Posttransplant Outcomes in Older Patients With Hepatocellular Carcinoma Are Driven by Non–Hepatocellular Carcinoma Factors

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The incidence of hepatocellular carcinoma (HCC) is growing in the United States, especially among the elderly. Older patients are increasingly receiving transplants as a result of HCC, but the impact of advancing age on long-term posttransplant outcomes is not clear. To study this, we used data from the US Multicenter HCC Transplant Consortium of 4980 patients. We divided the patients into 4 groups by age at transplantation: 18 to 64 years (n = 4001), 65 to 69 years (n = 683), 70 to 74 years (n = 252), and ≥75 years (n = 44). There were no differences in HCC tumor stage, type of bridging locoregional therapy, or explant residual tumor between the groups. Older age was confirmed to be an independent and significant predictor of overall survival even after adjusting for demographic, etiologic, and cancer-related factors on multivariable analysis. A dose-response effect of age on survival was observed, with every 5-year increase in age older than 50 years resulting in an absolute increase of 8.3% in the mortality rate. Competing risk analysis revealed that older patients experienced higher rates of non–HCC-related mortality ($P = 0.004$), and not HCC-related death ($P = 0.24$). To delineate the precise cause of death, we further analyzed a single-center cohort of patients who received a transplant as a result of HCC (n = 302). Patients older than 65 years had a

higher incidence of de novo cancer (18.1% versus 7.6%; $P = 0.006$) after transplantation and higher overall cancer-related mortality (14.3% versus 6.6%; $P = 0.03$). Even carefully selected elderly patients with HCC have significantly worse posttransplant survival rates, which are mostly driven by non–HCC-related causes. Minimizing immunosuppression and closer surveillance for de novo cancers can potentially improve the outcomes in elderly patients who received a transplant as a result of HCC.

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality in the world.[1] The incidence of HCC has been progressively increasing in patients aged older than 65 years.[2] These trends are expected to continue, with a predicted increase of 50.0% in the incidence of HCC during the next 10 years.[3,4] Liver transplantation (LT) offers the best chance for cure in patients with HCC and cirrhosis. As a result, the proportion of elderly patients with HCC who have received a transplant has increased from 17.4% in 2009 to 41.9% in 2019.[5]

Although there is no official upper age limit for transplantation, advanced age is associated with higher rates of removal from the waiting list as a result of death or tumor progression in patients with HCC.[6,7] However, the impact of age on long-term posttransplant survival in patients with HCC is not clear. Few studies have suggested that patients aged older than 60 years have lower posttransplant survival rates as a result of higher cardiovascular mortality.[7,8] Other studies failed to find any difference in outcomes in carefully selected elderly patients with HCC.[9,10] Despite these contradictory data on clinical outcomes, older patients are still likely to receive a transplant if they have low cardiovascular risk and good functional status. The long-term outcomes of elderly patients who receive a transplant and the predictors of outcomes in this subset are yet to be determined. Given the ongoing shortage of livers, additional research is needed to address this.

In this study, data from a large, multicenter HCC consortium with specific details on HCC staging, treatment, and explant tumor status were analyzed. We sought to evaluate the impact of increasing age on long-term posttransplant outcomes and identify risk factors associated with higher mortality among elderly patients aged ≥65 years. In addition, a single-center database with more granular details was evaluated to identify the specific causes that drive mortality in elderly patients.

Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; CI, confidence interval; CIF, cumulative incidence function; CNI, calcineurin inhibitor; CT, computed tomography; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; LT, liver transplantation; LRT, locoregional therapy; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; NS, not significant; OS, overall survival; P-splines, penalized splines; RFS, recurrence-free survival; TACE, transarterial chemoembolization; UMHTC, US Multicenter HCC Transplant Consortium; UNOS, United Network for Organ Sharing.

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Patients and Methods

PATIENT SELECTION

Details of the US Multicenter HCC Transplant Consortium (UMHTC) study, which was created to establish a multicenter database of patients with HCC who had undergone LT, were published previously.[11] Briefly, 4980 consecutively identified adult patients from 10 of the 11 United Network for Organ Sharing (UNOS) regions who received a transplant as a result of HCC between 2002 and 2013 were included in this study. Details on tumor staging, HCC treatment, and

explant residual tumor burden were available. Patients were stratified based on age at the time of LT: 18 to 64 years, 65 to 69 years, 70 to 74 years, and ≥75 years. To obtain additional detailed data on specific causes of death in the elderly, we also included a single-center retrospective study in adult patients with HCC who received a liver transplant at an academic transplant center (Stanford University Hospital) between 2008 and 2018.

DATA COLLECTION

The UMHTC database included patient demographics (age, sex, HCC etiology), tumor burden (Milan staging), type and number of locoregional therapies (LRTs), alpha-fetoprotein (AFP), and explant pathology (number/size of lesions, grade/differentiation, vascular invasion, T staging). Disease recurrence, location of recurrence, overall survival (OS), and recurrence-free survival (RFS) were also recorded. Patient data abstracted for the Stanford cohort of patients included general demographics, comorbid diseases, liver disease etiology, Child-Turcotte-Pugh score, initial HCC staging, LRTs received, imaging data, HCC recurrence, survival data, and cause of death. Explant pathologic variables were extracted from the standardized pathology reports and included total tumor number, maximum tumor diameter, grade, microvascular and macrovascular invasion, and American Joint Committee on Cancer tumor staging.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (IBM, Armonk, NY) was used to compare patient risk factors, demographics, and clinical outcomes. Categorical variables were described using frequencies and percentages, and statistical analyses of these variables were evaluated using Fisher's exact test or a chi-squared test. Continuous variables were described by correlation distributions using medians and interquartile ranges (IQRs). Kaplan-Meier curve analysis was used for survival analyses, with the log-rank test being used to compare outcomes. OS was defined as the duration between the date of LT and the date of death from any cause. RFS was defined as the duration between the date of LT and the date of recurrence or death from any cause. Univariable and multivariable Cox regression analyses were performed to investigate patient and tumour characteristics associated with tumor recurrence or death. Statistically significant variables were determined to have *P* values <0.05. However, a level of significance of 0.15 was used to determine the variables that would enter the multivariable analysis.

To evaluate the linearity of the relationship between age and OS effect we entered patient age as a continuous variable into the Cox proportional hazards regression using penalized splines (P-splines) in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).[12] Cause of death was classified into HCC-related and non–HCC-related. We used competing risk models to better estimate the risk of non–HCC-related death in the presence of a competing risk of HCC recurrence or death.[13,14] The failure event was represented by "death from non-HCC causes," whereas "HCC-related death or recurrence" represented the competing event and vice versa in cause-specific hazards function competing risk analysis performed using SAS 9.4 (SAS Institute, Cary, NC) to estimate cumulative incidences of the competing events of interest.

Results

DEMOGRAPHIC AND ETIOLOGIC TRENDS ASSOCIATED WITH AGE IN PATIENTS WITH HCC

The UMHTC database consists of a total of 4980 adult patients in the United States who received a transplant as a result of HCC at 20 centers from 10 UNOS regions between 2002 and 2013. The median age of transplantation for patients with HCC was 58.0 (IQR, 53.0-63.0), and the overall age distribution is shown in Fig. 1A. To understand the impact of age on LT, patients were categorized into the following clinically relevant groups at 5-year increments based on age at transplantation: 18 to 64 years (n = 4001), 65 to 69 years (n = 683), 70 to 74 years (n = 252), and ≥75 years (n = 44; Fig. 1B, Table 1). In this study, older patients are defined as those aged 65 years or older, unless otherwise noted. The median age at transplantation for each UNOS region is shown in Fig. 1C. Region 5 had the highest number of patients with HCC who underwent LT when they were older (21.3%; n = 209), followed by region 9 (18.2%; n = 178). The proportion of female sex progressively increased with higher age groups, with 32.4% (n = 96) of septuagenarians and 45.5% (n = 20) of those aged ≥75 years being female

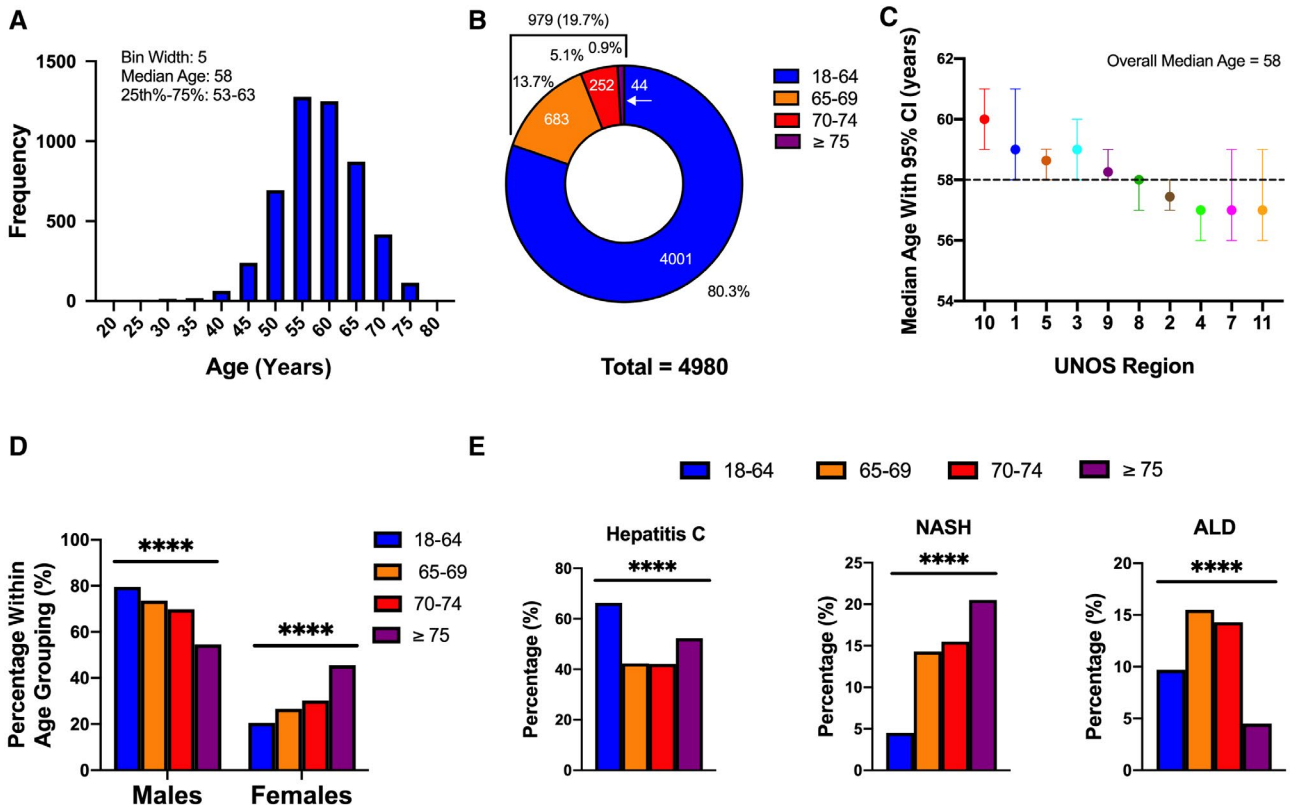

FIG. 1. Demographic and clinical features of elderly patients who received a transplant as a result of HCC. (A) Histogram showing age distribution at the time of transplantation in patients with HCC. (B) Proportional distribution of patients stratified by 5-year increments over age 65 years. (C) Median age (±95% CI) at transplantation stratified by UNOS regions. (D) Changes in sex distribution with increasing age in patients with HCC. (E) Changes in etiologic factors for HCC with increasing age. ****0.0001 > *P* > 0.00001.

(Fig. 1D). The incidence of nonalcoholic steatohepatitis (NASH) HCC also progressively increased with age ($P < 0.001$; Fig. 1E). In general, older cohorts also had a higher incidence of alcohol-related liver disease (ALD) HCC ($P < 0.001$) and cryptogenic HCC ($P < 0.001$) and a lower incidence of hepatitis C HCC ($P < 0.001$). The median physiologic Model for End-Stage Liver Disease (MELD) exemption score was lower than 15 in all 4 age groups but was slightly higher in those aged ≥75 years ($P = 0.001$). There was no difference in the median time from listing to transplantation between the 4 age groups ($P = 0.61$).

AGE DOES NOT IMPACT HCC TUMOR-SPECIFIC ATTRIBUTES

We evaluated the impact of patient age on tumor burden (Table 1). On comparison of pretransplant tumor burden between the different age groups, the proportion of patients who were within the Milan criteria at diagnosis was not statistically different ($P = 0.59$; Fig. 2A). Older patients had a lower median maximum AFP (13.4 [IQR, 5.9-71.7] versus [IQR, 19.1 7.0-87.1]; $P < 0.001$). However, the proportion of patients with AFP values >1000 was not significantly different between the age groups ($P = 0.36$). The median number of LRTs for older and younger patients was the same (1.0 [1.0-2.0] versus 1.0 [0.0-2.0]; $P = 0.10$) (Fig. 2B). Older patients were also more likely to be bridged with transarterial chemoembolization (TACE) ($P = 0.01$), whereas the receipt of the other modes of LRTs was not significantly different between the 4 groups (Table 1). On comparison of explant pathology, age did not appear to adversely impact residual tumor burden. The median number of tumors found in the explant was the same for all age groups ($P = 0.36$). The incidence of vascular invasion was not different between the age groups ($P = 0.45$). Pathologic grading and T staging were also not significantly different among all age groups ($P = 0.07$ and

TABLE 1. Demographic and Clinical Features Stratified by Age Groups

Variable	Subcategory	All Age Groups	Age Group				*P* Value
			18-64 (n = 4001)	65-69 (n = 683)	70-74 (n = 252)	≥75 (n = 44)	
Sex, n (%)	Male	3882 (77.9)	3179 (79.5)	502 (73.5)	176 (69.8)	24 (54.5)	<0.001
	Female	1099 (22.1)	822 (20.5)	181 (26.5)	76 (30.2)	20 (45.5)	
HCC etiology, n (%)	NASH	328 (6.6)	182 (4.5)	98 (14.3)	39 (15.5)	9 (20.5)	<0.001
	Hepatitis B	530 (10.6)	440 (11.0)	68 (10.0)	21 (8.3)	1 (2.3)	0.14
	Hepatitis C	3068 (61.6)	2650 (66.3)	289 (42.3)	106 (42.1)	23 (52.3)	<0.001
	Cryptogenic	210 (4.2)	127 (3.2)	54 (7.9)	24 (9.5)	4 (9.1)	<0.001
	ALD	532 (10.7)	388 (9.7)	106 (15.5)	36 (14.3)	2 (4.5)	<0.001
	Other	312 (6.3)	213 (5.3)	68 (10.0)	26 (10.3)	5 (11.4)	<0.001
MELD, median (IQR)	Physiologic	13.0 (9.6-19.0)	13.6 (10.0-20.0)	13.0 (10.0)	13.0 (9.0-18.0)	14.3 (8.6-26.0)	<0.001
	MELD exception	25.0 (22.0-29.0)	25.0 (22.0-29.0)	25.0 (22.0-28.0)	25.0 (22.0-28.0)	25.0 (22.0-31.0)	0.59
MELD exemption, n (%)		3158 (63.4)	2524 (63.3)	450 (66.1)	159 (63.3)	25 (56.8)	0.41
Milan, n (%)	Inside	3573 (71.7)	2852 (71.6)	500 (73.4)	188 (74.6)	32 (72.7)	0.59
	Outside but downstaged	465 (9.3)	373 (9.4)	70 (10.3)	19 (7.5)	3 (6.8)	0.57
	Outside but not downstaged	331 (6.6)	266 (6.7)	42 (6.2)	21 (8.3)	2 (4.5)	0.63
AFP, n (%)	>1000	131 (2.6)	110 (3.0)	12 (1.9)	6 (2.5)	2 (4.7)	0.36
Number of LRTs, n (%)	0	1398 (28.1)	1167 (29.2)	168 (24.6)	47 (18.7)	15 (34.1)	<0.001
	1	2163 (43.4)	1713 (42.8)	306 (44.8)	125 (49.6)	19 (43.2)	0.17
	2	874 (17.5)	692 (17.3)	129 (18.9)	48 (19.0)	5 (11.4)	0.46
	3	312 (6.3)	251 (6.3)	40 (5.9)	18 (7.1)	3 (6.8)	0.91
	≥4	122 (2.4)	174 (4.4)	40 (5.9)	14 (5.6)	2 (4.5)	0.32
Type of LRT, n (%)	TACE	2810 (56.4)	2214 (55.3)	410 (60.0)	160 (63.5)	26 (59.1)	0.01
	Thermal ablation	916 (18.4)	727 (18.2)	134 (19.6)	49 (19.4)	6 (13.6)	0.65
	Radioembolization	143 (2.9)	102 (2.5)	28 (4.1)	11 (4.4)	2 (4.5)	0.05
	Ethanol ablation	118 (2.4)	97 (2.4)	18 (2.6)	3 (1.2)	0 (0.0)	0.42
	Resection	159 (3.2)	127 (3.2)	26 (3.8)	5 (2.0)	1 (2.3)	0.54
	Other	180 (3.6)	155 (3.9)	18 (2.6)	6 (2.4)	1 (2.3)	0.26
Time to transplantation, median (IQR)		138.0 (43.0-335.0)	133.0 (41.0-320.3)	123.5 (40.0-260.0)	128.0 (38.0-288.0)	137.5 (21.8-444.5)	0.34
Incidental tumors, n (%)		595 (11.9)	495 (12.4)	69 (10.1)	24 (9.5)	7 (15.9)	0.17
Number of lesions in explant, median (IQR)		1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	0.36
Vascular invasion in explant, n (%)	None	3789 (76.1)	3031 (76.4)	527 (77.5)	194 (77.0)	37 (86.0)	0.46
	Microvascular	940 (18.9)	767 (19.3)	121 (17.8)	48 (19.0)	3 (7.0)	0.18
	Macrovascular	216 (4.3)	171 (4.3)	32 (4.7)	10 (4.0)	3 (7.0)	0.80

TABLE 1. *Continued*

Variable	Subcategory	All Age Groups	Age Group				*P* Value
			18-64 (n = 4001)	65-69 (n = 683)	70-74 (n = 252)	≥75 (n = 44)	
Pathologic tumor grade, n (%)	Well differentiated	1233 (24.8)	1003 (25.8)	168 (25.3)	48 (19.3)	14 (31.8)	0.07
	Moderate differentiation	2338 (46.9)	1870 (48.0)	323 (48.6)	122 (49.0)	22 (50.0)	
	Poor differentiation	432 (8.7)	340 (8.7)	55 (8.3)	36 (14.5)	1 (2.3)	
	Unknown differentiation	849 (17.0)	681 (17.5)	118 (17.8)	43 (17.3)	7 (15.9)	
Pathologic tumor stage, n (%)	T1	2192 (44.0)	1768 (44.2)	300 (43.9)	104 (41.3)	20 (45.5)	0.81
	T2	2280 (45.8)	1827 (45.7)	314 (46.0)	121 (48.0)	17 (38.6)	
	T3a	247 (5.0)	195 (4.9)	33 (4.8)	16 (6.3)	3 (6.8)	
	T3b	218 (4.4)	172 (4.3)	32 (4.7)	11 (4.4)	3 (6.8)	
	Unknown	44 (0.9)	39 (1.0)	4 (0.6)	0 (0.0)	1 (2.3)	

$P = 0.81$, respectively; Fig. 2C). Thus, tumor-specific attributes were not influenced by patient age.

OLDER AGE ASSOCIATED WITH POOR POSTTRANSPLANTATION CLINICAL OUTCOMES IN HCC

In the overall cohort, the 5-year posttransplant OS and RFS were 69.8% and 66.7%, respectively. The median follow-up time after LT was 3.9 years (IQR, 2.0-6.5). On univariable analysis, age was determined to be a strong predictor of both OS ($P = 0.001$) and RFS ($P = 0.001$; Fig. 3A, Supporting Fig. 1). The 5-year OS progressively decreased from 70.9% in those aged 18 to 64 years to 62.7% in patients aged ≥75 years, whereas the hazard ratio (HR) progressively increased from 1.0 in the youngest age group to 1.7 in those aged ≥75 years (P [trend] = 0.0001). To evaluate the linearity of the relationship between age and OS or RFS, we performed Cox proportional hazards regression using P-splines. Beyond the age of 50 years, the risk (log hazards) of mortality increased linearly with increasing age (Supporting Fig. 2). Also, a dose-response effect of age on survival was observed, with every 5-year increase in age >50 years resulting in an absolute increase of 8.3% in overall risk for both OS and RFS ($P < 0.001$ for both). Importantly, the absolute increase in mortality per 5-year period is the same for both OS and RFS, thus suggesting that the worse outcomes were not driven by HCC recurrence.

On multivariable analysis, age ≥ 65 years was confirmed to be an independent predictor of OS even after adjusting for multiple variables such as sex, etiology, HCC tumor stage, AFP, and HCC treatment (Table 2). Other variables found to predict poorer OS on multivariable analysis included hepatitis C (HR, 1.2 [$P = 0.02$]), prior resection (HR, 1.4 [$P = 0.04$]), AFP >1000 (HR, 1.5 [$P = 0.007$]), vascular invasion (HR, 1.3 [$P = 0.001$]), higher grade (moderate differentiation HR, 1.2 [$P = 0.03$] and poor differentiation HR, 1.4 [$P = 0.001$], respectively), and advanced pathologic stage (T3a HR, 1.5 [$P = 0.001$] and T3b HR, 1.9 [$P < 0.001$], respectively). Similar variables were found to predict poorer RFS (Table 3). In the overall cohort, the recurrence rate was 11.9% (n = 594). Of note, the recurrence rate ($P = 0.37$) and time to recurrence ($P = 0.23$) were not different between the 4 age groups (Fig. 3B, Supporting Table 1). To identify risk factors that predict survival in the elderly, we performed subgroup analysis in patients aged ≥65 years (Table 4). On multivariable

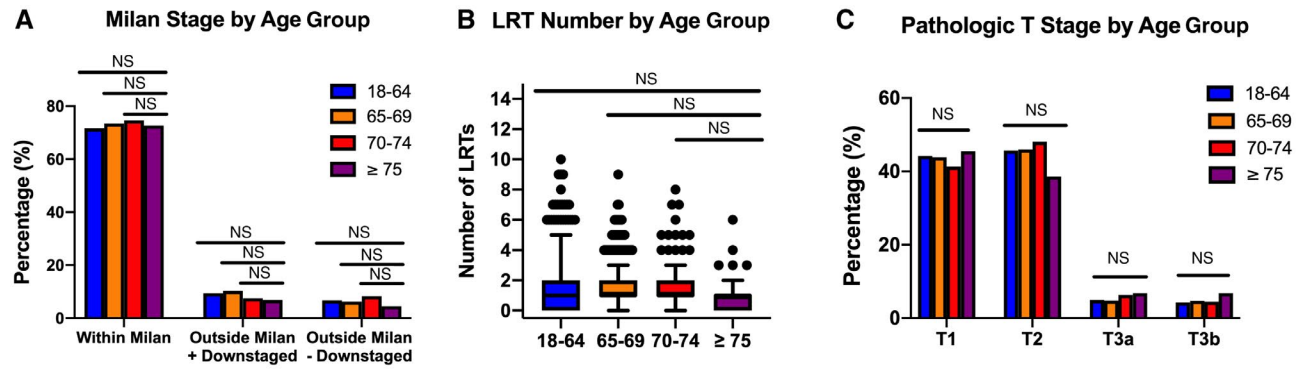

FIG. 2. Tumor-specific attributes in elderly patients who received a transplant as a result of HCC. (A) Changes in Milan staging with increasing age in patients with HCC. (B) LRT distribution comparison in older patients with HCC. (C) Changes in pathologic T staging with increasing age in patients with HCC.

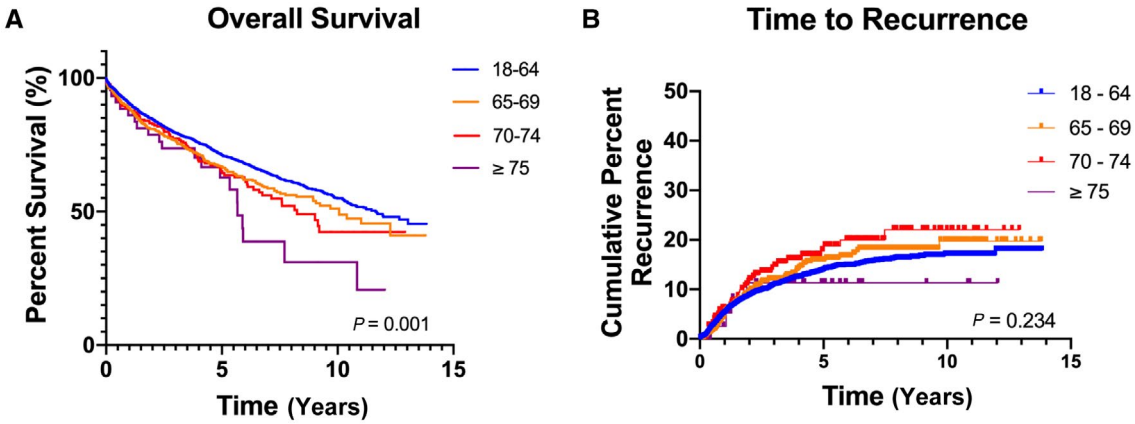

FIG. 3. Long-term posttransplant clinical outcomes in patients who received a transplant as a result of HCC. (A) OS stratified by age groups in patients who received a transplant as a result of HCC. (B) Time to recurrence stratified by age groups in patients who received a transplant as a result of HCC.

analysis for both OS and RFS, T3b stage tumors and vascular invasion were the only 2 variables predicting worse clinical outcomes (OS HR, 1.9 [$P = 0.02$] and HR, 1.5 [$P = 0.01$], respectively; RFS HR, 1.8 [$P = 0.03$] and HR, 1.5 [$P = 0.007$], respectively).

ELDERLY PATIENTS EXPERIENCE HIGHER NON–HCC-RELATED MORTALITY

We wanted to determine whether poor survival outcomes in older patients were attributable to HCC or non-HCC causes. We performed competing risk analysis to determine the cumulative incidence of non–HCC-related death versus HCC-related death or recurrence. We found that the cumulative incidence of HCC-related death or recurrence is not statistically different between the age-based cohorts ($P = 0.24$), whereas the cumulative incidence of death from non-HCC causes was statistically higher in the older age groups ($P = 0.004$; Fig. 4, Supporting Table 2). Thus, analysis of the large, multicenter HCC consortium data reveals that long-term posttransplant survival worsens progressively with increasing age, mostly driven by non–HCC-related mortality.

CAUSE OF DEATH IN ELDERLY TRANSPLANT PATIENTS

Using the large multicenter data, we show that older age was associated with poor survival attributed to non-HCC causes. To validate our findings and to

TABLE 2. Impact of Older Age on Posttransplant OS in Patients With HCC

		OS Univariable Analysis				OS Multivariable Analysis		
Variable	Subcategory	5-Year Survival	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	≥65 years	65.6 versus 70.8	1.3	1.1-1.4	<0.001	1.3	1.1-1.5	<0.001
Sex	Male				0.75	1.1	0.9-1.2	0.45
HCC etiology	NASH				0.46			
	Hepatitis B	65.2 versus 48.8	0.6	0.8-0.7	<0.001	0.7	0.5-0.9	0.002
	Hepatitis C	48.1 versus 54.3	1.3	1.2-1.4	0.001	1.2	1.0-1.4	0.02
	ALD				0.65			
	Cryptogenic				0.12	1.3	0.9-1.7	0.16
	Other	61.2 versus 49.8	0.7	0.5-0.8	0.001	0.7	0.5-0.9	0.01
LRT	0	70.4	1.0	–	–	1.0	–	–
	1	70.7	0.9	0.8-1.0	0.16	1.0	0.8-1.1	0.65
	2	69.6	1.0	0.8-1.2	0.87	0.9	0.8-1.1	0.44
	3	68.8	1.0	0.8-1.2	0.90	1.0	0.8-1.3	0.95
	≥4	54.7	1.5	1.2-1.9	<0.001	1.2	0.9-1.6	0.18
Type of bridging therapy	TACE				0.99			
	Thermal ablation				0.88			
	Radioembolization				0.17			
	Resection	37.8 versus 51.0	1.3	1.0-1.7	0.03	1.4	1.0-1.9	0.04
	Ethanol ablation				0.95			
	Other				0.69			
Milan	Within	71.3	1.0	–	–	1.0	–	–
	Outside but downstaged	64.3	1.2	1.0-1.4	0.04	1.1	0.9-1.3	0.55
	Outside not downstaged	60.6	1.4	1.2-1.7	<0.001	1.1	0.8-1.3	0.57
AFP	>1000	33.5 versus 50.9	1.9	1.5-2.4	<0.001	1.5	1.1-2.0	0.007
Vascular invasion		54.9 versus 74.5	1.9	1.7-2.1	<0.001	1.3	1.1-1.6	0.001
Grade	Well differentiated	75.8	1.0	–	–	1.0	–	–
	Moderate differentiation	68.2	1.3	1.1-1.4	<0.001	1.2	1.0-1.4	0.03
	Poor differentiation	56.6	2.0	1.7-2.3	<0.001	1.4	1.2-1.8	0.001
	Unknown differentiation	41.6	0.9	0.8-1.1	0.58	1.1	0.9-1.4	0.26
Focality (explant)	No lesions	76.2	1.0	–	–	1.0	–	–
	Single	73.0	1.1	0.8-1.6	0.41	1.2	0.8-2.0	0.39
	Multifocal	68.3	1.4	1.0-1.9	0.05	1.3	0.8-2.2	0.37
Maximum tumor diameter	0-2 cm	73.0	1.0	–	–	1.0	–	–
	2-5 cm	69.5	1.2	1.0-1.3	0.005	1.2	0.8-2.0	0.41
	>5 cm	56.2	1.7	1.5-2.1	<0.001	1.2	0.7-2.1	0.41
Pathologic T stage	T1	75.8	1.0	–	–	1.0	–	–
	T2	68.2	1.3	1.2-1.5	<0.001	1.1	1.0-1.3	0.09
	T3a	56.6	1.8	1.4-2.2	<0.001	1.5	1.2-2.0	0.001
	T3b	41.6	3.1	2.6-3.8	<0.001	1.9	1.5-2.6	<0.001

further understand the precise drivers of mortality in elderly patients who received a transplant as a result of HCC, we supplemented our analysis with another independent cohort of patients for whom detailed data were available from a single center. The single-center cohort had 302 patients of which 105 (34.8%) were aged ≥65 years. We first evaluated if metabolic comorbidities, performance status, or cardiovascular disease could explain why older patients have poor transplant outcomes because previous studies have suggested that older patients have higher rates of cardiovascular-related death.[7,8,15-17] Patients who were aged ≥65 years did not have statistical differences in race ($P = 0.22$), ethnicity ($P = 0.22$),

TABLE 3. Impact of Older Age on Posttransplant RFS in Patients With HCC

		RFS Univariable Analysis				RFS Multivariable Analysis		
Variable	Subcategory	5-Year Survival	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	≥65 years	62.6 versus 67.7	1.2	1.1-1.4	0.001	1.2	1.1-1.4	0.002
Sex	Male				>0.99	1.0	0.9-1.2	0.66
HCC etiology	NASH				0.31			
	Hepatitis B	64.2 versus 47.3	0.6	0.5-0.7	<0.001	0.7	0.6-0.9	0.01
	Hepatitis C	46.1 versus 53.9	1.3	1.2-1.4	<0.001	1.2	1.0-1.4	0.03
	ALD				0.52			
	Cryptogenic				0.26			
	Other	61.0 versus 48.3	0.7	0.5-0.8	0.001	0.7	0.5-0.9	0.009
LRT	0	68.3	1.0	–	–	1.0	–	–
	1	67.9	0.9	0.8-1.1	0.32	1.0	0.8-1.2	0.86
	2	65.7	1.1	0.9-1.2	0.34	1.0	0.8-1.2	0.86
	3	64.4	1.1	0.9-1.3	0.50	1.0	0.8-1.3	0.84
	4	45.0	1.7	1.4-2.1	<0.001	1.4	1.1-1.8	0.02
Type of bridging therapy	TACE				0.38			
	Thermal ablation				0.69			
	Radioembolization				0.29			
	Resection	38.6 versus 49.4	1.4	1.1-1.8	0.005	1.5	1.1-2.0	0.008
	Ethanol ablation				0.11	1.2	0.9-1.6	0.33
	Other				0.57			
Milan	Within	68.2	1.0	–	–	1.0	–	–
	Outside but downstaged	59.5	1.3	1.1-1.5	0.006	1.1	0.9-1.3	0.59
	Outside not downstaged	54.3	1.5	1.3-1.8	<0.001	1.1	0.9-1.3	0.55
AFP	≥1000	32.1 versus 49.4	2.2	1.7-2.8	<0.001	1.5	1.2-2.0	0.002
Vascular invasion		49.2 versus 72.1	2.1	1.9-2.3	<0.001	1.4	1.2-1.7	<0.001
Grade	Well differentiated	72.2	1.0	–	–	1.0	–	–
	Moderate differentiation	64.9	1.3	1.2-1.5	<0.001	1.2	1.0-1.4	0.01
	Poor differentiation	48.5	2.1	1.8-2.5	<0.001	1.5	1.2-1.8	<0.001
	Unknown differentiation	72.3	0.9	0.8-1.1	0.51	1.1	0.9-1.3	0.35
Focality (explant)	No lesions	73.0	1.0	–	–	1.0	–	–
	Single	70.9	1.2	0.9-1.6	0.28	1.2	0.8-2.0	0.38
	Multifocal	64.1	1.5	1.1-2.0	0.01	1.3	0.7-2.1	0.40

TABLE 3. *Continued*

Variable	Subcategory	5-Year Survival	RFS Univariable Analysis HR	95% CI	*P* Value	RFS Multivariable Analysis HR	95% CI	*P* Value
Maximum tumor diameter	0-2 cm	71.4	1.0	–	–	1.0	–	–
	2-5 cm	65.4	1.3	1.1-1.4	<0.001	1.1	1.0-1.3	0.09
	>5 cm	51.4	2.0	1.7-2.3	<0.001	1.4	1.1-1.8	0.01
Pathologic T stage	T1	74.0	1.0	–	–	1.0	–	–
	T2	64.5	1.4	1.3-1.5	<0.001	1.1	1.0-1.3	0.09
	T3a	49.4	2.1	1.7-2.5	<0.001	1.4	1.1-2.0	0.01
	T3b	35.9	3.5	3.0-4.3	<0.001	1.8	1.4-2.4	<0.001

diabetes mellitus (36.2% versus 29.9%; $P = 0.27$), hypertension (49.5% versus 39.6%; $P = 0.10$), hyperlipidemia (20.0% versus 13.7%; $P = 0.15$), obesity (26.7% versus 37.1%; $P = 0.07$), metabolic syndrome (16.2% versus 14.2%; $P = 0.65$), comorbid cardiac disease (4.8% versus 2.0%; $P = 0.18$), or smoking (39.0% versus 41.6%; $P = 0.66$; Supporting Fig. 3A). Older patients were more likely to have good functional status (Eastern Cooperative Oncology Group 0/1, 97.1% versus 89.8%; $P = 0.02$; Supporting Fig. 3B). The distribution of Child-Turcotte-Pugh stage was also not significantly different between the older and younger patients ($P = 0.06$; Supporting Fig. 3C). Similar to the UMHTC cohort, older and younger patients in the single-center cohort also had comparable tumor burden at diagnosis and transplantation. Despite these similarities, patients aged ≥65 years in this cohort did have significantly poorer OS (5-year survival 71.5% versus 85.0%; HR, 2.1 [$P = 0.005$]) and RFS (5-year survival 69.3% versus 81.3%; HR, 1.9 [$P = 0.009$]; Supporting Fig. 3D,E). Next, similar to the UMHTC cohort, the HCC recurrence rates were not significantly different in the older and younger patients (11.4% versus 8.1%; $P = 0.35$; Supporting Fig. 3F). Thus, poor posttransplant clinical outcomes in elderly patients cannot be directly attributed to pretransplant comorbidities, functional status, or HCC.

In the overall cohort, the major causes of death were cancer (9.3%; n = 28) and infection (3.0%; n = 9; Table 5). Patients aged ≥65 years had higher cancer-related mortality rates (14.3% [n = 15] versus 6.6% [n = 13]; $P = 0.03$), but HCC-related mortality was not statistically different (9.5% [n = 10] versus 4.6% [n = 9]; $P = 0.09$). The rate of other causes of death such as infection (2.9% versus 3.0%; $P = 0.52$), bleeding (1.0% versus 1.5%; $P > 0.99$), or cardiac causes (0.0% versus 1.0%; $P = 0.55$) were not higher in those aged ≥65 years. Patients who died from malignancy (n = 10) had de novo primary cancers of the lung (n = 4), gastrointestinal system (n = 3), blood (n = 1), genitourinary system (n = 1), and skin (n = 1), and did not die as a result of cancer recurrence. Of note, all of these patients had undergone standard screening for cancer prior to transplantation and had been cancer free for 5 years prior to LT. Lastly, older patients overall had a higher rate of de novo cancer (18.1% versus 7.6%; $P = 0.006$) in the posttransplant period. Primary sites for these de novo cancers in elderly patients included the gastrointestinal tract (esophageal [n = 1], pancreatic [n = 3],

TABLE 4. Subgroup Analysis of Predictors of Survival in Patients Aged ≥65 Years

		OS Subgroup Analysis in Patients Aged ≥65 Years						RFS Subgroup Analysis in Patients Aged ≥65 Years					
		Univariable			Multivariable			Univariable			Multivariable		
Variable	Subcategory	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Sex	Male			0.78	1.0	0.8-1.3	0.93			0.37	0.9	0.7-1.2	0.54
HCC etiology	NASH			0.69						0.90			
	Hepatitis B	0.6	0.4-0.9	0.01	0.5	0.3-0.8	0.006	0.6	0.4-0.9	0.02	0.5	0.3-0.9	0.006
	Hepatitis C	1.4	1.1-1.7	0.003	1.1	0.8-1.4	0.65	1.4	1.2-1.7	0.001	1.1	0.8-1.5	0.49
	ALD			0.12	0.6	0.4-0.8	0.003			0.11	0.6	0.4-0.9	0.006
	Cryptogenic			0.62						0.80			
	Other			0.15	0.5	0.3-0.8	0.004			0.13	0.5	0.3-0.8	0.006
LRT	0	1.0	–	–				1.0	–	–	1.0	–	–
	1			0.29						0.34			
	2			0.19						0.43			
	3			0.52						0.18			
	4			0.95						0.68			
Type of bridging therapy	TACE			0.54						0.98			
	Thermal ablation			0.74						0.72			
	Radioembolization			0.11	0.6	0.3-1.2	0.13			0.15	0.6	0.3-1.3	0.14
	Resection			0.42						0.35			
	Ethanol ablation			0.69						0.92			
	Other			0.43						0.46			
Incidental explant in lesion				0.59						0.98			
Milan	Within	1.0	—	—	1.0	—	—	1.0	—	—	1.0	—	—
	Outside but downstaged	1.1	0.8-1.6	0.67	1.0	0.6-1.4	0.81	1.2	0.8-1.7	0.33	1.0	0.7-1.5	0.97
	Outside not downstaged	1.5	1.1-2.2	0.02	1.4	0.9-2.1	0.10	1.6	1.1-2.3	0.008	1.4	0.9-2.2	0.10
AFP	≥1000			0.12	1.1	0.6-2.1	0.79			0.11	1.2	0.6-2.4	0.55
Vascular invasion		1.8	1.4-2.2	<0.001	1.5	1.1-2.0	0.01	1.8	1.5-2.3	<0.001	1.5	1.1-2.1	0.007
Grade	Well differentiated	1.0	–	–	1.0	–	–	1.0	–	–	1.0	–	–
	Moderate differentiation	1.1	0.9-1.5	0.37	1.1	0.8-1.4	0.70	1.1	0.9-1.5	0.33	1.1	0.8-1.5	0.48
	Poor differentiation	1.5	1.0-2.1	0.04	1.2	0.8-1.8	0.47	1.5	1.1-2.1	0.03	1.1	0.7-1.6	0.74
	Unknown differentiation	0.8	0.5-1.1	0.18	0.9	0.6-1.3	0.54	0.8	0.5-1.1	0.14	0.9	0.6-1.4	0.71
Focality (explant)	No lesions	1.0	–	–				1.0	–	–	1.0	–	–
	Single			0.38						0.28	2.4	0.6-9.9	0.21
	Multifocal			0.21						0.13	1.9	0.4-8.4	0.39

TABLE 4. *Continued*

Variable	Subcategory	OS Subgroup Analysis in Patients Aged ≥65 Years						RFS Subgroup Analysis in Patients Aged ≥65 Years					
		Univariable			Multivariable			Univariable			Multivariable		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Maximum tumor diameter	0-2 cm	1.0	–	–	1.0	–	–	1.0	–	–	1.0	–	–
	2-5 cm	1.2	1.0-1.6	0.09	1.3	1.0-1.8	0.06	1.3	1.0-1.6	0.06	1.2	0.9-1.6	0.29
	>5 cm	1.7	1.2-2.4	0.006	1.3	0.7-2.3	0.38	1.7	1.2-2.5	0.002	1.2	0.7-2.1	0.58
Pathologic T stage	T1	1.0	–	–	1.0	–	–	1.0	–	–	1.0	–	–
	T2	1.3	1.0-1.6	0.06	1.1	0.8-1.5	0.42	1.3	1.1-1.7	0.01	1.2	0.9-1.6	0.32
	T3a	1.8	1.2-2.7	0.006	1.5	1.0-2.5	0.07	2.0	1.3-3.0	0.001	1.8	1.1-2.8	0.02
	T3b	2.4	1.6-3.6	<0.001	1.9	1.1-3.3	0.02	2.6	1.8-3.9	<0.001	1.8	1.1-3.2	0.03

and colon [n = 2]), skin (n = 3 de novo and n = 5 recurrence), lung (n = 4), blood (n = 3), and genitourinary system (n = 2). Thus, elderly patients had a higher incidence of posttransplant cancer-related death.

Discussion

HCC is a leading indication for LT in the United States, and the proportion of older patients with HCC needing a transplant is projected to increase during the coming decade.[3,4] Even as transplant practices around the world continue to extend the upper limit for age to undergo transplantation, there are lingering concerns about the impact of older age on clinical outcomes. We used data from a large, US multicenter HCC cohort of 4980 adult patients, from 10 UNOS regions, to evaluate the impact of increasing age on posttransplant clinical outcomes. We found that older age at transplantation was significantly and independently associated with poor OS in patients with HCC, with every 5-year increment in age >50 years being associated with an 8.3% increase in the mortality rate. However, the higher mortality rate was not attributed to HCC-related causes or HCC recurrence but to non–HCC-related causes. Furthermore, we showed that patients aged ≥65 years are more likely to develop de novo cancers in the posttransplant period, which likely explains their worse outcomes.

We would like to emphasize that despite having worse outcomes than their younger counterparts, patients aged >65 years did overall enjoy relatively long survival with a 5-year survival rate of 66%. Given that even patients with early-stage HCC only have a median survival of 10 to 14 months if untreated,[18] it was clear that LT is still the best treatment option for elderly patients with cirrhosis. Tumor features that imply aggressiveness and are predictive of survival, such as stage, grade, vascular invasion, and AFP, were not different between older and younger patients with HCC. Also, older patients were as likely to receive LRTs and were also as likely to achieve a complete response before transplantation. Lastly, using competing risk analysis, we established that the cumulative incidence for death from HCC or from HCC recurrence was not higher in elderly patients compared with their younger counterparts. Thus, older age alone should not serve as a contraindication for LT in patients with HCC because LT offers the best curative option in patients with cirrhosis, regardless of age.

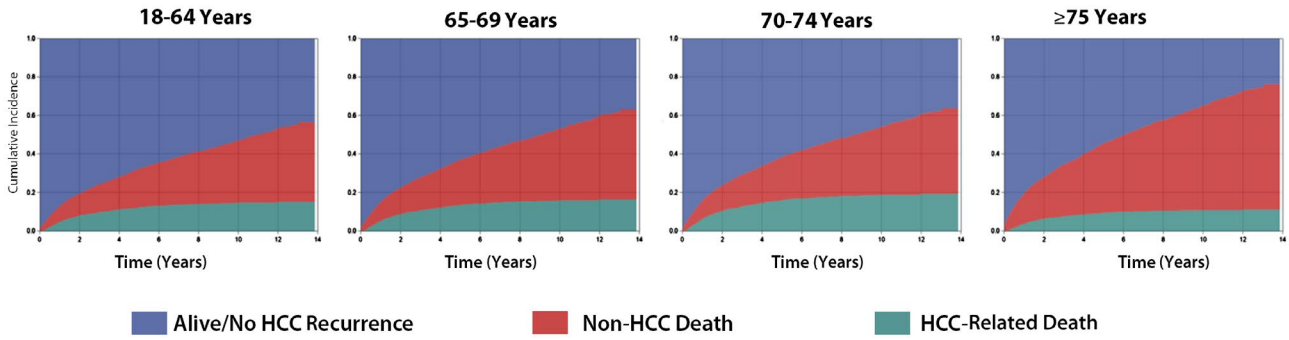

FIG. 4. Competing risk analysis for the impact of age on HCC-related and non–HCC-related death.

TABLE 5. Causes of Morbidity and Mortality in Older Patients Who Received a Transplant as a Result of HCC

Variable	Subcategory	Age <65 Years (n = 197; 65.2%)	Age ≥65 Years (n = 105; 34.8%)	*P* Value
Causes of death, n (%)	Cancer	13 (6.6)	15 (14.3)	0.03
	Infection	6 (3.0)	3 (2.9)	0.52
	Bleeding	3 (1.5)	1 (1.0)	>0.99
	Cardiac	2 (1.0)	0 (0.0)	0.55
	Other	7 (6.7)	7 (3.6)	0.22
Types of cancer causing death, n (%)*	Skin	1 (0.5)	0 (0.0)	>0.99
	Lung	1 (0.5)	3 (2.9)	0.24
	Blood	0 (0)	1 (1.0)	0.35
	Gastrointestinal	2 (1.0)	1 (1.0)	>0.99
	Genitourinary	0 (0.0)	1 (1.0)	0.35
	HCC	10 (9.5)	9 (4.6)	0.09
De novo cancer, n (%)	Any	15 (7.6)	19 (18.1)	0.006
	Skin	7 (3.6)	8 (7.6)	0.12
	Lung	4 (3.8)	4 (2.0)	0.46
	Gastrointestinal	4 (2.0)	5 (4.8)	0.29
	Blood	1 (0.5)	3 (2.9)	0.12
	Genitourinary	2 (1.9)	2 (1.0)	0.61

*One patient who was aged <65 years at the time of death succumbed from multiorgan system failure secondary to both non–small cell lung cancer and metastatic HCC.

In our study, we also showed that patients aged >65 years have higher posttransplant mortality despite careful patient selection based on cardiovascular risk profile and functional status. Although other studies have evaluated the impact of recipient age on posttransplant outcomes,[10,19] the precise cause of worse outcomes with older age has not been clarified. One of the limitations of such studies is the lack of access to granular data on the actual cause of death. In the multicenter database, cause of death was defined as HCC-related death versus non-HCC death. Using competing risk analysis, we determined that non-HCC causes of death were responsible for the increased mortality seen in elderly patients. We further validated these findings using a single-center study where more precise data on cause of death were available and that additionally showed that non-HCC de novo cancers were a clinically significant cause of death in elderly patients.

The finding that de novo cancers drive posttransplant mortality in older patients with HCC has important implications for posttransplant management. The worse outcomes can potentially be mitigated by rigorously following cancer surveillance guidelines and minimizing immunosuppression in elderly patients. Several societies have published detailed guidelines on posttransplant cancer surveillance,[20-22] but

further studies will be needed to clarify whether older patients should be under more frequent surveillance compared with their younger counterparts. In our study, skin cancer was the most common incident de novo cancer, but it was rarely associated with death. Gastrointestinal and lung cancers were the common causes of death in the patients with de novo cancer, and >80% of these patients had a history of tobacco smoking. We emphasize annual colorectal cancer screening for high-risk patients and lung cancer screening with low-dose computed tomography (CT) scans for at-risk smokers. The US Preventative Task Force now recommends lung cancer screening with yearly low-dose CT scans for patients aged >50 years with smoking histories of >20 packs per year. We need to follow these newer screening guidelines, especially in the vulnerable elderly patients who received a transplant as a result of HCC (Supporting Table 3).

The other strategy to improve outcomes in elderly patients who received a transplant as a result of HCC is to minimize posttransplant immunosuppression. Calcineurin inhibitors (CNIs) have been shown to have a dose-dependent risk for secondary malignancies, whereas sirolimus and related agents do not appear to have this risk. However, CNIs still remain the first line of posttransplant immunosuppression given their efficacy and the risk for cardiovascular mortality with sirolimus use.[23] We propose that a rational age-adapted immunosuppression regimen should be adapted after LT, as has been previously suggested.[24] Specifically, we recommend avoiding dual or triple immunosuppression regimens in elderly patients. Moreover, although similar doses of CNI might be needed at commencement, by the end of 1 year after LT, CNI dosages should be reduced to a minimum in elderly patients. Older patients have even been shown to tolerate withdrawal of immunosuppression therapy better than their younger counterparts.[25]

This study has some of the common limitations associated with retrospective studies, including potential coding errors, misclassification, and lack of access to donor data. However, the UMHTC database is 1 of the largest HCC-specific cohorts that has detailed data on bridging treatment and explant pathology. To understand the cause of poor clinical outcomes in elderly patients, we needed to understand the precise cause of death. The UMHTC cohort had information on whether the cause of death was related to HCC or not, but the specific cause of death was not available. To overcome this limitation, we supplemented the analysis using a second cohort of patients at Stanford University. Obtaining details on the causes of death from this database was particularly useful in validating the mortality results obtained from the UMTHC study and providing new insights into the drivers of mortality in the elderly patients. Larger studies with long-term follow-up and information on causes of death will be needed to confirm the generalizability of our findings.

Older patients are increasingly undergoing LT for HCC. We show here that the long-term posttransplant clinical outcomes of patients aged >65 years is worse than their clinically and physiologically comparable younger counterparts. These worse outcomes are mostly driven by increased non–HCC-related mortality. Importantly, we show that LT is still an effective curative option for HCC, even in elderly patients. Therefore, we stop short of defining a clear age cutoff for transplantation, but emphasize the importance of mitigating the risk of death from other causes to improve the OS in this cohort. Minimizing posttransplant immunosuppression and performing aggressive surveillance for de novo cancers in the posttransplant period are measures that can help improve outcomes in elderly patients undergoing LT for HCC.

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