ORIGINAL ARTICLE

Advanced donor age does not increase risk of hepatocellular carcinoma recurrence after liver transplantation: a retrospective two-centre analysis using competing risk analysis

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SUMMARY

The impact of donor age on the recurrence of hepatocellular carcinoma (HCC) after liver transplantation is still debated. Between 2002 and 2014, all patients transplanted for HCC in 2 European liver transplantation tertiary centres were retrospectively reviewed. Risk factors for HCC recurrence were assessed using competing risk analysis, and the impact of donor age < or ≥65 years and < or ≥80 years was specifically evaluated after propensity score matching. 728 patients transplanted with a median follow-up of 86 months were analysed. The 1-, 3- and 5-year recurrence rates were 4.9%, 10.7% and 13.9%, respectively. In multivariable analysis, recipient age (sHR: 0.96 [0.93; 0.98], $P < 0.01$), number of lesions (sHR: 1.05 [1.04; 1.06], $P < 0.001$), maximum size of the lesions (sHR: 1.37 [1.27; 1.48], $P < 0.01$), presence of a hepatocholangiocarcinoma (sHR: 6.47 [2.91; 14.38], $P < 0.01$) and microvascular invasion (sHR: 3.48 [2.42; 5.02], $P < 0.01$) were significantly associated with HCC recurrence. After propensity score matching, neither donor age ≥65 ($P = 0.29$) nor donor age ≥80 ($P = 0.84$) years increased the risk of HCC recurrence. In conclusion, donor age was not found to be a risk factor for HCC recurrence. Patients listed for HCC can receive a graft from an elderly donor without compromising the outcome.

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Key words
ECD graft, elderly graft, hepatocellular carcinoma, liver transplantation

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Introduction

Liver transplantation (LT) is the most effective treatment for hepatocellular carcinoma (HCC), with a 5-year overall survival of 65–75% for selected patients and a recurrence rate of 8–20% [1,2]. Consequently, with the increase in primary liver cancer worldwide, HCC has become one of the main indications for LT in most Western countries [3–5].

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At the same time, the growing gap between the number of candidates and patients actually transplanted has forced transplantation teams to increase the pool of donors by using more and more grafts from so-called 'extended criteria' donors (ECDs) [6,7]. These grafts mostly come from elderly donors, circulatory death donors (DCDs) or fatty liver graft donors and are commonly allocated to candidates listed for HCC (i.e. usually with a compensated liver disease and a low MELD score) [8].

However, the impact of these ECD grafts on HCC recurrence rates has been little studied and has yielded some controversial results, especially regarding donor age. Indeed, most studies identified donor's age as a risk factor of HCC recurrence [9–11], which is in contradiction with the current practice of most centres [8], thus raising issues on allocation policies to maintain good LT results in the treatment of HCC.

The aim of the present study was to analyse the influence of donor characteristics, especially their age, on HCC recurrence after transplantation in 2 European high-turnover centres.

Patients and methods

Patient selection

All liver transplantations performed between January 2002 and December 2014 in two European high-volume centres (Rennes University Hospital and Niguarda Ca' Granda Hospital in Milan) were retrospectively reviewed (n = 2213) (Fig. 1).

Only patients with HCC tumour confirmed on pathological findings of the explanted native liver were included (n = 792).

Patients transplanted with a living donor or a split liver graft (n = 28), with another associated organs (n = 7) or with missing data (n = 3) were excluded from the analysis. In order to avoid bias induced by the influence of a second graft, patients re-transplanted before postoperative day 30 (POD) were also excluded (n = 26).

The ' Milan criteria' [1] were initially used as selection criteria for LT in both centres. Since 2013, the 'AFP model' score [12] has been applied in the French centre.

Data collection

The following data were retrospectively retrieved and analysed:

-Recipient characteristics: age, gender, underlying liver disease and Child-Pugh and MELD scores.

-Tumour characteristics on pathological findings: the number and maximum size of lesions, micro- and macrovascular invasion, the presence of a hepatocholangiocarcinoma form, the presence of satellite lesions, complete tumoural necrosis found on specimens and alfafoetoprotein level (last values before LT).

-Donor characteristics: age, gender, BMI, cause of death, cold ischaemia time and biological parameters (last values before procurement).

-Outcomes: The date of point was set at the date of the latest news or the date of death. The date of HCC recurrence and its localization were also collected.

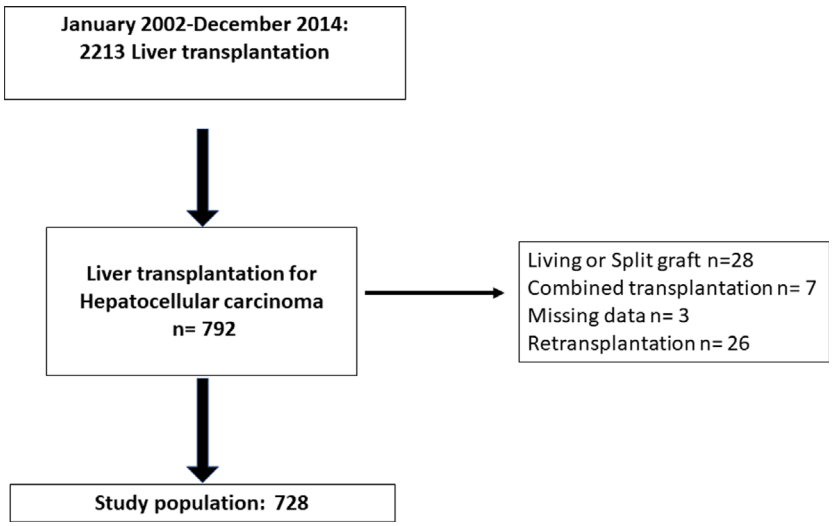

Figure 1 Flow chart of the study.

Surgical technique and postoperative care

All grafts were procured from donation after brain death (DBD).

After standard procurement, the graft was preserved in cold static phase, mainly with Celsior® or Custodiol®. No machine perfusion device was used.

All patients underwent orthotopic liver transplantation with inferior vena cava preservation.

After the procedure, patients were transferred to the intensive care unit (ICU) until graft function was satisfactory. Routine immunosuppression was similar in the two centres and based on calcineurin inhibitors (mostly tacrolimus), mycophenolate mofetil and a short course of corticosteroids (4 to 6 months).

After discharge, patients were followed up according to centre policy. AFP dosage and systematic imaging (i.e. Doppler ultrasound or CT scan) were carried out at least every 6 months in the first 3 years and yearly thereafter.

No significant change regarding the management of HCC during the waiting period, the surgical technic, the postoperative care (especially the immunosuppressive drugs) or the follow-up protocol was observed during the study period.

Ethics

Formal approval from both institutions' local ethics committees was obtained (n° 20.106). Data were retrieved from each centre's prospective database and anonymized prior to analysis.

Statistical analysis

Variable analysis

Quantitative variables were expressed as mean values ± standard deviation or as medians with extreme values (range) and compared using Student's t-test or Wilcoxon's test as appropriate.

Qualitative variables were expressed as numbers and percentages and compared using chi-square or Fisher's exact tests, as appropriate.

Competing risk analysis

Patients undergoing OLT for HCC are at risk of presenting mutually exclusive events. Indeed, since the occurrence of death (not related to HCC recurrence) precludes HCC recurrence, the usual Kaplan–Meier model is inappropriate to correctly estimate the HCC recurrence rate. Therefore, a competitive risk analysis using a Fine and Gray model [13] was used in order to specifically evaluate the risk factors of HCC recurrence and estimate the cause specific hazard also called sub-hazard ratio (sHR).

The 2 competing events were therefore HCC recurrence or death (without HCC recurrence). Patients were 'right-censored' at the latest update or the re-transplantation date (when occurring after POD 30).

All variables with a p-value < 0.1 in univariate competing risk analysis were included in a multivariable competing risk model. The final multivariable model was selected using a descending stepwise method retaining only significant variables.

Propensity score matching

In order to efficiently evaluate the impact of donor age and limit bias due to the differences of the subgroup characteristics, a competing risk analysis was also performed between patients transplanted with a graft from donors aged $<$ or ≥ 65 years and $<$ or ≥ 80 years using a propensity score matching (1/1 ratio). The quality of the matching process was assessed using the standardized differences.

All variables significantly associated (i.e. $P < 0.05$) with HCC recurrence in multivariable analysis, as well as demographic variables considered as clinically relevant, were used in the propensity score calculation.

Ultimately, the following variables were used for the propensity score calculation:
-transplantation centre, recipient age and gender, Child-Pugh and MELD scores, the underlying liver disease, cold ischaemia time, the number and maximum size of lesions, an hepatocholangiocarcinoma component, and the presence of microvascular invasion.

Exact matching was given priority, and the maximum distance allowed between two matched patients was set at 0.1 (calliper restriction).

A $P < 0.05$ was considered as significant. All statistical analyses were performed on R software version 3.1.3 using the 'Matching' v4.9-3 and 'survival' v3.1-12 packages.

Results

Population characteristics

Recipient characteristics

Our study population finally consisted of 728 patients transplanted between January 2002 and December

2014 with HCC confirmed on specimen analysis. The median recipient age was 58 years [17–73] with a majority of men (n = 648, 88.9%) and the median waiting time was 6 months [0.03; 66.3], without significant differences between the 2 centres (Table 1). There was a significant difference regarding the aetiology of the underlying liver disease, which was mostly viral infection for the patients in Milan (n = 241,

Table 1. Characteristics of the study population.

Variables	Entire population n = 728 (%)	Milan Niguarda Hospital n = 305 (%)	Rennes University Hospital n = 423 (%)	P -value
Recipient characteristics				
Gender (male)	648 (88.9%)	268 (87.9%)	380 (89.8%)	0.40
Age† (years)	58 [17; 73]	58 [35; 73]	59 [17; 73]	0.34
Waiting time† (months)	6 [0.03; 66.3]	6.4 [0.03; 66.3]	5.8 [0.03; 41]	0.16
Liver disease aetiology				
Viral	341 (46.8%)	241 (79%)	100 (23.6%)	<0.01
HCV	270 (37.1%)	183 (60%)	87 (20.6%)	
HBV	99 (13.6%)	87 (28.5%)	17 (3.3%)	
Alcohol	337 (46.3%)	51 (16.7%)	286 (67.6%)	
Metabolic*	25 (3.4%)	1 (0.3%)	24 (5.7%)	
Biliary and autoimmune	8 (1.1%)	6 (2%)	2 (0.5%)	
Others	17 (2.3%)	6 (2%)	11 (2.6%)	
Child-Pugh score†	6 [5; 14]	7 [5; 13]	6 [5; 14]	<0.01
MELD score†	11 [5; 39.8]	12 [5; 39]	10.8 [5.4; 39.8]	0.22
Downstaging treatment	104 (14.3%)	51 (16.7%)	53 (12.5%)	0.11
Pathological findings				
Number of nodules†	2 [1; 50]	2 [1; 15]	2 [1; 50]	0.13
Maximum size† (cm)	2.4 [0.1; 11]	2.4 [0.1; 8]	2.5 [0.1; 11]	0.55
Microvascular invasion	167 (23.6%)	75 (24.6%)	92 (21.7%)	0.16
Macrovascular invasion	23 (3.2%)	9 (3%)	14 (3.3%)	0.90
Presence of satellite lesion	87 (12%)	31 (10.2%)	56 (13.2%)	0.20
Hepatocholangiocarcinoma component	16 (2.2%)	3 (1%)	13 (3.1%)	0.06
Complete tumour necrosis	115 (15.8%)	61 (19.9%)	54 (12.8%)	<0.01
Alfa foeto-protein† (ng/mL)	8.4 [0; 847]	9.8 [0; 847]	7.5 [0.9; 700]	0.11
Donor characteristics				
Gender (male)	409 (56.2%)	167 (54.8%)	181 (42.8%)	0.51
Age† (years)	58 [10; 90]	62 [13; 89]	54 [10; 90]	<0.01
BMI†	25.5 [13.8;26]	25.9 [16.6; 56]	24.9 [13.8; 54.4]	<0.01
Cause of death				
Trauma	166 (22.8%)	60 (19.7%)	106 (25.1%)	0.26
Vascular	476 (65.4%)	205 (67.2%)	270 (63.8%)	
Anoxic	65 (8.9%)	28 (9.2%)	37 (8.7)	
Other	21 (2.8%)	12 (3.9%)	10 (2.4%)	
Cold ischaemia time† (min)	593 [183; 860]	600 [240; 860]	562 [183; 820]	0.04
Donor biological tests				
AST† (U/L)	33 [2;2111]	31 [2; 464]	34 [5; 2111]	0.13
ALT† (U/L)	27 [4;1544]	26.5 [5; 587]	27 [4; 1544]	0.38
GGT† (U/L)	30 [0;756]	31 [2; 611]	29 [0; 756]	0.32
ALP† (U/L)	64 [1;708]	66 [13; 699]	64 [1;708]	0.94
Total bilirubin level† (μmol/l)	11[1; 222.3]	11.6 [2; 222.3]	11[1; 121]	0.53
Sodium† (mmol/l)	145 [118; 192]	147 [121; 184]	144 [118; 192]	<0.01
Potassium† (mmol/l)	3.8 [1.9; 8]	3.8 [2.6; 6.3]	3.8 [1.9; 8]	0.50

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; Metabolic*, hemochromatosis, nonalcoholic steatohepatitis (NASH).

†Median value with [range].

79%), while it was alcohol (n = 286, 67.6%) for patients in Rennes. There was also a significant difference in the Child-Pugh scores between the 2 populations (7 vs 6, $P < 0.01$), while the MELD score was no similar.

Tumour characteristics

Downstaging treatment was necessary in 104 (14.3%) patients, without difference between centres ($P = 0.11$).

The median number of nodules was 2 [1; 50] and the median maximum size was 2.4 cm [0.1; 11], without significant differences between centres. Micro- and macrovascular invasion was present for, respectively, 23.6% (n = 167) and 3.2% (n = 23) in the entire cohort and the presence of a cholangiocarcinoma component was present for 2.2% (n = 16), without significant differences between centres. Complete tumoural necrosis was observed for 15.8% (n = 115) of the patients and was significantly higher in the Milan population (19.9% vs 12.8%, $P = 0.01$).

Donor characteristics

The median donor age was 58 [10; 90] with a significant increase over the study period (Fig. 2) and the median age was significantly older in the Italian cohort (62 vs 54 years, $P < 0.01$), as was the donor BMI (25.9 vs 24.9, $P < 0.01$) and the cold ischaemia time was longer (600 min vs 562 min, $P = 0.04$). There was no difference regarding the cause of donor death or biological parameters, except for sodium levels, which were significantly higher in the Milan cohort (147 mmol/L vs 144 mmol/L, $P < 0.01$).

Survival and oncological outcomes

The median follow-up was 86 months [0.1–215]. Overall patient survival was 91%, 80%, 73% and 58.6%, respectively, at 1, 3, 5 and 10 years post-transplantation (Fig. 3a).

During the study period, 122 (16.8%) patients presented HCC recurrence with a median time to recurrence of 20.3 months [0.4–186]. In competing risk analysis, the recurrence rates were 4.9%, 10.7%, 13.9% and 16.9%, respectively, at 1, 3, 5 and 10 years (Fig. 3b). The recurrence site was intra-hepatic for 17.2% (n = 21), extra-hepatic for 44.3% (n = 54) and both intra- and extra-hepatic for 38.5% (n = 47).

Risk factors for HCC recurrence

After multivariable competing risk analysis, recipient age (SHR: 0.96 [0.93; 0.98], $P < 0.01$), the number of lesions (SHR: 1.05 [1.04; 1.06], $P < 0.01$), the maximum size of the lesions (SHR: 1.37 [1.27; 1.48], $P < 0.01$), the presence of a hepatocholangiocarcinoma component (SHR: 6.47 [2.91; 14.38], $P < 0.01$) and the presence of microvascular invasion (SHR: 3.48 [2.42; 5.02], $P < 0.01$) were significantly associated with HCC recurrence. No characteristics related to the donors, and in particular to the donors' age, were found to be significant (Table 2).

Propensity score matching analysis

Impact of donor age ≥ 65 years

In the study population, 260 patients (35.6%) were transplanted with a graft from a donor aged 65 or over.

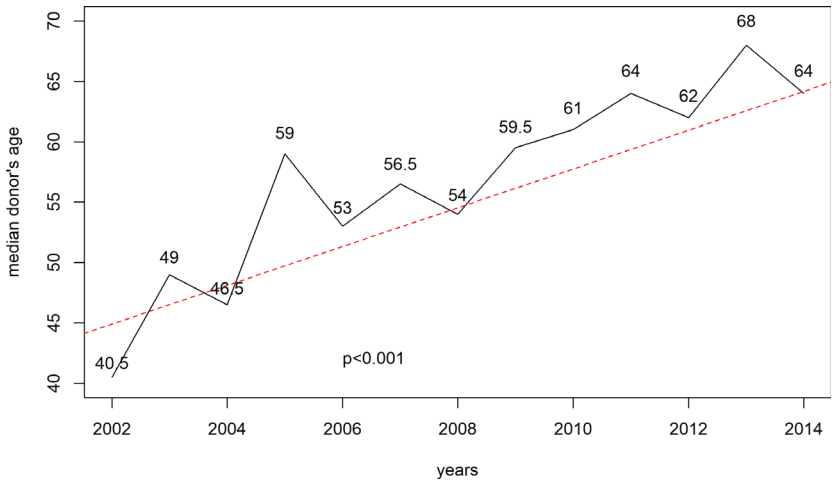

Figure 2 Evolution of donor age over the study period.

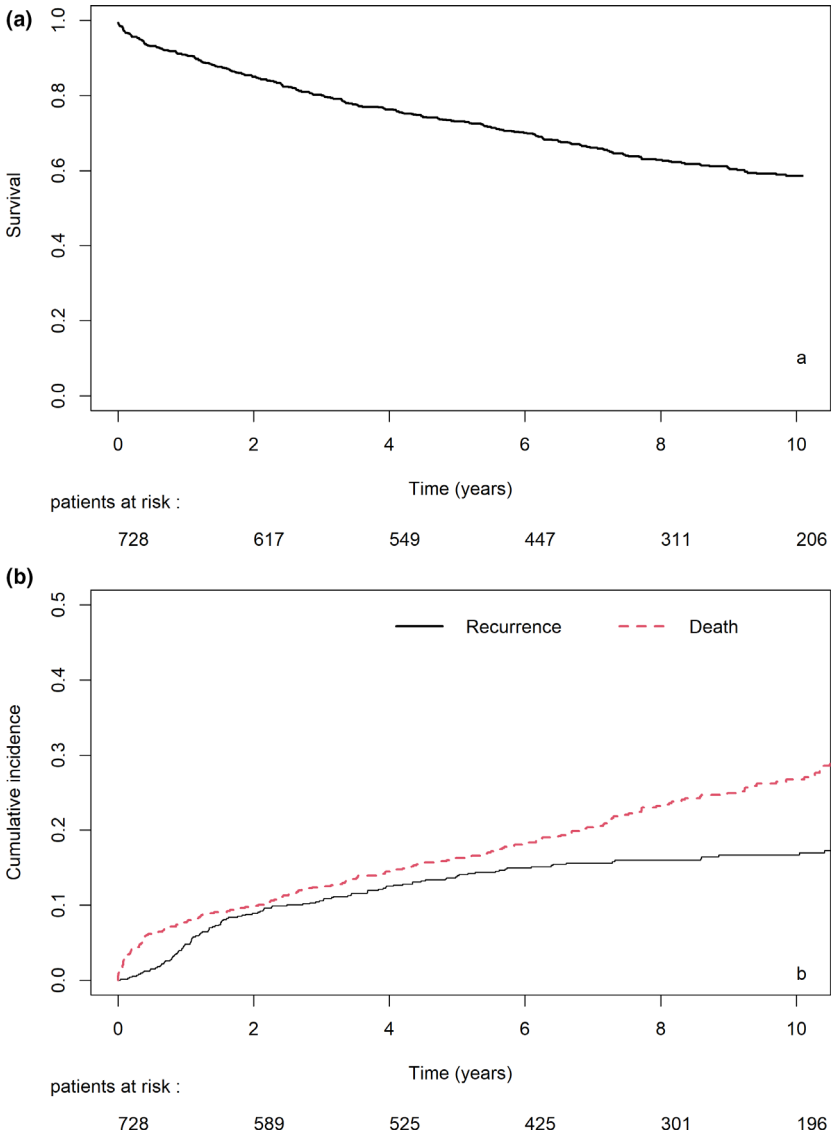

Figure 3 Outcomes for the entire cohort. (a) Overall patient survival. (b) Hepatocellular recurrence and death rate using a competing risk model.

After propensity score matching, 45 (17%) patients receiving a graft from donors aged ≥ 65 did not find a suitable control due to calliper restriction. The analysis was thus performed on 215 patients in each group (Table 3).

There was no difference regarding HCC recurrence ($P = 0.29$) or death ($P = 0.37$) between patients receiving a graft whether the donors were under 65 or 65 and over (Fig. 4a).

Impact of donor age ≥ 80 years

In the study population, 56 patients (7.7%) were transplanted with a graft from a donor aged 80 or over. After propensity score matching, 8 (14.3%) patients receiving a graft from donors aged ≥ 80 did not find a suitable control due to calliper restriction. The analysis was thus performed on 48 patients in each group (Table 4).

There was no difference regarding HCC recurrence ($P = 0.84$) or death ($P = 0.86$) between patients receiving a graft whether the donors were under 80 or 80 and over (Fig. 4b).

Discussion

Liver transplantation is the most effective treatment for HCC since it treats both the tumour and the underlying

Table 2. Risk factors for HCC recurrence (competing risk analysis).

	Univariable (competing risk)		Multivariable (competing risk)	
Variables	*P*	sHR [CI 95%]	*P*	sHR [CI 95%]
Transplantation centre	0.32	0.83 [0.58; 1.19]		
Recipient characteristics				
Gender	0.45	1.27 [0.68; 2.36]		
Age	<0.01	0.96 [0.94; 0.98]	<0.01	0.96 [0.93; 0.98]
Waiting time (months)	0.4	0.99 [0.97; 1.01]		
Liver disease aetiology	0.06		-†	
Alcohol	Reference = 1			
Metabolic*	0.65	1.27 [0.46; 3.56]		
Biliary/Autoimmune	0.26	2.24 [0.51; 9.79]		
Viral hepatitis	<0.01	1.73 [1.18; 2.54]		
Others	0.17	2.03 [0.71; 5.75]		
Child-Pugh score	0.09	0.93 [0.86; 1.01]	-†	
MELD score	0.041	0.96 [0.93; 1]	-†	
Downstaging treatment	0.72	1.1 [0.66; 1.82]		
Tumour characteristics				
Number of nodules	<0.01	1.04 [1.03; 1.05]	<0.01	1.05 [1.04; 1.06]
Maximum size	<0.01	1.43 [1.27; 1.61]	<0.01	1.37 [1.27; 1.48]
Microvascular invasion	<0.01	4.35 [3.04; 6.22]	<0.01	3.48 [2.42; 5.02]
Macrovascular invasion	<0.01	4.61 [2.43; 8.73]	-†	
Hepatocholangiocarcinoma component	<0.01	3.6 [1.59; 8.15]	<0.01	6.47 [2.91; 14.38]
Presence of satellite lesion	<0.01	2.28 [1.49; 3.47]		
Complete tumour necrosis	<0.01	0.36 [0.18; 0.75]	-†	
Alfa foeto-protein	0.98	1 [1; 1]		
Donor characteristics				
Gender	0.97	0.99 [0.69; 1.42]		
Age (continuous variable)	0.096	0.99 [0.98; 1]	-†	
Age (categorical variable)	0.86			
<64	Reference = 1			
65–79	0.63	0.91 [0.6; 1.36]		
≥80	0.74	0.88 [0.42; 1.84]		
BMI	0.99	1 [0.96; 1.04]		
Cause of death	0.99	1.03 [0.89; 1.18]		
Cold ischaemia time	0.73	1 [1; 1]		
AST	0.98	1 [1; 1]		
ALT	0.41	1 [1; 1]		
GGT	0.46	1 [1; 1]		
ALP	0.53	1 [1; 1]		
Total bilirubin	0.94	1 [0.97; 1.04]		
Sodium	0.86	1 [0.98; 1.02]		
Potassium	0.76	0.96 [0.73; 1.25]		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; Metabolic*, hemochromatosis, nonalcoholic steatohepatitis (NASH); sHR, sub-hazard ratio provided by competing risk analysis.

†Nonsignificant variable eliminated from the final multivariable model by the stepwise selection procedure.

disease. However, in the last 2 decades, an increased use of 'extended criteria donors' has given rise to major concerns regarding HCC recurrence after LT.

Using competing risk analysis on a large population from 2 European liver transplantation tertiary centres, it was found that donor age (tested as a continuous or categorical variable) was not a risk factor for HCC recurrence after liver transplantation. On the other hand, it was found that tumour characteristics, such as the number and maximum size of lesions, microvascular invasion and the presence of a hepatocholangiocarcinoma, were associated with a higher HCC recurrence

Table 3. Characteristics of patients transplanted with a donor age < or ≥65.

	Unmatched populations			Matched populations			
Variables	<65 *n* = 468(%)	≥65 *n* = 260(%)	*P*	<65 *n* = 215(%)	≥65 *n* = 215(%)	*P*	StD
Transplantation centre							
Milan	174 (37.2%)	131 (50.4%)	<0.01	86 (40%)	86 (40%)	1	<0.01
Rennes	294 (62.8%)	129 (49.6%)		129 (60%)	129 (60%)		
Recipient gender (male)	416 (88.9%)	232 (89.2%)	0.89	195 (90.7%)	193 (89.8%)	0.75	0.03
Recipient age† (years)	57 [17; 73]	60 [39; 73]	<0.01	59 [40; 73]	60 [39; 73]	0.92	<0.01
Liver disease aetiology							
Viral hepatitis	227 (48.5%)	114 (43.8%)	0.51	88 (40.9%)	86 (40%)	0.97	0.04
Alcohol	207 (44.2%)	130 (50%)		109 (50.7%)	114 (53%)		
Biliary/Autoimmune	15 (3.2%)	10 (3.8%)		11 (5.1%)	10 (4.7%)		
Metabolic*	6 (1.3%)	2 (0.8%)		3 (1.4%)	2 (0.9%)		
Others	13 (2.8%)	4 (1.5%)		4 (1.9%)	3 (1.4%)		
Child-Pugh score†	6 [5; 14]	6 [5; 14]	0.60	6 [5; 14]	6 [5; 14]	0.98	0.06
MELD score†	11 [5; 39.8]	11.1 [5.4; 34.5]	0.56	11.2 [5; 39.1]	11.1 [5.4; 34.5]	0.8	0.01
Number of nodules†	2 [1; 50]	2 [1; 20]	0.34	2 [1; 20]	2 [1; 20]	0.97	0.01
Maximum size † (cm)	2.5 [0.1; 11]	2.2 [0.3; 8]	0.33	2.2 [0.1; 11]	2.3 [0.3; 7.5]	0.80	0.01
Microvascular invasion	101 (21.6%)	66 (25.4%)	0.28	55 (25.6%)	57 (26.5%)	0.83	0.02
Macrovascular invasion	17 (3.6%)	6 (2.3%)	0.30	10 (4.7%)	4 (1.9%)	0.1	0.15
Hepatocholangiocarcinoma component	9 (1.9%)	7 (2.7%)	0.50	6 (2.8%)	7 (3.3%)	0.78	0.03
Cold ischaemia time† (min)	580 [183; 860]	600 [207; 814]	0.25	580 [205; 860]	600 [207; 814]	0.70	0.03

MELD, model for end-stage liver disease; Metabolic*, hemochromatosis, nonalcoholic steatohepatitis (NASH); PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; StD, standardized difference.

†Median value with [range].

rate. Conversely, recipient age was associated with a lower risk of recurrence, which could be explained by the fact that HCC occurring in young patients usually presents genetic alterations associated with a poorer prognosis. In addition, with a follow-up of at least 5 years for all living recipients over a 13-year study period, the present study confirms excellent results of LT for HCC, with a 5-year overall survival of 73% and a recurrence rate of 13.9%. It also shows that the median age of the donors allocated to HCC candidates significantly increased with time.

The risk factors and the prediction of HCC recurrence after LT have been widely studied, and several models or nomograms have been established [13–17]. While pretransplant parameters (such as tumour burden or AFP level) and post-transplant parameters (such as pathological findings on the specimen) have proved to be relevant, the influence of donor characteristics is still debated, especially regarding donor age, since most previous studies have reported that it was associated with more frequent HCC recurrence.

Indeed, Shama *et al.* [11] in a retrospective analysis of 94 patients found that donor age was a risk factor for HCC recurrence, along with the number and the size of the lesion. However, in their study, the median donor age was 38 (pointing to a small proportion of elderly donors). Using the UNOS database, Vagefi *et al.* [9] and Orci *et al.* [10] found that age over 60 was associated with a higher HCC recurrence rate. However, despite the large numbers of patients included, these studies should be interpreted with cautious, especially since the pathological findings on the specimens were not considered and the HCC recurrence rate was probably underestimated (6.5% over the study period for Vagefi *et al.* [9] and 7.8% at 5 years for Orci *et al.* [10]), as discussed by the authors [10]. On the contrary, by systematically reviewing and analysing data from the pathological analysis reports and completing a follow-up of at least 5 years for all patients, we report a 5-year recurrence rate of 13.9% which seems more in line with other reports [2,17–19]. These findings, associated with the use of accurate statistical methods, give credit to the present results. In particular, after appropriate propensity score matching (as confirmed by the low value of the standardized differences), it was observed that allocating a donor aged ≥ 65 (i.e. the most used cut-off for

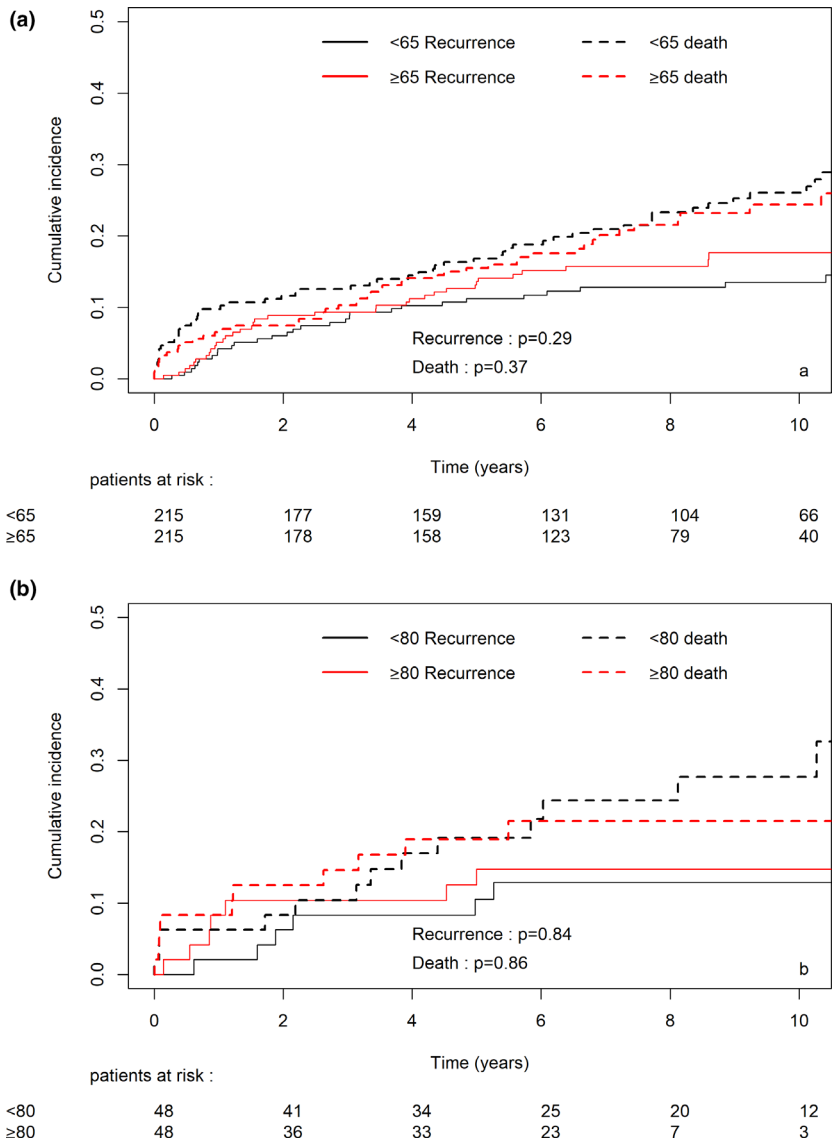

Figure 4 Impact of donor age on hepatocellular recurrence and death rate using competing risk model. a) impact of donor age < or ≥ 65 years and b) impact of donor age < or ≥ 80 years.

defining an extended criteria donor in recent studies) [20,21] or ≥ 80 (i.e. an octogenarian graft) [22] to an HCC candidate was not found to be associated with a higher risk of recurrence. This finding could be particularly interesting, since it gives credibility to most current MELD-based liver allocation policies, which mostly allocate non-ECD grafts to patients with decompensated liver disease and ECD grafts to HCC candidates [8,23]. Indeed, grafts from elderly donors, especially octogenarian donors, were found to be associated with increased postoperative risks unless careful selection of the recipients is performed [24,25]. As a consequence, HCC candidate seemed to be the most suitable candidate for elderly grafts since they usually present compensated liver disease. These policies are also supported by the contribution of machine perfusion, which reduces the risk of primary nonfunction of ECD grafts by improving the quality of conservation and reducing the consequences brought on by ischaemia–reperfusion [26].

However, the present study has some limitations. First, the retrospective and two-centre nature of the study population could be considered as a source of heterogeneity leading to potential bias. We nevertheless believe that merging 2 populations from 2 European tertiary centres could more efficiently reflect clinical practices and the characteristics of patients listed for HCC in Western centres (as shown by the equivalent proportions of HCV and alcohol liver disease across the

Table 4. Characteristics of patients transplanted with a donor age < or ≥80.

	Unmatched populations			Matched populations			
Variables	<80 *n* = 672(%)	≥80 *n* = 56(%)	*P*	<80 *n* = 48 (%)	≥80 *n* = 48 (%)	*P*	StD
Transplantation centre							
Milan	275 (40.9%)	30 (53.6%)	0.06	22 (45.8%)	22 (45.8%)	1	0.05
Rennes	397 (59.1%)	26 (46.4%)		26 (54.2%)	26 (54.2%)		
Recipient gender (male)	597 (88.8%)	51 (91.1%)	0.89	45 (93.8%)	44 (91.7%)	1	0.12
Recipient age† (years)	58 [57; 73]	60 [44; 71]	<0.01	58 [45; 73]	60.5 [44; 71]	0.13	0.21
Liver disease aetiology							
Viral hepatitis	317 (47.2%)	24 (42.9%)	0.88	20 (41.7%)	18 (37.5%)	0.83	0.14
Alcohol	307 (45.7%)	30 (53.6%)		28 (58.3%)	29 (60.4%)		
Biliary/Autoimmune	24 (3.6%)	1 (1.8%)		0 (0%)	1 (2.1%)		
Metabolic*	8 (1.2%)	0 (0%)		0 (0%)	0 (0%)		
Others	16 (2.4%)	1 (1.8%)		0 (0%)	0 (0%)		
Child-Pugh score†	6 [5; 14]	6 [5; 14]	0.83	6 [5; 12]	7 [5; 14]	0.82	0.01
MELD score†	11 [5; 39.8]	12 [5.5; 22.3]	0.88	10.1 [5; 39.1]	12.8 [5.5; 22.3]	0.33	0.1
Number of nodules†	2 [1; 50]	2 [1; 20]	0.82	2 [1; 9]	2 [1; 10]	0.65	0.05
Maximum size† (cm)	2.5 [0.1; 11]	2.2 [0.3; 7]	0.80	2.1 [0.5; 7.5]	2.2 [0.3; 7]	0.92	0.04
Microvascular invasion	150 (22.3%)	17 (30.4%)	0.21	17 (35.4%)	15 (31.2%)	0.66	0.07
Macrovascular invasion	21 (3.1%)	2 (3.6%)	0.70	3 (6.2%)	2 (4.2%)	1	0.07
Hepatocholangiocarcinoma component	15 (2.2%)	1 (1.8%)	1	1 (2.1%)	1 (2.1%)	1	0.06
Cold ischaemia time† (min)	591 [183; 860]	596 [207; 750]	0.73	592 [295; 800]	596 [207; 750]	0.50	0.07

MELD, model for end-stage liver disease; Metabolic*, hemochromatosis, nonalcoholic steatohepatitis (NASH); PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; StD, standardized difference.

†Median value with [range].

entire cohort) than a single centre or a national cohort. Second, the impact of graft histological parameters was not analysed (in particular liver steatosis). This choice was intentional, since steatosis evaluation is rarely available to clinicians at the time the proposal of a potential donor is accepted, and it is also known to be difficult to accurately evaluate [27]. Moreover, since most fatty liver grafts with macrosteatosis over 30% are generally refused, especially among elderly donors, the analysis could have been biased. Third, the subgroup analysis of impact of octogenarian grafts only contains 48 patients in each group and then may be associated with a lack of statistical power despite the matching process. This finding must then be confirmed on larger series before validation.

In conclusion, the present study reports a large two-centre analysis of HCC recurrence after LT, focusing on the impact of donor age. Using appropriate statistical methods, our results support the actual allocation policy of allocating an elderly grafts to HCC candidates. In our experience, this choice did not compromise the excellent results of LT for HCC.

Authors' contributions

MR, CC and LDC designed the study. MR and CC wrote the manuscript. MR, CC, RL, GBLS and LC gathered the data. MR and CJ performed the statistical analysis. All authors reviewed the manuscript.

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Conflict of interest

The authors declare no conflict of interest regarding this study.

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