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▶ **To cite this version:**

Lea Lerosey, Elea Ksiasek, Michal Abrahamowicz, Corinne Antoine, Sébastien Dharancy, et al.. Recipient age influences survival after liver transplant: Results of the French national cohort 2007–2017. Liver International, 2024, 44 (6), pp.1396-1408. 10.1111/liv.15867 . hal-04667801

HAL Id: hal-04667801
https://hal.inrae.fr/hal-04667801

Submitted on 5 Aug 2024

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Check for updates

Received: 2 June 2023 | Revised: 11 January 2024 | Accepted: 31 January 2024

DOI: 10.1111/liv.15867

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Recipient age influences survival after liver transplant: Results of the French national cohort 2007–2017

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Funding information
Société Nationale Française de Gastro-Entérologie

Handling Editor: Alejandro Forner

Abstract

Background: In recent years, age at liver transplantation (LT) has markedly increased. In the context of organ shortage, we investigated the impact of recipient age on post-transplantation mortality.

Methods: All adult patients who received a first LT between 2007 and 2017 were included in this cross-sectional study. Recipients' characteristics at the time of listing, donor and surgery data, post-operative complications and follow-up of vital status were retrieved from the national transplantation database. The impact of age on 5-year overall mortality post-LT was estimated using a flexible multivariable parametric model which was also used to estimate the association between age and 10-year net survival, accounting for expected age- and sex-related mortality.

Results: Among the 7610 patients, 21.4% were aged 60–65 years, and 15.7% over 65. With increasing age, comorbidities increased but severity of liver disease decreased. Older recipient age was associated with decreased observed survival at 5 years after LT ($p < .001$), with a significant effect particularly during the first 2 years. The linear increase in the risk of death associated with age does not allow any definition of an age's threshold for LT ($p = .832$). Other covariates associated with an increased risk of 5-year death were dialysis and mechanical ventilation at transplant, transfusion during

Abbreviations: BMI, body mass index; EMR, excess mortality rate; HCC, hepatocellular carcinoma; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; IQR, inter-quartile range; KM, Kaplan Meier; LL, log-linearity; LT, liver transplantation; MELD, model for end-stage liver-disease; NASH, non-alcoholic steatohepatitis; PH, proportional hazards; TD, time dependent; TIPS, transjugular intrahepatic portosystemic shunt; SD, standard deviation.

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LT, hepatocellular carcinoma and donor age. Ten-year flexible net survival analysis confirmed these results.

Conclusion: Although there was a selection process for older recipients, increasing age at LT was associated with an increased risk of death, particularly in the first years after LT.

KEYWORDS
liver transplantation, mortality, survival

1 | INTRODUCTION

Since its advent in 1963, the outcomes of liver transplantation (LT), including post-transplant survival and quality of life, have markedly improved. Advances in surgical and anaesthetic techniques, as well as in immunosuppressive therapies, have led to more liberal transplant policies, especially among elderly recipients. For instance, the most recent American guidelines state that age over 70 years is not a contraindication for LT.[1] European guidelines indicate that physiological rather than chronological age should be taken into consideration, although multidisciplinary discussion is needed for patients over 65–70 to exclude patients with major comorbidities before listing.[2]

In Europe, the proportion of recipients aged ≥65 years old increased from 5% in 2000 to 13% in 2015,[3] and in the United States, it rose from 8% in 2002 to 17% in 2014.[4] In France, the Biomedicine Agency reported that the mean age at LT increased from 49.7 to 53.2 years in 10 years, and the number of recipients aged >65 years increased fourfold between 2008 and 2018.[5] This can be explained by the ageing of the general population and by the increasing proportion of patients with hepatocellular carcinoma (HCC), who tend to be older.[4] In addition, ageing of LT recipients is expected to continue in the coming years with the widespread use of highly effective direct-acting antivirals (decreasing the number of new registrants for HCV-related cirrhosis), and with the growing proportion of non-alcoholic steatohepatitis (NASH)-related cirrhosis.[6–9]

However, there is a shortage of liver donors. In France, in 2019, there were 2.4 recipients for one liver graft.[5] In a context where demand far outweighs supply, it appears important to evaluate survival after LT in elderly recipients. Literature on the subject is scarce, comes mostly from US registries and is subject to debate because age was considered as a categorical variable, suggesting that there is an age threshold beyond which prognosis is changed, a hypothesis that deserves to be questioned. Indeed, while outcomes appear to be similar at 1 year in patients younger or older than 60 years old,[10] 5-year survival results are more controversial. Some studies have suggested that patients aged 65 or older have similar outcomes to their younger counterparts[11,12] while others have shown that 5-year survival is significantly lower (by around 10%–20%) among older recipients.[4,13–16] This increased risk of mortality in older recipients seems to be linked to certain comorbidities[17] and the severity of liver disease.[18] In any case, the lack of clear recommendations and conclusive studies has led to considerable heterogeneity in decision-making between transplant centres.

Key points

In patients undergoing liver transplantation, the age of the recipient at the time of transplantation was associated with the risk of death. The risk of death increases with increasing age in the first year after liver transplant, but decreases thereafter.

In this context, the aim of this study was to estimate the effect of recipient age on all-cause mortality within 5 years after a first LT. Secondary aims were to estimate the effect of recipient age on 5- and 10-year survival after a first LT, accounting for the corresponding age- and sex-specific mortality in the French general population.

2 | METHODS

2.1 | Study design

This cross-sectional study uses on data from the national transplantation database (CRISTAL), managed by the French Biomedicine Agency. This agency manages the national list of patients awaiting liver transplant and coordinates organ procurement, distribution and allocation in all French territories. The database was created in 1996 in order to collect data on all organ transplant candidates, recipients and donors in France together with candidate and recipient outcomes. Briefly, the database includes recipients' characteristics at the time of listing (age, sex, blood group, body mass index [BMI]) as well as their medical history and liver disease leading to LT. Data describing the recipient's disease severity are also collected at the time of LT, namely: hospitalisation prior to transplant, mechanical ventilation, dialysis and Model for End-Stage Liver Disease (MELD) score. Data relating to the corresponding donor (age, BMI, cause of death and medical history) as well as the description of the surgical procedure are also systematically collected. Additional available data include post-operative complications and annual follow-up of vital status. Data are entered into the database by a dedicated clinical research

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assistant in each transplant centre. Data collection is mandatory and is a pre-requisite for the transplant centre to obtain funding. The CRISTAL database complies with the European General Data Protection Regulation. For the purposes of the present study, anonymous data corresponding to our target population were provided by the team managing the CRISTAL database.

2.2 | Study population

We included all patients registered in the CRISTAL database, aged 18 years or older, who received a first LT between September 2007 and September 2017. Patients who underwent combined solid organ transplant, split transplantation, heterotopic graft or LT from a living donor or donation after circulatory determination of death (Maastricht categories I, II and III) were not included (Figure 1). In addition, recipients with missing data for age, vital status or at least one of the potential confounding variables identified in the literature (sex, diabetes, HCC, MELD score at transplant, location, dialysis and intubation at transplant, donor age) were excluded.

2.3 | Variables of interest

Six categories of age were considered for the descriptive analysis: [18–35[; [35–50[; 50–60[; [60–65[; [65–70[; ≥70. MELD score was calculated from laboratory parameters at LT (international normalized ratio [INR], bilirubin, and creatinine) according to a previously described algorithm.[19] In case of missing data at transplant, and if transplantation occurred less than 3 months after patient registration, the variables recorded at registration were used. Regarding the variable 'ascites history', if any information in the database indicated that the patient had refractory ascites, spontaneous bacterial peritonitis or hydrothorax at least once in the pre-transplant follow-up, then 'ascites history' was considered 'complicated'. For each covariable listed above, all inconsistent data were considered as missing data.

2.4 | Statistical analyses

Population characteristics are described as number and percentage for categorical variables, and as mean (± standard deviation [SD]) or median (interquartiles [IQR]) for continuous variables, according to their distribution. Patient and donor characteristics were compared by age group using the chi square test, analysis of variance or the Kruskal–Wallis test, as appropriate.

2.5 | All-cause mortality and net survival

For survival analyses, baseline was the date of LT. One- and 5-year survival probabilities were estimated using the Kaplan–Meier (KM) method. The association between age and 1-year risk of death

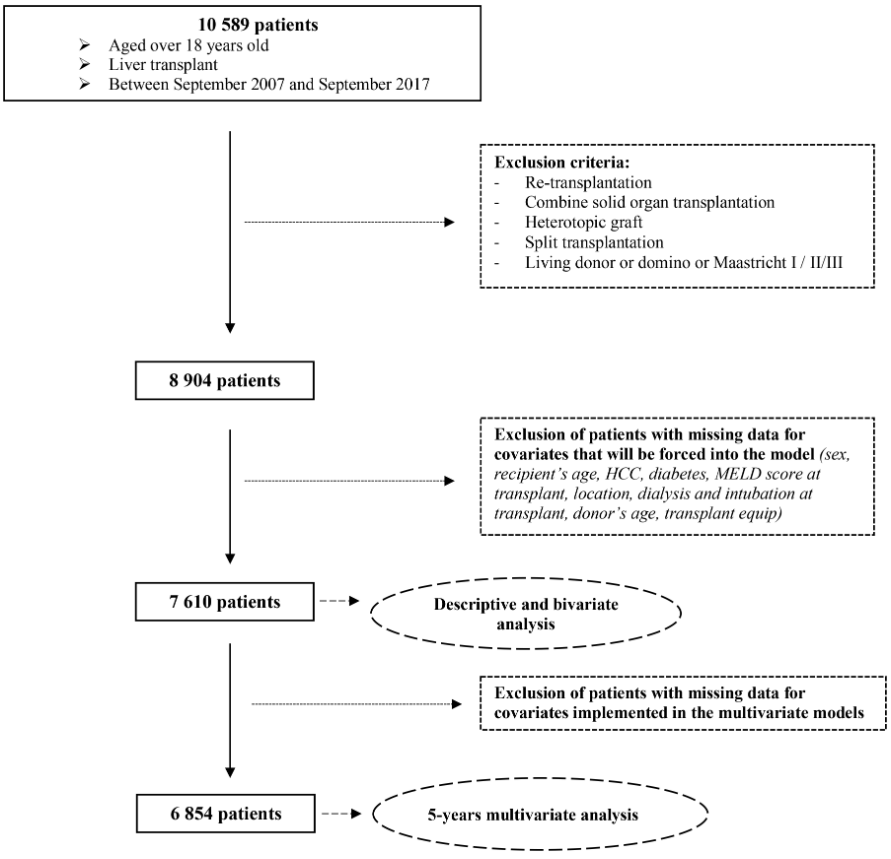

FIGURE 1 Flow chart of the study investigating the effect of recipient age on liver transplant outcomes in the French national cohort of liver transplanted patients between 2007 and 2017. HCC, hepatocellular carcinoma.

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was estimated using a conventional Cox proportional hazards (PH) model. This model was applied for each potential confounding factor. Next, a conventional multivariable Cox PH model was fitted, including recipient age, number of transplants performed in the centre (categorised according to tertiles of distribution), variables highly suspected to be prognostic factors in the literature (forced variables) and all variables associated with 1-year risk of death with a $p < .05$ in unadjusted analyses. A backward selection strategy was applied; only variables associated with the risk of death with a $p < .05$ were considered in the final model in addition to age at LT and forced variables. No imputation was performed for missing data.

In order to estimate the association between recipient age and 5-year and then, 10-year risk of death, we used the same flexible multivariable parametric model.[20,21] This flexible parametric model relies on the approximation of the log of the baseline hazard ratio by a restricted cubic spline and makes it possible to estimate non-proportional effects (also referred to as time-dependent effect or TD), which describe how the strength of the association between the predictor and the hazard varies during follow-up. They are modelled by forming multiplicative interactions with restricted cubic splines of baseline log cumulative hazard and the covariates of interest (a specific number of interior knots can be chosen for each covariate). The model also allows to estimate non-log-linear effects for continuous explanatory variables (e.g. for age: an increase of 5 years in age (from 40 to 45 years) may be associated with a significantly smaller effect than a 5-year increase from 70 to 75 years). It allows also to account for the expected mortality related to age and sex in the general population, when studying long-term survival and thus to estimate a 'net survival'. Indeed, long-term prognosis of patients affected by a specific disease is also affected by the other causes of death observed in the general population, and whose frequency increases with increasing age. And, in large cohorts like ours, the cause of death is often unreliable, and it is difficult to differentiate deaths specifically related to the disease of interest from other causes of death.

We used the following procedure to identify the variables associated with the risk of death: first, we defined the restricted cubic spline of the log baseline hazard function of the full model. We tested up to five interior knots for this spline, positioned according to the corresponding centiles of the observed distribution of uncensored event times (e.g. in case of 1 knot, it was located at the median; when two knots were considered they were positioned at the tertiles) and selected the number of knots allowing to obtain the minimal Akaike criterion (AIC—here two interior knots were retained). Then, we tested for the log-linearity (LL) of the relationship between each continuous covariable with the risk of death, separately in the full model (including all candidate variables), by using restricted cubic splines with up to five interior knots in order to capture any departure from LL. Knots were positioned according to the corresponding centiles of the sample distribution of the values of the considered continuous covariate. Third, we tested if any covariate in the full model had a TD effect. For all TD effects detected, 1 interior knot was retained. We concluded to a departure from LL and PH hypothesis when the corresponding likelihood ratio test yielded a $p < .02$. Finally, a flexible parametric model, including all significant TD effects, was fitted, and we applied a backward selection strategy to exclude unforced variables that were not associated with the risk of death with a minimal $p < .01$.

For the 10-year net survival analysis, expected mortality rates were derived from the observed mortality rates in the French general population, stratified by sex, current age and year of death (2007–2017), provided by the French national statistics institute (Institut National de la Statistique et des Etudes Economiques, INSEE).

The conventional Cox PH model was fitted using SAS 9.4 (SAS Institute Inc, Cary, NC), and the flexible parametric survival model was fitted using STATA release 14, stmp2 package (Stata College Station, TX, USA). To avoid false conclusions about significant associations given our sample size, a p-value below .001 was considered significant, and p-values between .001 and .01 were considered marginally significant.

3 | RESULTS

3.1 | Population

In total, 10 589 patients aged 18 years or older underwent LT in France between 2007 and 2017. Among them, 7610 patients met the inclusion criteria for the present analysis (Figure 1). Age ranged from 18.1 to 78.8 years, with a mean age at LT of 55.0 ± 10.5 years.

Table 1 shows the main characteristics of recipients at listing and at transplant, as well as the main donor and surgery characteristics by age. Among the 7610 patients included, 21.4% were aged 60–65 years, and 15.7% were aged over 65. From 50 years onwards, patients were increasingly frequently male. The proportion of patients with obesity and diabetes increased with age until 70 years.

Cirrhosis was the most frequent cause of LT in all age categories. However, the aetiology of cirrhosis varied with age: alcohol-related cirrhosis and hepatitis C decreased over time, whereas the proportion of 'other' aetiologies increased with age. Patients were more frequently transplanted for HCC when they were older than 60 years.

The severity of cirrhosis decreased with increasing age. The proportion of patients with Child-Pugh C cirrhosis decreased from 41% in patients aged 50–60 years to 24% in patients aged >70 years. A medical history of infection, ascites, the presence of a transjugular intrahepatic portosystemic shunt (TIPS) and hepatorenal syndrome were similar, regardless of recipient age, except in patients over 70, who were less likely to have a history of complicated ascites or hepatorenal syndrome. At transplant, MELD score decreased with increasing age, as did the risk of being hospitalised or admitted to the intensive care unit (ICU) and the risk of being under mechanical ventilation or dialysis (Table 1).

Time from listing to transplant increased with recipient's age. Older recipients had older donors with a cause of death more frequently related to vascular disease. Conversely, resuscitated cardiac

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TABLE 1 Recipient, donor and graft characteristics by age category, in the French national cohort of liver transplant patients from 2007 to 2017.

	Study population	[18–35[	[35–50[	[50–60[	[60–65[	[65–70[	[≥70]	*p*
N (%)	7610	469 (6.2)	1486 (19.5)	2834 (37.2)	1627 (21.4)	1069 (15.1)	125 (1.6)	
Recipients' characteristics at listing								
Sex, *N* (%); *n* = 7610								
Male	5678 (74.6)	244 (52.0)	1044 (70.3)	2191 (77.3)	1280 (78.7)	822 (76.9)	97 (77.6)	<.0001
Recipient BMI (kg/m^2), N (%); *n* = 7599								
<18.5	219 (2.9)	50 (10.7)	62 (4.2)	72 (2.5)	24 (1.5)	10 (0.9)	1 (0.8)	<.0001
[18.5–25]	3108 (49.9)	296 (63.3)	753 (50.8)	1119 (39.5)	526 (32.4)	369 (34.6)	45 (36.3)	
[25–30]	2641 (34.8)	87 (18.6)	417 (28.1)	1036 (36.6)	651 (40.0)	398 (37.3)	52 (41.9)	
≥30	1631 (21.5)	35 (7.5)	250 (16.9)	604 (21.3)	425 (26.1)	291 (27.3)	26 (21.0)	
Diabetes, *N* (%); *n* = 7610	1746 (22.9)	8 (1.7)	154 (10.4)	645 (22.8)	508 (31.2)	390 (36.5)	41 (32.8)	<0.0001
Aetiology for LT[a], *N* (%); *n* = 7610								
Cirrhosis	7039 (92.5)	335 (71.4)	1305 (87.8)	2693 (95.0)	1567 (96.3)	1023 (95.7)	116 (92.8)	<.0001
Alcoholic cirrhosis	4127 (54.2)	34 (7.3)	675 (45.4)	1699 (60.0)	1039 (63.9)	625 (58.5)	55 (44.0)	<.0001
HCV-cirrhosis	1535 (20.2)	9 (1.9)	327 (22.0)	772 (27.2)	259 (15.9)	145 (13.6)	23 (18.4)	<.0001
HBV and/or HDV cirrhosis	481 (6.3)	38 (8.1)	126 (8.5)	172 (6.1)	74 (4.6)	66 (6.2)	5 (4.0)	.0002
Auto-immune cirrhosis	202 (2.7)	54 (11.5)	54 (3.6)	49 (1.7)	29 (1.8)	13 (1.2)	3 (2.4)	<.0001
Biliary cirrhosis	442 (5.8)	94 (20.0)	116 (7.8)	127 (4.5)	51 (3.1)	46 (4.3)	8 (6.4)	<.0001
Other causes of cirrhosis	1405 (18.5)	143 (30.5)	248 (16.7)	369 (13.0)	330 (20.3)	278 (26.0)	37 (29.6)	<.0001
Acute liver failure	381 (5.0)	109 (23.2)	123 (8.3)	83 (2.9)	30 (1.8)	30 (2.8)	6 (4.8)	<.0001
Tumours other than HCC	142 (1.9)	19 (4.1)	47 (3.2)	41 (1.5)	21 (1.3)	11 (1.0)	3 (2.4)	<.0001
Others	85 (1.1)	14 (3.0)	3 (1.6)	28 (1.0)	14 (0.9)	6 (0.6)	0 (0.0)	.0003
HCC, *N* (%); *n* = 7610	3046 (40.0)	33 (7.0)	287 (19.3)	1140 (40.2)	874 (53.7)	640 (59.9)	72 (57.6)	<.0001
MELD exception, *N* (%); *n* = 7610	1036 (13.6)	120 (25.6)	199 (13.4)	362 (12.8)	192 (11.8)	151 (14.1)	12 (9.6)	<.0001
Recipient medical history, N (%)								
TIPS (*n* = 7542)	461 (6.1)	15 (3.2)	78 (5.3)	202 (7.2)	97 (6.0)	60 (5.7)	9 (7.3)	.0110
Previous abdominal surgery (*n* = 7428)	1846 (24.9)	110 (24.4)	324 (22.6)	625 (22.5)	421 (26.4)	325 (31.0)	41 (33.6)	<.0001
Portal vein thrombosis (*n* = 7523)	592 (7.9)	21 (4.5)	96 (6.6)	213 (7.6)	150 (9.3)	97 (9.1)	15 (12.2)	.0007
Gastrointestinal bleeding (*n* = 7751)	864 (11.4)	36 (7.7)	179 (12.2)	335 (11.9)	193 (11.9)	104 (9.8)	17 (13.8)	.0390
Hepatorenal syndrome (*n* = 7532)	768 (10.2)	32 (6.9)	158 (10.8)	298 (10.6)	166 (10.3)	105 (9.9)	9 (7.4)	.1738
Porto-pulmonary-hypertension (*n* = 7469)	186 (2.5)	7 (1.5)	41 (2.8)	76 (2.7)	40 (2.5)	20 (1.9)	2 (1.6)	.4132
Infections (*n* = 7549)	628 (8.3)	43 (9.3)	134 (9.1)	257 (9.1)	113 (7.0)	72 (6.8)	9 (7.3)	.0407

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TABLE 1 (Continued)

	Study population	[18–35[	[35–50[	[50–60[	[60–65[	[65–70[	[≥70]	*p*
Ascites history, *N* (%); *n* = 7607								
Absent	3289 (43.2)	293 (62.6)	612 (41.2)	1107 (39.1)	696 (42.8)	510 (47.7)	71 (56.8)	<.0001
Moderate	1608 (21.1)	85 (18.2)	349 (23.5)	622 (22.0)	334 (20.5)	192 (18.0)	26 (20.8)	
Complicated	2710 (35.6)	90 (19.2)	525 (35.3)	1103 (39.0)	597 (36.7)	367 (34.3)	28 (22.4)	
Child-Pugh score, N (%); *n* = 5445								
A	546 (10.0)	18 (5.7)	60 (5.9)	220 (10.8)	124 (10.6)	106 (13.1)	18 (18.6)	<.0001
B	2790 (51.2)	157 (49.7)	456 (45.0)	983 (48.1)	650 (55.7)	488 (60.3)	56 (57.7)	
C	2109 (38.7)	141 (44.6)	498 (49.1)	839 (41.1)	393 (33.7)	215 (26.6)	23 (23.7)	
Recipients' characteristics at transplant								
Location, *N* (%); *n* = 7610								
Not hospitalised	5327 (70.0)	226 (48.2)	926 (62.3)	2035 (71.8)	1224 (75.2)	816 (76.3)	100 (80.0)	<.0001
Hospitalized out of ICU	960 (12.6)	66 (14.1)	213 (14.3)	384 (13.6)	174 (10.7)	119 (11.1)	4 (3.2)	
Hospitalised in ICU	1323 (17.4)	177 (37.7)	347 (23.4)	415 (14.6)	229 (14.1)	134 (12.5)	21 (16.8)	
Mechanical ventilation, *N* (%); *n* = 7610	538 (7.1)	87 (18.6)	165 (11.1)	159 (5.6)	66 (4.1)	57 (5.3)	4(3.2)	<.0001
Dialysis, N (%); *n* = 7610	372 (4.9)	55 (11.7)	100 (6.7)	112 (4.0)	53 (3.3)	51 (4.8)	5 (4.0)	<.0001
MELD score, mean (±SD); *n* = 7610	19.5 (±9.9)	23.8 (±11.5)	22.5 (±10.4)	19.4 (±9.5)	17.8 (±9.2)	16.8 (±9.1)	15.9 (±9.8)	<.0001
Transplant characteristics								
Time from listing to transplant, median (IQR); *n* = 7610	112.0 (223.9)	38.0 (179.0)	58.0 (175.0)	107.5 (246.0)	143.0 (274.0)	190.0 (317.0)	318.0 (378.0)	<.0001
Cold ischemia time (h), mean (±SD); *n* = 7536	7.7 (±2.3)	7.4 (±1.9)	7.9 (±2.2)	7.8 (±2.3)	7.7 (±2.3)	7.6 (±2.3)	7.8 (±2.2)	.0008
Transfusion during surgery, *N* (%); *n* = 7273	5819 (80.0)	357 (78.6)	1182 (83.1)	2159 (80.0)	1242 (79.8)	790 (77.2)	89 (76.1)	.0104
Transplant centre volume, *N* (%); *n* = 7610								
<400	1174 (15.4)	57 (12.2)	235 (15.8)	459 (16.2)	246 (15.1)	151 (14.1)	26 (20.8)	.0024
400–800	3998 (52.5)	226 (48.2)	742 (49.9)	1509 (53.3)	879 (54.0)	580 (54.3)	62 (49.6)	
>800	2438 (32.0)	186 (39.7)	509 (34.3)	866 (30.6)	502 (30.9)	338 (31.6)	37 (29.6)	
Characteristics of donors								
Age, mean (±SD); *n* = 7610	57.1 (±18.0)	49.4 (±18.2)	54.7 (±17.3)	57.1 (±18.0)	59.1 (±17.7)	60.1 (±17.9)	64.1 (±16.4)	<.0001
Cause of death, *N* (%); *n* = 7610								

(Continues)

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TABLE 1 (Continued)

	Study population	[18–35[	[35–50[	[50–60[	[60–65[	[65–70[	[≥70]	p
Anoxia	1036 (13.6)	68 (14.5)	212 (14.3)	401 (14.2)	208 (12.8)	135 (12.6)	12 (9.6)	.0206
Trauma	1738 (22.8)	129 (27.5)	337 (22.7)	658 (23.2)	361 (22.2)	227 (21.2)	26 (20.8)	
Vascular	4643 (61.0)	258 (55.0)	885 (59.6)	1707 (60.2)	1020 (62.7)	690 (64.6)	83 (66.4)	
Other	193 (2.5)	14 (3.0)	52 (3.5)	68 (2.4)	38 (2.3)	17 (1.6)	4 (3.2)	
Resuscitated cardiac arrest, *N* (%); *n* = 7595	1901 (25.0)	136 (29.1)	394 (26.6)	717 (25.4)	393 (24.2)	239 (22.4)	22 (17.6)	.0135
Medical history, *N* (%)								
Alcohol (*n* = 7610)	1247 (16.4)	77 (16.4)	221 (14.9)	468 (16.5)	282 (17.3)	174 (16.3)	25 (20.0)	.4427
Smoking (*n* = 7610)	2846 (37.4)	199 (42.4)	593 (39.9)	1069 (37.7)	570 (35.0)	373 (34.9)	42 (33.6)	.0051
Hypertension (*n* = 7531)	2852 (37.9)	114 (24.6)	493 (33.5)	1051 (37.6)	677 (41.9)	457 (43.1)	60 (48.4)	<.0001
Diabetes (*n* = 7399)	654 (8.8)	20 (4.4)	111 (7.8)	246 (8.9)	170 (10.7)	99 (9.5)	8 (6.5)	.0007

Abbreviations: BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; ICU, intensive care unit.; LT, liver transplant; MELD, model for end-stage liver disease; TIPS, Transjugular intrahepatic portosystemic shunt. n=data available; N=number of cases for eac variable

[a]Total % may exceed 100% because patients could have up to three aetiologies.

arrest and history of smoking and diabetes decreased among donors of older patients.

3.2 | Cause of death

During the first year after transplant, 946 (12.4%) patients died, and 738 additional deaths (i.e. 22.1% of total patients) were observed in the following 4 years. At 10 years after LT, 5603 (73.6%) patients were still alive.

Figure 2 shows available causes of death according to recipient's age and time of death after LT. At 1 year post LT, patients aged 50–70 years mostly died from infectious (33%–42%), cardiovascular (22%–25%) and hepatic (22%–31%) causes. Conversely, patients aged over 70 more frequently died from cardiovascular disease (28%) and cancer (14%, half of which were hematologic cancers) and less frequently from hepatic causes (21%). The proportion of deaths from infectious causes was the same (35%).

Beyond the first year post LT, patients aged 50–70 mostly died from cancer (30%–37%) and hepatic (33%–37%) causes (infectious and cardiovascular causes accounted for respectively 10–15% and 10%–13%). Patients over 70 years old died more frequently from cancer (50%, of which 12.5% were hematologic cancers) and cardiovascular disease (25%), and less frequently from hepatic causes (12%) and infection (0%).

3.3 | 1-year survival after transplantation

One-year survival probability decreased with increasing age, from 90.0% in patients aged 35–50 year, to 86.1% in those aged 60–65; 84.5% in those aged 65–70; and 83.2% in those aged >70 years.

Bivariate associations with the 1-year risk of death are presented in Table S1. Multivariable Cox regression showed that recipient age was an independent risk factor for death (hazard ratio [HR] = 1.02; 95% confidence interval = 1.01–1.03, $p < 10^{-4}$, Table 2), and the log-linearity hypothesis was not found to be violated ($p = .707$). For illustrative purpose, we estimated the HR for each age category (Table S2). Patients aged 60–65, 65–70 and over 70 years old had respectively a 61% ($p < .0001$), 73% ($p < .0001$) and 81% ($p = .023$) increase in the risk of death during the first year after LT, compared to those aged 35–50 (Table S2). The other main variables significantly associated with 1-year mortality were portal vein thrombosis, hospitalization in ICU, mechanical ventilation and transfusion during surgery.

3.4 | 5-year survival after transplantation

Five-year survival probabilities estimated using K–M method decreased with recipient age, from 81.7% for patients aged 18–35 years, to 70.7% for those aged 65–70 years. Bivariate associations with the 5-year risk of death are presented in Table S3.

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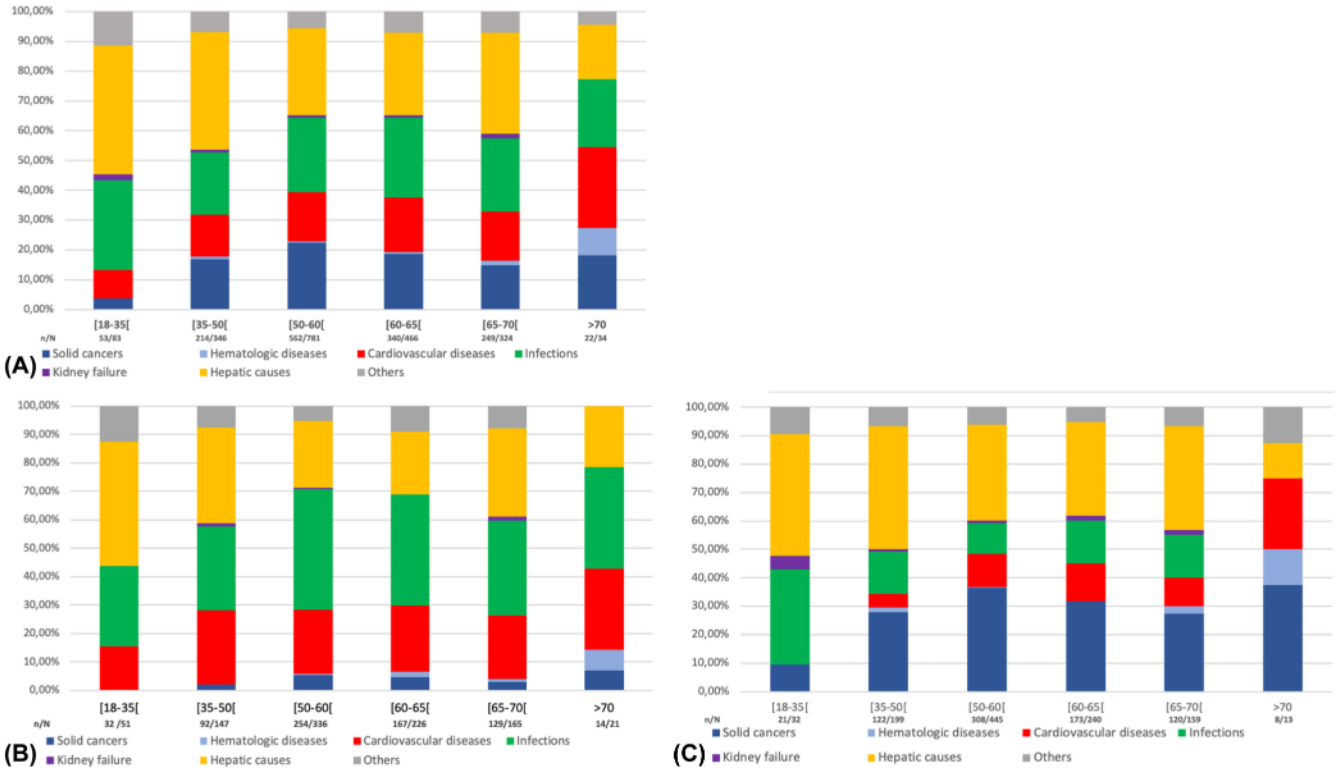

FIGURE 2 Causes of death by age category of liver transplant recipients. Deaths occurring during the whole period after liver transplantation (A), deaths occurring in the first year after liver transplantation (B) and deaths occurring beyond the first year following liver transplantation (C). *n/N*, data available/number of deaths by age category. Hepatic causes = hepatocellular carcinoma, graft rejection, surgical or graft complications and other hepatic disease such as relapse of the initial disease.

We fitted the parametric survival model described in the method section to test and model both TD and non-log-linear effects. This analysis showed no significant violation of the LL assumption for any continuous variable, including age at LT ($p = .832$). This result implies that a 1-year increase in age is associated with the same relative risk of death over the 5 years following LT, regardless of whether we compare subjects aged 36 versus 35 years or those aged 70 versus 69 years. Conversely, the age at LT had a TD effect (p-value for the PH test <.001), whereby the impact of older age was higher during the first year following the LT and then decreased sharply until 2 years of follow-up (Figure 3A), and then more slowly, remaining significant at 5 years ($p < .001$). In addition, six covariates had a TD effect on the risk of death (p-value for departure from the PH hypothesis <.001 for all except for dialysis at LT which had $p = .007$): donor age, mechanical ventilation and dialysis at transplant as well as transfusion during surgery decreased over time (Figure 3B,E,F,G). The relative risk of death in patients in ICU peaked at 2 years to become null around 3 years (Figure 3D) while the risk of death in patients with HCC increased over times (Figure 3C). Two other covariates were found to be marginally associated with the 5 years risk of death, but without any TD effect: previous abdominal surgery and cold ischaemia time ($p = .007$ and .002, respectively).

3.5 | 10-year net survival

In order to account for the expected mortality in the general population according to age, we applied the same model, but accounting for the general mortality according to sex and age, adjusted for the same covariates (including their TD effects when necessary) as those included in the final flexible parametric model obtained when studying factors associated with the 5-year overall risk of death. This analysis showed an overall effect of recipient age at transplant ($p < .0001$) while accounting for its time-dependency, with a major effect in the first 2 years following LT (Figure 4). No violation of the LL hypothesis for recipient age was identified ($p = .7403$).

4 | DISCUSSION

Our study found a significant effect of recipient age on observed survival at 1 year after LT. This effect was still significant at 5 years ($p < .001$). However, when analysed using a flexible model, we show that, in fact, the effect of recipient age was particularly significant during the first 2 years after LT, decreasing thereafter. To the best of our knowledge, this study is the first to show a significant effect

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TABLE 2 Estimation of the effect of age on the risk of death within the first year after liver transplantation (Cox model) in the French national cohort of liver transplant patients between 2007 and 2017.

Variables	HR	[99.9% confidence interval]	*p*-value
Recipient age at transplant (per additional year of age)	**1.02**	**1.01–1.03**	**<.001**
Sex (male)	1.08	[0.82–1.42]	.375
Diabetes	1.14	[0.87–1.50]	.122
HCC	0.92	[0.69–1.23]	.362
History of portal vein thrombosis	**1.48**	**[1.03–2.13]**	**<.001**
Previous abdominal surgery	*1.26*	*[0.97–1.64]*	*.004*
MELD score at transplant	1.00	[0.98–1.02]	.969
Location at transplant			
Not hospitalised	1.00	—	—
Hospitalised out of ICU	1.29	[0.87–1.90]	.034
ICU	**1.75**	**[1.14–2.69]**	**<.001**
Mechanical ventilation at transplant	**1.97**	**[1.25–3.09]**	**<.001**
Dialysis at transplant	*1.46*	*[0.91–2.34]*	*.009*
Transfusion during surgery	**1.48**	**[1.02–2.16]**	**<0.001**
Cold ischemia time (h)	*1.05*	*[0.99–1.11]*	*.002*
Donor age	1.00	[0.99–1.01]	.080
Donor hypertension	*1.24*	*[0.95–1.61]*	*.008*
Transplant centre volume			
<400			
[400–800]	0.89	[0,63–1.25]	.268
>800	0.92	[0,64–1.33]	.459

Note: Sex, diabetes, Hepatocellular carcinoma (HCC), MELD score at transplant, location at transplant, dialysis and mechanical ventilation at transplant, donor age and the volume of activity in the LT centre were forced in the model. *p*-values between .001 and .01 are considered marginally significant (in italics). $p < .001$ are considered significant (in bold).

Abbreviations: HCC, hepato-cellular carcinoma; ICU, intensive care unit; MELD, model for end-stage liver disease.

of age in the early period after LT. A previous study suggested outcomes seemed to be similar at 1 year between patients younger than 60 years and those older than 60.[10] Other studies have reported similar outcomes at 5 years between patients aged younger than versus those older than 60–65 years, but most were single-centre studies,[10,12,22,23] and many of them took place before the MELD-attribution era.[10,12,23] Some more recent studies have shown that 5-year survival was significantly lower (by around 10%–20%) among older recipients,[4,13–15] but all of these results relied on the PH assumption, which is questionable. In our study, recipient age proved to have a time-dependent effect, whereby the risk of death in older recipients was increased in the first years following LT, and then decreased thereafter. In addition, previous studies used arbitrary categories for recipient age, thus losing information. Our flexible analysis did not reveal any non-log-linear effect for recipient age. This linear increase in risk has never before been demonstrated and precludes the definition of an age threshold for LT.

Some series suggested that the decrease in long-term survival with increasing recipient age was simply due to the fact that older persons have, by definition, fewer years of life remaining than younger persons.[11] However, our net survival analysis confirmed the negative, time-dependent effect of recipient age, with a major effect in the first 2 years following LT. To the best of our knowledge, this is the first European multicentre study, using systematic national collection of patients with LT, and assessing the effect of recipient age on survival post-LT, after accounting for sex-and-age-expected mortality rates in the general population. As expected in such large cohort, data concerning the cause of death were often missing (32% of total number of deaths in the whole period, Figure 2). The net survival analysis enabled us to differentiate deaths related specifically to LT from other causes of death. In addition, the characteristics of our study sample (6854/8904 eligible individuals) were very similar to our target population, which argues in favour of its representativeness.

Other variables found to be significantly associated with 1-year survival in our study were portal vein thrombosis, location in ICU and mechanical ventilation at transplant, and transfusion during LT. Interestingly, these latter three variables were also significant at 5 years, but with a TD effect, which was especially notable during the first year after LT for mechanical ventilation at transplant, and for transfusion during LT, as well as dialysis at LT and donor age. These results are consistent with those of previous studies.[15,17,24]

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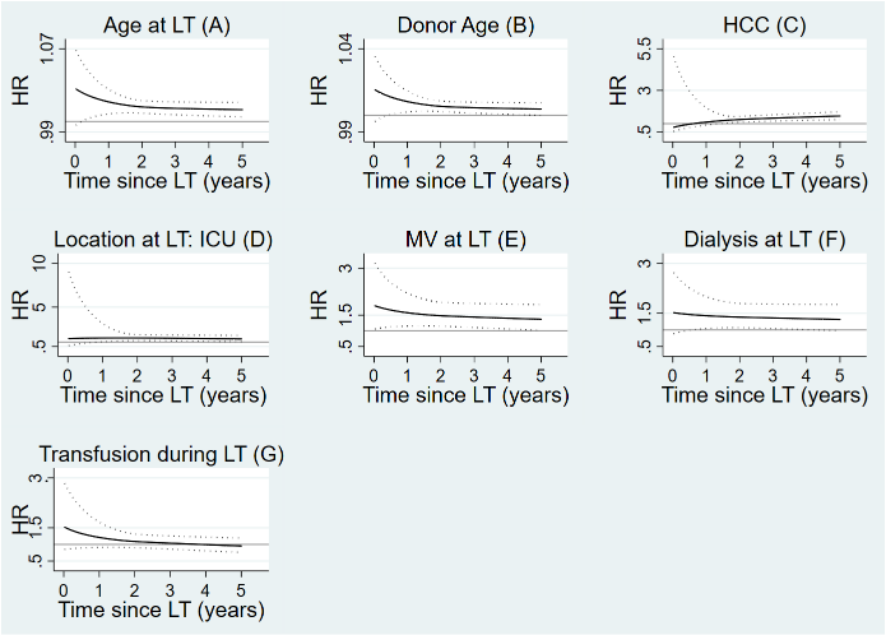

FIGURE 3 Adjusted time-dependent effect over time of recipient age (A), Donor age (B), HCC (C), location at LT: ICU (D), MV (mechanical ventilation) at LT (E), dialysis at LT (F) and transfusion during LT (G) on 5-year survival post LT, in the French national cohort of liver transplant patients between 2007 and 2017. HCC, hepatocellular carcinoma; LT, liver transplant.

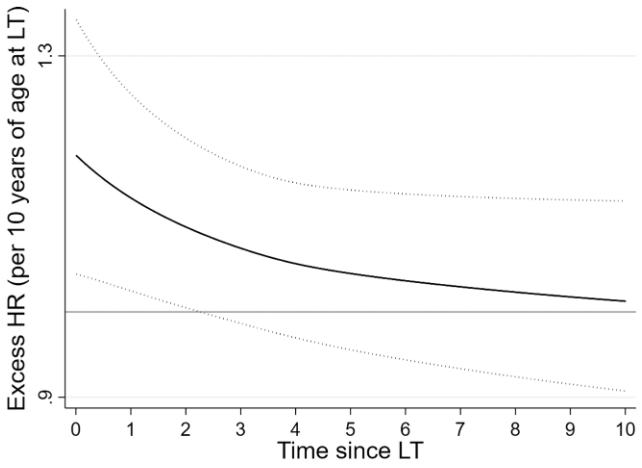

FIGURE 4 Predicted time-dependent effect of recipient age over the 10 years following liver transplant (multivariable net survival model), in the French national cohort of liver transplant patients between 2007 and 2017. LT, Liver transplant.

Conversely, the risk of death in patients with HCC peaked at 3 years and then decreased, probably linked to HCC recurrence after LT.

Some studies suggested that the accumulation of risk factors (hospitalisation in ICU, ventilation, diabetes, kidney failure, dialysis) leads to an increased risk of death after LT, especially in older recipients.[16,17,24] These data suggested that by improving recipient selection, similar results could be achieved in young and old recipients. As previously shown,[4,15,16,18] we found in our series that recipient characteristics were different among older recipients versus their younger counterparts. The aetiology of cirrhosis leading to LT varied with age, whereby older patients were less frequently transplanted for alcoholic cirrhosis and more often for 'other causes of cirrhosis'. These can be assumed to be mostly NASH cirrhosis since this category was not available in the CRISTAL database during the study period. We also showed that there was already some selection among older recipients. Indeed, they were less frequently transplanted for decompensated cirrhosis, but more often for HCC. In addition, beyond 60 years of age, recipients were less likely to be hospitalised, intubated and ventilated, or under dialysis. Nevertheless, 17% of patients older than 70 years were hospitalised in the ICU at the time of the transplant.

The addition of immunosuppressant therapy to a recipient's history of cardiovascular risk factors (for instance diabetes and hypertension) and neoplastic risk factors (tobacco and alcohol) may explain the observed excess mortality associated with recipient's age. Several studies have reported that the most frequent causes of death in older recipients were cardiovascular events and cancer.[4,10,15,22] Indeed, we found that the proportion of patients with obesity and diabetes increased with age until 70 years. Data concerning the cause of death in this large cohort are to be taken with caution, in view of the high rate of missing data and the small number of patients over 70 years. Nonetheless, we found that in the older age category, cancer (both hematologic and solid) and cardiovascular disease were the main causes of death at 5 years, but also at 1 year post LT, despite the pre-operative assessment, which can be assumed to have been more extensive in these at-risk patients.

Aloia et al.[24] suggested that a combined recipient and donor age of 120 years or more was significantly associated with poorer survival, and other studies[25–28] have shown that older donor age was associated with worse post-transplant outcomes. We also found that the donor's age was significantly associated with the 5-year risk of death in our multivariable flexible model (Table 3). Conversely, we found donor age to increase in line with recipient age, suggesting that the donor's age is not taken into consideration when a graft is attributed to an older recipient.

A strength of our study is the large size and homogeneity of the population study: within the MELD era, excluding retransplantation

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TABLE 3 Final multivariable flexible model for 5-year survival after liver transplantation in the French national cohort of liver transplant patients between 2007 and 2017.

n = 6854	Final flexible model		
Variables	HR	(99.9% confidence interval)	*p*-value
Recipient's age (per 1 year)	Figure 3A		**<.001**
Sex (male vs. female)	0.86	[0.73–1.01]	.014
Diabetes (yes vs. no)	1.10	[0.94–1.28]	.127
HCC (yes vs. no)	Figure 3C		**<.001**
Previous abdominal surgery (yes vs. no)	*1.17*	*[1.01–1.36]*	*.007*
MELD score at transplant	0.99	[0.98–1.00]	.021
Location at transplant			
Not hospitalised	**1.00**	—	—
Hospitalised out of ICU	**1.37**	**[1.11–1.71]**	**<.001**
ICU	Figure 3D		**<.001**
Mechanical ventilation at transplant (yes vs. no)	Figure 3E		**<.001**
Dialysis at transplant (yes vs. no)	Figure 3F		*.007*
Transfusion during surgery (yes vs. no)	Figure 3G		**<.001**
Cold ischaemia time (h)	1.04	*[1.01–1.07]*	*.002*
Donor age (per 1 year)	Figure 3B		**<.001**
Transplant centre volume			
<400	1.00	—	—
400–800	0.89	[0.73–1.07]	.107
>800	0.90	[0.74–1.11]	.206

Note: Sex, diabetes, HCC, MELD score at transplant, location at transplant, dialysis and mechanical ventilation at transplant, donor age and the volume of activity in the LT centre, were forced in the model. For associations, *p*-values between .001 and .01 are considered marginally significant (in italics). $p < .001$ are considered significant (in bold).

Abbreviations: HCC, hepatocellular carcinoma; ICU, intensive care unit; MELD, model for end-stage liver disease; PH, proportional hazards.

or complex transplantation. However, it is important to note that AFP score[29] has been implemented during the study period for patients with HCC. This change has been effective in January 2013 and has concerned a minority of listed patients (around 15% according to Biomedecine Agency). Overall survival has not significantly changed after, so we don't think it has influenced the results of our study. Another limitation is that LT with DCD donation and living-related LT were excluded, preventing any extrapolation of the results to those specific cases. However, it avoided to gather populations with different medical context and prognosis.

The main limitation of this study is the absence of data concerning other cardiovascular risk factors in LT recipients (history of smoking, HTA, dyslipidaemia, cardiovascular diseases). These data would have been useful as Sonny et al. previously showed that pre-transplant coronary artery disease is a predisposing factor to 30-day and 1-year mortality in recipients aged >60 years old.[4,15,16,18] Moreover, as the EASL guidelines recommend that physiological age should be taken into consideration when listing a patient for LT, it would have been interesting to adjust our survival analyses for frailty or nutritional status. Unfortunately, the CRISTAL database did not record these variables at the time of this study. Finally, in their multicentre study from the American registry, Su et al.[4] showed that increasing recipient age was associated with lower post-transplant survival, but also with reduced survival before transplantation, and thus, the survival benefit from LT was similar in younger and older recipients, at similar Meld score, proving the benefit of LT in older recipients at individual level. Given our results, and to explore further, it would be interesting to combine mortality risk factors identified here (mechanical ventilation, dialysis or ICU admission etc.) with recipient age in a score that could help to determine a profile of recipients for whom LT should not be considered, as suggested by Asrani et al.[17]

5 | CONCLUSION

In conclusion, although there was a selection process for older recipients, increasing age at LT was associated with an increased risk of death, particularly in the first 2 years after LT. This negative, time-dependent effect of age was confirmed after accounting for age-and-sex-related expected mortality in the French population. Therefore, the lower survival in older patients cannot be attributed to the inherent risk of death linked to age. However, the linear increase in the risk of death associated with age precludes any

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definition of a threshold age for LT. These results clearly indicate that selection of older recipients should be more stringent, and that further studies are warranted to define the profile of individuals who should not be considered for LT in a context of organ shortage.

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ACKNOWLEDGEMENTS

French liver transplantation study group: Julio Abba—CHU Grenoble; Pietro Addeo—CHU Strasbourg; Teresa Antonini—Hospices Civils de Lyon; Thierry Artzner—CHU Strasbourg; Daniel Azoulay—CHU Henri Mondor, Créteil; Louise Barbier—CHU Tours; Edouard Bardou Jacquet—CHU Rennes; Hélène Barrault—CHU Tours; Damien Bergeat—CHU Rennes; Olivier Boillot—Hospices Civils de Lyon; Emmanuel Boleslawski—CHU Lille; Patrick Borentain—CHU Marseille; Karim Boudjema—CHU Rennes; Emmanuel BUC—CHU de Clermont Ferrand; Petru Bucur—CHU Tours; Daniel Cherqui—Hôpital Paul Brousse—Paris; Laurence Chiche—CHU Bordeaux; Mircea Chirica—CHU Grenoble; Mathilde Derrider—CHU Strasbourg; Federica Dondero—Hôpital Beaujon, Paris; Safi Dokmak—Hôpital Beaujon, Paris; François Durand—Hôpital Beaujon, Paris; Mehdi El Amrani—CHU Lille; Stéphanie Faure—CHU Montpellier; Édouard Girard—CHU Grenoble; Claire Goumard—Hôpital Pitié-Salpêtrière, Paris; Emilie Gregoire—CHU Marseille; Jean Gugenheim—CHU Nice; Astrid Herrero—CHU Montpellier; Jean-Baptiste Hiriard—CHU Bordeaux; Caroline Jezequel—CHU Rennes; Guillaume Lassailly—CHU Lille; Fanny Lebosse—Hospices Civils de Lyon; Jean-Yves Mabrut—Hospices Civils de Lyon; Maxime Mallet—Hôpital Pitié-Salpêtrière, Paris; Charlotte Maulat—CHU Toulouse; Alessandra Mazzola—Hôpital Pitié-Salpêtrière, Paris; Baptiste Michard—CHU Strasbourg; Guillaume Millet—CHU Lille; Fabrizio Panaro—CHU Montpellier; Jean-Marie Peron—CHU Toulouse; Gabriella Pittau—Hôpital Paul Brousse, Paris; Michel Rayar—CHU Rennes; Fabien ROBIN—CHU Rennes; Olivier Roux—Hôpital Beaujon, Paris; Didier Samuel—Hôpital Paul Brousse, Paris; Éric Savier—Hôpital Pitié-Salpêtrière, Paris; Olivier Scatton—Hôpital Pitié-Salpêtrière, Paris; Laurent Sulpice—CHU Rennes; Christine Sylvain—CHU Poitiers; Nicolas Tabchouri—CHU Tours; Stéphanie Truant—CHU Lille; José Ursic-Bedoya—CHU Montpellier; Claire Vanlemmens—CHU Besançon; Emmanuel Weiss—Hôpital Beaujon, Paris. This work was published using data from the French liver transplant registry (CRISTAL, ABM) and with the support of the French Biomedicine Agency. This study was supported by a grant of the French National Society of Gastroenterology (scholarship MAHGE). We thank Marie-Eve BEAUCHAMPS (Research Institute of the McGill University Health Centre, Montreal, Canada) for her assistance throughout the study, Gaëlle ROMAIN and Valérie JOOSTE (Digestive cancers registry of Burgundy & UMR1231-EPICAD team, Dijon, France) for their assistance in the net survival modelling. We also thank Suzanne RANKIN for critical revision of the manuscript.

FUNDING INFORMATION

Lea Lerosey, as a Master 2 student, received a scholarship from the French National Society of Gastroenterology (SNFGE).

CONFLICT OF INTEREST STATEMENT

The authors do not have any disclosures to report.

DATA AVAILABILITY STATEMENT

All the data used for this analysis are presented in the document and supplementary material.

ETHICS STATEMENT

This study uses anonymised data from the French national liver transplant database, which is compliant with the General Data Protection Regulation and French legislation regarding data privacy.

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How to cite this article: Lerosey L, Ksiasek E, Abrahamowicz M, et al. Recipient age influences survival after liver transplant: Results of the French national cohort 2007–2017. *Liver Int*. 2024;44:1396-1408. doi:10.1111/liv.15867

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