Impact of donor age on liver transplant outcomes in patients with hepatocellular carcinoma: Analysis of the SRTTR dataset

Jie Zhou

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University, School of Medicine

Zhichao Huang

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University, School of Medicine

Zheng Chen

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University, School of Medicine

Fangshen Xu

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University, School of Medicine

Rongliang Tong

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University, School of Medicine

Shusen Zheng (✉ shusenzheng@zju.edu.cn)

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University, School of Medicine

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Abstract

Background: Donor age is an important predictor for liver transplant recipients. Studies have not fully explored its impact on transplant outcomes in hepatocellular carcinoma (HCC) patients, and its involvement in tumor recurrence has not yet been fully explored.

Methods: HCC recipients who received liver transplants from 2010–2017 from the Scientific Registry of Transplant Recipients database were included. The recipients were divided into four groups on the basis of donor age: I (18–34 years), II (35–49 years), III (50–64 years), and IV (≥ 65 years). Transplant outcomes, including the overall survival (OS), tumor recurrence, and risks, were evaluated.

Results: A total of 13,276 HCC recipients were included in this study. The OS was significantly different among four groups. The best 5-year survival was 76.0% in group I, followed by 73.5% in group II, 72.8% in group III, and 69.2% in group IV ($P < 0.001$). Donor age, recipient age, recipient race, recipient serum creatinine, sum of tumor diameter, and α -fetoprotein (AFP) were found to be independent predictors of OS. In subgroup analysis, OS was significantly different in hepatitis C virus (HCV) recipients, but there was no significant difference between recipients with hepatitis B virus (HBV), alcoholic diseases and nonalcoholic steatohepatitis (NASH). The cumulative tumor recurrence rates and the mean time to recurrence post-transplantation did not differ among the four groups.

Conclusions: Older donor age was associated with decreased OS in HCC recipients, but it was not correlated with post-transplant tumor recurrence. Older donor age also had different effects in patients with different underlying liver diseases

Background

Hepatocellular carcinoma (HCC) accounts for more than 700,000 deaths annually, which is the fourth most common cancer-related death worldwide, and its incidence continues to increase [1-3]. Only a minority of HCC patients are feasible candidates for hepatectomy, which is largely because most patients were diagnosed at the advanced stages and often presented with poor liver function. Tumor recurrence after hepatectomy remains high. Liver transplantation is the only curative option to treat HCC patients. However, due to the disparity between the large number of candidates on the waiting list and the relative shortage of donor livers, many patients dropped out of the waiting list before they could match with a feasible donor graft.

To expand the donor pool, marginal donor usage has been suggested. Elderly donors are the most commonly used marginal donors. The number of elderly liver donors is increasing due to the ageing population [4]. However, there are concerns regarding the application of old liver grafts in clinical practice, as liver tissue from older donors would undergo a series of morphological and physiological changes, making it more vulnerable to ischemia–reperfusion injury (IRI) during transplantation [5]. These pathophysiological changes would then lead to adverse effects on recipient prognosis. Feng et al. evaluated the effects of donor-related variables on transplant outcomes and demonstrated that donor age was an independent predictor of overall survival (OS) in the recipient [6]. They also created a model known as the donor risk index (DRI) to stratify the risk of transplant outcomes based on a series of donor variables. However, with an increasing application of liver grafts from elderly donors and improved surgical techniques and perioperative managements, a number of

studies have recently shown the safety of use of old donor livers, even using livers from octogenarian donors [7].

Despite this, the effect of donor age on liver transplantation specifically in HCC has not yet been fully elucidated. Tumor recurrence after liver transplantation is an important concern in such patients. We have already established recipient selection criteria so that donors are matched with the most feasible patients to obtain favorable transplant outcomes [8,9]. However, currently, practical experience with regard to how donor variables such as donor age could affect transplant outcomes, including tumor recurrence, in HCC patients is scarce. Although previous studies have demonstrated the association of donation after cardiac death (DCD) and post-transplant mortality in HCC recipients, they have not focused on tumor recurrence [10]. Orci et al. previously evaluated the effect of donor characteristics on tumor recurrence after liver transplantation based on the Scientific Registry of Transplant Recipients (SRTR) [11]. Their study included patients from 2004–2011. Policies surrounding treatment of HCC have changed during this time, with improvements in liver transplantation and increased use of marginal donors. Therefore, it is important to re-evaluate donor characteristics on the transplant outcomes in HCC patients in this setting.

Here, we use renewed data from the SRTR to evaluate the effect of donor age on liver transplant outcomes, especially OS and tumor recurrence, in patients with HCC.

Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government [12]. Organs from executed prisoners were not used in this study. The protocol for the present study was in accordance to Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, China (approval number 2019-1020).

We included patients with HCC who received liver transplantation from through January 1, 2010, to December 31, 2017. The inclusion criteria included recipients ≥ 18 years of age, with a primary diagnosis of “hepatocellular carcinoma” or “hepatoma” at transplant. Patients with a previous liver transplantation, those who received transplant for benign liver disease or liver tumor other than HCC, and those < 18 years of age were excluded from participation in this study. Among all the liver transplant recipients during this time period, a total of 13,276 recipients were eligible based on the inclusion and exclusion criteria. Figure 1 illustrates the patient selection flowchart.

To assess how donor age affects transplant outcomes, we divided recipients into four groups according to donor age: group I, donor age ≤ 34 years (N = 4,723); group II, donor age 35–49 years (N = 3,572); group III,

donor age 50–64 years (N = 3,743); group IV, donor age ≥ 65 years (N = 1,238). The donor and recipient data as well as tumor characteristics were compared among the four groups.

For long-term outcomes, we firstly compared post-transplant OS among four groups, which was evaluated from the time of LT and defined recipient death as the endpoint. OS was also assessed according to recipient underlying liver diseases including hepatitis C virus (HCV), hepatitis B virus (HBV), alcoholic liver diseases and nonalcoholic steatohepatitis (NASH). The post-transplant HCC recurrence was then compared among the four different groups, and the definition of post-transplant HCC recurrence was in accordance with the report by Samoylova et al. [13]. The detailed identification procedure was performed in accordance with that described in the study by Orci et al. [11].

Statistical analysis

Donor and recipient data and tumor characteristics were compared using one-way ANOVA analysis of variance for continuous variables and the chi-square test for binomial variables. OS was assessed by the Kaplan-Meier method and log-rank test was used to compare differences among the groups. Univariable analysis was used to identify potential predictors for OS, and those with $P < 0.05$ were further analyzed using the Cox proportional hazard ratios (HRs) model to adjust for potential confounders. Time-dependent effects were evaluated based on Schoenfeld’s residuals, and cubic spline functions were also introduced in the model [14]. The cumulative tumor recurrence rates were evaluated using a competing risk model. A two-tailed P value < 0.05 was considered statistically significant. All the analyses were conducted with SPSS version 22.0 (IBM, Armonk, NY, United States) and R for Windows (version 4.0.2).

Results

Baseline characteristics

The median follow-up time was 36 months (interquartile range, 18–60 months) for the entire study population. Donor characteristics, including donor height, weight, race, ABO blood type, sex, cause of death, deceased donor type (DCD or not) significantly differed among the four age groups. For recipient characteristics, the recipient age, race, ABO blood type, presence of underlying liver disease, height, weight, cold ischemia time, BMI, calculated laboratory model for end-stage liver disease (MELD) score, pretransplant laboratory albumin, bilirubin, international normalized ratio (INR), and creatinine were all statistically different among the four groups, while the donor warm ischemia time and pretransplant laboratory sodium level were comparable among all four groups. Analysis of tumor characteristics revealed that the pre-transplant treatment, including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), chemotherapy, cryoablation, surgery, number of tumors, largest tumor diameter, sum of tumor diameters, tumor staging, and pre-transplant α -fetoprotein (AFP) level were all similar among four groups. Table 1 presents a summary of the data in detail.

Table 1 Baseline characteristics

	Donor age group I (= $\leq$ 34, N = 4,723)	Donor age group II (35-49, N = 3,572)	Donor age group III (50-64, N = 3,743)	Donor age group IV ($\geq$ 65, N = 1,238)	P
Donor variables					
Race					<0.001
White	3051 (64.6%)	2269 (63.5%)	2378 (63.5%)	872 (70.4%)	
Black or African American	814 (17.2%)	647 (18.1%)	757 (20.2%)	188 (15.2%)	
Asian	82 (1.7%)	96 (2.7%)	114 (3.0%)	51 (4.1%)	
Hispanic/Latino	725 (15.4%)	524 (14.7%)	465 (12.4%)	123 (9.9%)	
Other	51 (1.1%)	36 (1.0%)	29 (0.8%)	4 (0.3%)	
ABO					<0.001
A	1752 (37.1%)	1361 (38.1%)	1346 (36.0%)	467 (37.7%)	
B	667 (14.1%)	490 (13.7%)	506 (13.5%)	129 (10.4%)	
O	2129 (45.1%)	1584 (44.3%)	1796 (48.0%)	620 (50.1%)	
AB	175 (3.7%)	137 (3.8%)	95 (2.5%)	22 (1.8%)	
Gender					<0.001
M	3226 (68.3%)	2048 (57.3%)	2013 (53.8%)	619 (50.0%)	
F	1497 (31.7%)	1524 (42.7%)	1730 (46.2%)	619 (50.0%)	
Cause of Death					<0.001
Anoxia	1812 (39.4%)	1262 (36.5%)	1045 (28.3%)	202 (16.3%)	
Cerebrovascular/stroke	429 (9.3%)	1285 (37.1%)	2003 (54.2%)	815 (65.9%)	
Head trauma	2234 (48.6%)	801 (23.1%)	586 (15.8%)	205 (16.6%)	
CNS tumor	27 (0.6%)	25 (0.7%)	12 (0.3%)	1 (0.1%)	
Other	94 (2.0%)	88 (2.5%)	52 (1.4%)	14 (1.1%)	
DCD	494 (10.5%)	302 (8.5%)	153 (4.1%)	1 (0.1%)	<0.001
Height (cm)	172.58 $\pm$ 11.56	171.48 $\pm$ 10.11	170.32 $\pm$ 10.13	168.83 $\pm$ 10.18	<0.001
Weight (kg)	78.71 $\pm$ 20.49	86.30 $\pm$ 21.54	84.02 $\pm$ 20.75	79.67 $\pm$ 18.30	<0.001
Recipient variables					
Sex					<0.001
M	3599 (76.2%)	2854 (79.9%)	2929 (78.3%)	909 (73.4%)	
F	1124 (23.8%)	718 (20.1%)	814 (21.7%)	329 (26.6%)	
Age	59.62 $\pm$ 7.31	59.49 $\pm$ 7.16	59.89 $\pm$ 6.75	61.55 $\pm$ 6.64	<0.001
Race					<0.001
White	3074 (65.1%)	2400 (67.2%)	2524 (67.4%)	825 (66.6%)	
Black or African American	500 (10.6%)	373 (10.4%)	332 (8.9%)	85 (6.9%)	
Asian	332 (7.0%)	203 (5.7%)	253 (6.8%)	109 (8.8%)	
Hispanic/Latino	753 (15.9%)	552 (15.5%)	590 (15.8%)	201 (16.2%)	
Other	64 (1.4%)	44 (1.2%)	44 (1.2%)	18 (1.5%)	
ABO					<0.001
A	1733 (36.7%)	1344 (37.6%)	1328 (35.5%)	462 (37.3%)	
B	684 (14.5%)	509 (14.2%)	498 (13.3%)	131 (10.6%)	
O	2062 (43.7%)	1532 (42.9%)	1780 (47.6%)	609 (49.2%)	
AB	244 (5.2%)	187 (5.2%)	137 (3.7%)	36 (2.9%)	
Underlying liver disease					<0.001
HCV	3147 (66.6%)	2389 (66.9%)	2372 (63.4%)	556 (44.9%)	
HBV	329 (7.0%)	228 (6.4%)	271 (7.2%)	152 (12.3%)	
Alcohol	412 (8.7%)	347 (9.7%)	366 (9.8%)	184 (14.9%)	
NASH	396 (8.4%)	309 (8.7%)	363 (9.7%)	171 (13.8%)	
Other	439 (9.3%)	299 (8.4%)	371 (9.9%)	175 (14.1%)	
Hight (cm)	172.39 $\pm$ 10.04	173.06 $\pm$ 9.85	172.75 $\pm$ 9.99	170.91 $\pm$ 9.96	<0.001
Weight (kg)	85.07 $\pm$ 18.82	86.72 $\pm$ 18.52	86.75 $\pm$ 18.66	84.40 $\pm$ 17.84	<0.001
Warm ischemia time (min)	40.11 $\pm$ 20.31	40.29 $\pm$ 18.80	40.86 $\pm$ 19.69	40.61 $\pm$ 21.13	0.646
Cold ischemia time (h)	6.21 $\pm$ 2.65	6.06 $\pm$ 2.52	6.21 $\pm$ 2.50	6.02 $\pm$ 2.21	0.006
BMI	28.55 $\pm$ 5.47	29.00 $\pm$ 7.73	29.04 $\pm$ 6.24	28.83 $\pm$ 5.40	0.001
MELD	15.40 $\pm$ 8.77	15.40 $\pm$ 8.53	14.74 $\pm$ 7.97	14.01 $\pm$ 6.83	<0.001

Albumin		3.21±0.69	3.23±0.69	3.25±0.70	3.27±0.67	0.01
Bilirubin		4.05±7.32	3.91±7.01	3.56±6.39	3.21±5.62	<0.001
INR		1.53±0.73	1.55±0.79	1.51±0.74	1.46±0.68	0.002
Creatinine		1.23±1.13	1.19±1.01	1.12±0.86	1.04±0.62	<0.001
Sodium		137.12±4.51	137.16±4.42	137.28±4.40	137.17±4.45	0.389
Treatment						
	TACE	2577 (64.9%)	1990 (65.5%)	2140 (65.6%)	757 (69.0%)	0.093
	RFA	489 (12.3%)	341 (11.2%)	365 (11.2%)	108 (9.8%)	0.107
	Chemotherapy	123 (3.1%)	89 (2.9%)	116 (3.6%)	32 (2.9%)	0.482
	Cryoablation	12 (0.3%)	13 (0.4%)	14 (0.4%)	2 (0.2)	0.54
	Surgery	39 (1.0%)	31 (1.0%)	43 (1.3%)	18 (1.6%)	0.207
Tumor Staging						0.592
	within Milan	3680 (97.4%)	2795 (96.8%)	3026 (97.1%)	1023 (97.2%)	
	beyond Milan	99 (2.6%)	92 (3.2%)	91 (2.9%)	30 (2.8%)	
Tumor nubmer		1.24±0.55	1.24±0.54	1.24±0.56	1.25±0.55	0.197
Largest tumor diameter (cm)		1.54±1.40	1.57±1.61	1.57±1.40	1.57±1.44	0.463
Sum of tumor diameters (cm)		1.88±1.81	1.91±1.98	1.91±1.80	1.94±1.88	0.381
AFP value (ng/ml)		8 (4, 24)	8 (4, 27)	8 (4, 24)	7 (4, 20)	0.781

OS

We compared OS among the four groups. The 1-, 3-, and 5-year OS were 91.4%, 82.3%, and 76.0% in group I; 90.6%, 81.2%, and 73.5% in group II; 89.5%, 80.0%, and 72.8% in group III; and 89.2%, 76.8%, and 69.2% in group IV, respectively ($P < 0.001$; Figure 2). We also compared the survival between two age groups at a time, and observed that the survival of group I recipients was significantly better than that of the other three groups (group I vs. group II, $P = 0.049$; group I vs. group III, $P = 0.002$; group I vs. group IV, $P < 0.001$). The survival of group II recipients was comparable to that of group III ($P = 0.308$) but significantly better than that of group IV recipients ($P = 0.004$). The survival of group III recipients was also better than that of group IV ($P = 0.038$).

Next, we analyzed the survival according to underlying liver diseases in the recipient. The OS significantly differed among the recipients with HCV, with the 1-, 3-, and 5-year OS at 91.4%, 82.1%, and 75.8% in group I; 90.2%, 79.8%, and 72.1% in group II; 89.1%, 78.6%, and 71.4% in group III; and 89.3%, 75.1%, and 68.1% in group IV, respectively ($P < 0.001$; Figure 3a). However, there were no significant differences in the survival rates among the four groups of patients in subsets with HBV, alcoholic liver diseases and NASH. The 1-, 3-, and 5-year OS rates were 93.3%, 87.5%, and 84.1% in group I; 90.3%, 85.2%, and 80.6% in group II; 91.5%, 85.0%, and 82.0% in group III; and 92.1%, 83.1%, and 77.1% in group IV in recipients with HBV ($P = 0.564$; Figure 3b). For recipients with alcoholic liver diseases, the 1-, 3-, and 5-year OS rates were 89.7%, 81.0%, and 75.4% in group I; 92.4%, 84.1%, and 76.0% in group II; 91.2%, 83.0%, and 75.8% in group III; and 90.2%, 79.4%, and 71.2% in group IV in ($P = 0.850$; Figure 3c). And the corresponding OS rates in recipients with NASH were 88.3%, 80.8%, and 73.9% in group I; 89.0%, 82.7%, and 72.9% in group II; 90.0%, 83.0%, and 76.4% in group III; and 83.5%, 76.3%, and 68.2% in group IV ($P = 0.442$; Figure 3d).

Univariable analysis for OS

We then performed univariable analyses to identify potential risk factors for recipient OS. Donor characteristics, including donor age and cause of death; recipient characteristics, including recipient age, race, underlying liver diseases, pre-transplant laboratory MELD score, albumin, bilirubin, INR, creatinine, sodium; and

tumor characteristics such as the number of tumors, largest tumor diameter, sum of tumor diameters, tumor staging, and pre-transplant AFP level, were all found to be significantly associated with the OS. Table 2 presents this information in greater detail.

Table 2 Univariable analysis

	HR	P value
Donor variables		
Age (reference Group I)		<0.001
Group II	1.097 (1.000 - 1.203)	0.050
Group III	1.153 (1.053 - 1.262)	0.002
Group IV	1.319 (1.164 - 1.493)	<0.001
Race (reference White)		0.778
Black or African American	1.008 (0.917 - 1.108)	0.868
Asian	0.983 (0.783 - 1.235)	0.885
Hispanic/Latino	1.011 (0.910 - 1.124)	0.832
Other	0.750 (0.483 - 1.165)	0.200
ABO (reference A)		0.123
B	0.925 (0.824 - 1.039)	0.189
O	1.053 (0.974 - 1.139)	0.196
AB	0.961 (0.782 - 1.181)	0.706
Gender	1.005 (0.969 - 1.042)	0.781
Cause of Death (reference Anoxia)		0.002
Cerebrovascular/stroke	1.112 (1.019 - 1.214)	0.017
Head trauma	0.960 (0.874 - 1.055)	0.397
CNS tumor	0.452 (0.215 - 0.950)	0.036
Other	0.955 (0.722 - 1.263)	0.747
DCD	1.052 (0.916 - 1.208)	0.476
Hight (cm)	0.997 (0.994 - 1.000)	0.085
Weight (kg)	1.000 (0.999 - 1.002)	0.587
Recipient variables		
Age	1.018 (1.013 - 1.024)	<0.001
Sex (F vs. M)	0.972 (0.931 - 1.015)	0.195
Race (reference White)		<0.001
Black or African American	1.177 (1.050 - 1.320)	0.005
Asian	0.756 (0.645 - 0.885)	<0.001
Hispanic/Latino	0.852 (0.767 - 0.946)	0.003
Other	0.965 (0.706 - 1.320)	0.826
ABO (reference A)		0.226
B	0.946 (0.844 - 1.061)	0.345
O	1.044 (0.965 - 1.130)	0.28
AB	0.927 (0.773 - 1.111)	0.41
Underlying liver disease (reference HCV)		<0.001
HBV	0.687 (0.586 - 0.804)	<0.001
Alcohol	0.905 (0.796 - 1.029)	0.126
NASH	1.014 (0.890 - 1.154)	0.839
Other	1.038 (0.922 - 1.169)	0.535
Hight (cm)	1.003 (1.000 - 1.007)	0.071
Weight (kg)	1.000 (0.998 - 1.002)	0.849
Warm ischemia time (min)	1.000 (0.998 - 1.003)	0.674
Cold ischemia time (h)	0.999 (0.986 - 1.013)	0.915
BMI	0.997 (0.990 - 1.003)	0.303
MELD	1.016 (1.012 - 1.020)	<0.001
Albumin	0.893 (0.848 - 0.940)	<0.001
Bilirubin	1.013 (1.008 - 1.017)	<0.001
INR	1.084 (1.040 - 1.131)	<0.001
Creatinine	1.086 (1.061 - 1.111)	<0.001
Sodium	0.991 (0.983 - 0.999)	0.034
Tumor Staging (beyond vs. within Milan)	1.420 (1.160 - 1.738)	0.001
Tumor nubmer	1.113 (1.043 - 1.187)	0.001
Largest tumor diameter (cm)	1.065 (1.045 - 1.086)	<0.001
Sum of tumor diameters (cm)	1.061 (1.043 - 1.079)	<0.001
AFP value (ng/ml) >400	1.928 (1.599 - 2.325)	<0.001

Multivariable analysis for OS

The multivariable Cox regression analysis showed that donor age, recipient age, recipient race, underlying liver diseases, pre-transplant MELD score, creatinine, sum of tumor diameters, and AFP level were all independent predictors of OS. Table 3 presents this information in greater detail.

Table 3 Multivariable analysis

	HR (95% CI)	P value
Donor age (reference Group I)		0.002
Group II	1.074 (0.963 - 1.199)	0.201
Group III	1.101 (0.984 - 1.232)	0.094
Group IV	1.343 (1.158 - 1.558)	<0.001
Recipient age	1.021 (1.015 - 1.028)	<0.001
Recipient Race (reference White)		0.010
Black or African American	1.139 (0.998 - 1.3)	0.053
Asian	0.88 (0.728 - 1.065)	0.190
Hispanic/Latino	0.875 (0.777 - 0.986)	0.029
Other	1.199 (0.865 - 1.662)	0.277
Underlying liver diseases (reference HCV)		0.007
HBV	0.716 (0.589 - 0.869)	0.001
Alcoholic liver diseases	0.918 (0.789 - 1.068)	0.268
NASH	0.868 (0.74 - 1.018)	0.082
Other	0.977 (0.851 - 1.121)	0.736
MELD	1.011 (1.005 - 1.018)	0.001
Recipient serum creatinine	1.051 (1.009 - 1.094)	0.016
Sum of tumor diameters	1.05 (1.031 - 1.069)	<0.001
AFP (≥ 400 ng/ml vs. < 400 ng/ml)	1.957 (1.617 - 2.367)	<0.001

Time-dependent effect of donor age on OS

We specifically analyzed the time-dependent HR of donor age on the recipient OS and observed that the HR remained generally stable in the transplant recipient during the follow-up, but it tended to increase in the early transplant months and decrease over the years (Figure 4), suggesting that although donor age was a constant independent predictor of decreased OS, the negative effect of older donor age on the transplant recipient may tend to decrease over time.

Post-transplant tumor recurrence

Five hundred and sixty seven recipient suffered HCC recurrence in the post-transplant periods. The general tumor recurrence rates were comparable among the four age groups (218 in group I, 142 in group II, 150 in group III and 57 in group IV, $P = 0.375$). The median time to recurrence after transplantation was 22 months (interquartile range, 10 – 33 months) in group I, 22.5 months (12 – 35 months) in group II, 21.5 months (12 – 35.5 months) in group III and 22 months (11 – 37 months) in group IV. To further analyze the cumulative tumor recurrence rates, we introduced a competing risk model. We observed that the cumulative recurrence rate in the four age group recipients was also similar ($P = 0.382$), with 5-year cumulative recurrence rate at 5.54% in group I, 4.98% in group II, 4.80% in group III and 5.84% in group IV, indicating that donor age had slight effect on post-transplant tumor recurrence (Supplemental Figure 1).

As no difference was observed in terms of recurrence rates among the groups, additional Cox regression model and competing regression model were not used. However, we further investigated the time-dependent effect of donor age on tumor recurrence in a sensitive analysis. The effect of donor age also remained generally stable in the early transplant years, and showed a decreasing trend over the long-term follow-up period (Supplemental Figure 2).

Discussion

In this study, we demonstrated that the OS significantly differed in HCC liver transplant recipients categorized according to different donor ages, whereas donor age had no effect on post-transplant tumor recurrence. With regard to underlying liver diseases, there were differences in OS in HCV recipients, but not in recipients with HBV, alcoholic liver diseases and NASH.

The impact of donor age on transplant outcomes has been evaluated for decades, in an attempt by clinicians to expand the donor pool by using organ grafts from older donors. However, there are controversies surrounding the safety and feasibility of grafts from older donors compared with grafts from younger donors. Several studies have shown that older donor age is associated with an increased risk of post-transplant graft loss and poor patient survival. One study investigated the correlation of donor-related variables with post-transplant outcomes, and derived the DRI model [6]. In this model, donor age was reported to be an independent predictor of post-transplant survival, with a 1-year survival of 85–86% in recipients whose donors were <40 years of age versus 61–76% in recipients whose donors were over 70 years old. This DRI model was also validated in a European study [15]. Other modified models based on DRI have also been proposed [16,17]. Studies have shown that the impact of donor age is especially important in recipients with underlying HCV infection, leading to more advanced hepatic fibrosis after transplantation as well as decreased survival [18–20]. While these studies almost always showed the negative association of older donor age with survival, several centers have reported early experiences of successful use of septuagenarian and even octogenarian donors, whose transplant outcomes were comparable with those of younger donors. Clinicians who believed that adequate selection of donor liver and donor-recipient matching are the keys to successful use of liver grafts from older donors have endeavored to push the age limits of eligible liver graft donors [4,7]. Other studies have pointed out that the main difference in transplant outcomes between grafts from older and young donors mainly presents in the first transplant year, and this difference may stabilize in the subsequent years after the transplant [21,22].

While the impact of donor age on transplant outcomes has been widely investigated, little is known about how donor age affects tumor recurrence in recipients with HCC. Liver grafts are likely to undergo senescence (both morphological, synthetic, and functional) with age, seen as shrinking in size and a decrease in metabolic and immune cell functions [23]. Therefore, pathophysiological changes during IRI in liver grafts from old donors differ considerably from those in liver grafts from young patients. In fact, studies have shown that liver grafts from older donors would be more vulnerable to IRI, with deregulation in liver cell mitochondrial alteration, inflammatory response, and autophagic flux [5]. The study by Reese and Gao showed that special attention should be paid to cold ischemia time in cases where the age of the graft donor is greater than 70 years [24,25]. Increased IRI was also found to be associated with tumor recurrence. Man et al. demonstrated that more severe early-phase IRI in small-for-size liver grafts has a higher probability of late-phase tumor recurrence,

which might be due to post-transplant mobilization of endothelial progenitor cells and regulatory T cells [26,27]. Thus, there is a potential that older donor age can lead to higher tumor recurrence rate after transplantation. In fact, in a previous study by Orci et al., which also evaluated the association of donor-related variables and HCC recurrence using SRTTR data observed that older donor age was associated with higher HCC recurrence [11]. However, their data included recipients who received a liver transplant from 2004 to 2011, and the transplant policies for HCC patients have been modified in the past decade, with different indications for liver diseases, new transplant techniques, and improved post-transplant management. Indeed, significant progress has been made in the field of transplantation over the past decades, with improvements in patients, graft survival, and fewer disparities in recipients who received grafts from donors >60 years compared with recipients of grafts from donors below 60 years of age [25]. Considerable progress has been made in treating HCC, with the development of new targeted therapies and immune therapies [3]. Therefore, it is worth re-investigating the impact of donor age on HCC patients in the current transplant era.

We found that although there were significant differences in the OS among transplant recipients from donors of different age groups, no difference was observed with regard to tumor recurrence. We also evaluated the time-dependent HR of donor age during transplant follow-up for both OS and tumor recurrence. The HR for OS remained relatively stable over time and showed an increasing trend in the early transplant months and a decreasing trend with longer transplant years. This might indicate that donor age remained to be the independent predictor for recipient OS although its effects might lessen with longer transplant follow-up time. The HR for post-transplant tumor recurrence also remained stable during the transplant follow-up years, indicating that the probability of tumor recurrence would not increase with longer follow-up time. As the cumulative tumor recurrence risk did not differ among the four age groups, we only performed sensitivity analysis and did not perform the competing risk model to assess the risk of tumor recurrence. This might reflect improvements in the management of HCC in transplant recipients.

We observed the differential effects of donor age on recipients with different underlying liver diseases. In patients with HCV, older donor age was associated with decreased OS, while in patients with HBV, alcoholic diseases and NASH, donor age did not affect post-transplant survival. This result is in accordance with that reported by Lake et al. [28], who reported that donor age did not have any effect on post-transplant outcomes in recipients with HBV. Their study also showed that transplants from donors >60 years were associated with decreased survival in patients with underlying liver diseases other than HBV and HCV. However, they did not sub-classify these diseases, which we think is important in the current transplant status, as the number of patients with NASH has shown an increasing trend in the past few years and it has become one of the leading indications of liver transplantation in current clinical practice [29,30]. Therefore, our preliminary results on the impact of donor age on liver transplant recipients with HCC with different underlying liver diseases would benefit from validation and further exploration in a larger population so as to study the different causes of liver diseases in transplant recipients.

Recipient age was an independent predictor for OS in HCC recipients, which is in accordance with that reported previously, where older recipient age was associated with inferior long-term survival, particularly in those with higher MELD scores [31-34]. Patients with HCC are generally older than other waiting list candidates [30,33,35]. Factors associated with older age, including cardiovascular diseases, functional status such as frailty as well as higher extrahepatic tumor risks were all the negative predictors associated with older age, which lead to

adverse outcomes in HCC recipients. Our study also observed that a higher MELD score was an independent predictor of OS. Further studies could evaluate the association between recipient age and HCC recurrence after transplantation.

Our study also found that sum of tumor diameters and pre-transplant AFP level were independent predictors of OS, reflecting the importance of the candidate selection process in HCC patients, which we should not only evaluate the general status of the recipient but also study the tumor characteristics using HCC selection criteria, such as the Milan Criteria and etc [8,36]. However, in our previous study we mainly focused on the tumor recurrence based on HCC selection criteria. Our study showed that in addition to tumor recurrence, tumor physical status (sum of tumor diameter) and tumor biological status (AFP) were vital in pre-transplant evaluation of recipient OS. With the development of new technologies, new biological markers such as molecular and gene signatures and circulating tumor cells determined by liquid biopsy should be included in routine transplant practice to better predict post-transplant outcomes.

Our study has several limitations. First, as it is based on a large dataset, we could not analyze the possible confounding variables as well as include new variables related to new therapeutic advances in HCC treatment, such as the use of targeted therapies before or after transplantation. This is important because the prognosis of HCC patients has considerably improved in recent years with the development of targeted therapy and immunotherapy. Secondly, although our study included recipients from 2010 through 2017, there is a potential that a relatively short follow-up would confound the true risk of tumor recurrence after transplantation, especially as currently the development of new treatments for HCC are ongoing, and these might delay or diminish the recurrence of HCC. Nonetheless, our study presents the largest study to date based on the latest transplantation recipient cohort to evaluate the effect of donor age on transplant outcomes in HCC patients. In the future, prospective studies with long follow-up time should be performed to investigate the effect of donor age on HCC transplant recipients so as to expand the donor pool to benefit more candidates on the waiting list.

Conclusions

Our study demonstrated that older donor age was associated with inferior OS in transplant recipients with HCC, but donor age did not affect post-transplant tumor recurrence in these patients. Older donor age also had different effects in recipients with different underlying liver diseases, with inferior OS in recipients with HCV but with no influence in recipients with HBV, alcoholic diseases and NASH. These findings may be useful for clinicians in decision-making with regards to marginal donor allocation and recipient selection to achieve favorable transplant outcomes.

List Of Abbreviations

DCD, Donation after cardiac death; DRI, Donor risk index; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HR, Hazard ratios; INR, International normalized ratio; IRI, Ischemia–reperfusion injury; MELD, Model for end-stage liver disease; NASH, Nonalcoholic steatohepatitis; OPTN, Organ Procurement and Transplantation Network; OS, Overall survival; RFA, Radiofrequency ablation; SRTR, Scientific Registry of Transplant Recipients; TACE, Transarterial chemoembolization.

Declarations

Ethics approval and consent to participate

With Data Release Agreement with the Scientific Registry of Transplant Recipients database, all data in this study were released from SRTR. The protocol for the present study was in accordance to Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, China (approval number 2019-1020). And no additional patient consent was required for the measurements in the data analysis.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the Scientific Registry of Transplant Recipients database, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Scientific Registry of Transplant Recipients database.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J.Z and Z.C.H retrieved the associated data from the SRTR database. J.Z, Z.C.H and Z.C performed the statistical analysis. J.Z wrote the first draft of the manuscript. Z.C.H, F.S.X and R.L.T contributed intellectual content. All authors contributed to critical revisions to the manuscript. S.S.Z is the corresponding author. All authors approved the final manuscript.

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Authors' information

1. Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University, School of Medicine,
2. NHC Key Laboratory of Combined Multi-organ Transplantation
3. Key Laboratory of the diagnosis and treatment of organ Transplantation, Research Unit of Collaborative Diagnosis and Treatment For Hepatobiliary and Pancreatic Cancer, Chinese Academy of Medical Sciences
2019RU019
4. Key Laboratory of Organ Transplantation, Research Center for Diagnosis and Treatment of Hepatobiliary Diseases, Zhejiang Province, Hangzhou 310003, China

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Figures

Figure 1

Flow chart of patient selection process.

Figure 2

Overall survival of HCC recipients categorized by different donor age groups.

Figure 3

Overall survival of HCC recipients according to underlying liver diseases: a) HCV; b) HBV; c) alcoholic liver diseases; d) NASH.

Figure 4

Cox - derived estimates of the time-dependent hazard ratio of donor age for overall survival in HCC recipients.

Supplementary Files

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