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Post-Transplant Outcomes in Older Patients with Hepatocellular Carcinoma (HCC) are Driven by non-HCC Factors

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Abstract

The incidence of hepatocellular carcinoma (HCC) is growing in the US, especially among the elderly. Older patients are increasingly getting transplanted for HCC, but the impact of advancing age on long-term post-transplant outcomes is not clear. To study this, we used data from the US Multicenter HCC Transplant Consortium (UMHTC) of 4980 patients. We divided the patients into 4 groups by age at transplantation- 18–64 (n = 4001), 65–69 (n = 683), 70–74 (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 over 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 transplanted for HCC (n = 302). Patients older than 65 years had a higher incidence of de-novo cancer (18.1% vs 7.6%, p = 0.006) after transplantation and higher overall cancer-related mortality (14.3% vs 6.6%, p = 0.03).

Conclusion ––—Even carefully selected elderly patients with HCC have significantly worse post-transplant survival, which are mostly driven by non-HCC related causes. Minimizing immunosuppression and closer surveillance for *de novo* cancers can potentially improve outcomes in elderly patients transplanted for HCC.

Keywords

Age; Mortality; Malignancy; Transplant; HCC

INTRODUCTION

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 older than 65 years [2]. These trends are expected to continue, with a predicted increase of 50.0% in the incidence of HCC over 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 getting transplanted has increased from 17.4% in 2009 to 41.9% in 2019 [5].

While there is no official upper age limit for transplantation, advanced age is associated with higher rates of waiting list removal due to death or tumour progression in patients with HCC [6,7]. However, the impact of age on long-term post-transplant survival in patients with HCC is not clear. Few studies have suggested that patients older than 60 years have lower post-transplant survival rates due to 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 be transplanted if they have low cardiovascular risk and good functional status. The long-term outcomes of transplanted elderly patients 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 analysed. We sought to evaluate the impact of increasing age on long-term post-transplant outcomes and to identify risk factors associated with higher mortality among elderly patients ≥ 65 years. Additionally, a single-center database with more granular details was evaluated to identify the specific causes that drive mortality in elderly patients.

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, 4,980 consecutively identified adult patients from 10 of the 11 United Network for Organ Sharing (UNOS) regions who were transplanted for 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 liver transplantation: 18 – 64 years, 65 – 69 years, 70 – 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 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-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, micro- and macro-vascular invasion, and American Joint Committee on Cancer (AJCC) tumor staging.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, IBM) 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 analysis was used for survival analyses, with the log-rank test being used to compare outcomes. Overall survival was defined as the duration between the date of LT and the date of death from any cause. Recurrence-free survival 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.

In order to evaluate the linearity of the relationship between age and overall survival 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 (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 (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 US Multicenter HCC Transplant Consortium (UMHTC) database consists of a total of 4980 adult patients transplanted in the US for HCC at 20 centres from ten 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 Figure 1A. To understand the impact of age on liver transplantation, patients were categorized into the following clinically relevant groups at five-year increments based on age at transplantation - a. 18 – 64 years (n = 4001); b. 65 – 69 years (n = 683); c. 70 – 74 years (n = 252) and d. ≥ 75 years (n = 44) (Figure 1B, Table 1). In this study, older patients are defined as those 65 or older, unless otherwise noted. The median age at transplantation for each UNOS region is shown in Figure 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 gender progressively increased with higher age groups, with 32.4% (n = 96) of septuagenarians and 45.5% (n = 20) of those ≥ 75 being female (Figure 1D). The incidence of non-alcoholic steatohepatitis (NASH)-HCC also progressively increased with age ($p < 0.001$) (Figure 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 exemption (MELD) score was lower than 15 in all four age groups but was slightly higher in those ≥ 75 years ($p = 0.001$). There was no difference in the median time from listing to transplantation between the four 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 pre-transplant tumor burden between the different age groups, the proportion of patients who were within the Milan criteria at diagnosis was not statistically different ($p = 0.59$) (Figure 2A). Older patients had a lower median maximum AFP (13.4 (IQR 5.9 – 71.7) vs 19.1 (7.0 – 87.1), $p < 0.001$). However, the proportion of patients with AFP values above 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) vs (1.0 (2.0); $p = 0.10$) (Figure 2B). Older patients were also more likely to be bridged with transarterial chemoembolization (TACE) ($p = 0.01$), while the receipt of the other modes of LRTs was not significantly different between the four 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 amongst all age groups ($p = 0.07$ and $p = 0.81$, respectively) (Figure 2C). Thus, tumor-specific attributes were not influenced by patient age.

Older age associated with poor post-transplantation clinical outcomes in HCC

In the overall cohort, the 5-year post-transplant 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) (Figure 3A, Supplementary Fig 1). The 5-year OS progressively decreased from 70.9% in those aged 18 – 64 to 62.7% in patients ≥ 75, while the HR progressively increased from 1.0 in the youngest age group to 1.7 in those ≥ 75 (p (trend) = 0.0001). To evaluate the linearity of the relationship between age and OS or RFS, we performed Cox proportional hazards regression using penalized splines (P-splines). Beyond the age of 50 years, the risk (log Hazards) of mortality increased linearly with increasing age (Supplementary Figure 2). Also, a dose-response effect of age on survival was observed, with every 5-year increase in age over 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 was confirmed to be an independent predictor of OS even after adjusting for multiple variables like gender, 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 (HR 1.2 p = 0.03; HR 1.4 p = 0.001, respectively), and advanced pathologic stage (HR 1.5 p = 0.001; 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 four age groups (Figure 3B, Supplementary Table1). To identify risk factors that predict survival in the elderly, we performed subgroup analysis in patients ≥ 65 (Table 4). On multivariable analysis for both OS and RFS, T3 stage tumors and vascular invasion were the only two variables predicting worse clinical outcomes (OS HR 1.9 p = 0.02; HR 1.5 p = 0.01, respectively; RFS HR 1.8, p = 0.03; 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), while the cumulative incidence of death from non-HCC causes was statistically higher in older age groups (p = 0.004) (Figure 4, Supplementary Table 2). Thus, analysis of the large multicenter HCC data reveals that long-term post-transplant 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 due to non-HCC causes. To validate our findings and to further understand the precise drivers of mortality in elderly patients transplanted for HCC, we supplemented our analysis with another independent cohort of patients for whom detailed data was available from a single-center. The single-center cohort had 302 patients of which 105 (34.8%) were 65 years or older. We first evaluated if metabolic comorbidities, performance status or cardiovascular

disease could explain why older patients have poor transplant outcomes, since previous studies have suggested that older patients have higher cardiovascular-related death [7,8,15–17]. Patients who were ≥ 65 or younger did not have statistical differences in race (p = 0.22), ethnicity (p = 0.22), diabetes (36.2% vs 29.9%, p = 0.27), hypertension (49.5% vs 39.6%, p = 0.10), hyperlipidemia (20.0% vs 13.7%, p = 0.15), obesity (26.7% vs 37.1%, p = 0.07), metabolic syndrome (16.2% vs 14.2%, p = 0.65), comorbid cardiac disease (4.8% vs 2.0%, p = 0.18), or smoking (39.0% vs 41.6%, p = 0.66) (Supplementary Figure 3A). Older patients were more likely to have good functional status (Eastern Cooperative Oncology Group (ECOG) 0/1, 97.1% vs 89.8%, p = 0.02) (Supplementary Figure 3B). The distribution of Child Pugh stage was also not significantly different between older and younger patients (p = 0.06) (Supplementary Figure 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 ≥ 65 in this cohort did have significantly poorer OS (5-year survival 71.5% vs 85.0%, HR 2.1, p = 0.005) and RFS (5-year survival 69.3% vs 81.3%, HR = 1.9, p = 0.009) (Supplementary Figures 3D/3E). Next, similar to the UMHTC cohort, HCC recurrence rates were not significantly different in older and younger patients (11.4% vs 8.1%, p = 0.35) (Supplementary Figure 3F). Thus, poor post-transplant clinical outcomes in elderly patients cannot be directly attributed to pre-transplant comorbidities, functional status, or HCC.

In the overall cohort, the major causes of death were cancer (9.6% (n = 29)) and infection (3.3% (n = 10)) (Table 5). Patients ≥ 65 had higher cancer-related mortality (14.3% (n = 15) vs 6.6% (n = 13), p = 0.03), but HCC-related mortality was not statistically different (9.5% (n = 10) vs 4.6% (n = 9), p = 0.09). The rate of other causes of death like infection, (2.9% vs 3.0%, p = 0.52), bleeding (1.0% vs 1.5%, p > 0.99), or cardiac causes (0.0% vs 1.0%, p = 0.55) were not higher in those ≥ 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 due to 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% vs 7.6%, p = 0.006) in the post-transplant period. Primary sites for these *de novo* cancers in older living patients included the gastrointestinal tract (esophageal (n = 1), pancreatic (n = 3), 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 post-transplant cancer-related death.

DISCUSSION

HCC is a leading indication for liver transplantation in the US, and the proportion of older patients with HCC needing a transplant is projected to increase over 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 use data from a large US multicenter HCC cohort of 4,980 adult patients, from ten UNOS regions, to evaluate the impact of increasing age on post-transplant clinical outcomes. We found that older age at transplantation was significantly and independently associated with poor overall survival in patients with HCC, with every 5-year

increment in age over 50 years being associated with 8.3% increase in the mortality rate. However, the higher mortality was not due to HCC-related causes or HCC recurrence, but due to non-HCC-related causes. Further, we show that patients ≥ 65 years are more likely to develop *de novo* cancers in the post-transplant period, which likely explains their worse outcomes.

We would like to emphasize that despite having worse outcomes than their younger counterparts, patients older than 65 years did overall enjoy relatively long survival with a 5-year survival of 66%. Given that even patients with early stage HCC only have a median survival of 10–14 months if untreated [18], it is clear that LT still is the best treatment option for elderly patients with cirrhosis. Tumor features which imply aggressiveness and are predictive of survival, like 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 establish that cumulative incidence for death from HCC or from HCC recurrence was not higher in elderly patients compared to their younger counterparts. Thus, older age alone should not serve as a contraindication for LT in patients with HCC since LT offers the best curative option in patients with cirrhosis, regardless of age.

In our study, we also show that patients older than 65 years have higher post-transplant mortality, despite careful patient selection based on cardiovascular risk profile and functional status. While other studies have evaluated the impact of recipient age on post-transplant outcomes [19,20], 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 determine 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 was available, and which additionally showed that non-HCC *de novo* cancers were an important cause of death in elderly patients.

The finding that *de novo* cancers drive post-transplant mortality in older patients with HCC has important implications for post-transplant management. The worse outcomes can potentially be mitigated by rigorously following cancer surveillance guidelines and minimizing immunosuppression in the elderly patients. Several societies have published detailed guidelines on post-transplant cancer surveillance [21–23], but further studies will be needed to clarify whether older patients should be under more frequent surveillance compared to their younger counterparts. In our study, skin cancer was the most common incident *de novo* cancer but it was rarely associated with death. GI and lung cancers were the common cause of death in the patients with *de novo* cancer, and more than 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 CT scans for at risk smokers. The United States Preventative Task force (USPSTF) now recommends lung cancer screening with yearly low dose CT scans for patients with > 20 pack years smoking history

over the age of 50. We need to follow these newer screening guidelines, especially in the vulnerable elderly patients transplanted for HCC (Supplementary Table 3).

The other strategy to improve outcomes in elderly patients transplanted for HCC is to minimize post-transplant immunosuppression. Calcineurin inhibitors (CNIs) have been shown to have a dose-dependent risk for secondary malignancies, while sirolimus and related agents do not appear to have this risk. However, CNIs still remain the first line of post-transplant immunosuppression given their efficacy and also the risk for cardiovascular mortality with sirolimus use [24]. We propose that a rational age-adapted immunosuppression regime should be adapted after liver transplantation, as has been previously suggested [25]. Specifically, we would recommend avoiding dual or triple IS regimens in elderly patients. Moreover, while similar doses of CNI might be needed at commencement, by the end of the one year post LT, CNI dosages should be reduced to a minimum in elderly patients. Older patients have even been shown to tolerate withdrawal of IS therapy better than their younger counterparts [26].

This study does have 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 one 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 did have 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 cause of death will be needed to confirm the generalizability of our findings.

Older patients are increasingly undergoing liver transplantation for HCC. We show here that the long-term post-transplant clinical outcome of patients older than 65 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 liver transplant is still an effective curative option for HCC, even in elderly patients. Therefore, we stop short of defining a clear age cut-off for transplantation, but emphasize the importance of mitigating the risk of death from other causes to improve the overall survival in this cohort. Minimizing post-transplant immunosuppression and performing aggressive surveillance for *de novo* cancers in the post-transplant period are measures that can help improve outcomes in elderly patients undergoing liver transplantation for HCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AFP	alpha-fetoprotein
AASLD	American Association for the Study of Liver Diseases
ALD	alcohol related liver disease
CI	confidence interval
CIF	cumulative incidence function
CNI	calcineurin inhibitors
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
HCC	hepatocellular carcinoma
IQR	interquartile range
LT	Liver transplantation
LRT	locoregional therapy
MELD	model for end-stage exemption
NASH	non-alcoholic steatohepatitis
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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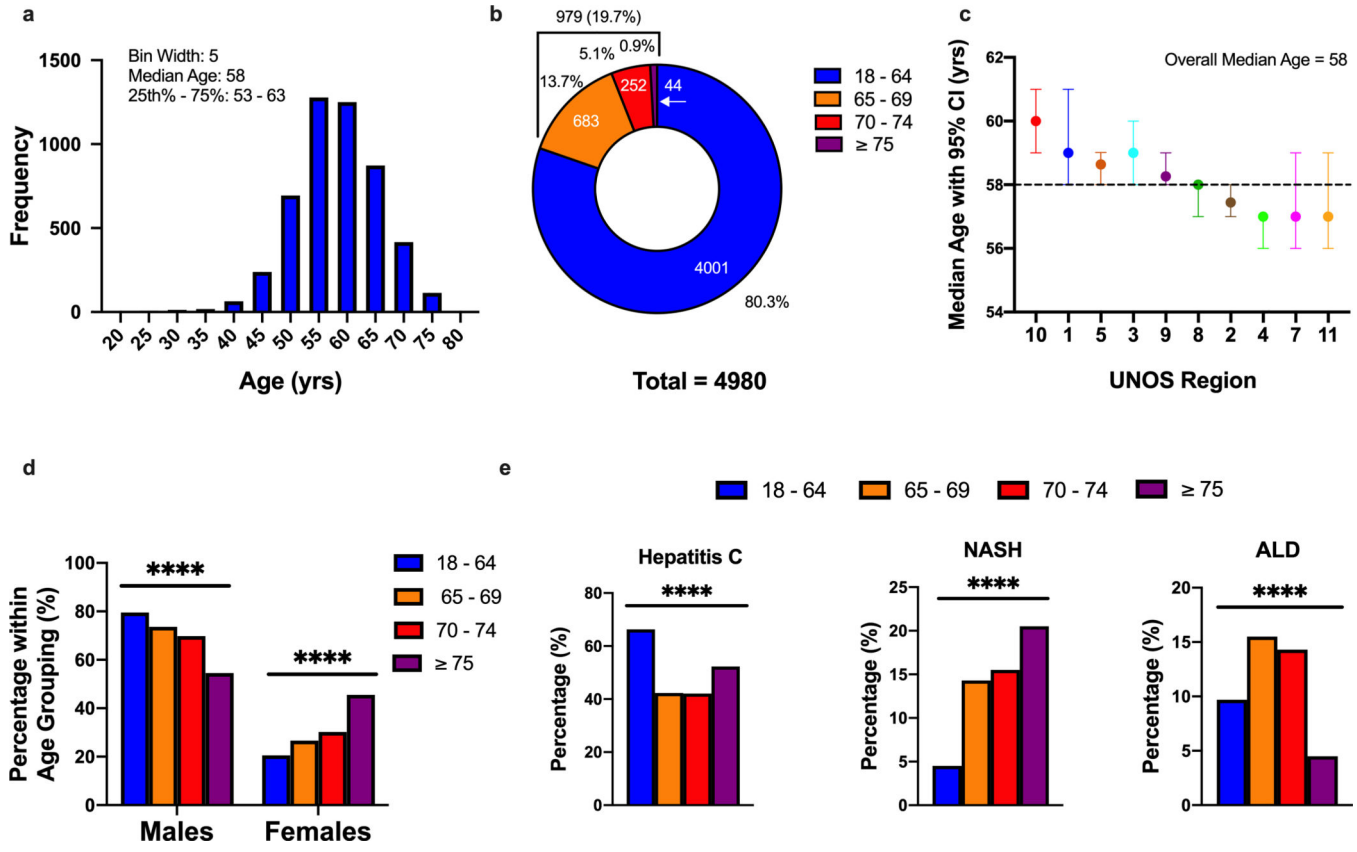

Figure 1. Demographic and clinical features of elderly patients transplanted for HCC

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.

ALD = alcoholic liver disease, HCC = hepatocellular carcinoma, NASH = non-alcoholic steatohepatitis, UNOS = United Network for Organ Sharing

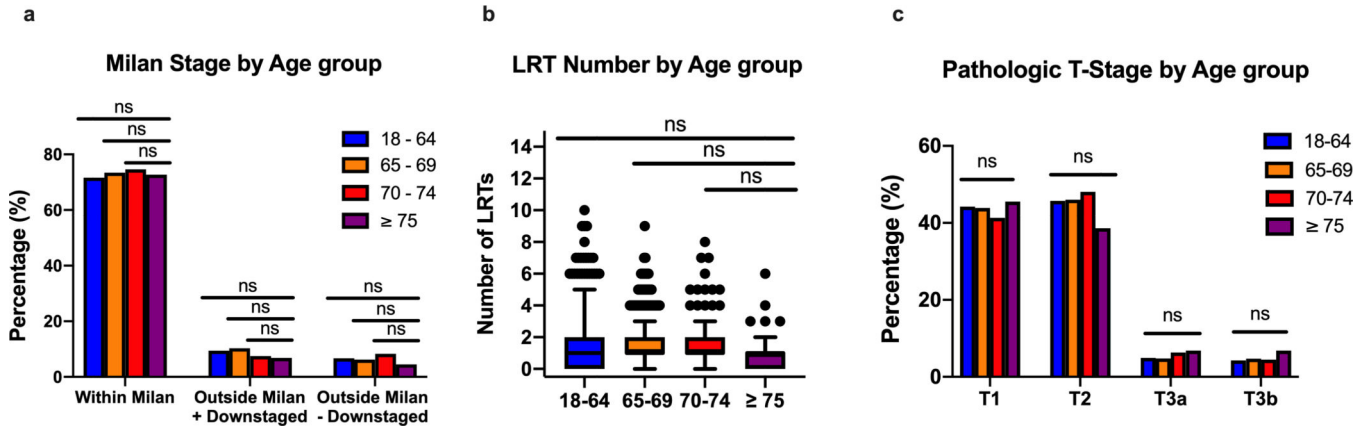

Figure 2. Tumor-specific Attributes in Elderly Patients Transplanted for HCC

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.

HCC = hepatocellular carcinoma, LRT = Locoregional Therapy

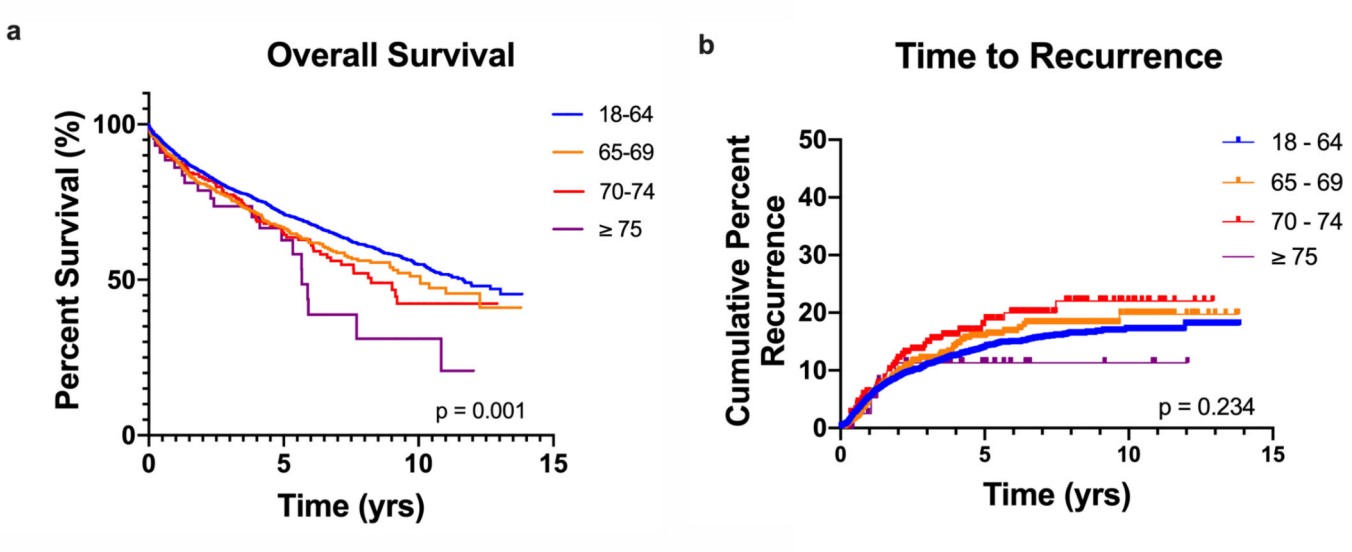

Figure 3: Long-term post-transplant clinical outcomes in patients transplanted for HCC

a. Overall survival stratified by age groups in patients transplanted for HCC.

b. Time to Recurrence stratified by age groups in patients transplanted for HCC

HCC = hepatocellular carcinoma, OS = overall survival, RFS = recurrence-free survival

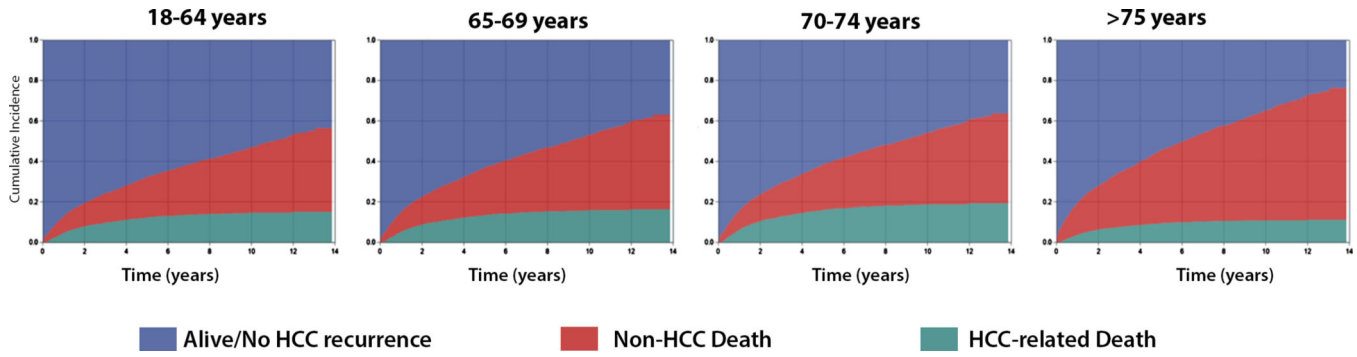

Figure 4. Competing Risk Analysis for the Impact of Age on HCC-Related and Non-HCC-Related Death

CI = confidence interval, CIF = cumulative incidence function, HCC = hepatocellular carcinoma

Table 1

Demographic and clinical features stratified by age groups

Variables	Sub-Category	All Age Groups	Age Groups				
			18–64 n = 4001	65–69 n = 683	70–74 n = 252	≥ 75 n = 44	P-value
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 (9.5)	13.6 (10.0)	13.0 (10.0)	13.0 (9.0)	14.3 (17.4)	**< 0.001**
	MELD Exception	25.0 (7.0)	25.0 (7.0)	25.0 (6.0)	25.0 (6.0)	25.0 (9.0)	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 Locoregional Therapies, 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 Locoregional Therapies, 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

Variables	Sub-Category	All Age Groups	Age Groups				
			18–64 n = 4001	65–69 n = 683	70–74 n = 252	≥ 75 n = 44	P-value
Time to Transplantation, median (IQR)		138.0 (285.0)	133.0 (279.3)	123.5 (220.0)	128.0 (250.0)	137.5 (422.8)	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
Pathologic Tumor Grade, n (%)	Well-differentiated	1233 (24.8)	1003 (25.8)	168 (25.3)	48 (19.3)	14 (31.8)	0.07
	Moderate Differentated	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)	

AFP = alpha-fetoprotein, ALD = alcoholic liver disease, HCC = hepatocellular carcinoma, MELD = Model for End Stage Liver Disease, NASH = non-alcoholic steatohepatitis, TACE = transarterial chemoembolization

Table 2

Impact of older age on post-transplant overall survival in patients with HCC

Variable	Subcategory	Overall Survival Univariable Analysis				Overall Survival Multivariable Analysis		
		5-year survival	HR	CI (95%)	p value	HR	CI (95%)	p value
Age	**≥ 65**	65.6 vs 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 vs 48.8	0.6	0.8–0.7	<0.001	**0.7**	**0.5–0.9**	**0.002**
	Hepatitis C	48.1 vs 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 vs 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 vs 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 vs 50.9	1.9	1.5–2.4	<0.001	**1.5**	**1.1–2.0**	**0.007**
Vascular Invasion		54.9 vs 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**

Variable	Subcategory	Overall Survival Univariable Analysis				Overall Survival Multivariable Analysis		
		5-year survival	HR	CI (95%)	p value	HR	CI (95%)	p value
	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
	Mutlfocial	68.3	1.4	1.0–1.9	0.05	1.3	0.8–2.2	0.37
1Maximum Tumor Diameter	**0cm-2 cm**	73.0	1.0	--	--	1.0	--	--
	2cm-5cm	69.5	1.2	1.0–1.3	0.005	1.2	0.8–2.0	0.41
	>5cm	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**

AFP = alpha-fetoprotein, ALD = alcoholic liver disease, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, LRT = locoregional therapy, NASH = non-alcoholic steatohepatitis, TACE = transarterial chemoembolization

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Table 3

Impact of older age on recurrence-free survival in patients with HCC

Variable	Subcategory	Recurrence-Free Survival Univariable Analysis				Recurrence-Free Survival Multivariable Analysis		
		5-year survival	HR	CI (95%)	p value	HR	CI (95%)	p value
Age	**≥ 65**	62.6 vs 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 vs 47.3	0.6	0.5–0.7	<0.001	**0.7**	**0.6–0.9**	**0.01**
	Hepatitis C	46.1 vs 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 vs 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 vs 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 vs 49.4	2.2	1.7–2.8	<0.001	**1.5**	**1.2–2.0**	**0.002**
Vascular Invasion		49.2 vs 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**

Variable	Subcategory	Recurrence-Free Survival Univariable Analysis				Recurrence-Free Survival Multivariable Analysis		
		5-year survival	HR	CI (95%)	p value	HR	CI (95%)	p value
	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
	Mutlfocial	64.1	1.5	1.1–2.0	0.01	1.3	0.7–2.1	0.40
Maximum Tumor Diameter	**0cm-2 cm**	71.4	1.0	--	--	1.0	--	--
	2cm-5cm	65.4	1.3	1.1–1.4	< 0.001	1.1	1.0–1.3	0.09
	>5cm	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**

AFP = alpha-fetoprotein, ALD = alcoholic liver disease, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, LRT = locoregional therapy, NASH = non-alcoholic steatohepatitis, TACE = transarterial chemoembolization

Table 4

Subgroup analysis of predictors of survival in patients ≥ 65 years.

Variable	Subcategory	Overall Survival SubGroup Analysis in Patients ≥ 65						Recurrence-Free Survival SubGroup Analysis in Patients ≥ 65					
		Univariable			Mulivariable			Univariable			Mulivariable		
		HR	CI (95%)	p value	HR	CI (95%)	p value	HR	CI (95%)	p value	HR	CI (95%)	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	--	--

Variable	Subcategory	Overall Survival SubGroup Analysis in Patients ≥ 65						Recurrence-Free Survival SubGroup Analysis in Patients ≥ 65					
		Univariable			Mulivariable			Univariable			Mulivariable		
		HR	CI (95%)	p value	HR	CI (95%)	p value	HR	CI (95%)	p value	HR	CI (95%)	p value
	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
	Mutlfocial			0.21						0.13	1.9	0.4–8.4	0.39
Maximum Tumor Diameter	**0cm-2cm**	1.0	--	--	1.0	--	--	1.0	--	--	1.0	--	--
	2cm-5cm	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
	>5cm	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**

AFP = alpha-fetoprotein, ALD = alcoholic liver disease, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, LRT = locoregional therapy, NASH = non-alcoholic steatohepatitis

Table 5

Causes of morbidity and mortality in older patients transplanted for HCC.

Variable	Sub-Category	< 65 n = 197 (65.2%)	≥ 65 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
	Bleed	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
	GI	2 (1.0)	1 (1.0)	> 0.99
	GU	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
	GI	4 (2.0)	5 (4.8)	0.29
	Blood	1 (0.5)	3 (2.9)	0.12
	GU	2 (1.9)	2 (1.0)	0.61

Note: one patient who was <65 at the time of death succumbed from mutli-organ system failure secondary to both non-small cell lung cancer and metastatic HCC.

GI = gastrointestinal, GU = genitourinary, HCC = hepatocellular carcinoma