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Age Matching of Elderly Liver Grafts With Elderly Recipients Does Not Have a Synergistic Effect on Long-term Outcomes When Both Are Carefully Selected

Nicholas Gilbo, MD,[1,2] Ina Jochmans, PhD,[1,2] Mauricio Sainz-Barriga, PhD,[1,2] Frederik Nevens, PhD,[3] Schalk van der Merwe, PhD,[3] Wim Laleman, PhD,[3] Chris Verslype, PhD,[3] David Cassiman, PhD,[3] Len Verbeke, PhD,[3] Hannah van Malenstein, PhD,[3] Tania Roskams, PhD,[4] Jacques Pirenne, PhD,[1,2] and Diethard Monbaliu, PhD[1,2]

Background. Older donors and recipients are increasingly considered for liver transplantation. Both donor and recipient age have a negative impact on outcomes. Large registry analyses show that older donors are frequently matched to older recipients. Whether age-related risks accumulate in a synergic negative effect on outcomes because of donor-recipient age matching is poorly understood. **Methods.** We investigated the impact of donor-recipient age interaction on patient and death-censored graft survival in multivariate Cox regressions in 849 transplants (January 2000 to December 2015). **Results.** Donors 70 years or older did not affect long-term patient or graft survival. Recipient age independently increased the risk of death (hazard ratio [HR], 1.03; 95% confidence interval [CI], 1.02-1.05, $P < 0.0001$), but donor-recipient age interaction was noninfluential. The negative impact of recipient age on patient survival was significant as early as 6 months after transplantation (HR, 1.06; 95% CI, 1.03-1.09; $P = 0.00008$). The adjusted risk of death was significant for patients aged 60 to 69 years (HR, 1.995; 95% CI, 1.40-2.85; $P < 0.0001$) and 70 years or older (HR, 2.001; 95% CI, 1.10-2.66; $P = 0.04$). In contrast, the risk of graft loss was not influenced by recipient age (HR, 1.02; 95% CI, 0.996-1.04; $P = 0.11$) or age interaction. **Conclusions.** Older livers can be safely used in older recipients without jeopardizing graft and patient survival if other risk factors are minimized.

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Liver transplantation (LT) is increasingly being offered to older candidates as a consequence of a combination of increasing life expectancy[1] and improved care of elderly.[2,3] At the same time, grafts from older donors are increasingly accepted to satisfy the ever-growing demand for LT.[4,5]

Because both donor and recipient age are well-known risk factors for transplant failure, the question arises whom these older livers are best offered to. It is generally accepted that recipients with lower likelihood of success, that is, older patients with higher Model for End-stage Liver Disease (MELD) score, should not face the risk of failure associated

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[1] *Department of Microbiology and Immunology, Laboratory of Abdominal Transplant Surgery, KU Leuven, Leuven, Belgium.*

[2] *Abdominal Transplant Surgery, University Hospitals Leuven, Leuven, Belgium.*

[3] *Department of Gastroenterology and Hepatology, KU Leuven, Leuven, Belgium.*

[4] *Department of Imaging and Pathology, Translational Cell and Tissue Research, KU Leuven, Leuven, Belgium.*

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Correspondence: Diethard Monbaliu, MD, PhD, Abdominal Transplant Surgery and Coordination, University Hospitals, Leuven Herestraat 49, B-3000 Leuven, Belgium. (diethard.monbaliu@uzleuven.be).

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with donors of suboptimal quality, that is, older donors with higher Donor Risk Index (DRI).[6] Conversely, younger recipients are believed to endure the transplantation of high-risk grafts with no or minimal impact on outcomes.[6] Surprisingly, recent large registry analyses have shown that older donors are frequently matched with older recipients.[3,5,7,8]

Aging induces functional changes in both graft and recipient, affecting the pathophysiology of ischemia-reperfusion injury and postoperative course. Aged livers are more frequently fibrotic and have lower regeneration capacities,[9,10] resulting in more severe injuries after graft reperfusion.[11] Unsurprisingly, donor age is the risk factor with the highest weight in the DRI score.[12,13] Nevertheless, several single-center reports showed that careful selection of older donors can mitigate the risks associated with advanced donor age.[7,14-17]

Senescence impairs the innate immunity in older recipients, increasing the susceptibility to infections, whereas the adaptive response is hyperactivated with exaggerated production of proinflammatory cytokines and aggravation of ischemia-reperfusion injury.[18,19] Older liver transplant candidates typically have more comorbidities, lower likelihood of success of surgical procedures,[2] and are more carefully selected for LT. Previous studies have associated recipient age with both poor survival[3,5,20] and satisfactory results after transplantation.[21]

It is not clear if matching older donor livers to older transplant candidates affects long-term outcomes because of synergic amplification or age-related risks. We assessed if the interaction of donor and recipient age influences long-term patient and death-censored graft survival after adjustment for other predictors of poor outcomes.

MATERIALS AND METHODS

Study Population and Design

A prospectively collected clinical database was retrospectively reviewed to identify all deceased-donor LTs performed between January 1, 2000, and December 31, 2015, at the University Hospitals of Leuven (Belgium). Pediatric recipients, partial grafts, and combined transplantations were excluded. This study was approved by the local ethical committee (s60518).

Older donors were defined as being 70 years or older ($D \geq 70$) based on the most commonly accepted definition in recently published literature.[5,7,20,22-24] Recipient age was considered as a continuous variable. In post hoc subgroup analyses, recipients were divided into the following age groups: younger than 60 years, between 60 and 69 years, and equal to or older than 70 years.

Donor and recipient demographics, transplant data, posttransplant complications, and graft and patient survival were collected. The effect of the interaction of donor and recipient age on patient and graft survival was investigated in the entire cohort in multivariate analyses. Survival of recipients was censored at the time of death or at the time of last follow-up (August 31, 2016). Graft loss was defined as retransplantation or failure of the graft leading to recipient's death.

Statistical Analyses

Continuous data are expressed as median (interquartile range), and the difference between groups was estimated with the Mann-Whitney U test. Categorical variables are expressed as numbers (percentage), and the difference in incidence was evaluated with the χ^2 test or Fisher exact test. Bonferroni correction for multiple testing was applied when appropriate. The correlation between donor and recipient age was investigated with Spearman's rho.

The existence of age interaction was assessed first visually with interpolation plots. Dot plots were used to visualize the effect of age interaction on outcomes. Mean patient/graft survival (Y-axis) was plotted per recipient age (X-axis) with dots of different colors representing either younger (black) or older donors (gray). Next, interpolation lines were fitted separately for younger and older donors, the slope of which represented the effect of age interaction so that equal slopes (or parallel lines) would indicate absence of relevant interaction.

The effect of age interaction on the risk of recipient's death and graft loss was assessed in univariate analysis with moderated Cox regressions, in which the only variables considered were recipient age, donor 70 years or older, and their interaction product. This effect was further adjusted for other predictors in multivariate Cox regressions. Variables that were significantly associated with the risk of patient's death or graft loss in univariate analysis were considered and retained in the final multivariable models based on backward stepwise selection. The DRI was calculated for every transplant to estimate donor quality, but in multivariate regression only its single components (type, age, race, height, cause of death, cold ischemia, allocation, graft type) were considered to avoid excessive collinearity with donor age. Recipient age, donor 70 years or older, and their interaction product were added to the multivariate models irrespectively from their performance in univariate analyses.

Additionally, an explorative multivariate Cox regression was performed to identify predictors of patient's death in the subgroup of recipients 60 years or older. Finally, given the longevity of the study period, analyses were repeated, adjusting for the effect of transplant era.

Survival curves were plotted based on adjusted hazard ratios (HRs). A 2-sided P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (SPSS Inc. Chicago, IL, version 20).

RESULTS

Characteristics of the Study Population

Eight hundred forty-nine deceased-donor LTs meeting the inclusion criteria were performed between January 1, 2000, and December 31, 2015. Donor and recipient demographics are summarized in Table 1; posttransplant outcomes in Table 2. A significant correlation between donor and recipient age was observed in our center, although the strength of this association was weak (Spearman rho = 0.23, $P < 0.0001$) (**SDC, Figure S1,** http://links.lww.com/TXD/A196).

Median donor age was 52 years (41–62 years). One hundred fifteen donors were 70 years or older (13.60%). Donation after circulatory death (DCD) donors accounted for 12% of LTs. In DCD, total donor warm ischemia time was 19 minutes (15–25 minutes). Cold ischemia time was 7.88 hours (6.23–9.50 hours). No difference in the duration of cold ischemia time was observed between $D < 70$ and $D \geq 70$ (Table 1).

Compared to younger donors, $D \geq 70$ were more often female, died more frequently of cerebrovascular events, had shorter hospitalization in intensive care before donation,

TABLE 1.

Overview of donor and recipient demographics of the study population and transplants performed with grafts from donors younger or older than 70 years

Characteristics	Overall (n = 849)	D < 70 (n = 734)	D ≥ 70 (n = 115)	*P*
Donor				
Age, y	52 (41–62)	49 (38–58)	77 (72–80)	<0.0001
Age ≥70 y, n (%)	115 (13.60)	—	—	—
Sex, n (%)				0.003
Male	472 (55.60)	423 (57.60)	49 (42.60)	
Female	377 (44.40)	311 (42.40)	66 (57.4)	
DCD, n (%)	102 (12.01)	100 (13.60)	2 (1.70)	<0.0001
Total warm ischemia[a], min	19 (15–25)	19 (14–25)	19 (17–19)	0.98
Functional warm ischemia[b], min	10 (6–16)	10 (6–16)	10 (8–11)	0.98
Asystolic warm ischemia[c], min	8 (8–10)	8 (8–10)	8 (8–8)	0.98
Hospitalization in ICU, d	2 (1–5)	2 (1–6)	2 (1–3)	0.004
BMI	24 (22–26)	24 (22–26)	25 (23–27)	0.001
DRI	1.99 (1.61–2.38)	1.89 (1.56–2.22)	2.63 (2.43–2.87)	<0.0001
ET-DRI				
Height, cm	171 (165–180)	174 (167–180)	165 (160–175)	<0.0001
Highest AST, IU/L	44 (27–80)	48 (28–88)	33 (24–48)	<0.0001
Highest ALT. IU/L	31 (19–61)	34 (20–68)	20 (15–29)	<0.0001
Cause of death, n (%)				<0.0001
Trauma	225 (26.60)	205 (28.00)	20 (17.40)	
Cerebrovascular accident	468 (55.30)	379 (51.80)	89 (77.40)	
Cardiac arrest	36 (4.30)	34 (4.70)	2 (1.70)	
Hypoxia	72 (8.50)	69 (9.40)	3 (2.60)	
Others	45 (5.30)	44 (6.00)	1 (0.90)	
Procurement team, n (%)				0.00006
Local	437 (51.50)	357 (48.60)	80 (69.60)	
Regional	224 (26.40)	200 (27.20)	24 (20.90)	
Interregional	188 (22.10)	177 (24.10)	11 (9.60)	
Donor of thoracic organ(s)[d], n (%)	503 (59.60)	487 (66.80)	16 (13.90)	<0.0001
Cold ischemia time[e], h	7.88 (6.23–9.50)	7.94 (6.30–9.52)	7.32 (5.91–9.25)	0.10
Recipient				
Age, y	57 (49–64)	57 (48–64)	62 (55–68)	<0.0001
Sex, n (%)				0.92
Male	530 (62.40)	459 (62.50)	71 (61.70)	
Female	319 (37.60)	275 (37.50)	44 (38.30)	
BMI	26 (22–-29)	26 (23–29)	26 (23–29)	0.93
Laboratory MELD score	15 (11–23)	15 (11–23)	15 (10–23)	0.58
UNOS score, n (%)				0.13
ICU	102 (13.30)	88 (13.40)	12 (12.50)	
Ward	162 (21.10)	44 (21.90)	18 (16.10)	
Continuous care	226 (29.40)	183 (27.90)	43 (38.40)	
Home	279 (36.30)	242 (26.80)	37 (33.00)	
History of hypertension, n (%)	372 (43.90)	317 (43.30)	55 (47.80)	0.37
History of diabetes, n (%)	206 (24.30)	176 (24.00)	30 (26.10)	0.64
Renal replacement therapy, n (%)	29 (3.70)	26 (3.90)	3 (2.80)	0.79
Portal vein thrombosis, n (%)	69 (8.10)	58 (7.90)	11 (9.60)	0.58
Indication[f], n (%)				
Postethyl cirrhosis	107 (12.60)	148 (20.20)	27 (23.50)	0.46
Posthepatitis B cirrhosis	31 (3.70)	30 (4.10)	1 (0.90)	0.11
Posthepatitis C cirrhosis	41 (4.80)	40 (5.40)	1 (0.90)	0.03
NASH	44 (5.20)	36 (4.90)	8 (7.00)	0.52
Acute liver failure	50 (5.90)	47 (6.40)	3 (2.60)	0.14
Cholestatic diseases	92 (10.80)	81 (11.00)	11 (9.60)	0.75
Metabolic diseases	35 (4.10)	32 (4.40)	3 (2.60)	0.61
Budd-Chiari syndrome	14 (1.60)	13 (1.80)	1 (0.90)	0.71
Hepatic artery thrombosis	21 (2.50)	18 (2.50)	3 (2.60)	0.76

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TABLE 1. (Continued)

Characteristics	Overall (n = 849)	D < 70 (n = 734)	D ≥ 70 (n = 115)	P
Primary nonfunction	3 (0.40)	2 (0.30)	1 (0.90)	0.35
HCC	257 (30.27)	155 (21.20)	40 (34.80)	0.002
Others	154 (18.14)	132 (17.28)	16 (13.91)	
Retransplantation, n (%)	72 (8.48%)	64 (8.70)	8 (7.00)	0.72

[a] Total warm ischemia was defined in DCDs as the time between withdrawal of therapy and initiation of the cold flush in situ during organ procurement.

[b] Functional warm ischemia was defined in DCDs as the time between the drop of systemic blood pressure below 60 mmHg and initiation of cold flush in situ during organ procurement.

[c] Asystolic warm ischemia was defined in DCDs as the time between the occurrence of circulatory arrest and initiation of cold flush in situ during organ procurement.

[d] Donors were considered also donors of thoracic organ(s) when either heart, lungs, or heart and lungs were procured.

[e] Cold ischemia was defined as the time between the initiation of the cold flush in situ during organ procurement and the liver graft being placed in the recipient abdomen.

[f] Indications are not mutually exclusive.

Data are expressed as median (IQR) if not otherwise indicated.

ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; DCD, donation after circulatory death; DRI, Donor Risk Index; ET-DRI, Eurotransplant Donor Risk Index; HCC, hepatocellular carcinoma; ICU, intensive care unit; IQR, interquartile range; MELD, model for end-stage liver disease score; NASH, nonalcoholic steatohepatitis; UNOS, United Network for Organ Sharing.

higher DRI [D ≥ 70: 2.63 (2.43–2.87), D < 70: 1.89 (1.56–2.22); $P < 0.0001$], and were more frequently procured by our own team. DCDs were less common in D ≥ 70 (1.70%) than in D < 70 (13.60%, $P < 0.0001$). Predonation peak-transaminases were lower in D ≥ 70 (Table 1).

Recipients were aged 57 years (49–64 years) and were transplanted with a median laboratory MELD at the time of LT of 15 points (11–23). The two most frequent indications for transplantation were hepatocellular carcinoma (HCC; 30.27%) and postethyl cirrhosis (12.60%) (Table 1).

The median follow-up was 5.26 years (2.38–9.35 years). Patient survival was 90% at 1 year and 75.60% at 5 years after transplantation, whereas graft survival was 97.80% and 90% at 1 and 5 years after LT, respectively (Table 2).

Older Recipients Are at Higher Risk of Death Independently of Age Matching

Figure 1A depicts the interpolation plot for patient survival, in which divergent interpolation lines suggest the existence of significant interaction of age. In univariate analysis, recipient age was associated with higher risk of death after transplantation (HR, 1.04 per additional year; 95% confidence interval [CI], 1.02-1.05, $P < 0.0001$), whereas patient survival was not influenced by D ≥ 70 (HR, 5.96; 95% CI, 0.45-79.09; $P = 0.18$) or age interaction (HR, 0.97; 95% CI,: 0.93-1.01; $P = 0.17$).

The effect of older donors, recipient age, and age interaction on patient survival was further tested against other predictors in multivariate Cox regression (Table 3). Among the variables significantly associated with worse patient survival

TABLE 2.

Overview of postoperative outcomes after transplantation of the study population and after LT of grafts procured from donors younger or older than 70 years

Characteristics	Overall (n = 849)	D < 70 (n = 734)	D ≥ 70 (n = 115)	P
Outcomes				
Peak AST within 1st week, IU/L	669 (349–1313)	689 (361–1342)	568 (305–1148)	0.11
Peak ALT within 1st week, IU/L	678 (332–1234)	682 (347–1305)	626 (284–1003)	0.07
Primary nonfunction, n (%)	3 (0.40)	3 (0.40)	0 (0.00)	1.00
Early allograft dysfunction[a], n (%)	225 (26.50)	188 (25.60)	31 (27.00)	0.73
Acute kidney injury[b], n (%)	193 (23.00)	172 (23.80)	21 (18.30)	0.23
Hospitalization in ICU, d	4 (2–7)	4 (2–7)	4 (2–8)	0.32
Total hospitalization, d	20 (15–30)	20 (15–31)	21 (15–29)	0.22
Nonanastomotic biliary strictures[c], n (%)	119 (14.00)	109 (14.90)	10 (8.70)	0.08
Biliary leak, n (%)	41 (4.80)	39 (5.30)	2 (1.70)	0.11
Patient survival, %				
1 y	90.00	89.90	92.20	0.40
5 y	75.60	76.00	74.40	0.99
Death-censored graft survival, %				
1 y	97.80	93.90	98.20	0.06
5 y	90.00	89.70	91.50	0.27

[a] Early allograft dysfunction was defined as peak of AST or ALT >2000 IU/dL within the first week posttransplant, and/or bilirubin ≥10 mg/dL on day 7 post-LT, and/or INR ≥ 1.6 on day 7 post-LT.[25]

[b] Acute kidney injury was defined as at least 1.5-fold increase of posttransplant peak creatinine compared to baseline and calculated within the first week after LT.

[c] Nonanastomotic strictures were defined as clinically relevant narrowing of the intrahepatic bile duct confirmed radiologically in the absence of hepatic artery thrombosis.

Data are expressed as median (IQR) if not otherwise indicated.

ALT, alanine transferase; AST, aspartate transferase; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation.

in univariate analysis, the United Network for Organ Sharing score, transplantation for HCC, redo-LT, and cold ischemia remained independent predictors for patient's death in multivariate analysis. Donors in which thoracic organs were also donated (either heart, lungs, or heart and lungs) were associated with better survival after transplantation. D ≥ 70 did not affect patient survival (adjusted HR, 2.15; 95% CI, 0.14-34.26; $P = 0.59$). In contrast, recipient's age independently increased the risk of death after transplantation (adjusted HR, 1.03 per additional year; 95% CI, 1.02-1.05; $P < 0.0001$), but matching older donors to older recipients did not confer additional risk (adjusted HR of the interaction product, 0.98; 95% CI, 0.94-1.03, $P = 0.47$) (Table 3).

Results remained unchanged when introducing the era of the transplant in the multivariate model, which had no effect on patient survival (adjusted HR, 0.98; 95% CI, 0.93-1.03; $P = 0.35$).

After stratification per recipient age, the adjusted risk of patient's death was significant for patients aged 60 to 69 years (HR, 1.995; 95% CI, 1.40-2.85; $P < 0.0001$) and for recipients 70 years or older (HR, 2.001; 95% CI, 1.10-2.66; $P = 0.02$) (Figure 2; **SDC, Table S1,** http://links.lww.com/TXD/A197).

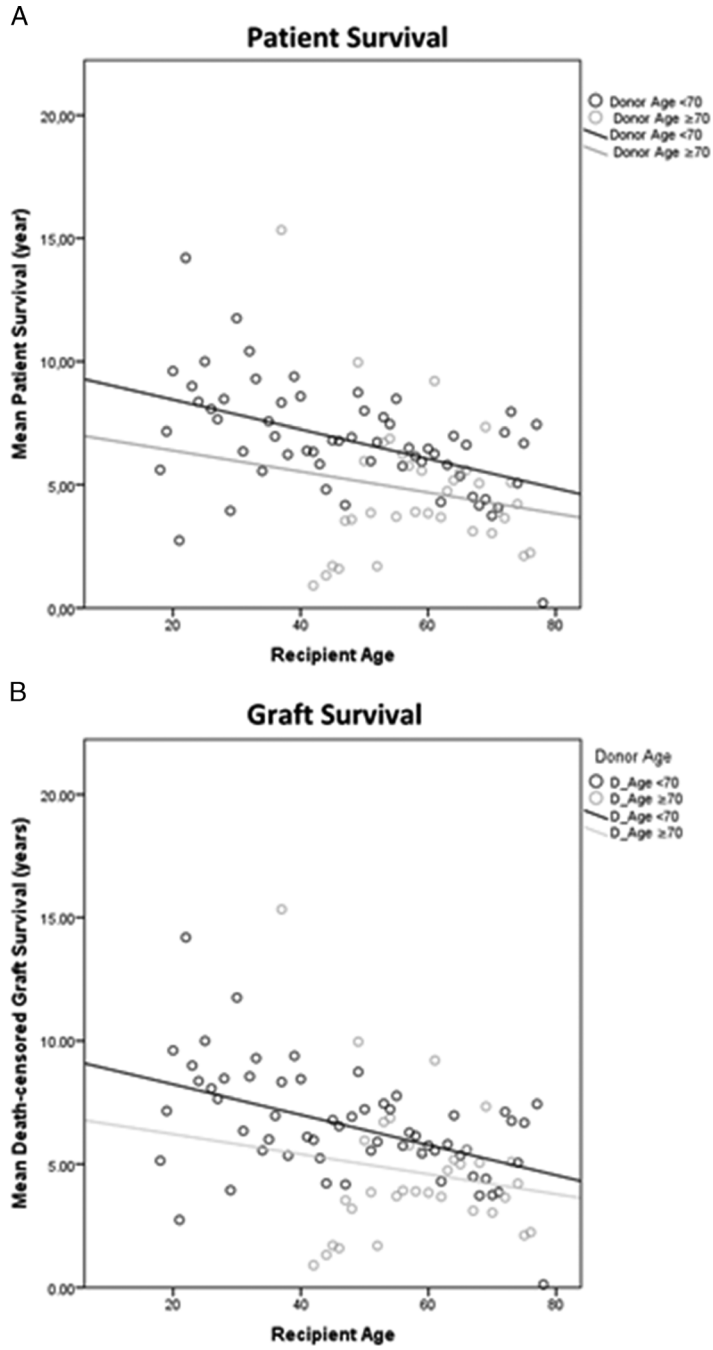

FIGURE 1. Interpolation plots depicting the interaction between recipient age and donors of younger (<70 years) or older age (≥70 years). The mean patient survival (A) and graft survival (B) are plotted per every age of recipients (x-axis), and dots represent either younger (in black) or older donors (in gray). The slope of the interpolation lines fitted separately for donors of different age corresponds to the effect of age interaction on the outcome measured, where equal slopes (or parallel lines) would represent a nonsignificant interaction.

The adjusted negative effect of recipient age on patient survival was significant already 6 months (HR, 1.06 per additional year; 95% CI, 1.03-1.09; P = 0.00008) and 1 year after transplantation (HR, 1.06 per additional; 95% CI, 1.03-1.09, P = 0.00003) (**SDC, Table S2,** http://links.lww.com/TXD/A198).

Five-year patient survival in recipients 70 years or older transplanted with grafts from D ≥ 70 years was 72.60%. The absolute difference on 5-year patient survival of recipients transplanted with grafts procured from younger or older donors was similar between recipients younger than 60 years (7%) or 70 years or older (8%, P = 0.53), further confirming the absence of significant interaction of donor and recipient age (Figure 3).

Older Recipients Are Not at Higher Risk of Graft Loss

Figure 1B depicts the interpolation plot for graft survival, in which divergent interpolation lines suggested the existence of significant interaction of age. However, in univariate analysis, the risk of graft loss was not associated with recipient age (HR, 1.02 per additional year; 95% CI, 0.997-1.04; P = 0.09), D ≥ 70 (HR, 1.56; 95% CI, 0.11-222.57; P = 0.86), or age interaction (HR, 0.99; 95% CI, 0.91-1.07; P = 0.75).

The effect of older donors, recipient age, and age interaction on graft survival was further tested against other predictors in multivariate Cox regression (Table 3). Among the predictors associated with graft loss in univariate analysis, retransplantation and recipient with a history of diabetes remained significant predictors in multivariate regression, whereas the risk of graft loss was not influenced by D ≥ 70 (adjusted HR, 1.09; 95% CI, 0.01-88.01; P = 0.97), recipient age (adjusted HR, 1.02; 95% CI, 0.996-1.04; P = 0.11), or age interaction (adjusted HR, 0.993; 95% CI, 0.92-1.07; P = 0.85) (Table 3).

Older Recipients Exhibited a Low-risk Profile Pretransplantation

To identify predictors of worse outcomes in older recipients, donor and recipient demographics, transplant characteristics, and postoperative complications were compared post hoc between the age group showing the best outcomes, that is, recipients younger than 60 years (R < 60, n = 514 LT), and the 2 age groups showing a significantly increased risk of death after LT, that is, recipients of 60 to 69 years (R60-69, n = 289 LT) and recipients 70 years or older (R ≥ 70, n = 46 LT).

Both R60-69 and R ≥ 70 were transplanted with grafts procured from older donors. Cold ischemia was significantly shorter in both R60-69 (7.64 hours [6.02–9.34], P = 0.002) and R ≥ 70 (6.55 hours [5.14–8.27], P = 0.002) than R < 60 (8.03 hours [6.45–9.67]). DCD grafts were more frequently transplanted in R60-69 (17.30%) than R < 60 (9.30%, P = 0.004) (Table 4).

Older recipients had a more stable disease when compared to R < 60. Indeed, both R60-69 and R ≥ 70 were transplanted more frequently for HCC within Milan criteria,[26] had lower laboratory MELD score at the time of LT [R < 60: 16 (11–25); versus R60-69: 14 (11–21), P = 0.004; versus R ≥ 70: 12 (8–25), P = 0.004], and were less frequently admitted to the intensive care at the time of organ offer (R < 60: 16.90%; versus R60-69: 8.40%, P = 0.02; versus R ≥ 70: 4.50%, P = 0.06). Additionally, R60-69 needed renal replacement therapy before LT less frequently than R < 60 (Table 4).

There was no difference between groups in the incidence of primary nonfunction, early allograft dysfunction,[25] acute kidney injury, and nonanastomotic biliary strictures. R60-69 and R ≥ 70 showed higher frequencies of diabetes than R < 60, and R60-69 showed a higher frequency of arterial hypertension. Nevertheless, there was no difference in death rate caused by either cardiac or cerebrovascular events, nor a more prevalent cause of death in R60-69 or R ≥ 70 could be identified (Table 4).

An explorative analysis of risk factors for patient death in older recipients (R ≥ 60, n = 335 LT) identified hospitalization in the intensive care at the time of organ offer as the only predictor of poor patient survival (adjusted HR, 2.91; 95% CI, 1.53-5.52; P = 0.001), whereas D ≥ 70 did not influence the risk of death after LT (adjusted HR, 0.66; 95% CI, 0.39-1.11; P = 0.12) (**SDC, Table S3,** http://links.lww.com/TXD/A199).

DISCUSSION

This single-center retrospective analysis of 849 deceased-donor LTs shows that matching older donor livers to older liver transplant recipients does not affect long-term outcomes because there was no synergic amplification of age-related risks when other risk factors are minimized. Advanced recipient age was an independent predictor of patient's death but did not influence the risk of graft loss. Lastly, older donors were not associated with worse outcomes, in contrast with results from large registry studies[12,13] but in line with previously published single-center analyses.[7,14-17]

Previous studies have assessed the risk of death/graft loss of transplants with different combinations of donor and recipient age.[27-29] In a large retrospective analysis, Chapman et al[27] did not observe any difference in patient and graft survival in LTs matched or mismatched per age, but the actual interaction product of donor and recipient age was not considered. Using a similar approach, Pagano et al[28] observed worse graft and patient survival in multivariate analysis in age mismatched LT, but the absence of correction for donor and recipient age, the small sample size, and small number of events do not allow to draw any solid conclusion on the relevance of age interaction. Very recently, Bittermann and Goldberg[29] observed in a large-registry analysis that the detrimental effect of increasing donor age was greater in younger (<40 years) than older recipients (≥60 years), and younger recipients transplanted with older grafts (≥60 years) had significantly worse outcomes in multivariate analysis. These results led the authors to conclude that donor and recipient age have a significant synergic interaction influencing outcomes after LT, although it is not clear if recipient age was a risk factor for death and if analyses were adjusted for donor age. In the absence of such adjustment, a higher risk of death/graft loss in transplants in which older grafts are used might reflect the detrimental effect of advanced donor age rather than indicating a significant effect of true interaction of age. Furthermore, in the study by Bitterman and Goldberg, donors younger than 40 years constituted almost 50% of the donor pool, and only 17% were older donors (≥60 years), whereas in our cohort, they accounted for 20% and 30%

TABLE 3.

Univariate and multivariate Cox regression for patient and death-censored graft survival

	Patient survival				Graft survival			
	Univariate		Multivariate[a]		Univariate		Multivariate[b]	
Characteristics	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Donor age ≥70 y (reference: no)	5.96 (0.45–79.09)	0.38	2.15 (0.14–34.26)	0.59	1.56 (0.11–222.57)	0.86	1.09 (0.01–88.01)	0.97
Recipient age, y	1.04 (1.02–1.05)	<0.0001	1.03 (1.02–1.05)	<0.0001	1.02 (0.997–1.04)	0.09	1.02 (0.996–1.04)	0.11
Age interaction	0.97 (0.93–1.01)	0.17	0.98 (0.94–1.03)	0.47	0.99 (0.91–1.07)	0.75	0.993 (0.92–1.07)	0.85
Donor sex (reference: male)	0.98 (0.77–1.25)	0.88	—	—	1.25 (0.82–1.90)	0.29	—	—
DCD (reference: no)	1.03 (0.67–1.61)	0.89	—	—	1.65 (0.91–2.99)	0.10	—	—
Total warm ischemia[c], min	1.003 (0.98–1.02)	0.79	—	—	1.03 (1.002–1.05)	0.04	—	—
Functional warm ischemia[d], min	1 (0.97–1.03)	0.94	—	—	1.04 (1.002–1.07)	0.04	—	—
Asystolic warm ischemia[e], min	0.99 (0.95–1.04)	0.75	—	—	1.05 (0.99–1.12)	0.10	—	—
Donor ICU hospitalization, d	1 (0.99–1.01)	0.43	—	—	0.99 (0.97–1.02)	0.60	—	—
Donor BMI	1.01 (0.98–1.1)	0.5	—	—	1.00 (0.94–1.07)	1.00	—	—
Donor height, cm	0.997 (0.98–1.01)	0.70	—	—	0.997 (0.97–1.02)	0.78	—	—
Donor highest AST, IU/L	1 (1–1.002)	0.14	—	—	1 (0.99–1.001)	018	—	—
Donor highest ALT, IU/L	1 (0.998–1.001)	0.58	—	—	1.00 (0.99–1.001)	0.14	—	—
Donor cause of death (reference: others)	1	0.04	—	—	1	0.13	—	—
Trauma	0.58 (0.35–0.95)	0.03	—	—	0.37 (0.16–0.85)	0.02	—	—
Cerebrovascular accident	0.68 (0.42–1.09)	0.11	—	—	0.56 (0.27–1.19)	0.13	—	—
Cardiac arrest	0.84 (0.38–1.84)	0.66	—	—	0.94 (0.31–2.87)	0.94	—	—
Hypoxia	0.70 (0.38–1.32)	0.27	—	—	0.59 (0.21–1.62)	0.59	—	—
Procurement team (reference: local)	1	0.65	—	—	1	0.53	—	—
Regional	1.01 (0.75–1.35)	0.96	—	—	1.31 (0.80–2.15)	0.28	—	—
Interregional	1.16 (0.86–1.56)	0.34	—	—	1.22 (0.71–2.08)	0.47	—	—
Donor of thoracic organ(s)[f] (reference: no)	0.68 (0.53–0.86)	0.001	0.59 (0.44–0.79)	<0.0001	0.89 (0.58–1.35)	0.57	—	—
Cold ischemia time[g], h	1.07 (1.01–1.13)	0.02	1.2 (1.03–1.17)	0.003	1.08 (0.98–1.19)	0.11	—	—
Duration of transplantation, h	1.07 (0.99–1.15)	0.1	—	—	1.09 (0.97–1.24)	0.16	—	—
Recipient sex (reference: male)	0.79 (0.61–1.02)	0.07	—	—	1.05 (0.68–1.60)	0.83	—	—
Recipient BMI	1.01 (0.98–1.03)	0.66	—	—	1.00 (0.95–1.04)	0.81	—	—
Recipient laboratory MELD score (point)	1.02 (1.01–1.03)	0.006	—	—	1.006 (0.98–1.03)	0.64	—	—
Recipient UNOS score (reference: home)	1	0.0001	1	<0.0001	1	0.70	—	—
ICU	2.47 (1.65–3.7)	<0.0001	3.44 (2.24–5.30)	<0.0001	0.81 (0.35–1.86)	0.70	—	—
Ward	1.70 (1.16–2.49)	0.007	1.88 (1.25–2.82)	0.002	1.30 (0.73–2.30)	0.70	—	—
Continuous care	1.56 (1.12–2.2)	0.01	1.42 (1.004–2.02)	0.048	1.04 (0.61–1.78)	0.88	—	—
Recipient history of arterial hypertension (reference: no)	1.16 (0.91–1.48)	0.23	—	—	1.10 (0.70–1.60)	0.74	—	—
Recipient history of diabetes (reference: no)	1.30 (0.99–1.71)	0.06	—	—	1,93 (1.12–3.33)	0.02	1.68 (0.96–2.94)	0.07
Recipient renal replacement therapy (reference: no)	1.64 (0.92–2.92)	0.10	—	—	1.95 (0.79–4.80)	0.15	—	—
Recipient portal vein thrombosis (reference: no)	0.69 (0.47–1.01)	0.06	—	—	1.20 (0.58–2.50)	0.62	—	—
Indication								
Post-ethyl cirrhosis	0.89 (0.66–1.2)	0.47	—	—	0.90 (0.53–1.53)	0.70	—	—
Post-hepatitis B cirrhosis	0.91 (0.53–1.63)	0.75	—	—	0.84 (0.26–2.66)	0.77	—	—
Post-hepatitis C cirrhosis	0.82 (0.47–1.43)	0.47	—	—	0.60 (0.19–1.91)	0.39	—	—
NASH	0.82 (0.44–1.60)	0.55	—	—	0.96 (0.35–2.62)	0.93	—	—
Acute liver failure	0.78 (0.44–1.39)	0.40	—	—	0.19 (0.03–1.37)	0.10	—	—
Cholestatic diseases	0.65 (0.42–1.02)	0.06	—	—	1.41 (0.78–2.55)	0.25	—	—
Metabolic diseases	1.10 (0.63–1.90)	0.76	—	—	1.10 (0.40–2.99)	0.86	—	—
Budd-Chiari syndrome	0.93 (0.35–2.50)	0.90	—	—	1.45 (0.36–5.88)	0.61	—	—
Hepatic artery thrombosis	1.60 (0.80–3.30)	0.18	—	—	1.76 (0.56–5.76)	0.34	—	—
Primary nonfunction	3.32 (0.80–13.40)	0.09	—	—	0.05 (0.00–51.00)	0.75	—	—
HCC	1.52 (1.19–1.95)	0.001	1.74 (1.26–2.40)	0.001	0.98 (0.62–1.56)	0.93	—	—
Retransplantation (no. transplant)	1.53 (1.13–2.10)	0.006	1.74 (1.25–2.43)	0.001	1.73 (1.08–2.76)	0.02	1.65 (1.01–2.71)	0.047

[a] Results from a multivariate model predicting patient survival based on 224 events in 763 subjects. Covariates were retained in the multivariate analysis after backwards stepwise selection; donor ≥70 years, recipient age, and their interaction product were introduced in the model irrespectively from their performance at univariate analysis.

[b] Results from a multivariate model predicting death-censored graft survival based on 87 events in 838 subjects. Covariates were retained in the multivariate analysis after backwards stepwise selection; donor ≥70 years, recipient age, and their interaction product were introduced in the model irrespectively from their performance at univariate analysis and model reduction.

[c] Total warm ischemia was defined as the time between withdrawal of therapy and initiation of the cold flush in situ during organ procurement.

[d] Functional warm ischemia was defined as the time between the drop of systemic blood pressure below 60 mm Hg and initiation of cold flush in situ during organ procurement.

[e] Asystolic warm ischemia was defined as the time between the occurrence of circulatory arrest and initiation of cold flush in situ during organ procurement.

[f] Donors were considered also donors of thoracic organ(s) when either heart, lungs, or heart and lungs were procured.

[g] Cold ischemia was defined as the time between the initiation of the cold flush in situ during organ procurement and the liver graft being placed in the recipient abdomen.

ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; ICU, intensive care unit; MELD, model for end-stage liver disease score; NASH, nonalcoholic steatohepatitis; UNOS, United Network for Organ Sharing.

of LTs, respectively. Such difference in the donor pool resulted in a more stringent selection of older donors in our population (shorter hospitalization, small number of DCDs with shorter warm ischemia time, and more frequent local procurement/allocation), making direct comparison of results difficult. When clustering the transplants according to different age matches similarly to the study by Bittermann and Goldberg, our results did not change: older recipients were at higher risk of death independently from various combinations of donor and recipient age (**SDC, Table S4,** http://links.lww.com/TXD/A200).

Despite the fact that older patients were at higher risk of death, our adjusted analysis showed that LT in older recipients achieves 5-year patient survival more than 80% (Figure 2), which is in line with the best achievable results identified in a recent benchmark analysis in LT.[30] Although the benefit in years-gain after LT should be quantified based on the expected survival on the waiting list rather than on the absolute value of post-LT survival,[6] our data justify the conclusion that LT in older candidates can achieve excellent results. Indeed, their remarkable 80% patient survival at 5 years after transplantation is likely to be superior to the expected 5-year survival of age peers suffering from end-stage liver disease still on the waiting list and is substantially greater than the 60% cutoff generally accepted as threshold to overcome the harm of a futile transplant.[31] Therefore, older candidates should not be excluded from LT a priori based on "chronological" age; rather, a more comprehensive risk stratification and evaluation of their health status should guide the decision for listing.

Older recipients exhibited a pretransplant profile, suggesting a high likelihood of success (they were transplanted mostly for HCC within Milan criteria,[26] with a low laboratory MELD score, and short cold ischemia), yet they had higher risk of death. Although the effect of recipient age remained largely unexplained in our analyses, it did not seem related to graft failure since recipient age did not influence death-censored graft survival. We do acknowledge, however, that our analysis may have been less precise for this outcome due to the small number of graft loss observed in our cohort (n = 87). Lastly, the adjusted effect of recipient age on patient's death was significant as early as 6 months after LT; therefore, the negative effect of recipient age cannot be related solely to the expected inferior longevity of older recipients.

Cardiovascular diseases have been associated with mortality after solid organ transplantation in older patients[2] but did not seem to play a major role in our series. The incidence of the most common risk factors for cardiovascular events was similar in older and younger recipients, with the exception of diabetes mellitus. We could not evaluate the incidence of risk factors for metabolic syndrome,[32] which is closely related to the risk of both cardiac and cerebrovascular events.[33,34] Nevertheless, patients of advanced age in this series underwent full cardiological assessment (including MIBI myocardial perfusion image test or coronary angiography when appropriate) on single-case basis before listing, and we did not observe higher incidence of fatal cardiac or cerebrovascular accidents in older recipients.

Recipient's age may be a surrogate marker of other factor(s) not adequately captured in our analysis. For instance, recipient's global fitness and functional reserves rather than "chronological age" may determine the increased risk of death observed in older recipients. "Physical frailty" is a syndrome of the geriatric population characterized by increased vulnerability to external stressors and predisposes to adverse outcomes and death.[35] The loss of muscular mass, the impairment of muscular performance, and the malnutrition almost invariably associated with liver cirrhosis are also hallmarks of the frailty syndrome.[36] The recently developed "liver frailty index," which evaluates the extrahepatic manifestation of cirrhosis (nutritional status, extremity strength, and neuromotor function) with 3 straightforward performance tests (grip strength, chair stands, and balance),[37] quantifies patient's functional reserves, predicts waitlist mortality better than MELD,[37] and, more importantly, correlates with post-LT mortality in preliminary studies.[38,39] We hypothesize that older recipients in our cohort suffered from unknown degrees of physical frailty, which, in turn, might have predisposed them to worse outcomes despite the favorable pretransplant profile. Indeed, an explorative analysis identified hospitalization in intensive care as the only predictors of patient's death in recipients 60 years or older (**SDC, Table S3,** http://links.lww.com/TXD/A199), which may also reflect the more fragile phenotype of these patients. To date, the pretransplant assessment of (older) candidates suffering from end-stage liver disease focuses mostly on quantifying their probability to survive surgery mainly by stratifying their risk of cardiovascular events.[2] The systematic and objective quantification of functional reserves of older transplant candidates might allow us not only to improve risk stratification and selection of older recipients but also to prompt targeted rehabilitation therapies aiming to improve their global fitness and endurance before LT, ultimately improving results in the long-term.

Our study is a single-center retrospective analysis in which donors ≥70 years with a low-risk profile were selected and, as such, donor-related risk factors as donor type and warm ischemia were not associated with worse outcomes. It may be argued that an unequal distribution between younger and older DCD donors in our cohort may confound our findings on the safety of using well-selected older donors. However, DCD grafts of 50 or older or 60 years or older can be safely used without impact on long-term graft survival, provided that other risk factors are minimized.[40,41] We repeated our analysis excluding DCD liver transplants, and the results did not change (**SDC, Table S5,** http://links.lww.com/TXD/A201).

The low median laboratory MELD of the transplants included in our study (15 [11–23]) may also be considered as a limitation to the generalizability of our results. However, de Boer et al analyzing the utilization of older grafts for LTs performed within the Eurotransplant region in the same period considered in our study (2000–2015) reported a similar median laboratory MELD score of 16 points (11–27). Therefore, we believe that the LTs included in our study are a fair representation of the current practice in LTs in the majority of Europe.

Older recipients had more stable disease than younger patients, and the intrinsic effect of recipient's age after adjustment for other predictors in our analysis might have been underestimated. Additionally, the effects of other factors, such as the severity of hepatic steatosis and physical deconditioning and malnutrition, were not considered in this study, and we might have overestimated the effect of recipient's age on long-term outcomes. Therefore, some degree of caution is warranted while interpreting our results.

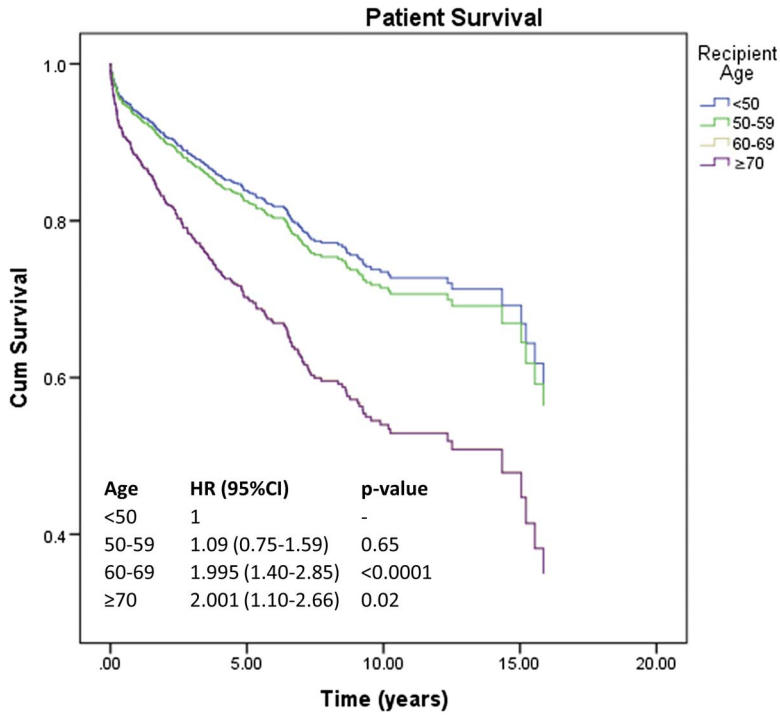

FIGURE 2. Adjusted patient survival according to different subgroups of recipient age. Survival curves are plotted based on HR from a multivariable Cox regression predicting the risk of patient's death and adjusted for D ≥ 70, donor cause of death, DRI, cold ischemia time, recipient laboratory MELD score, recipient UNOS score, transplantation for HCC, and retransplantation (**SDC, Table S1,** http://links.lww.com/TXD/A197). CI, confidence interval; DRI, Donor Risk Index; HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing.

We acknowledge that the experience of our center with older donors[17] may partially influence the good results obtained with this type of graft and that carefully selecting and matching older donors and recipients may limit the generalizability of our study. Nonetheless, this strategy reflects a real-life practice aiming to use older donor grafts without jeopardizing outcomes by minimizing other risk factors well known to influence long-term results. For example, we preferably but not exclusively accept D ≥ 70 with normal liver function tests predonation, a short intensive care stay (≤3 days), procured by our own team allowing us to minimize the duration of cold ischemia. Similar observations have been made in 2 registry analyses. Indeed, Halazun et al observed that adjusting for cold ischemia (>8 hours) and some recipient characteristics (>60 years, hepatitis C, pretransplant hospitalization, retransplantation, previous abdominal surgery) resulted in similar patient survival after transplantation of ≥70 and <70 years donor grafts.[20] Similar to our findings, Segev et al identified a subgroup of "low-risk" recipients (nonurgent first transplant for HCC or indications other than hepatitis C, >45 years, cold ischemia <8 hours) in which posttransplant outcomes were not

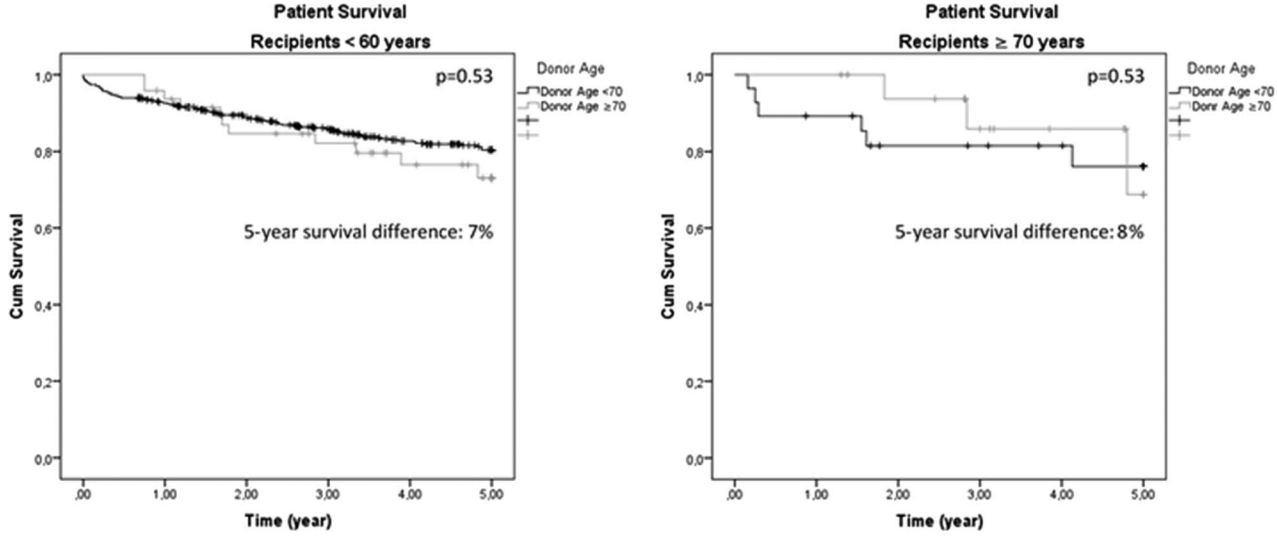

FIGURE 3. Unadjusted 5-year patient survival of recipients younger than 60 years (A) and ≥70 years (B) stratified per donor's age. The absolute difference in 5-year survival between the 2 groups of recipients was comparable, showing no relevant interaction of donor and recipient age.

TABLE 4.

Comparison of donor and recipient demographics and posttransplant results between recipients that achieved the best patient survival (R < 60 years) and 2 age groups at higher risk of worse outcomes (R60-69 years and R ≥ 70 years)

Characteristics	R < 60 (n = 514)	R60-69 (n = 289)	P[a]	R ≥ 70 (n = 46)	P[b]
Donor					
Age, y	49 (39–59)	56 (44–65)	<0.0001	63 (50–77)	<0.0001
Sex, n (%)			1		1
Male	291 (56.60)	156 (54.00)		25 (54.30)	
Female	223 (43.40)	133 (46.00)		21 (45.70)	
DCD, n (%)	48 (9.3)	50 (17.30)	0.004	4 (8.7)	1
Total warm ischemia[c], min	19 (15–26)	19 (14–24)	0.62	13 (11–20)	0.15
Functional warm ischemia[d], min	10 (6–17)	10 (5–15)	0.53	8 (4–11)	0.35
Asystolic warm ischemia[e], min	9 (8–10)	8 (7–10)	0.23	8 (4–9)	0.32
Hospitalization in ICU, d	2 (1–5)	2 (1–6)	0.11	2 (1–3)	0.11
BMI	24 (22–26)	24 (22–26)	1	24 (22–26)	1
DRI	1.9 (1.56–2.26)	2.14 (1.71–2.56)	0.0004	2.29 (1.86–2.78)	0.0004
ET-DRI					
Height, cm	173 (165–180)	170 (165–180)	0.08	170 (165–180)	0.68
Highest AST, IU/L	44 (27–79)	46 (26–85)	1	39 (27–74)	1
Highest ALT, IU/L	31 (19–60)	31 (19–66)	0.48	24 (17–50)	0.48
Cause of death, n (%)			0.82		0.66
Trauma	148 (28.80)	68 (23.60)		9 (20.50)	
Cerebrovascular accident	277 (53.90)	165 (57.30)		26 (59.10)	
Cardiac arrest	18 (3.50)	14 (4.90)		4 (9.10)	
Hypoxia	46 (8.90)	23 (8.00)		3 (6.80)	
Others	25 (4.90)	18 (6.20)		2 (4.50)	
Procurement team, n (%)			0.11		0.28
Local	246 (47.90)	163 (56.40)		28 (60.90)	
Regional	141 (27.40)	71 (24.60)		12 (26.10)	
Interregional	127 (24.70)	55 (19.00)		6 (13.00)	
Donor of thoracic organ(s)[f], n (%)	329 (64.50)	155 (53.80)	0.006	19 (41.30)	0.004
Cold ischemia time[g], h	8.03 (6.45–9.67)	7.64 (6.02–9.34)	0.002	6.55 (5.14–8.27)	0.002
Duration of transplantation, h	5.67 (4.75–6.90)	5.64 (4.58–6.75)	0.62	5.42 (4.64–6.58)	1
Recipient					
Age, y	51 (43–56)	65 (63–68)	<0.0001	73 (72–76)	<0.0001
Sex, n (%)			0.02		1
Male	304 (59.10)	197 (68.00)		29 (63.00)	
Female	210 (40.90)	92 (32.00)		17 (37.00)	
BMI	25 (22–29)	27 (24–30)	0.77	25 (22–27)	1
Laboratory MELD score	16 (11–25)	14 (11–21)	0.004	12 (8–25)	0.004
UNOS score, n (%)			0.02		0.16
ICU	78 (16.90)	22 (8.40)		2 (4.50)	
Ward	98 (21.20)	57 (21.70)		7 (15.90)	
Continuous care	126 (27.30)	86 (32.70)		14 (31.80)	
Home	160 (27.30)	98 (37.20)		21 (47.70)	
History of hypertension, n (%)	204 (39.80)	148 (51.40)	0.004	20 (43.50)	1
History of diabetes, n (%)	92 (17.90)	98 (34.00)	<0.0001	16 (34.80)	0.02
Renal replacement therapy, n (%)	25 (5.30)	4 (1.50)	0.02	0 (0.00)	0.52
Portal vein thrombosis, n (%)	33 (6.40)	31 (10.70)	0.08	5 (10.90)	0.46
Indication[h], n (%)					
Post-ethyl cirrhosis	116 (22.60)	58 (20.00)	0.84	1 (2.20)	0.0006
Post-hepatitis B cirrhosis	22 (4.30)	8 (2.80)	0.68	1 (2.20)	1
Post-hepatitis C cirrhosis	26 (5.10)	14 (4.80)	1	1 (2.20)	1
NASH	21 (4.10)	21 (7.30)	0.14	2 (4.30)	1
HCC	87 (17.00)	89 (30.80)	<0.0001	19 (41.30)	0.0006
Acute liver failure	40 (7.80)	9 (3.10)	0.02	1 (2.20)	0.48
Cholestatic diseases	66 (12.80)	19 (6.60)	0.01	7 (15.20)	1.00
Metabolic diseases	25 (4.90)	9 (3.10)	0.56	1 (2.20)	0.71
Budd-Chiari syndrome	14 (2.70)	0 (0.00)	0.006	0 (0.00)	1.00

Continued next page

TABLE 4. (Continued)

Characteristics	R < 60 (n = 514)	R60-69 (n = 289)	P[a]	R ≥ 70 (n = 46)	P[b]
Hepatic artery thrombosis	15 (2.90)	4 (1.40)	0.46	2 (4.30)	0.64
Primary nonfunction	2 (0.40)	1 (0.30)	1.00	0 (0.00)	1.00
Retransplantation, n (%)	44 (8.56)	22 (7.61)	1	6 (13.04)	1
Outcomes					
Peak AST within 1st week, IU/L	695 (375–1433)	632 (338–1263)	0.16	520 (275–1010)	0.12
Peak ALT within 1st week, IU/L	725 (360–1400)	612 (303–1063)	0.004	518 (303–845)	0.02
Primary nonfunction, n (%)	1 (0.20)	2 (0.70)	0.30	0 (0.00)	1
Early allograft dysfunction[i], n (%)	133 (25.90)	75 (26.00)	1	11 (23.90)	1
Acute kidney injury[j], n (%)	110 (21.60)	77 (27.20)	0.08	6 (13.00)	0.38
Hospitalization in ICU, d	4 (2–7)	4 (2–7)	0.21	3 (2–5)	0.38
Total hospitalization, d	19 (14–29)	21 (15–33)	0.01	19 (13–29)	1
Nonanastomotic biliary strictures[k], n (%)	75 (14.60)	39 (13.50)	0.75	5 (10.90)	1
Biliary leak, n (%)	21 (4.10)	16 (5.60)	0.38	4 (8.70)	0.28
Cause of death, n (%)					
Sepsis	22 (4.28)	19 (6.57)	0.30	4 (8.70)	0.34
De novo tumors	27 (5.25)	25 (8.65)	0.12	2 (4.35)	1
Cardiovascular event	9 (1,75)	7 (2.42)	1	0 (0.0)	1
Cerebrovascular event	5 (0.97)	5 (1.73)	0.70	1 (2.17)	0.88
Recurrence HCC	14 (2.72)	10 (3.46)	1	2 (4.35)	1
Recurrence hepatic disease	13 (2.53)	6 (2.08)	1	1 (2.17)	1
Nonanastomotic biliary strictures	1 (0.20)	6 (2.08)	0.04	0 (0.00)	0.26
Others	38 (7.39)	23 (7.96)	0.26	5 (10.87)	1
Unknown	6 (1.20)	11 (3.81)	0.46	0 (0.00)	1

[a] R < 60 vs R 60-69; level of significance after Bonferroni correction for multiple testing.

[b] R < 60 vs R ≥ 70; level of significance after Bonferroni correction for multiple testing.

[c] Total warm ischemia was defined as the time between withdrawal of therapy and initiation of the cold flush in situ during organ procurement.

[d] Functional warm ischemia was defined as the time between the drop of systemic blood pressure below 60 mmHg and initiation of cold flush in situ during organ procurement.

[e] Asystolic warm ischemia was defined as the time between the occurrence of circulatory arrest and initiation of cold flush in situ during organ procurement.

[f] Donors were considered also donors of thoracic organ(s) when either heart, lungs, or heart and lungs were procured.

[g] Cold ischemia was defined as the time between the initiation of the cold flush in situ during organ procurement and the liver graft being placed in the recipient abdomen.

[h] Indications are not mutually exclusive.

[i] Early allograft dysfunction was defined as peak of AST or ALT >2000 IU/dL within the first week posttransplant, and/or bilirubin ≥10 mg/dL on day 7 post-LT, and/or INR ≥1.6 on day 7 post-LT.[25]

[j] Acute kidney injury was defined as at least 1.5-fold increase of posttransplant peak creatinine compared to baseline and calculated within the first week after LT.

[k] Nonanastomotic strictures were defined as clinically relevant narrowing of the intrahepatic bile duct confirmed radiologically in the absence of hepatic artery thrombosis.

Data are expressed as median (IQR) if not otherwise indicated.

ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; DCD, donation after circulatory death; DRI, Donor Risk Index; ET-DRI, Eurotransplant Donor Risk Index; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; UNOS, United Network for Organ Sharing.

affected by older donor age.[5] Such findings were recently confirmed in a Eurotransplant registry analysis.[42] However, our results also highlight that older "low-risk" recipients have a considerable increased risk of death independent of age matching, stressing the emergent need to improve the preoperative risk stratification of these patients.

In conclusion, older livers can be safely used in older recipients without jeopardizing graft and patient survival if other risk factors are minimized. However, carefully selected older recipients have higher risk of death after LT, although their 5-year survival can be excellent. The preoperative evaluation of older liver transplant candidates should include the objective assessment of their global fitness and functional reserves because it might improve stratification of risks, allow targeted pretransplant rehabilitation, and ultimately further ameliorate long-term outcomes.

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