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The Future Frontier of Liver Transplantation Exploring Young Donor Allocation Strategies for HCC Recipients

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Background. The role of donor age in liver transplantation (LT) outcomes for hepatocellular carcinoma (HCC) is controversial. Given the significant risk of HCC recurrence post-LT, optimizing donor/recipient matching is crucial. This study reassesses the impact of young donors on LT outcomes in patients with HCC. **Methods.** A retrospective review of 11 704 LT cases from the United Network for Organ Sharing database (2012–2021) was conducted. The study focused on the effect of donor age on recurrence-free survival, using hazard associated with LT for HCC (HALT-HCC) and Metroticket 2.0 scores to evaluate post-LT survival in patients with HCC. **Results.** Of 4706 cases with young donors, 11.0% had HCC recurrence or death within 2 y, and 18.3% within 5 y. These outcomes were comparable with those of non-young donors. A significant correlation between donor age and post-LT recurrence or mortality ($P = 0.04$) was observed, which became statistically insignificant after tumor-related adjustments ($P = 0.32$). The Kaplan-Meier curve showed that recipients with lower HALT-HCC scores (<9) and Metroticket 2.0 scores (<2.2) significantly benefited from young donors, unlike those exceeding these score thresholds. Cox regression analysis showed that donor age significantly influenced outcomes in recipients below certain score thresholds but was less impactful for higher scores. **Conclusions.** Young donors are particularly beneficial for LT recipients with less aggressive HCC, as indicated by their HALT-HCC and Metroticket 2.0 scores. These findings suggest strategically allocating young donors to recipients with less aggressive tumor profiles, which could foster more efficient use of the scarce donor supply and potentially enhance post-LT outcomes.

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Liver transplantation (LT) is the preferred treatment for patients with hepatocellular carcinoma (HCC) and background liver disease.[1-4] LT for HCC is not universally accepted and is limited to early-stage patients with HCC because of a notable percentage of recipients experiencing recurrence despite the scarcity of donor livers. Post-LT recurrence was reported in between 8% and 20% of cases, even when strict selection criteria were applied.[5-11] Recurrence of HCC post-LT has a poor prognosis, with treatments still being challenging. As such, to ensure recipients benefit the most from the limited available donor resources, it is crucial to minimize the risk of HCC recurrence or mortality after LT, through optimal matching of donors and recipients.

Potential negative factors affecting the prognosis post-LT in patients with HCC include various donor factors, such as donor age, alongside tumor and recipient factors.[9,12] In the early 2010s, several studies asserted the significant role of donor age as an independent risk factor influencing post-LT prognosis in patients with HCC.[13,14] However, this standpoint has recently been challenged. Critics argue that most of the earlier studies relied on the United States registry database gathered before 2012, before the final pathological findings of liver grafts were released.[14] A more recent study considering these pathological factors contradicted previous beliefs, highlighting the lack of a consensus in the current disclosure.[14,15] Moreover, the last decade has witnessed several policy changes for treating HCC, with a rising preference for using marginal donors.[16,17] Therefore, it becomes essential to reevaluate how donor characteristics influence transplant outcomes for patients with HCC.

In the various components of donor organ quality, younger donor age has been proven as the most significant indicator of favorable quality.[18-20] In LT for HCC, although younger donor

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The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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organs may provide oncological survival benefits compared with older ones, prioritizing young, high-quality donors for HCC recipients with a high risk of post-LT recurrence may not be the best way to maximize their benefits. Therefore, given the present practice in LT for patients with HCC, reassessing the suitable donor allocation strategy while considering its potential influence on post-LT recurrence will be critical. We hypothesize that by considering pathological tumor factors, recipients with varying tumor factors may experience different levels of benefits when receiving transplants from young donors, with a particular "hot spot" where the advantages can be maximized. Our study aimed to reevaluate the implications of donor characteristics on post-LT recurrence in patients with HCC, focusing on the potential benefits of allocating young donors specifically.

MATERIALS AND METHODS

Study Population

The study used data from the United Network for Organ Sharing (UNOS) Transplant Analysis and Research database between 2012 and 2021. The study focused on adult (age 18 y or older) recipients who underwent LT because of HCC, with organs from deceased donors aged between 18 and 70 y. The selection criteria required that all reports must contain HCC explant data for the cases to be included in the study. LT cases involving donations after circulatory death donors were not included. To examine the evolution of donor characteristics because of changes in the HCC allocation policy, the study segmented the study population into 3 distinct periods: 2012–2014; 2015–2018, during the HCC "cap and delay" policy; and 2019–2021, after the implementation of the median Model for End-Stage Liver Disease (MELD) at transplantation minus 3 policy. In this study, donors younger than 40 y were classified as "young livers."[19,21-23] The primary objective was to assess the number of young donors used in LT where recipients experienced post-LT recurrence or death within 2 and 5 y, regardless of HCC recurrence. The secondary objective was to analyze how young donors might influence the outcomes post-LT in unadjusted scenarios and when adjusted for tumor-related factors. Subsequently, we attempted to assess the recurrence-free survival (RFS) benefits of using young donors based on varying levels of tumor factors. Our aim was also to determine the most effective strategy for allocating organs from young donors to facilitate better outcomes in LT. All the analyses were conducted with the approval of the institutional review board at Stanford University (No. 69532).

Statistical Analyses

Statistical analyses were conducted using R version 4.3.1 (https://cran.r-project.org/). Donor and recipient demographics were documented, reporting the frequencies of various characteristics as percentages alongside median values and interquartile ranges. Differences between categorical values were estimated using the chi-square test. Differences between continuous values were assessed with the Mann-Whitney *U* test or Kruskal-Wallis tests as appropriate. The cumulative incidence of HCC recurrence or mortality post-LT was evaluated, categorizing donors into young (younger than 40 y) and non-young donors (40–70 y). This assessment was further conducted by adjusting for tumor-related factors, such as pre-LT alpha-fetoprotein (AFP) levels, tumor number, and tumor size.

To confirm the merits of using young donors based on the severity of tumor factors, the study population was classified using 2 published scores that are preoperatively used to evaluate post-LT survival rates in patients with HCC.[24] One is the hazard associated with LT for HCC (HALT-HCC) score, which is guided by the formula: the HALT-HCC score = (1.27 × tumor burden score) + (1.85 × lnAFP) + (0.26 × MELD-Na).[25] In this formula, the tumor burden score is derived through the Pythagorean theorem, which represents the hypotenuse calculated using the maximum tumor size and tumor number.[25] The other one is the Metroticket 2.0 score, consisting of tumor size, number, and AFP, which was examined to mitigate the influence of MELD-Na embedded in the HALT-HCC score. After the stratification through both HALT-HCC and Metroticket 2.0 scores, Kaplan-Meier survival curves for LT using both young and non-young donors were compared, emphasizing the 2-y and 5-y RFS.

Multivariable Cox regression analysis was performed to identify prognostic factors affecting RFS. The influence of each factor derived from this analysis was visualized using a Sankey diagram. In this model, the z-value conveys the influence exerted by each factor.[26] The z-value within the Cox regression model is a standardized statistic based on the null hypothesis that every coefficient's estimated value equates to zero. The size of the z-value's absolute value indicates the statistical significance of the coefficient, which guides the decision to reject or retain the null hypothesis. Statistical significance was established at a P value of <0.05.

RESULTS

Study Population

During the study period, a total of 11 704 LT for patients with HCC were included. Among them, 4706 individuals (40.2%) received organs from donors aged between 18 and 40 y (Table 1). In the group receiving LT from young donors, there was a significantly higher proportion of male donors (65.2 versus 55.6%, $P < 0.01$). The young donor group had a lower median body mass index (26.3 versus 28.4 kg/m^2, $P < 0.01$). The prevalence of diabetes was notably lower in the young donor group (4.4% versus 21.7%, $P < 0.01$), and a slightly longer median cold ischemic time was recorded for this group as well (6.0 versus 5.9 h, $P < 0.01$).

Regarding recipient characteristics, no significant difference was observed between the groups in age (62 versus 62, $P = 0.07$). The distribution of male individuals was likewise comparable (78.9% in the young donor group versus 77.8% in the non-young donor group, $P = 0.18$). The median body mass index showcased a similar trend (28.4 kg/m^2 in the young donor group versus 28.7 kg/m^2 in the non-young donor group, $P = 0.08$). The median MELD-Na score was similar between the 2 groups (11 versus 11, $P = 0.31$). The proportions of pre-LT locoregional therapies were comparable; in the young donor group, 52.6% had 1 therapy, 25.4% had 2, and 10.6% had ≥3, whereas in the non-young donor group, the distribution was 52.6%, 24.6%, and 11.5%, respectively ($P = 0.42$).

When examining the pathological tumor factors, no statistically significant variation was identified between the groups. The median maximum tumor size remained consistent across

TABLE 1.

The characteristics difference according to donor age

Characteristics	Donor age <40 y (N = 4706)	Donor age ≥40 y (N = 6998)	*P*
Donor characteristics			
Sex, male	3066 (65.2)	3889 (55.6)	<0.01
History of diabetes, yes	208 (4.4)	1517 (21.7)	<0.01
BMI, kg/m^2	26.3 (23.1–30.7)	28.4 (24.8–33.0)	<0.01
Cold ischemic time, h	6.00 (4.67–7.65)	5.85 (4.60–7.25)	<0.01
Recipient characteristics			
Age, y	61 (58–66)	62 (58–66)	0.07
Sex, male	3711 (78.9)	5444 (77.8)	0.18
BMI, kg/m^2	28.4 (25.2–32.3)	28.7 (25.4–32.6)	0.08
Maximum tumor size, cm	2.5 (1.6–3.6)	2.5 (1.6–3.8)	0.15
Tumor number	1 (1–3)	1 (1–3)	0.79
Vascular invasion, yes	654 (14.8)	996 (15.1)	0.56
Poorly differentiation, yes	344 (7.3)	480 (6.9)	0.37
AFP, ng/mL	7.0 (4.0–17.0)	6.0 (4.0–15.0)	0.38
Locoregional therapy			
0	373 (8.2)	567 (8.4)	0.42
1	2474 (54.5)	3680 (54.3)	
2	1195 (26.3)	1724 (25.4)	
MELD-Na score	11 (8–16)	11 (8–16)	0.31

Continuous variables are presented as median (IQR) and categorical variables are presented as number (%).
AFP, alpha-fetoprotein; BMI, body mass index; IQR, interquartile range; MELD, Model for End-Stage Liver Disease.

both groups at 2.5 cm ($P = 0.15$). Similarly, the median tumor count was equivalent between the groups (1 versus 1, $P = 0.79$). There was no substantial difference in the instances of vascular invasion ($P = 0.56$). The proportions of cases with poorly differentiated tumors were 7.3% in the young donor group and 6.9% in the non-young donor group ($P = 0.37$). The pre-LT median AFP levels were 7.0 ng/mL in the young donor group and 6.0 ng/mL in the non-young donor group ($P = 0.38$).

The Impact of Using Young Donors on Post-LT RFS

At 2 y post-LT, 11.0% (or 517 individuals) of patients who received organs from young donors faced either HCC recurrence or death. By 5 y post-LT, this increased to 18.3% (or 861 individuals) of the patients in this group. Figure 1A and B reveal that using young donors for LT did not noticeably reduce the rate of HCC recurrence or death compared with using organs from non-young donors.

The cumulative incidence of either HCC recurrence or mortality was significantly lower in the group that received organs from young donors ($P = 0.04$; Figure 1C). However, when adjustments were made considering tumor factors, the distinction between the 2 groups was found to be not statistically significant ($P = 0.32$; Figure 1D).

Advantages of Using Young Donors According to the HALT-HCC Scores

The study population was grouped according to their preoperative HALT-HCC scores, which were determined through imaging assessments. The distribution pattern of these scores is illustrated in Figure S1A (**SDC,** http://links.lww.com/TXD/A664). The Kaplan-Meier survival analysis of the entire study population reveals a significant difference in RFS between the cohorts who received organs from young donors and those from non-young donors ($P = 0.02$).

However, a distinct pattern emerged on dividing the study population into 3 equal groups based on their HALT-HCC scores. Although the group with the lowest HALT-HCC group (<9) exhibited a significant difference ($P < 0.01$), the other 2 groups did not display any significant difference at the 2-y RFS endpoint ($P = 0.40$ and 0.30, respectively; Figure 2A–C). A similar trend was noted at the 5-y RFS endpoint (**Figures S2A–C, SDC,** http://links.lww.com/TXD/A664).

The multivariable Cox regression analysis was performed to explore the potential prognostic factors (Table 2). Setting the endpoint to the 2-y RFS, it was found that, in the group with the lowest HALT-HCC scores, the donor age category emerged as a significant prognostic factor ($P < 0.01$). Conversely, donor age did not manifest as a significant prognostic factor in the middle-scoring group. For the group with the highest HALT-HCC scores, the HALT-HCC score was identified as a robust prognostic factor ($P < 0.01$). A parallel trend persisted when the analysis used the 5-y RFS endpoint (Table 2). The fluctuations in the weight of each factor as a prognostic factor of the 2-y RFS were vividly depicted in Figure 3A, and similarly for the 5-y RFS in Figure S3A (**SDC,** http://links.lww.com/TXD/A664.

Advantages of Using Young Donors According to the Metroticket 2.0 Scores

A similar analysis was conducted using the Metroticket 2.0 scores as the stratifying factor to exclude the potential impact of MELD-Na scores on the study outcomes (**Figure S1B, SDC,** http://links.lww.com/TXD/A664). Even when categorized using the Metroticket 2.0 score, a marked difference was observed in the 2-y RFS in the group with the lowest Metroticket 2.0 scores, exhibiting a significant discrepancy between the groups ($P < 0.01$; Figure 2D–F). This observed

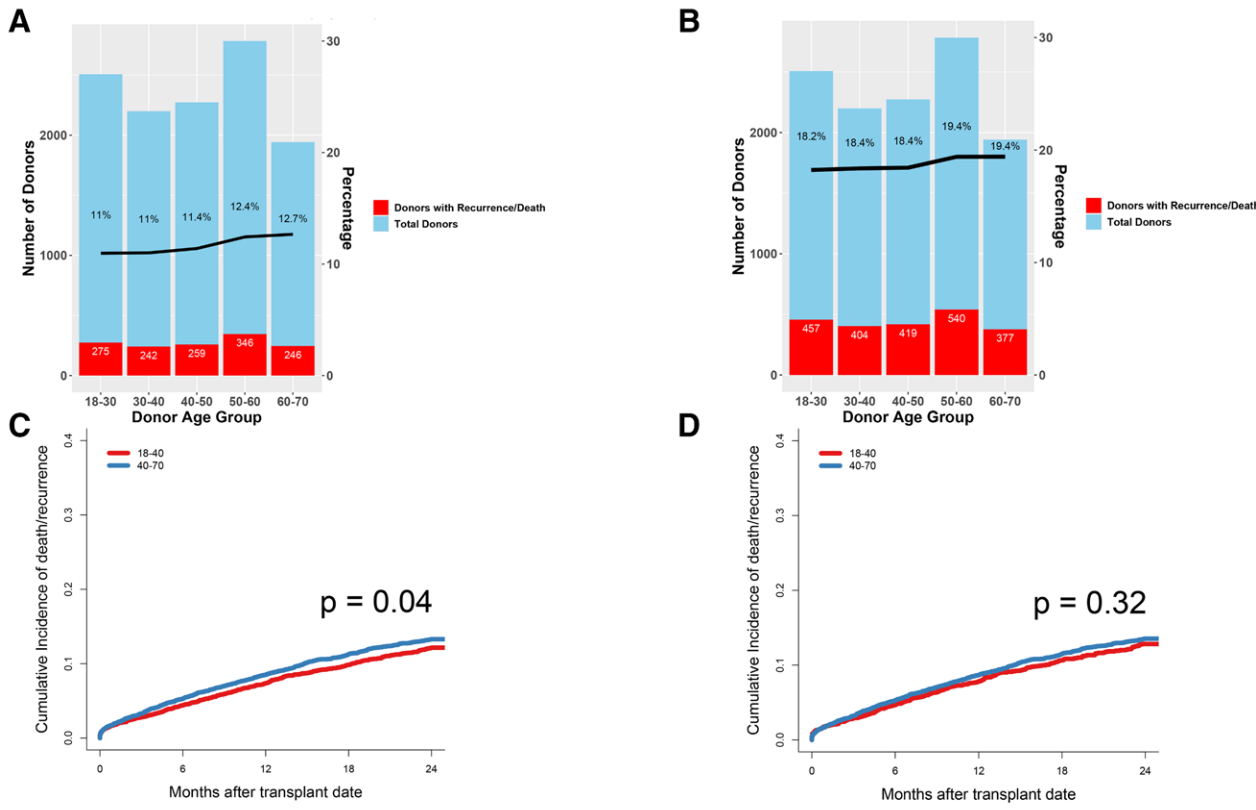

FIGURE 1. The relationship between LT using young donors and post-LT RFS. A, This figure displays the data on the number of donors used and the cases of HCC recurrence or mortality 2 y after the transplant, breaking this down based on the age categories of the donors. The black curve shows the percentage of patients who faced either HCC recurrence or death among those who received donors. B, This part displays data similar to that in (A) but looks at a time frame of 5 y after LT. C, This graph shows the cumulative incidence of HCC recurrence or mortality across different donor age groups without considering the influence of tumor characteristics ($P = 0.04$). D, In contrast to (C), this graph includes the adjustment for tumor characteristics while showing the cumulative incidence of HCC recurrence or mortality across different donor age groups ($P = 0.32$). HCC, hepatocellular carcinoma.

trend remained consistent at the 5-y RFS (**Figure S2D–F, SDC,** http://links.lww.com/TXD/A664).

A multivariable Cox regression analysis was performed to identify prognostic factors (**Table S1, SDC,** http://links.lww.com/TXD/A664). When analyzing the 2-y RFS, it was discerned that donor age emerged as a significant prognostic factor in the subset with the lowest Metroticket 2.0 scores ($P < 0.01$). However, in the middle-scoring group, donor age did not retain its statistical significance. Remarkably, in the bracket with the highest Metroticket 2.0 scores, the score itself was isolated as a potent prognostic factor ($P < 0.01$). This pattern of fluctuating prognostic relevance of different factors persisted even when the endpoint was defined at 5-y RFS (**Table S1, SDC,** http://links.lww.com/TXD/A664). These pronounced variations in the significance of different factors throughout both the 2-y and 5-y RFS intervals were visualized in Figure 3B and Figure S3B (**SDC,** http://links.lww.com/TXD/A664), respectively.

The Subanalysis in Light of Policy Changes

A Cox regression analysis was conducted for each phase to evaluate the potential impacts of policy changes. A discernible pattern emerged from this analysis in any period: as the HALT-HCC or Metroticket 2.0 scores rose, the influence of the donor age diminished. Meanwhile, the relative importance of the HALT-HCC or Metroticket 2.0 score factor itself became more pronounced as its value escalated (**Figures S4 and S5, SDC,** http://links.lww.com/TXD/A664).

DISCUSSION

This study aimed to analyze cases where patients with HCC underwent LT from young, high-quality donors but had a short RFS period. The goal was to identify the best recipient group for young donors to maximize their benefits. Our statistical analysis showed that young donors were used in 4706 cases, accounting for 40.2% of the total. After LT, 11.0% experienced HCC recurrence or death within 2 y, and 18.3% within 5 y. These figures were not noticeably lower than the corresponding rates observed when non-young donors were used. An initial observation suggested a trend of increasing post-LT HCC recurrence or mortality correlating with increasing donor age ($P = 0.04$). However, after adjusting for tumor-related factors, this trend was no longer statistically significant ($P = 0.32$). These findings led us to hypothesize that the influence of donor age diminishes in the presence of strong tumor factors. As such, allocating young, high-quality donors to recipients with aggressive tumor profiles might not maximize the benefit derived from the youth of the donors. Instead, it can be speculated that it seems more promising to pair young donors with recipients presenting less severe tumor factors, where the inherent advantages of younger organs could potentially offer more substantial benefits.

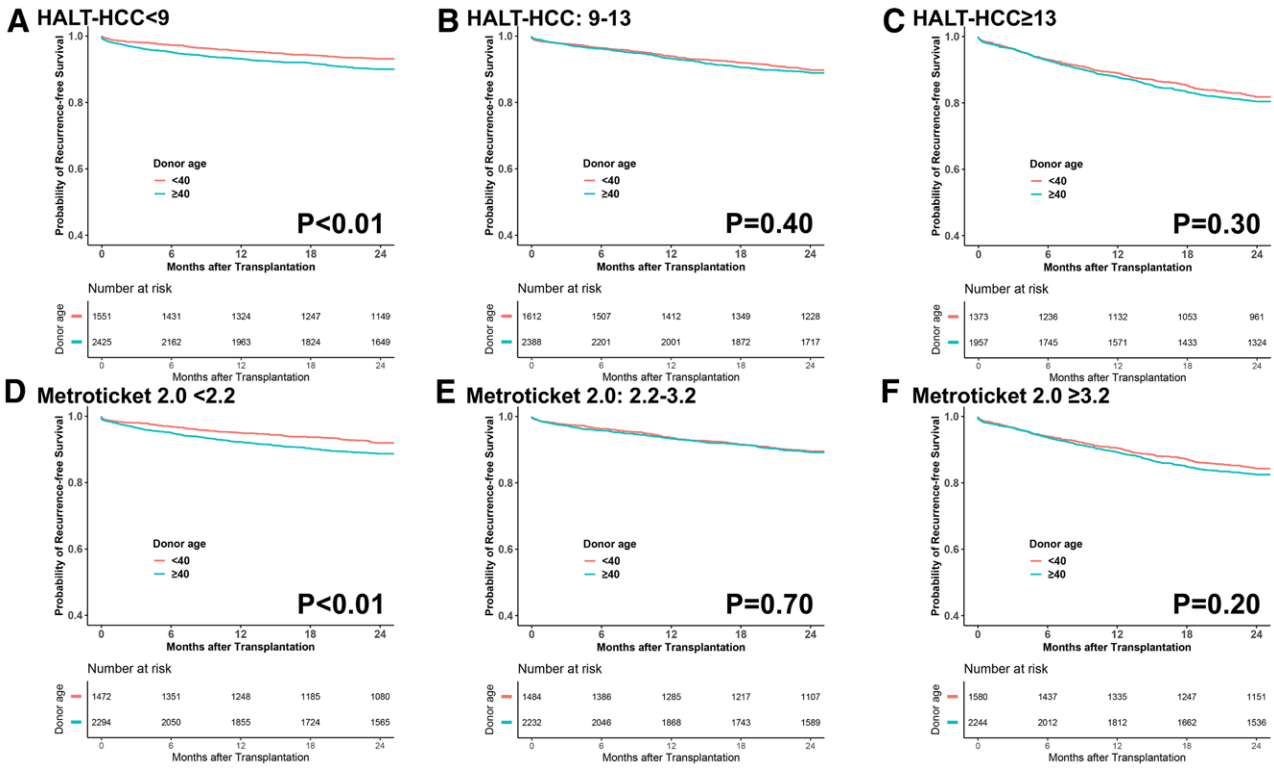

FIGURE 2. Kaplan-Meier curves for the 2-y RFS, grouped by donor age: (A) HALT-HCC score: <9; (B) HALT-HCC score: 9–13; (C) HALT-HCC score: ≥13; (D) Metroticket 2.0 score: <2.2; (E) Metroticket 2.0 score: 2.2–3.2; and (F) Metroticket 2.0 score: ≥3.2. HALT-HCC, hazard associated with liver transplantation for hepatocellular carcinoma; RFS, recurrence-free survival.

The effect of donor age on the results of organ transplants has been debated for a long time, with differing opinions on whether using organs from old donors is safe and effective. Some research suggests that organs from older donors might be linked to a lower survival rate for the recipients, yet there are also reports of successful transplants involving donors in their 70s and 80s.[19,27-31] The way donor age influences HCC recurrence in recipients remains unclear. For example, a study by Sharma et al[32] involving 94 patients indicated that older donor age might increase the risk of HCC recurrence. Ussing the UNOS database, other researchers found a higher HCC recurrence rate in cases where donors were older than 60 y.[13,14] However, these studies might overlook detailed tissue sample analysis. A recent analysis that considered pathological factors showed that donor age did not necessarily increase the risk of HCC recurrence. This suggests that people on the waitlist because of HCC could potentially receive organs from older donors without negatively affecting their prognosis.[15] Given these insights, we aimed to identify the best group of recipients who could benefit most from younger donors, factoring in the tumor characteristics. Allocating young, high-quality organs properly is extremely vital, considering the current shortage of donors. Our study seeks to answer pressing clinical questions: How often are young donor livers allocated to individuals who later experience HCC recurrence or death, and would it be more beneficial to direct young organs to a different group of recipients?

An interesting finding was identified when categorizing the study population by their HALT-HCC scores. The group with a HALT-HCC score <9 had a clear difference in RFS based on donor age. However, this was not the case for the group with a HALT-HCC score of ≥9. The HALT-HCC model is a continuous risk score in patients with HCC. This score looks at morphological, biological, and recipient disease data before LT.[24] Therefore, it can be posited that patients with elevated HALT-HCC scores are likely to exhibit a heightened risk of recurrence in preoperative evaluations, indicative of high-risk HCC. Our results show that donor age makes a difference for patients with low HALT-HCC scores but not those with high scores. This finding may imply that for cases of high-risk HCC recurrence, the beneficial impact of using young-aged donors might be negated by the substantial adverse effects of tumor factors; however, there is more to consider. The HALT-HCC score also considers MELD-Na, which is another factor; thus, to make sure that our results remained consistent with this additional component, a similar analysis was conducted with the Metroticket 2.0 score. This score only considers factors such as AFP level, tumor size, and tumor number. Our findings were consistent: only those with a Metroticket 2.0 score <2.2 showed a clear difference in RFS based on donor age. Considering all these, it seems there is a certain range or "hotspot" where the benefits of younger donors shine through, especially when tumor-related risks are not too high compared with donor age. From a practical standpoint, given the influence of the donor age variable is more pronounced than that of the tumor variable in individuals with HALT-HCC scores <9 and Metroticket 2.0 scores <2.2, corresponding to the first third quartile of the study population, it would be advantageous to prioritize young donors. However, if the HALT-HCC or Metroticket 2.0 score surpasses the thresholds mentioned, using non-young donors is considered to potentially maximize benefits. This insight will aid clinicians in making informed decisions for donor/recipient matching to achieve better outcomes and enhance the sophistication of current practices.

TABLE 2.

Multivariable Cox regression analysis of prognostic factors for 2-y/5-y RFS according to HALT-HCC scores

	2-y RFS		5-y RFS	
	Multivariable HR (95% CI)	***P***	**Multivariable HR (95% CI)**	***P***
HALT-HCC score: <9				
Recipient age >65 y	1.60 (1.27-2.00)	<0.01	1.49 (1.24-1.78)	<0.01
Donor age ≥40 y	1.42 (1.11-1.81)	<0.01	1.23 (1.02-1.49)	0.03
Cold ischemic time	0.99 (0.94-1.04)	0.64	1.00 (0.97-1.03)	0.94
Recipient BMI	1.00 (0.98-1.02)	0.82	1.00 (0.98-1.02)	0.87
Donor BMI	1.01 (0.99-1.03)	0.29	1.01 (1.00-1.02)	0.11
Recipient sex, male	1.04 (0.79-1.36)	0.81	1.04 (0.84-1.28)	0.74
Donor sex, male	0.90 (0.72-1.14)	0.39	1.02 (0.85-1.22)	0.85
History of diabetes	1.18 (0.88-1.58)	0.28	1.05 (0.82-1.34)	0.71
HALT-HCC score	1.09 (1.01-1.19)	0.04	1.09 (1.02-1.16)	<0.01
Locoregional therapy >2×	0.93 (0.63-1.38)	0.72	0.88 (0.64-1.22)	0.46
HALT-HCC score: 9–13				
Recipient age >65 y	1.42 (1.15-1.75)	<0.01	1.38 (1.17-1.63)	<0.01
Donor age ≥40 y	1.01 (0.82-1.25)	0.91	1.04 (0.89-1.22)	0.63
Cold ischemic time	1.00 (0.96-1.04)	0.96	0.99 (0.96-1.02)	0.58
Recipient BMI	0.99 (0.97-1.01)	0.56	1.00 (0.98-1.01)	0.78
Donor BMI	1.01 (0.99-1.02)	0.45	1.00 (0.99-1.01)	0.71
Recipient sex, male	1.18 (0.92-1.52)	0.21	1.24 (1.02-1.50)	0.03
Donor sex, male	0.96 (0.79-1.18)	0.73	0.91 (0.78-1.07)	0.25
History of diabetes	1.21 (0.92-1.60)	0.17	1.13 (0.91-1.40)	0.26
HALT-HCC score	1.04 (0.95-1.14)	0.37	1.05 (0.98-1.13)	0.13
Locoregional therapy >2×	1.53 (1.16-2.01)	<0.01	1.52 (1.22-1.88)	<0.01
HALT-HCC score: ≥13				
Recipient age >65 y	1.21 (1.00-1.46)	0.04	1.25 (1.07-1.46)	<0.01
Donor age ≥40 y	1.03 (0.87-1.22)	0.76	1.00 (0.86-1.15)	0.95
Cold ischemic time	0.99 (0.96-1.03)	0.64	0.99 (0.97-1.02)	0.44
Recipient BMI	0.98 (0.97-1.00)	0.02	0.99 (0.98-1.00)	0.10
Donor BMI	1.00 (0.99-1.01)	0.95	1.00 (0.99-1.01)	0.94
Recipient sex, male	1.17 (0.95-1.44)	0.15	1.20 (1.01-1.43)	0.04
Donor sex, male	0.92 (0.78-1.10)	0.36	0.92 (0.80-1.06)	0.26
History of diabetes	1.16 (0.92-1.47)	0.20	1.03 (0.84-1.25)	0.80
HALT-HCC score	1.05 (1.04-1.07)	<0.01	1.05 (1.04-1.07)	<0.01
Locoregional therapy >2×	1.00 (0.99-1.00)	0.26	1.14 (0.95-1.38)	0.17

BMI, body mass index; CI, confidence interval; HALT-HCC, hazard associated with liver transplantation for hepatocellular carcinoma; HR, hazard ratio; RFS, recurrence-free survival.

Our observations from the Cox analysis and the Sankey diagram, which visually maps the strength of each factor's influence, provide a compelling validation for our hypothesis. Essentially, it is observed that donor age is a dominant factor affecting the groups with HALT-HCC scores <9 and Metroticket 2.0 scores <2.2. However, this dominance diminishes in cases where the HALT-HCC score is ≥9 and the Metroticket 2.0 score is ≥2.2. In scenarios with even higher scores—specifically, HALT-HCC scores ≥13 and Metroticket 2.0 scores ≥3.2—we notice that the influence of the HALT-HCC and Metroticket 2.0 scores surges, overtaking that of the donor age. This trend generally holds true across different subgroups defined by each HCC allocation policy.

The limitations of this study include its retrospective nature. Additionally, this analysis does not use a competing risk analysis, which would differentiate between HCC recurrence and post-LT mortality. This is rooted in the understanding that whether the outcome is HCC recurrence or mortality after LT, in both circumstances, the valuable organs from younger donors are lost without being fully used. Therefore, we focused on RFS as the endpoint for our study. A potential issue could be that HCC recurrence was logged either at the time it happened or at the time of death resulting from the recurrence, which may delay recording events in the cumulative incidence curves. However, as previously discussed, any misclassification of HCC recurrence happens randomly, which suggests that donor-related factors do not systematically influence the recording of HCC recurrence.[13] Moreover, the population in our study spans a broad period from 2012 to 2021. Despite this wide time frame potentially introducing variability, we conducted a subanalysis grounded in the policy changes during those years to adequately account for any confounding effects arising from the differences in eras. Our study focused on the period after 2012, when the UNOS database began incorporating the final pathological reports. This approach amplifies the robustness of our findings and is a prominent strength of our research setup.

In conclusion, LT using young donors demonstrates an 11.0% occurrence of HCC recurrence or death 2 y post-LT, and 18.3% at 5 y. These rates are fairly similar to those observed when non-young donors are used. Although there was a trend that higher donor age correlated with increased post-LT HCC recurrence or death, this became nonsignificant

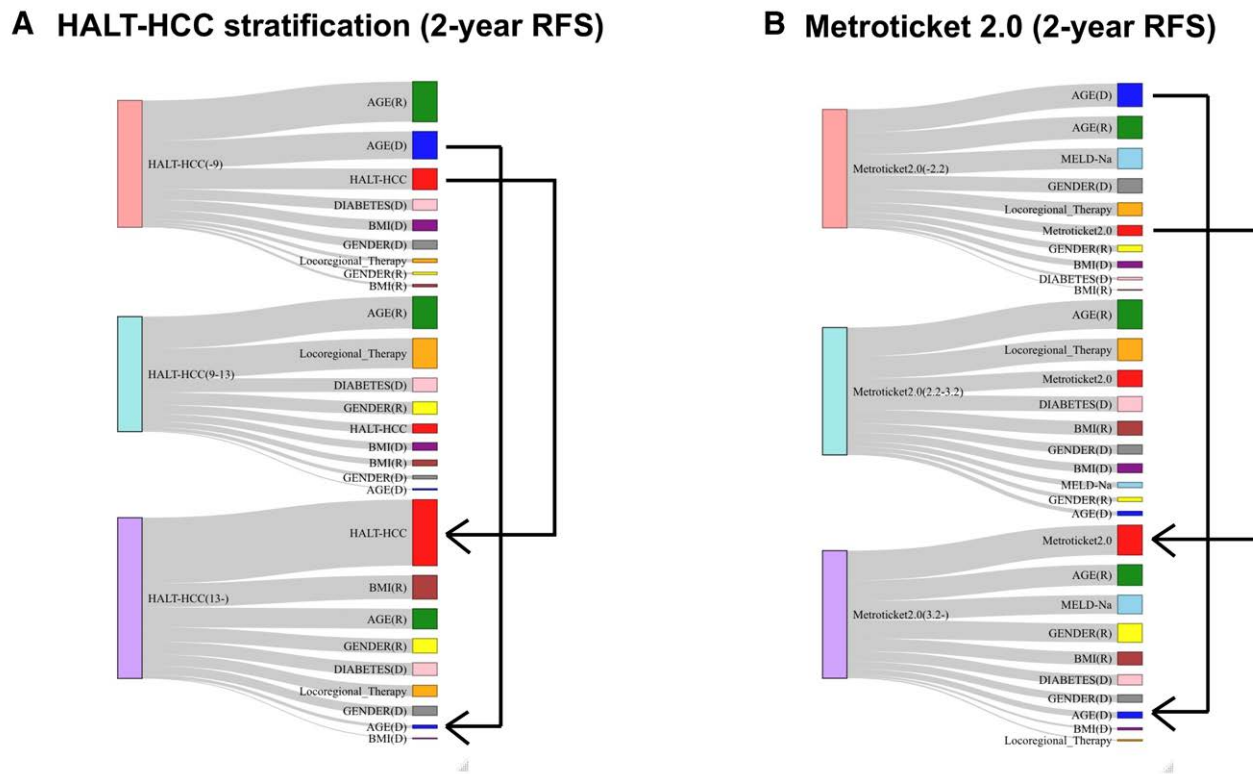

FIGURE 3. Sankey diagrams mapping the influence of each factor on the 2-y RFS. A, The Sankey diagram visualizes the influence of each factor on the 2-y RFS based on HALT-HCC scores. Factors are arranged top to bottom based on their influence, determined through the absolute values derived from a Cox regression analysis. The z-value influences both the order of the factors and the length of their respective boxes; higher absolute z-values indicate a stronger influence and result in longer boxes. This diagram illustrates that in the group with HALT-HCC scores <9, the age of the donor is a dominant influence on 2-y RFS. However, for scores of ≥13, the donor age becomes less influential, with the HALT-HCC score itself becoming the most crucial factor. "D" and "R" are used to denote "donors" and "recipients," respectively. B, The Sankey diagram illustrating the influence of each factor on the 2-y RFS based on Metroticket 2.0 scores. BMI, body mass index; HALT-HCC, hazard associated with liver transplantation for hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; RFS, recurrence-free survival.

after accounting for tumor factors. Recipients with HALT-HCC scores <9 or Metroticket 2.0 scores <2.2 can benefit from younger donors. However, those with HALT-HCC scores ≥9 or Metroticket 2.0 scores ≥2.2 see limited benefits, making the allocation of non-young donors a potentially better choice for this group. These insights are crucial for optimizing the allocation of scarce donor resources, aiming for better transplant outcomes.

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