living donors. Donor's characteristics (age, weight and BMI) were collected. The presence of HCC was recorded (before LT and from histological analysis of liver explant).

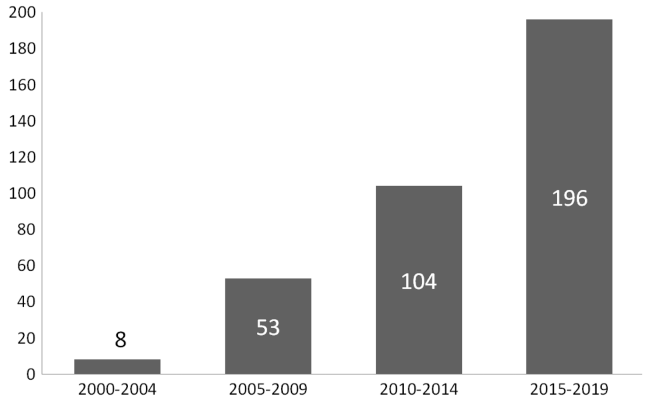

FIGURE 1 Evolution of Patients transplanted for NAFLD cirrhosis in France and Geneva between 2001 and 2019.

2.3 | Follow-up after LT

Initial immunosuppressive regimen was based on a calcineurin-inhibitor (CNI): cyclosporine (CYA) or tacrolimus (TAC). Induction therapy by polyclonal antibodies or anti-interleukin-2 receptor antibodies was mainly administered in case of acute kidney injury. Starting on postoperative day 1, methylprednisolone was tapered to reach a maintenance dose of 0 to 5 mg/day at 6 months post-transplantation. Azathioprine (AZA), mycophenolate mofetil (MMF) or sirolimus/everolimus (mTor inhibitor [mTor-i]) were either administered as part of an initial triple immunosuppressive regimen or introduced during follow-up as a maintenance immunosuppressive agent. Outpatient follow-up visits were usually conducted once a week during the first month after discharge from the hospital, twice

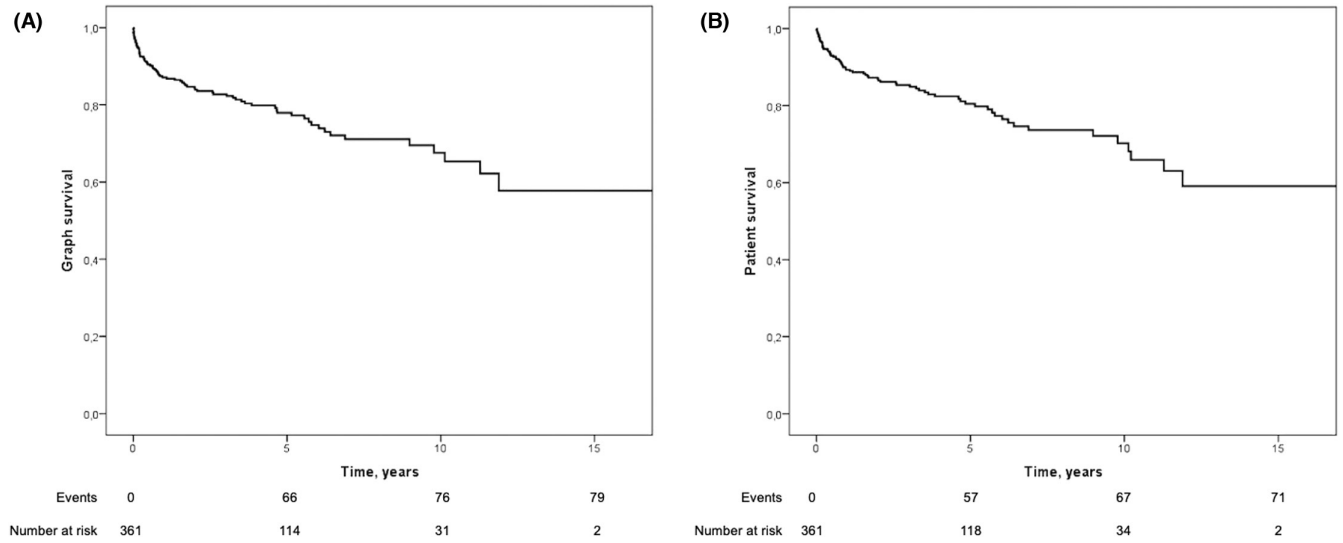

FIGURE 2 Graft (A) and overall patient (B) survival (According to Kaplan–Meier estimates). (A) Graft survival at 1, 5 and 10 years after was 86.8%, 77.2% and 65.3% respectively. (B) Patient survival at 1, 5 and 10 years after LT was 89.3%, 79.8% and 68.1% respectively.

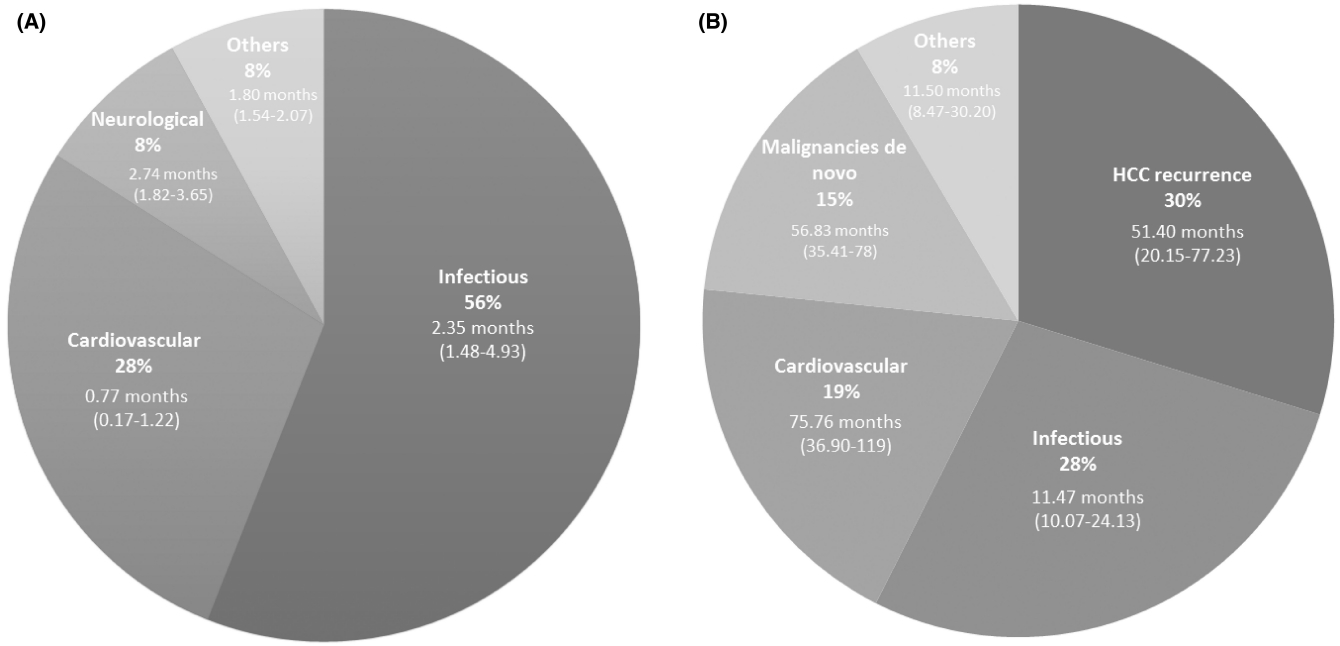

FIGURE 3 Characteristics of deaths after LT according to the period: before 6 months (A) and after 6 months (B) Median delay from LT (range).

a month during the second and third months, monthly for the rest of the first year, and every 3 or 12 months thereafter, regardless of the length of the observation period after LT. Additional visits were made when necessary. A complete laboratory investigation, including haematology, liver parameters, coagulation, electrolytes, total protein, renal parameters, fasting blood glucose, a lipid profile and blood calcineurin inhibitor trough levels or mTor-i levels, was conducted at each visit.

We collected systematically for each patient occurrence of significant infections (defined by hospitalization, prolongation of hospitalization or resulted in significant morbidity or mortality), biliary and hepatic vascular complications, diabetes, arterial hypertension, CV events and malignancies. Stage 3 chronic kidney disease (CKD) was defined by a Glomerular Filtration Rate (GFR) less than 60 ml/min/1.73m^2 using the Modification of Diet in Renal Disease equation (MDRD) and stage 4 by a GFR less than 30 ml/min/1.73m^2.

The end of follow-up corresponded to death, the last medical examination or date of loss of follow-up. All data were retrospectively collected until 31 June 2020.

2.4 | Statistical analysis

All data were analysed using SPSS software, version 23.0 (IBM, Armonk, NY, US). Data were described in their totality using median with interquartile range [IQR] or mean with standard deviation (SD) for continuous variables and number (percentage) for categorical variables. 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. Patient survival was calculated from the date of LT to that of death or the last clinical visit. Graft survival was calculated from the date of LT to that of re-liver transplantation (re-LT), death or last visit if no re-LT. 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 multivariate models. All significant variables in the univariate analysis with a level set at $p < .1$ were incorporated into multivariate models. A p value less than .05 was considered statistically significant.

Competent survival analysis was performed with the RStudio software, version 2022.02.2 Build 485 (RStudio Inc., Boston, US).

3 | RESULTS

3.1 | Population characteristics (Table 1)

Three hundred sixty-one patients were included. Patients were transplanted between January 2001 and December 2019. Between 2004 and 2018, the number of LT for NAFLD cirrhosis increased by 720%, from 5 to 36 patients per year (Figure 1). The study population consisted in a majority of men (69.8%). The median [IQR] age at LT time was 62.3 years [57.4–65.9]; more than half of the patients had an HCC, with a neoadjuvant treatment in the majority of case. Ninety-two patients had history of CV events (25.5%). All patients had a CV check-up before LT with at least a TTE. One-quarter of patients underwent an ICA during the pre-LT CV check-up, with 19 angioplasties. The median [IQR] BMI at LT time was 30.9 kg/m^2 [26.8–34.1 kg/m^2].

TABLE 2 Risk associated to overall death

Factors	*p*-value	Multivariate analysis OR (95% CI)	*p*-value
Clinical characteristics before LT			
Sex (M/F)	.632		
Age	.039		
Age ≥ 50 years	.117		
Age ≥ 55 years	.116		
Age ≥ 60 years	**.037**	1.294 (0.671–2.497)*	.0442
Age ≥ 62 years	**.009**	1.333 (0.772–2.459)*	.358
Age ≥ 65 years	.179		
MELD score	.408		
≥ 15	.262		
≥ 20	.476		
≥ 25	.489		
≥ 30	.751		
≥ 35	.550		
HCC at LT time	.959		
Refractory ascites	.546		
Higher BMI	.237		
BMI ≥35 kg/m^2	.560		
BMI at LT time	**.002**		
≥ 20 kg/m^2	.651		
≥ 25 kg/m^2	.274		
≥ 30 kg/m^2	**.031**	0.598 (0.337–1.061)**	.079
≥ 31 kg/m^2	**.022**	0.557 (0.307–1.010)**	.054
≥ 32 kg/m^2	**.003**	**0.440 (0.232–834)****	**.012**
≥ 35 kg/m^2	.301		
Pre-LT diabetes	.272		
HbA1c ≥ 7%	.297		
Pre-LT insulin therapy	.627		
Pre-LT arterial hypertension	.445		
Pre-LT metabolic syndrome	.862		
Active smoking before LT	.900		
CV history	.523		
Pre-LT ICA	.639		
Pre-LT Angioplasty (during LT check-up time)	**.003**	**2.916 (1.226–6.935)*****	**.016**
Angioplasty or coronary bypass history	**.074**	1.429 (0.553–3.692)***	.461
Angioplasty or coronary bypass at any time	**.007**	2.045 (0.942–4.442)***	.071
GFR≤60 ml/min	**.051**	1.261 (0.707–2.248)	.432
GPR≤30 ml/min	.387		
Dialysis before LT	.938		
ICU at LT time	.585		
Donors characteristics			
Age of the donor (years)	.566		
Age ≥ 60 years	**.054**	**1.794 (1.002–3.211)***	**.049**
Age ≥ 70 years	.131		
Donors age + recipients age (years)	.413		
≥ 120 years	.149		
≥ 135 years	**.035**	**2.020 (1.052–3.877)***	**.035**
Donor BMI (kg/m^2)	.856		
Graft steatosis (≥ 5%)	.265		
Grade ≥2 steatosis	.778		
Induction Immunosuppressive regimen			
Tacrolimus	.428		
MMF	.105		
Cyclosporine	.472		
CST	.208		
mTor-i	.585		

Note: Each variable was tested in univariate analysis. All variables with a *p*-value <.010 were retained for the multivariate model. */**/*** Because these variables are not independent, different multivariate analysis models were performed.

Abbreviations: BMI, Body Mass Index; CST, corticosteroid; CV, Cardiovascular; GFR, Glomerular Filtration Rate; HCC, Hepatocellular Carcinoma; ICA, Invasive coronary angiography; ICU, Intensive Care Unit; LT, Liver Transplantation; MELD, Model for End-Stage Liver Disease; MMF, Mycophenolate Mofetil; mTor-i, mTor inhibitor.
Values in bold are statistically significant values.

At the end of follow-up, the majority of patients received a double immunosuppressive therapy (76.3%). The combination of TAC and MMF was in the majority of patients. Twenty-six patients (8.4%) had corticosteroids (CST) 6 months after LT. Median [IQR] (range) follow-up after LT was 38.6 months [15.6–72.4 months] (0–224 months).

3.2 | Extra-hepatic complications

Septic episodes occurred in 60.9% of patients with a mean number of 1.9 episodes per patient (range 1–5). The median [IQR] (range) delay between LT and the first septic event was 17.5 days [5–117.3 days] (0 day-16.1 years). Leading locations of sepsis were lung (21.7%), biliary tract (13.2%) and urinary tract (10.1%).

Two-hundred-and nine CV events occurred in 138 patients (38.2%) after LT: the incidence of CV events at 1, 5 and 10 years was 22.5%, 39.1% and 66.8% respectively. The median [IQR] (range) time between the LT and the first CV event was 5.2 months [0.2–36.8 months] (0–162.5 months). Atrial fibrillation and coronary heart disease (including acute myocardial infarction or chronic CAD) were

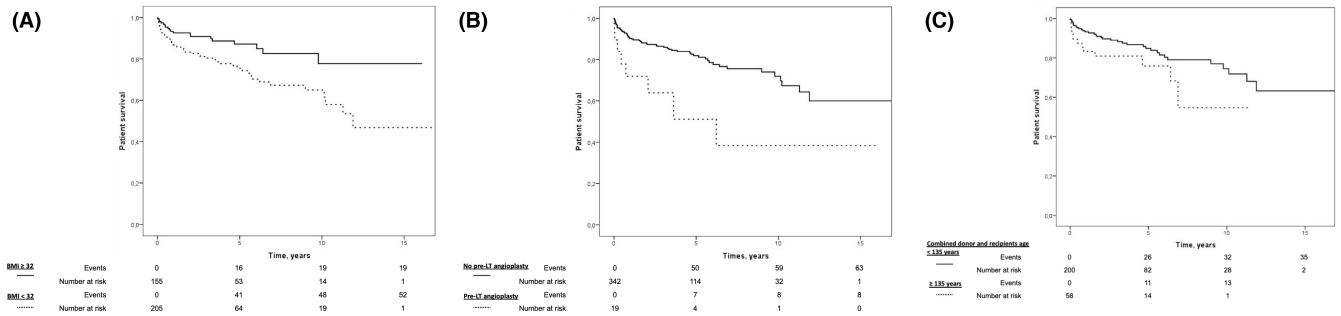

FIGURE 4 Patient overall survival according to three independent prognostic factors: BMI ≥32 kg/m^2 at LT time (A), combined recipient and donor age ≥ 135 years (B) and pre-LT angioplasty (C). (According to Kaplan–Meier estimates). (A) Patient survival according to BMI at LT time (greater than or equal to 32 kg/m^2). Patient survival at 1, 5 and 10 years was 92.6%, 87.2% and 77.8%, respectively, in the group with a BMI greater than 32 kg/m^2. In the group with a BMI less than 32 kg/m^2, patient survival was 86.8%, 75.5% and 61.6% at 1, 5 and 10 years respectively ($p = .003$). (B) Patient survival according to the presence of history of pre-LT angioplasty. In patients without angioplasty during CV check-up before LT, survival was 90.2%, 81.9% and 71.9% at 1, 5 and 10 years respectively. In patient with a history of pre-LT angioplasty, survival was 71.9% at 1 year, 51.1% at 5 years and 38.3% at 10 years ($p = .003$). (C) Patient survival according to the combined recipients and donors age at LT time. In the group with a combined age less than 135 years, patient survival was 93.3% at 1 year, 84.8% at 5 years and 74.5% at 10 years. In the group with a combined age greater than 135 years, patient survival at 1, 5 and 10 years was, respectively, 83.3%, 75.9% and 54.7% ($p = .035$).

the most frequent CV events after LT. The only risk factor found in multivariate analysis was the age over than 62 years at LT time (OR: 2.058; 95%CI: 1.387–3.053; $p = .0001$). In multivariate analysis, pre-LT BMI or pre-LT MS did not impact the occurrence of CV events. A history of CAD was significantly associated with CV events in univariate analysis but not in multivariate analysis. No difference on CV events was found between patients with or without HCC.

The incidence of stage III CKD was 48.8%, 81.4% and 90.6% at 1, 5 and 10 years respectively. Forty patients (11.1%) developed stage IV CKD. Seventeen patients were under chronic haemodialysis at the end of follow-up. One patient underwent kidney transplantation at 72.4 months after LT. Four patients were listed for kidney transplantation at the end of follow-up. Female sex (OR: 1.506; 95%CI: 1.107–2.048; $p = .009$), age over 60 years at time of LT (OR: 1.520; 95%CI: 1.111–2.082; $p = .009$) and creatinine level over 84 µmol/L before LT (OR: 1.908; 95%CI: 1.385–2.269; $p = .0001$) were associated in multivariate analysis with risk to develop stage III CKD. BMI before LT or MS did not influence the incidence of CKD.

Seventy-two patients (19.9%) developed one or several malignancies with a median [IQR] (range) delay of 37.3 months after LT [13.8–67.4 months] (14 days-191.7 months). Twenty-six patients had HCC recurrence after LT. Forty-eight patients (13.3%) developed one or several de novo malignancies after LT with a median [IQR] (range) time between LT and malignancies diagnosis of 44.1 months [17.6–71.1 months] (14 days-154.3 months). Main de novo malignancies were non-melanoma skin carcinoma (45.8%), prostate cancer (20.8%) and pancreatic cancer (6.3%).

3.3 | Graft survival

Graft survival at 1, 5 and 10 years after was 86.8%, 77.2% and 65.3% respectively (Figure 2A). A total of 18 re-LT were performed in 16 patients (4.4%) with a median [IQR] (range) delay of 60 days after LT [6–156.5] (2 days-56.5 months). Main causes of re-LT were as follows: ischaemic cholangitis ($n = 6$; 33.3%), primary no function ($n = 6$; 33.3%); acute or chronic rejection ($n = 3$; 16.7%); nodular regenerative hyperplasia ($n = 2$; 11.1%) and arterial thrombosis ($n = 1$; 5.6%). No re-LT for NAFLD cirrhosis recurrence was performed. Two patients had two re-LT; they both died, the first from sepsis and the second for a cerebral ischaemia. Of 14 patients who underwent a unique re-LT, eight died during the follow-up (57.1%) after a median delay of 10.8 months after the second LT.

3.4 | Patient survival

Patient survival at 1, 5 and 10 years after LT was 89.3%, 79.8% and 68.1% respectively (Figure 2B). Seventy-two patients died after LT with a median [IQR] (range) time to death of 11.5 months [2.7–56.3 months] (1 day-18.8 years); 30-day and 90-day mortality rate after LT was, respectively, 2.5% and 5.8%. The main causes of death were infectious diseases (37.5%), malignancies (29.2%) and CV events (22.2%). During the first 30 days after LT, 4 of 9 deaths (44.4%) that occurred were of CV origin. Main causes of deaths are summarized in Figure 3.

In multivariate analysis, significant risk factors for overall mortality after LT were a BMI < 32 kg/m^2 at LT time (OR: 2.272; 95%CI: 1.199–4.306; $p = .012$), pre-LT angioplasty during CV check-up (OR: 2.916; 95%CI: 1.226–6.935; $p = .016$) and a combined donor and recipient age over 135 years (OR: 2.020; 95%CI: 1.052–3.877; $p = .035$) (Table 2 and Figure 4).

Risk factors of early deaths after LT (in the first 3 months) found in multivariate analysis were only combined recipients and donor age over 135 years (OR: 3.194; 95%CI: 1.072–9.515; $p = .037$) (Table 3). Pre-LT BMI and angioplasty were considered as a risk factor in univariate analysis but not in multivariate analysis. We find the same risk factor for death at 6 months: combined

TABLE 3 Risk factors associated to early deaths

	Before 3 months			Before 6 months		
		Multivariate analysis			Multivariate analysis	
Factors	***p-value***	**OR (95% CI)**	***p-value***	***p-value***	**OR (95% CI)**	***p-value***
Clinical characteristics before LT						
Sex (M/F)	.913			.303		
Age				**.056**		
Age ≥ 50 years	.687			.479		
Age ≥ 55 years	.201			.098		
Age ≥ 60 years	**.017**	2.510 (0.545–11.568)*	.238	**.028**	1.371 (0.363–5.170)*	.641
Age ≥ 62 years	**.005**	2.386 (0.642–8.874)*	.194	**.014**	1.951 (0.592–6.340)*	.272
Age ≥ 65 years	.123			.313		
MELD score				.103		
≥ 15	.178			.141		
≥ 20	.861			.492		
≥ 25	.642			.793		
≥ 30	.825			.769		
≥ 35	.533			.468		
HCC at LT time	.198			.116		
Refractory ascites	.652			.316		
Higher BMI				.301		
BMI ≥35 kg/m^2	.887			.407		
BMI at LT time				.126		
≥ 20 kg/m^2	.741			.701		
≥ 25 kg/m^2	.964			.602		
≥ 30 kg/m^2	.162			.156		
≥ 31 kg/m^2	**.037**	0.453 (0.137–1.490)**	.192	**.064**	0.462 (0.158–1.356)*	.160
≥ 32 kg/m^2	**.046**	0.574 (0.176–1.876)**	.358	.108		
≥ 35 kg/m^2	.277			.569		
Kidney function before LT						
GPR ≤80 ml/min	.682			.323		
GPR ≤60 ml/min	.503			.324		
GPR ≤30 ml/min	.309			.801		
Dialysis before LT	.431			.362		
ICU at LT time	.339			.886		
Metabolic characteristics before LT						
Pre-LT diabetes	.197			.187		
HbA1c ≥ 7%	.359			.141		
Pre-LT insulin therapy	.287			**.051**	3.100 (0.973–9.875)*	.056
Pre-LT arterial hypertension	.188			**.090**	1.787 (0.228–14.002)*	.580
Pre-LT metabolic syndrome	.700			.763		
CV check-up before LT						
Pre-LT CV history	.658			.539		
Pre-LT ICA	.791			.143		
Pre-LT angioplasty	**.028**	3.157 (0.966–14.252)***	.135	**.008**	2.003 (0.446–9.000)***	.365
Angioplasty or coronary bypass history	.272			.174		
Angioplasty or coronary bypass at any time	**.024**	2.388 (0.647–8.809)***	.191	**.022**	1.308 (0.352–4.868)***	.688

(Continues)

TABLE 3 (Continued)

	Before 3 months			Before 6 months		
		Multivariate analysis			Multivariate analysis	
Factors	*p-value*	OR (95% CI)	*p-value*	*p-value*	OR (95% CI)	*p-value*
Donors characteristics						
Age of the donor (years)				**.013**		
Age ≥ 60 years	**.047**	3.492 (0.958–12.737)*	.058	**.010**	**3.600 (1.006–12.880)***	**.049**
Age ≥ 70 years	**.003**	**4.783 (1.553–14.729)***	**.006**	**.004**	**4.761 (1.665–13.617)***	**.004**
Donors age + recipients age (years)				**.010**		
≥ 120 years	.141			**.034**	2.457 (0.777–7.766)*	.126
≥ 135 years	**.032**	**3.194 (1.072–9.515)***	**.037**	**.029**	**3.185 (1.137–8.918)***	**.027**
Donor BMI (kg/m^2)				**.081**		
Graft steatosis (≥ 5%)	.966			.892		
Grade ≥2 steatosis	.489			.726		

Note: Each variable was tested in univariate analysis. All variables with a *p*-value <.010 were retained for the multivariate model. */**/*** Because these variables are not independent, different multivariate analysis models were performed.

Abbreviations: BMI, Body Mass Index; CST, corticosteroid; CV, Cardiovascular; GFR, Glomerular Filtration Rate; HCC: Hepatocellular Carcinoma; ICU: Intensive Care Unit; LT, Liver Transplantation; MELD, Model for End-Stage Liver Disease; MMF, Mycophenolate Mofetil.

Values in bold are statistically significant values.

recipients and donor age over 135 years (OR: 3.185, 95%CI: 1.137–8.918; $p = .027$) (Table 3).

Concerning risk of death after 12 months, univariate analysis disclosed that recipient age > 62 years old, recipient BMI below 32 kg/m^2, an HCC at LT time, a GPR below 60 ml/min, long-term corticoids use and HCC recurrence were significant predictive factors. In multivariate analysis, significant risk factors for death after 12 months included a GFR below 60 ml/min (OR: 4.278; 95%CI: 1.246–14.691; $p = .021$), a long-term corticoid use (OR: 9.737; 95%CI: 2.356–37.379; $p = .001$) and HCC recurrence (OR: 7.242; 95%CI: 1.913–27.418; $p = .0004$) (Table 4). In addition, use of statins therapy (OR: 0.234; 95%CI: 0.058–0.940; $p = .041$) was considered as protective factors.

A combined score was built to predict the overall mortality of patients after LT. This score includes BMI at LT, angioplasty during CV check-up before LT and cumulative donor and recipient age greater than 135 years (Figure 5). There was a significant difference between the group of patients with at least one risk factor and the group without risk factors ($p = .005$).

Figure S1 shows overall competitive survival as a function of cardiovascular mortality: this analysis confirms that early mortality is of cardiovascular origin.

4 | DISCUSSION

Herein, we report the first European cohort study and the largest worldwide cohort, based on individual data, on outcome after LT for NAFLD. Overall patient survival was 89.3%, 79.8% and 68.1% at 1, 5 and 10 years after LT, respectively, close to available data.[7,10,11] We identified as independent three prognostic factors: a combined donor and recipient age over 135 years, an angioplasty performed during pre-LT CV check-up and BMI < 32 kg/m^2 at LT time.

The first major result of our study is the absence of negative impact of recipient pre-LT high BMI on patient survival after LT. Although international guidelines do not consider BMI alone to be a contraindication to LT, results on the impact of recipient pre-LT BMI on outcome after LT has been conflicting.[12] In 2015, a meta-analysis of 13 studies found no impact of pre-LT BMI on patient survival after LT for all LT indications.[13] Another US study from UNOS registry of simultaneous liver-kidney transplants confirmed that a BMI greater than 40 was not an independent risk factor for mortality.[14] In an US registry study from UNOS registry, patients transplanted for NAFLD with a BMI greater than 30 kg/m^2 had a reduced risk of graft loss and mortality at 10 years when compared with patients with a BMI less than 30 kg/m^2.[15] However, class 3 obesity was associated with increased mortality in patients transplanted for a cause other than NAFLD.[15] One of the hypotheses proposed by the authors to explain this better survival would be an improvement in insulin resistance after LT, resulting in an improvement of CV profile of these obese patients with NASH compared with other indications for LT.[16] In the ELTR study, a BMI greater than 40 kg/m^2 was associated with an increasing mortality in patients transplanted for NAFLD cirrhosis without HCC.[7] This could suggest that the highest BMI could be particularly deleterious in patients with decompensated cirrhosis. In our study, we did not find a difference in patient survival after LT according to pre-LT BMI classes. Since there were few patients with class 3 obesity (21 patients, 5.8%), these results must be taken with caution for this category of patients. Nevertheless, a BMI higher than 32 kg/m^2 before LT was independently associated with a better patient's survival. There are several hypotheses to explain this difference. First, the selection for LT of obese patients, especially

TABLE 4 Risk associated to death after 12 months

Factors	*p-value*	Multivariate analysis OR (95% CI)	*p-value*
Clinical characteristics before LT			
Sex (M/F)	.174		
Age			
Age ≥ 50 years	.034		
Age ≥ 55 years	.200		
Age ≥ 60 years	.099		
Age ≥ 62 years	**.042**	1.053 (0.302–3.672)	.935
Age ≥ 65 years	.200		
MELD score	.471		
≥ 15	.530		
≥ 20	.628		
≥ 25	.558		
≥ 30	.471		
≥ 35	.427		
HCC at LT time	**.061**	1.947 (0.477–7.954)	.353
BMI at LT time	**.002**		
≥ 20 kg/m^2	.358		
≥ 25 kg/m^2	.478		
≥ 30 kg/m^2	.376		
≥ 31 kg/m^2	.305		
≥ 32 kg/m^2	**.013**	0.484 (0.153–1.530)	.216
≥ 35 kg/m^2	.397		
Pre-LT diabetes	.377		
HbA1c ≥ 7%	.497		
Pre-LT insulin therapy	.966		
Pre-LT arterial hypertension	.331		
Pre-LT metabolic syndrome	.807		
Active smoking before LT	.966		
CV history	.137		
Pre-LT ICA	.780		
Pre-LT Angioplasty (during LT check-up time)	.132		
Angioplasty or coronary bypass history	.629		
Angioplasty or coronary bypass at any time	.201		
GPR ≤80 mL/min	.468		
GPR ≤60 mL/min	**.050**	**4.278 (1.246–14.691)**	**.021**
Creatinaemia Level ≥ 133 µmol/L	.352		
Dialysis before LT	.330		
ICU at LT time	.749		
Donors characteristics			
Age of the donor (years)	.566		
Age ≥ 60 years	.608		
Age ≥ 70 years	.793		
Donors age + recipients age (years)	.413		
≥ 120 years	.571		
≥ 135 years	.767		
Donor BMI (kg/m^2)	.250		
Graft steatosis (≥ 5%)	.327		
Grade ≥2 steatosis	.275		
Metabolic events after LT			
BMI at 1 years after LT	.169		
≥ 30 kg/m^2	.547		
≥ 32 kg/m^2	.891		
≥ 35 kg/m^2	.927		
Diabetes post-LT	.324		
Arterial hypertension post-LT	**.0001**	0.171 (0.026–1.134)	.067
Triglycerides ≥1.7 mmol/L post-LT LDLc ≥3.90 mmol/L	.788		
HDLc <1.15 mmol/L	.129		
HbA1c ≥ 7%	**.074**	0.792 (0.263–2.388)	.679
HbA1c ≥ 8%	.170		
Long Immunosuppressive regimen			
Tacrolimus	.617		
MMF	**.002**	0.588 (0.188–1.841)	.362
Cyclosporine	.760		
mTor-i	**.002**	0.913 (0.292–2.849)	.875
CST	**.0001**	**9.737 (2.356–37.379)**	**.001**
AZA	.610		
Therapies after LT			
Statins therapy	**.002**	**0.234 (0.058–0.940)**	**.041**
Fibrates therapy	.234		
Insulin therapy	.865		
Comorbidities after LT			
Smoking after LT	.685		
CV events	.705		
Infectious events	.883		
Neoplasia de novo	.518		
HCC recurrence	**.0001**	**7.242 (1.913–27.418)**	**.004**
Grade 3 CKD	.390		
Dialysis after LT	.469		

Note: Each variable was tested in univariate analysis. All variables with a *p*-value <.010 were retained for the multivariate model.

Abbreviations: AZA, Azathioprine; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CST, corticosteroid; CV, Cardiovascular; GFR, Glomerular Filtration Rate; HCC, Hepatocellular Carcinoma; HDL-c, High-Density Lipoproteins Cholesterol; ICA, Invasive coronary angiography; ICU, Intensive Care Unit; LDL-c, Low-Density Lipoproteins; LT, Liver Transplantation; MELD, Model for End-Stage Liver Disease; MMF, Mycophenolate Mofetil; mTor-i, mTor inhibitor. Values in bold are statistically significant values.

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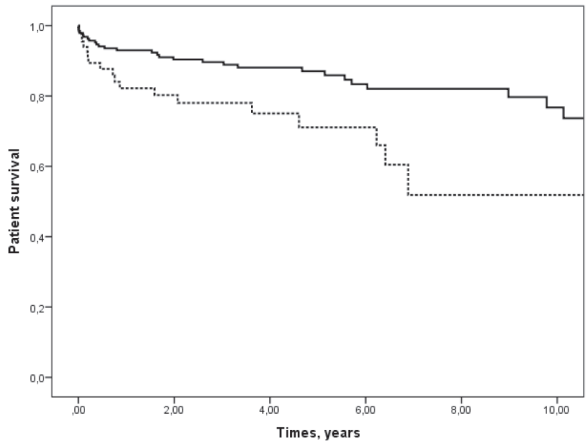

No risk factors	Events	0	17	20	25	25	28
	Number at risk	189	134	96	62	40	24
One or more risk factors	Events	0	12	14	16	18	18
	Number at risk	67	36	23	13	4	2

FIGURE 5 Patient survival after LT according to the absence or presence of one or more risk factors. (According to Kaplan–Meier estimates). Risk factors considered for analysis: BMI less than 32 kg/m^2, pre-LT angioplasty and combined donor and recipient age greater than 135 years. In the group of patients without risk factors, patient survival was 93.0% at 1 year, 85.9% at 5 years and 73.7% at 10 years. With risk factors, patient survival was 82.2%, 71.1% and 51.8% at 1, 5 and 10 years respectively. The difference is significant between the two groups of patients ($p = .005$).

after exhaustive cardiovascular evaluation, may be more thorough and would explain this better survival. Second, the impact of sarcopenia in these patients is major: a recent Chilean study based on adults over 60 years found an inverse correlation between obesity and sarcopenia in NAFLD patients[17]: only 2% of obese patients had sarcopenia. Comprehensive data on sarcopenia in NAFLD cirrhotic patients especially those awaiting LT are lacking. We were not able to investigate this in our population because sarcopenia evaluation was not systematically performed during the study period. Pre-LT BMI estimate may be modified by the presence of ascites, even if we recorded 'dry weights'. Finally, it has been reported that morbid obesity and presence of diabetes could be associated with a higher frequency of dropout from the LT waiting list or mortality rate on waiting list[18]: this high dropout rate can be explained by a higher mortality of patients with poor prognostic factors and therefore a selection of good candidates for LT. We did not investigate mortality and removal from the LT waiting list in our study.

Despite the lack of negative impact of pre-LT high BMI on patient survival, patients with NAFLD cirrhosis have a higher risk of CV events than other aetiologies of cirrhosis.[19] Median recipient's age was relatively high in our cohort, which is by itself a CV risk factor. This seems related to the NAFLD indication; in the large report of the ELTR registry, median age of NAFLD patients was 60 years, significantly higher to other LT aetiologies (55 years).[7] This is also in accordance with a 2012 French study on the epidemiology of cirrhosis in general hospitals: patients with complicated NAFLD cirrhosis (decompensation, HCC) were older than other aetiologies with a mean age of 66 years.[20] In non-transplant NAFLD patients, reported leading cause of death is CV, followed by extrahepatic cancers and finally liver-related complications.[21] Independently of CV risk factors, NAFLD, in non-transplant patients, is associated with an increase in CV events and complications, mainly cardiomyopathy, valvular calcifications and cardiac arrhythmia.[22] In our study, 77.3% of patients had diabetes before LT, 83.4% a history of arterial hypertension and 56.8% a MS. In addition, a quarter had a CV history before LT. CV disease was the 3rd cause of overall death after LT in our study, but the 2nd cause of early death. A history of angioplasty before LT was a risk factor for overall mortality and late mortality. This mortality is mainly related to angioplasties performed during the pre-LT CV check-up: these patients must be carefully evaluated and have CV monitoring on LT waiting list and after LT. Two previous cohort studies did not find an impact of CAD on post-LT survival.[11,23] The mean age in these two studies was 56 years, younger than the age in our study. In addition, in Barritt's study, only 5 patients out of 118 had significant CAD before LT (defined by a coronary stenosis greater than 50%).[23] In Bhagat's study, the impact of CAD on patient survival after LT has not been studied.[11] These elements may explain the lack of impact of CAD on survival in these two studies.

There are no recommendation on CV screening before LT and CV risk stratification, especially in the high-risk NAFLD patients.[24] In our study, all patients had a TTE, 142 (39.3%) a dobutamine stress echocardiography (DSE) and 39 patients (10.8%) had coronary artery bypass or angioplasty before LT, including 19 with an angioplasty during CV pre-LT check-up. Current international recommendations are to perform a TTE in all patients awaiting LT, and to use a non-invasive test according to risk factors without specific examination for NAFLD patients.[12] The place of invasive coronary angiography (ICA) in these patients remains debated. An algorithm published by cardiology group from Chicago group stratifies CV risk and whether or not ICA should be performed.[25] In another study, systematically performing a ICA before LT was associated with a reduction of myocardial infraction and patient cardiac mortality.[26] Nevertheless, performing ICA is an invasive procedure in cirrhotic patients who often have impaired renal function. The protocol of CV examinations before LT requires prospective studies to specify the necessary examinations and their order, especially in this specific population with CV history. Interestingly, although the share of cardiovascular mortality is significant throughout the follow-up after LT, it is particularly predominant in the early postoperative period.

More interesting and new in this LT indication, we found that donor age had a strong impact on both short-term and overall survival. Interestingly, combined donor and recipient age greater than 135 years was an independent pejorative prognostic factor for overall mortality, and especially on early death (<3 or 6 months). Moreover, regarding this factor, the age of the donor seems to have a greater impact than the age of the recipient: the recipient age alone was not a factor significantly associated with early mortality, whereas the donor age was. Several studies have found a pejorative impact of donor age on graft loss and long-term survival in recipients over 40 years: the impact of donor age mainly occurs during the first year after LT.[27–29] The impact of donor age has been largely studied in LT for HCV, and was associated with a decrease in graft and patient survival: this deleterious effect was probably related to more severe recurrent HCV on the graft before direct-acting antivirals became available.[30–32] A recent Chinese study confirmed these data in patients transplanted for HCC: overall survival was significantly decreased in recipients of a liver from a donor older than 65 years.[33] Within the donor risk index, donor age is one of the seven independent predictors of graft loss after LT.[34] There is an increase in the risk of graft loss with each decade of donor age over 40 years. In a study from UNOS Registry covering the period 1994–2005, combined donor and recipient age greater than 120 years was found to be an independent factor in mortality after LT in recipients over 60 years of age (and therefore receiving grafts from donors over 60 years of age).[35] A combined recipient and donor age greater than 120 years was associated with a 20% reduction of patient survival.[35] Recipients in this study were similar in age to those of our study with a median age at LT of 62 years. Many hypotheses can explain these results and the temporal impact after LT. Increased pro-inflammatory cytokines and vascular or biliary complications may explain the increased early mortality after LT.[35] One hypothesis is based on the hepatocellular senescence, characterized by thickening of the arteriolar walls leading to a decrease in the fenestration of endothelial cells and a decrease in hepatic blood flow increasing ischaemia–reperfusion processes after LT.[29] In addition, an increase in the production of pro-inflammatory cytokines is described in the elderly donors with a decrease in cytochrome P450 activity may lead to increased inflammation post-LT with donors over 60 years of age and may lead to liver damage.[36] The effect of ageing on the arterial wall may intuitively lead to a higher risk of vascular and biliary complications in the context of LT: young grafts tend to have better vascular compliance, lower vascular resistance and fewer complications after LT.[37] In the context of living donors, one study found that donor age over 20 years was significantly associated with higher recipient mortality.[38] The late impact of donor age on survival can be explained by a decrease in regenerative capacity and cellular senescence. The capacity of gluconeogenic of the liver decreases with age with an increased risk of lipid accumulation, insulin resistance and steatosis.[39] With age, mitochondrial dysfunctions increase, and apoptosis capacities decrease leading to an increase in fibrosis, potentiated by pro-inflammatory mechanisms increased by age.[40] The impact of the donor's age must therefore be considered in daily practice, especially since the proportion of donors over 60 years increased between 1990 and 2014 in USA and in France, the average age of donors increased from 50 to 57 between 2007 and 2017 with an average age of 57.6 years in 2020.[41,42]

In conclusion, we report here the first European cohort study of LT for NAFLD and the largest worldwide cohort, not registry-based. We confirm a good mid-term survival of patients after LT, but several criteria must be taken into account in the selection of patients and grafts: high BMI does not have a negative impact in our study but CV history and donor age were significant risk factors for early and overall mortality.

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CONFLICT OF INTEREST

No conflict of interest to declare for all authors.

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SUPPORTING INFORMATION

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