OPEN

Beyond 75: Graft Allocation and Organ Utility Implications in Liver Transplantation

Miho Akabane, MD,[1] Allison Kwong, MD,[2] Yuki Imaoka, MD, PhD,[1] Carlos O. Esquivel, MD, PhD,[1] W. Ray Kim, MD,[2] Marc L. Melcher, MD, PhD,[1] and Kazunari Sasaki, MD[1]

Background. The global surge in aging has intensified debates on liver transplantation (LT) for candidates aged 75 y and older, given the prevalent donor scarcity. This study examined both the survival benefits and organ utility of LT for this age group. **Methods.** A total of 178 469 adult LT candidates from the United Network for Organ Sharing database (2003–2022) were analyzed, with 112 266 undergoing LT. Post-LT survival outcomes and waitlist dropout rates were monitored across varying age brackets. Multivariable Cox regression analysis determined prognostic indicators. The 5-y survival benefit was assessed by comparing LT recipients to waitlist candidates using hazard ratios. Organ utility was evaluated through a simulation model across various donor classifications. **Results.** Among candidates aged 75 y and older, 343 received LT. The 90-d graft and patient survival rates for these patients were comparable with those in other age categories; however, differences emerged at 1 and 3 y. Age of 75 y or older was identified as a significant negative prognostic indicator for 3-y graft survival (hazard ratio: 1.72 [1.20-2.42], $P < 0.01$). Dropout rates for the 75 y and older age category were 12.0%, 24.1%, and 35.1% at 90 d, 1 y, and 3 y, respectively. The survival benefit of LT for the 75 y and older cohort was clear when comparing outcomes between LT recipients and those on waitlists. However, organ utility considerations did not favor allocating livers to this age group, regardless of donor type. Comparing 3-y patient survival between LT using donors aged 60 y and younger and older than 60 y showed no significant difference ($P = 0.50$) in the 75 y or older cohort. **Conclusions.** Although LT offers survival benefits to individuals aged 75 y and older, the system may need rethinking to optimize the use of scarce donor livers, perhaps by matching older donors with older recipients.

(*Transplantation Direct* 2024;10: e1661; doi: 10.1097/TXD.0000000000001661.)

Liver transplantation (LT) is the definitive treatment for end-stage liver disease.[1] By 2030, forecasts suggest that individuals aged 70 y and older will account for 15% of the US population, mirroring a global aging trend.[2] Concurrently, many patients are diagnosed with end-stage liver disease at a later stage.[3,4] Although there has been no technical age limit to LT, generally accepted age thresholds have increased since the 1980s, from 50 to 70 y, and occasionally, even older.[5-8] This expansion, despite the higher comorbidities in the elderly, reflects advancements in surgical methodologies, intensive care, postoperative management, and improved donor/recipient matching.[9] In addition, the burden of liver disease due to metabolic dysfunction-associated steatohepatitis is growing and presents in older age.[10] Accordingly, LT rates among older patients may be expected to climb further.[11]

Current guidelines from the American Association for the Study of Liver Diseases emphasize that age alone should not be the sole exclusionary factor for LT. However, the definition of "elderly" varies, and emerging evidence suggests potential complications in older LT recipients, specifically those older than 70 y.[12] Although some data from the Organ Procurement and Transplantation Network highlight reduced 5-y graft survival for those older than 65 y, other studies report comparable results between different age groups.[12-14] Consequently, the utility of LT in advanced age is still debated.

The demographic trends in the United States have been characterized by a significant extension of the average lifespan.[15] From 1974 to 2019, the lifespan of the US population increased from 72 to 79 y.[16] Notably, life expectancy for those aged 65 and 75 y stands at 19.6 and 12.4 y, respectively, highlighting the potential longevity in a health-selected elderly

Received 21 February 2024. Revision received 5 March 2024.

Accepted 7 March 2024.

[1] Division of Abdominal Transplant, Department of Surgery, Stanford University Medical Center, Stanford, CA.

[2] Division of Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA.

The authors declare no funding or conflicts of interest.

M.A. and K.S. participated in research design and data analysis. M.A., A.K., M.L.M., and K.S. participated in writing the article. M.A., A.K., Y.I., C.O.E., W.R.K., M.L.M., and K.S. participated in the critical review.

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

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Kazunari Sasaki, MD, Division of Abdominal Transplant, Department of Surgery, Stanford University, 1265 Welch Rd, Stanford, CA 94305. (sasakik@stanford.edu).

Copyright © 2024 The Author(s). Transplantation Direct. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001661

subgroup.[17] This suggests that being of an age close to the average life expectancy at birth does not necessarily diminish the potential benefits of LT. Nonetheless, the majority of excess mortality post-LT in elderly recipients stems from nonhepatic causes. Therefore, we should focus on maximizing organ utility.[18,19]

Given these dynamics, it is pertinent to critically examine the practical merits and organ utility of LT for those aged 75 y and older. This scrutiny becomes more pressing given the increasing LT demand against limited donor availability. This study seeks to evaluate the appropriateness of LT for those aged 75 y and older, aiming to discern survival benefits and organ utility implications of graft allocation to this age group.

MATERIALS AND METHODS

Study Population

The study used data from the United Network for Organ Sharing (UNOS) database between 2003 and 2022. The study cohort consisted of adult (older than 17 y) candidates enlisted on the LT waiting list. Exclusions included multiorgan transplant recipients, patients with status 1, those undergoing retransplantation, and procedures involving living donors. Recipient ages were segmented as 18–49, 50–59, 60–64, 65–69, 70–74, and 75 y and older. The primary objective was to elucidate the characteristics of recipients and donors used in LT among those aged 75 y and older and to compare these characteristics with other age categories. The secondary objective was to clarify the survival benefits of LT across different age groups. The survival benefits were calculated by comparing the dropout rates from the waitlist with post-LT mortality to determine whether LT conferred a survival advantage over remaining on the waitlist. Additionally, the expected organ utility was assessed. This concept involves maximizing the overall survival rate of the entire recipient pool, which includes both those who ultimately undergo LT and those who do not, during the 2013 to 2022 period, whenever a donor offer is made. 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 range. Differences between categorical values were estimated using the chi-square test. Differences between continuous values were assessed with the Mann-Whitney *U* test or the Kruskal-Wallis test as appropriate.

Post-LT graft and patient survival rates were calculated using the Kaplan-Meier technique during the 2013–2022 period. Differences in the Kaplan-Meier survival curves were statistically analyzed using the log-rank test. Furthermore, an in-depth exploration of the effects of advanced age on short-term and long-term outcomes was facilitated through multivariable Cox regression for the 2013–2022 span.

LT survival time was calculated from the time of transplant until death or the date of the last follow-up during a follow-up time. Conversely, waitlist survival time was defined as the number of days from registration until death before LT, LT, removal from the waiting list for other reasons, or the last day of follow-up, whichever occurred first. The cumulative incidence of death on the waitlist was computed through competing-risk analysis, with LT considered as a competing risk. Patient mortality post-LT was estimated via the Kaplan-Meier method. Waitlist patients and transplant recipients were stratified on the basis of their initial and final laboratory Model for End-stage Liver Disease (MELD)-Na scores on the waiting list, respectively. In each age group, the 5-y survival benefit was assessed by comparing the mortality of LT recipients using the hazard ratio (HR) to waitlist candidates using the sub-HR for death.[20-22] A significant survival benefit stemming from LT was identified when the HR, accompanied by a 95% confidence interval, was found to be statistically <1.0.[23] The mortality rate was calculated by dividing the number of deaths per 1000 patient-years. For waitlist mortality analyses, removal from the waitlist due to death or deterioration in medical condition (ie, too sick for transplantation) was considered waitlist mortality.[24-26] Given the significance of the time era, with improved outcomes observed after the introduction of effective antiviral therapy for hepatitis C, analyses focused on the 2013–2022 interval.

In evaluating organ utility, we devised a simulation scale to capture the organ utility of LT based on the age category of the recipient. The term "organ utility" in this study refers to the maximization of the overall survival rate for the entire recipient pool. This pool includes those who receive LT and those who do not when a donor offer is made. This approach treats the population as 1 entity, and the expected organ utility is calculated as the sum of each age group's survival rates (range, 0–1) multiplied by its proportion within the entire pool (also range, 0–1). In other words, if the survival rate of all age groups were 100%, this value would be 1.0. Therefore, the organ utility value moves between 0 and 1, with values closer to 1.0 indicating a higher expected overall survival rate from a single donor offer and those closer to 0.0 indicating a lower rate. In this context, all age categories in the waiting recipient pool are treated equally without weighting. The calculation is a straightforward score predicting the expected overall survival rate of the entire recipient pool based on the allocation of the donor offer to a specific age group. This model does not account for various factors, such as potential differences in medical costs for the same treatment across age groups. Specifically, when a liver donor offer is presented, and a recipient from a specific age group accepts, we estimate post-LT patient survival outcomes at 90 d, 1 y, and 3 y. These outcomes are derived from Kaplan-Meier curves and subsequently adjusted by the respective age category's percentage representation in the total waitlist pool. If a particular age category declines the offer, the projected survival outcomes on the waitlist, also drawn from Kaplan-Meier curves (with LT treated as a censored event and both death and "too sick" status considered as dropout events), are used. These waitlist outcomes are further adjusted by representing the declining age category in the total waitlist pool at the same intervals. The cumulative simulation scale for the entire cohort when an organ offer is presented represents the organ utility—it is the aggregate of the simulation scales across all age categories.[27] To elucidate further:

$$Simulation\ scale = (Proportion^{i})x^{i} + \sum_{j=1}^{6}(Proportion^{j})x^{j} \quad (j \neq i)$$

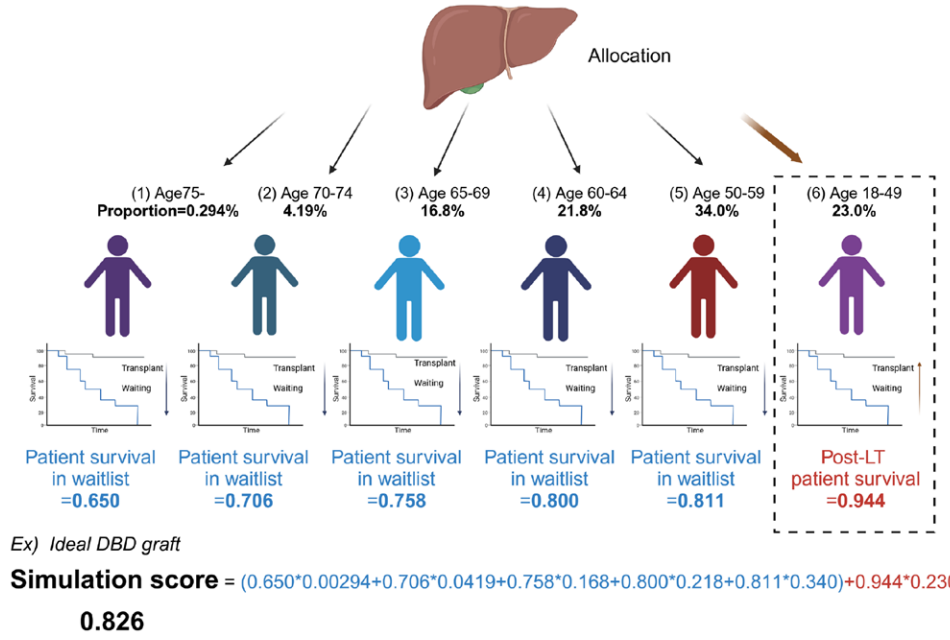

FIGURE 1. Conceptualizing the organ utility of LT. This figure represents the principle of organ utility derived from LT. When a liver donation is available, transplant surgeons can consider determining the optimal recipient age group to maximize organ utility. The methodology underpinning the calculation of organ utility is depicted through an example calculation. DBD, donation after brain death; LT, liver transplantation.

Here, i is the age group accepting the offer, with $proportion^i$ denoting the fraction of this age group in the total waitlist pool. X^i represents the post-LT patient survival for group^i. j is the age group foregoing the offer, with $proportion^j$ denoting its share in the total waitlist pool, and X^j symbolizing the waitlist survival for group^j. Age groups are numerically designated from 1 to 6, aligning with the 6 aforementioned age categories. This formula was applied to various donor liver scenarios, including donors after circulatory death (DCD), ideal donors after brain death (DBD), steatotic DBD, elderly DBD, and high body mass index (BMI) DBD. Criteria for steatotic DBD, elderly DBD, and high BMI DBD were macrosteatosis >30%, age older than 65 y, and BMI >35, respectively. Ideal DBDs did not meet these conditions. This methodology is depicted in Figure 1, which shows 1 example of the calculation. In all the analyses, statistical significance was established a P value of <0.05.

RESULTS

Study Population

During the 2003–2022 period, a cohort of 178 469 candidates was identified. Of these, 112 266 underwent LT. Among 444 candidates aged 75 y and older, 343 received LT (Table 1). **Figure S1A and B** (**SDC,** http://links.lww.com/TXD/A668) shows the age category distribution among the waitlist and transplanted cohorts.

Of the transplanted group (aged 75 y and older), 24 (7.0%) received DCD donors, closely paralleling the 6.9% (7778 patients) in the entire cohort; 214 (62.4%) were recipients of male donor organs, with an observed cold ischemic time of 6.0 h; and the main cause of donor death was cerebrovascular accidents (39.4%). This cohort had a median donor age of 46 y, with an observed trend of increasing donor age correlating with recipient age. The median waiting duration for this group was 99 [23–271] d. This duration ascended concomitantly with recipient age brackets, evidenced by 41, 83, 118, 130, and 143 d for ages 18–49, 50–59, 60–64, 65–69, and 70–74, respectively. Notably, as recipient age escalated, MELD-Na scores declined. The 75 y or older recipient group had a median score of 18. Liver malignancies, including hepatocellular carcinoma and cholangiocarcinoma, were most prevalent in the 75 y or older cohort (42.9%).

The chronological trend of recipient and donor characteristics in those aged 75 y or older was assessed (**Table S1, SDC,** http://links.lww.com/TXD/A668). The BMI for recipients and donors has steadily increased, and the median recipient MELD-Na score has also increased. Meanwhile, the cold ischemic time has steadily decreased. Regarding the underlying diseases in recipients, the proportion of cases with hepatitis C has decreased, whereas the proportion of cases with metabolic dysfunction-associated steatotic liver disease has increased.

Survival Outcomes

In the 2013–2022 cohort, the 75 y or older cohort exhibited comparable 90-d post-LT survival outcomes to other age categories, as evidenced by graft/patient survival rates of 95.3%/96.9%, 95.1%/96.3%, 94.8%/96.0%, 94.2%/95.2%, 93.9%/94.9%, and 94.2%/95.7% for ages 18–49, 50–59, 60–64, 65–69, 70–74, and 75 y or older, respectively (Figure 2). However, as time progressed post-LT, the 75 y or older cohort displayed a notable divergence, showcasing graft/patient survival rates of 84.4%/85.7% and 74.7%/75.8% at the 1-y and 3-y milestones, respectively (both $P < 0.01$; Figure 2). A similar analysis using the 2003–2022 cohort showed the same results ($P < 0.01$; **Figure S2, SDC,** http://links.lww.com/TXD/A668).

The multivariable Cox regression analysis discerned recipient age 75 y or older as a significantly worse prognostic indicator for 3-y graft survival (HR: 1.72 [1.20-2.42], $P < 0.01$), although this association was not significant for the 90-d endpoint (HR: 1.18 [0.61-2.08], $P = 0.59$; Table 2).

TABLE 1.

Recipient and donor characteristics in the transplanted population stratified by recipient age

	Recipient age						
	18–49 y (N = 27 048)	**50–59 y (N = 43 466)**	**60–64 y (N = 21 975)**	**65–69 y (N = 15 318)**	**70–74 y (N = 4116)**	**≥75 y (N = 343)**	***P***
Donor							
Male, %	16 520 (61.1)	26 479 (60.9)	13 104 (59.6)	9028 (58.9)	2432 (59.1)	214 (62.4)	<0.01
BMI, median (IQR)	26.3 (23.0–30.4)	26.6 (23.3–30.9)	26.7 (23.4–31.1)	26.9 (23.4–31.2)	26.8 (23.4–31.2)	26.6 (23.2–30.9)	<0.01
CIT,	6.15 (4.95–8.00)	6.12 (4.92–8.00)	6.00 (4.80–7.66)	6.00 (4.70–7.43)	5.93 (4.75–7.45)	6.00 (4.98–7.33)	<0.01
h, median (IQR)							
MP, %	115 (0.4)	176 (0.4)	121 (0.6)	102 (0.7)	35 (0.9)	4 (1.2)	<0.01
DCD, yes, %	1508 (5.6)	2935 (6.8)	1687 (7.7)	1234 (8.1)	390 (9.5)	24 (7.0)	<0.01
COD, %							
Anoxia	30.3	28.8	33.0	33.4	33.9	30.9	<0.01
CVA	32.2	35.8	34.3	35.5	36.8	39.4	
Trauma	34.9	32.9	30.2	28.5	26.6	27.4	
Age, y, median (IQR)	39 (26–52)	42 (28–54)	43 (28–55)	44 (29–57)	46 (30-59)	46 (30–60)	<0.01
Recipient							
Male, %	17 452 (64.5)	30 436 (70.0)	14 813 (67.4)	9778 (63.8)	2633 (64.0)	228 (66.5)	<0.01
BMI, median (IQR)	27.6 (23.9–32.5)	28.7 (25.2–32.9)	28.5 (25.2–32.5)	28.4 (25.1–32.3)	27.8 (24.9–31.3)	26.6 (23.9–29.7)	0.97
Waiting days, median (IQR)	41 (8–193)	83 (17–274)	118 (25–320)	130 (27–324)	143 (33–327)	99 (23–271)	<0.01
MELD-Na, median (IQR)	27 (19–35)	23 (15–32)	21 (12–30)	20 (11–29)	19 (11–28)	18 (10–29)	<0.01
Underlying disease, %							
HCV	3626 (13.4)	9724 (22.4)	3643 (16.6)	1798 (11.7)	357 (8.7)	29 (8.5)	<0.01
HBV	608 (2.2)	698 (1.6)	295 (1.3)	195 (1.3)	61 (1.5)	5 (1.5)	
Alcohol	9171 (33.9)	10 794 (24.8)	3643 (16.6)	1798 (11.7)	397 (9.6)	32 (9.3)	
MASLD	1673 (6.2)	4148 (9.5)	3125 (14.2)	2814 (18.4)	818 (19.9)	49 (14.3)	
Malignancy,[a] yes, %	2155 (8.0)	9588 (22.1)	6722 (30.6)	5177 (33.8)	1563 (38.0)	147 (42.9)	<0.01

Continuous variables are presented as median (IQR). Categorical variables are presented as number (%).

[a]Malignancy includes hepatocellular carcinoma and cholangiocarcinoma.

BMI, body mass index; CIT, cold ischemic time; COD, cause of death; CVA, cerebrovascular accident; DCD, donation after cardiac death; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-stage Liver Disease; MP, machine perfusion.

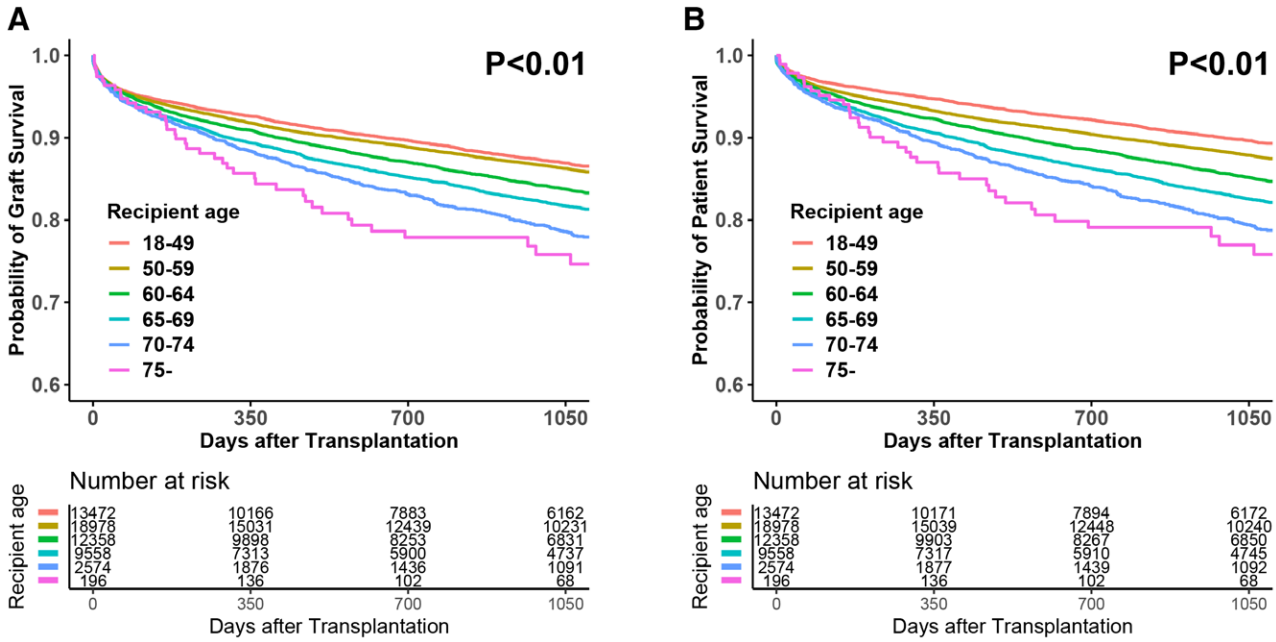

FIGURE 2. Kaplan-Meier survival curves categorized by recipient age (2013–2022): (A) 3-y graft survival and (B) 3-y patient survival.

TABLE 2.

Univariable and multivariable Cox regression analysis of prognostic factors for 90-d/3-y graft survival

	Univariable HR	*P*	Multivariable HR	*P*
90 d				
Recipient sex, male	0.94 (0.87-1.02)	0.11	0.94 (0.87-1.02)	0.13
MELD-Na score ≥25	1.13 (1.05-1.22)	<0.01	1.15 (1.06-1.24)	<0.01
CIT >6.5 h	1.41 (1.31-1.52)	<0.01	1.43 (1.32-1.54)	<0.01
Recipient age ≥75 y	1.14 (0.58-1.99)	0.68	1.18 (0.61-2.08)	0.59
Donor sex, male	0.94 (0.87-1.02)	0.15	0.96 (0.89-1.04)	0.33
Donor age	1.00 (1.00-1.01)	0.08	1.00 (1.00-1.01)	0.03
Donor BMI	1.01 (1.00-1.01)	0.06	1.01 (1.00-1.01)	0.07
3 y				
Recipient sex, male	1.06 (1.01-1.12)	0.03	1.06 (1.01-1.12)	0.02
MELD-Na score ≥25	0.96 (0.92-1.01)	0.12	0.99 (0.94-1.04)	0.65
CIT >6.5 h	1.20 (1.14-1.26)	<0.01	1.22 (1.16-1.28)	<0.01
Recipient age ≥75 y	1.70 (1.19-2.39)	<0.01	1.72 (1.20-2.42)	<0.01
Donor sex, male	0.95 (0.91-1.00)	0.06	0.96 (0.91-1.01)	0.12
Donor age	1.01 (1.00-1.01)	<0.01	1.01 (1.00-1.01)	<0.01
Donor BMI	1.00 (0.99-1.00)	0.64	1.00 (0.99-1.00)	0.05

BMI, body mass index; CIT, cold ischemic time; HR, hazard ratio; MELD, Model for End-stage Liver Disease.

A competing-risk analysis of the 2013–2022 waitlist dropout rates illuminated a directly proportional relationship between candidate age and dropout incidence. Specifically, the 75 y or older age category manifested dropout rates of 12.0%, 24.1%, and 35.1% at 90 d, 1 y, and 3 y, respectively (Figure 3).

Survival Benefit

The 5-y transplant-related survival benefit for each age category was calculated as a ratio comparing the mortality rate of LT recipients with candidates on the waitlist for 5 y after LT or listing (ie, HR).[20,21] The patient survival of LT recipients is greater than that of their waitlisted counterparts during the 2013–2022 period (Figure 4A). Notably, even for the 75 y or older cohort, the upper limit of the 95% confidence interval remains <1.0, underscoring the survival benefit conferred by LT. Because older age recipients had lower MELD-Na scores, outcomes were also examined for only the MELD-Na <25 strata to limit potential confounding, which yielded a similar result, strengthening the survival benefit thesis for the 75 y or older cohort (Figure 4B).

Organ Utility

A simulation model was used to calculate organ utility correlated with 90-d, 1-y, and 3-y survival post-LT across various donor classifications, including DCD, ideal DBD, steatotic DBD, elderly DBD, and high BMI DBD donors. As shown in Table 3, the 75 y or older cohort registered the lowest organ utility score irrespective of donor type. Conversely, cohorts aged 50–59 and 18–49 consistently demonstrated the highest organ utility scores across all temporal endpoints (90 d, 1 y, and 3 y), suggesting that liver allocations to the 75 y or older demographic might yield diminished organ utility.

Liver Allocation to Patients Aged 75 y and Older

In the cohort comprising patients aged 75 y and older, the 3-y patient survival outcomes were compared between LT using donors aged 60 y and younger and older than 60 y. As illustrated in **Figure S3** (**SDC,** http://links.lww.com/TXD/A668), there was no statistically significant difference between the 2 groups ($P = 0.50$).

DISCUSSION

The present study was conducted to evaluate the merits of LT for candidates aged 75 y and older, considering both individual survival benefits and organ utility in light of the prevailing donor scarcity. Our results indicate that although individuals aged 75 y and older can derive survival benefits from LT, allocating livers to this age demographic might not

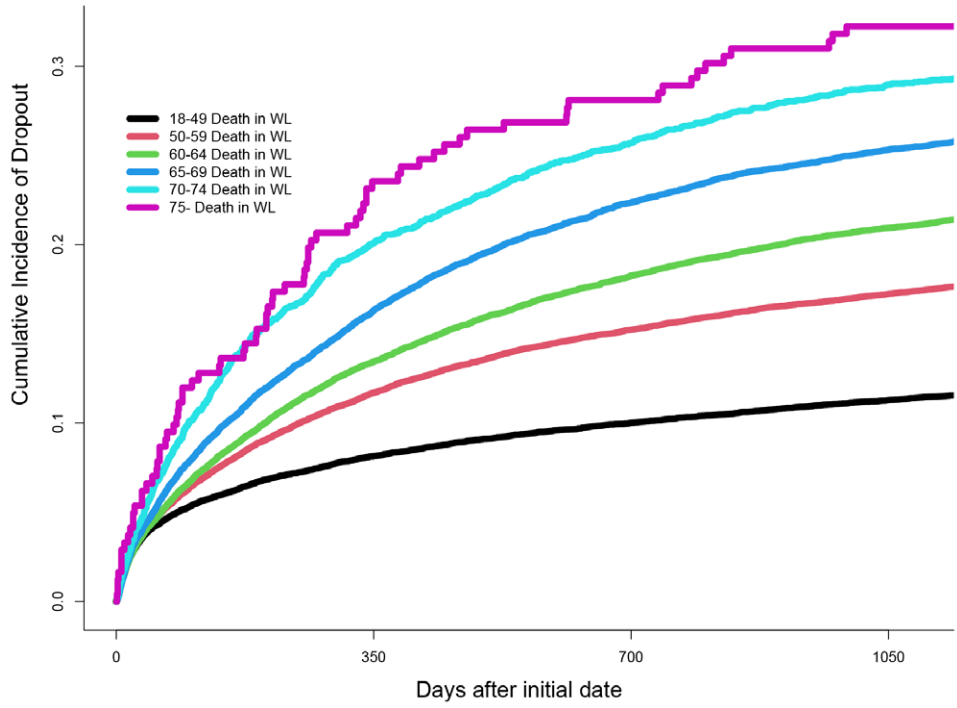

FIGURE 3. Cumulative incidence analysis of WL dropout competing risks. This graph showcases the relationship between the increasing cumulative incidence of WL dropout as recipient age rises. WL, waitlist.

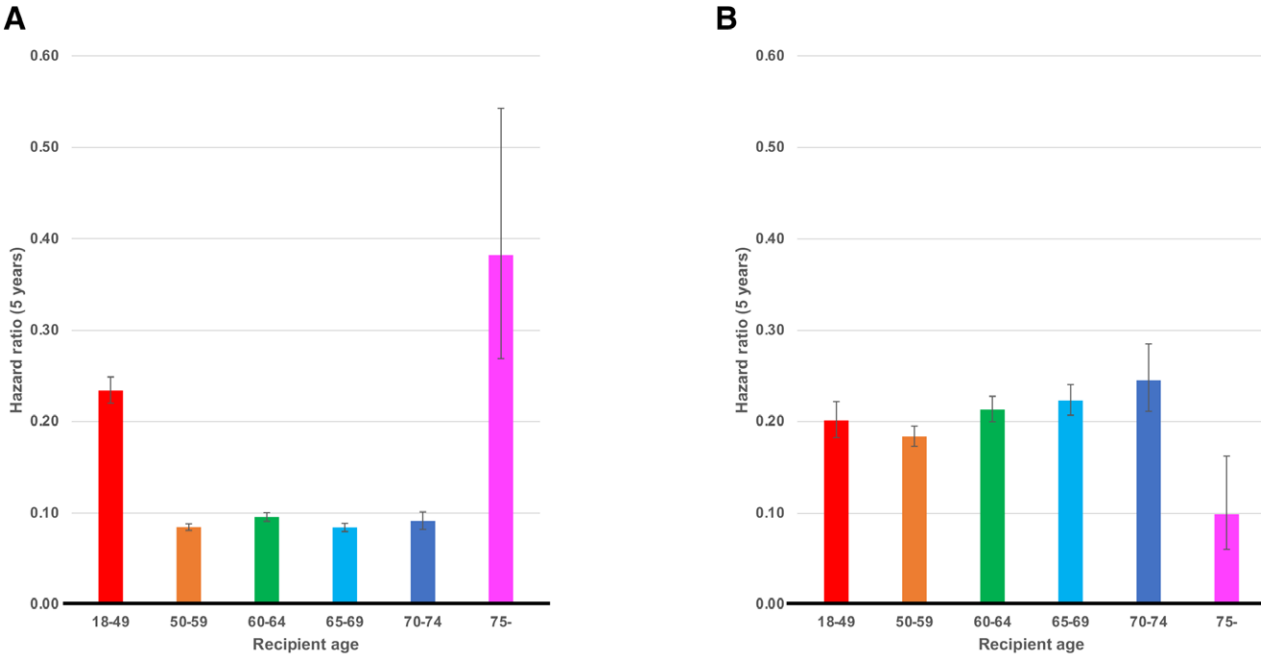

FIGURE 4. Liver transplantation survival benefits categorized by recipient age. A, The HRs of undergoing LT in comparison with remaining on the waitlist. An upper 95% CI limit of <1.0 indicates a significant survival benefit from LT. Analysis was performed across the entire study population. B, A parallel analysis was executed for individuals with a MELD-Na score of <25. CI, confidence interval; HR, hazard ratio; LT, liver transplantation; MELD, Model for End-stage Liver Disease.

yield the highest organ utility, especially when considering the value of a single liver donation. This highlights the potential need for a more stratified approach to organ allocation without excluding this age bracket from LT consideration.

Historically, LT for the elderly has been a contentious issue, with the definition of "elderly" being inconsistent across studies. The literature is mixed; while some support LT for the elderly, citing comparable survival outcomes, others caution given the associated risks. This has left the community without a definitive consensus.[14] However, limited research has been dedicated to optimizing liver donation from the donor perspective considering organ utility—the aggregate

TABLE 3.

Predictive value of patient survival based on donor type allocation across different recipient age categories

	Donor type				
	DCD	Ideal DBD	Steatotic DBD	Old DBD	High BMI DBD
90 d					
18-49	0.933	0.932	0.932	0.931	0.939
50–59	0.935	0.936	0.926	0.937	0.936
60–64	0.929	0.929	0.926	0.931	0.930
65–69	0.930	0.929	0.926	0.931	0.930
70–74	0.925	0.924	0.922	0.925	0.925
75–	0.922	0.922	0.922	0.922	0.922
1 y					
18–49	0.828	0.826	0.830	0.832	0.835
50–59	0.847	0.847	0.835	0.845	0.835
60–64	0.828	0.832	0.828	0.833	0.828
65–69	0.830	0.829	0.827	0.830	0.832
70–74	0.812	0.813	0.812	0.814	0.822
75–	0.806	0.806	0.806	0.806	0.805
3 y					
18–49	0.633	0.618	0.643	0.618	NA[a]
50–59	0.674	0.676	0.672	0.673	NA[a]
60–64	0.645	0.650	0.655	0.648	NA[a]
65–69	0.646	0.644	0.646	0.641	NA[a]
70–74	0.608	0.603	0.605	0.604	NA[a]
75–	0.588	0.588	0.588	0.588	NA[a]

[a]The analysis about liver transplantation using high BMI DBD donors was omitted because of the lack of enough follow-up time.
BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory death.

survival benefits to the society derived from a single liver offer. Although the MELD score informs liver allocation by gauging LT urgency, it was not designed to predict post-LT survival.[28] Naturally, both waitlist and post-LT mortality significantly correlate with increased age.[5,29,30] The concept of survival benefit, which integrates LT urgency with post-LT survival expectations, remains incomplete.[24] Given the stark imbalance between the available donors and recipients requiring LT, a comprehensive approach that ensures efficient resource utilization and maximizes organ utility is imperative.

Our analysis indicated that recipients 75 y and older can still achieve survival benefits from LT, similar to younger cohorts. Even after accounting for potential biases from MELD-Na scores by examining those with lower MELD-Na scores, we found consistent survival benefits post-LT. The observed survival benefit in the cohort aged 75 y and older can be contextualized by the concomitant impact of advancing age on both post-LT and waitlist survival rates, considering that the group aged 75 y and older manifested the highest dropout rate and the most subdued survival outcomes at 5 y post-LT.

From the perspective of organ utility derived from a single liver donation, our research makes a notable finding: allocating a liver to a recipient aged 75 y and older offers the lowest organ utility value. This disparity in organ utility among groups widens progressively from 90 d to 1 y and then 3 y. LT recipients inherently represent a medically vetted group equipped to endure LT. This includes the 75 y and older cohort, which is an even more severely selected healthier subset because they face heightened vulnerability to complications arising from surgeries, including potential heart or kidney issues, owing to their advanced age. Surprisingly, individuals 75 y and older undergoing LT often have a shorter median wait time than those aged 60–64, 65–69, or 70–74 y. This challenges the idea that they might have missed earlier transplantation chances. Instead, indicators such as low MELD-Na scores and a higher incidence of liver malignancies, including hepatocellular carcinoma, hint at relatively stable patients undergoing LT. Despite the anticipated selection bias favoring the 75 y and older cohort, allocating a liver to them does not seem to fully optimize organ utility. Additionally, the economic aspects of LT further validate our findings. Although older recipients typically present with better health profiles, they are more prone to complications, such as infections or organ failures postsurgery. Earlier research indicated that older recipients required more intensive interventions like mechanical ventilation and renal replacement therapy during the perioperative phase than younger patients.[31] Therefore, advanced age can be linked to increased medical expenses and a higher likelihood of readmission postdischarge.[32,33]

In previous work, younger recipients, specifically those 45 y or younger, who survived at least 5 y post-LT, showed inferior long-term survival rates when the age gap with their donor exceeded 10 y as opposed to those with <10-y age difference, whereas older recipients (those aged 65 y and older) demonstrated no survival disparity based on donor age.[34] This underscores the potential of matching older recipients with livers from relatively older donors without jeopardizing their post-LT outcomes while also ensuring optimal graft compatibility for younger recipients sensitive to age mismatches, as illustrated in **Figure S3** (**SDC**, http://links.lww.com/TXD/A668). With this understanding, we propose revising the allocation strategy to promote age-matched pairings, a critical need given the current organ scarcity.

The limitations of the current study include its retrospective nature. Additionally, the UNOS database inherently introduces selection bias, as transplanted patients expected to have better post-LT outcomes are preferentially selected. However, this bias would support our findings—even with a pr2-selected group of healthier individuals, allocating livers to recipients aged 75 y and older does not maximize organ utility. Moreover, the simulation model was built on the present proportions of each age group in the waitlist. This proportion is not static and is subject to change over time in real-world clinical scenarios. With the rapid aging of our population, we anticipate a growth in the future in demographics of patients aged 60–70 y. Consequently, the outcomes of age groups such as 18–49 y and 50–59 y, which currently peak in our simulation model results, might more closely approximate the outcomes of the older age groups. Furthermore, real-world clinical situations may involve factors not considered in our model. Considering this challenge, we have tried to keep the current model simple and understandable. Although there is an ongoing debate about the transformative potential of machine perfusion in transplant medicine, our stance is that its introduction, while potentially enhancing recipient-side survival benefits, may not significantly shift the dynamics of liver allocation from a donor perspective. The primary purpose of this study is to highlight the need for a more precise simulation model for LT in recipients aged 75 y and older, considering a variety of factors. Thus, it is important to note that applying the findings of this study to future allocation decision-making may not be prudent at this stage. Additionally, the study presented the matching of elderly recipients and donors as just 1

example of a recipient/donor match. This is merely a case in point, and future research should consider more complex factors for appropriate matching. This is likely the next challenge in determining suitable LT for recipients aged 75 y and older. A more sophisticated study will be warranted after accumulating more case studies with granular data. Finally, our findings are rooted in the contemporary state of the UNOS database. As the medical landscape evolves, it will be essential to continually reassess and update our understanding, ensuring our conclusions remain valid and relevant.

In conclusion, the discourse on LT for the advanced age is multifaceted. Although individuals aged 75 y and older can derive survival benefits from LT, the organ utility implications of allocating scarce donor livers to this age group might not provide the highest cumulative benefit. We are not suggesting that this age should not be transplanted. Instead, this analysis underscores the pressing need for a more refined allocation system. As the societal age profiles shift, it will be crucial to revisit and adapt our recommendations periodically.

REFERENCES

1. Tejedor M, Selzner N, Berenguer M. Are MELD and MELDNa still reliable tools to predict mortality on the liver transplant waiting list? *Transplantation*. 2022;106:2122–2136.
2. Bureau UC. *Statistical Abstract of the United States*. Statistical Abstract of the Un; 2009.
3. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547–555.
4. Haugen CE, Holscher CM, Garonzik-Wang J, et al. National trends in liver transplantation in older adults. *J Am Geriatr Soc*. 2018;66:2321–2326.
5. Keswani RN, Ahmed A, Keeffe EB. Older age and liver transplantation: a review. *Liver Transpl*. 2004;10:957–967.
6. Lipshutz GS, Hiatt J, Ghobrial RM, et al. Outcome of liver transplantation in septuagenarians: a single-center experience. *Arch Surg*. 2007;142:775–781.
7. Aduen JF, Sujay B, Dickson RC, et al. Outcomes after liver transplant in patients aged 70 years or older compared with those younger than 60 years. *Mayo Clin Proc*. 2009;84:973–978.
8. Starzl TE, Todo S, Gordon R, et al. Liver transplantation in older patients. *N Engl J Med*. 1987;316:484–485.
9. Fernandez TMA, Gardiner PJ. Critical care of the liver transplant recipient. *Curr Anesthesiol Rep*. 2015;5:419–428.
10. Clayton-Chubb D, Kemp WW, Majeed A, et al. Metabolic dysfunction-associated steatotic liver disease in older adults is associated with frailty and social disadvantage. *Liver Int*. 2024;44:39–51.
11. Kwong AJ, Ebel NH, Kim WR, et al. OPTN/SRTR 2021 annual data report: liver. *Am J Transplant*. 2023;23(2 Suppl 1):S178–S263.
12. Gómez Gavara C, Esposito F, Gurusamy K, et al. Liver transplantation in elderly patients: a systematic review and first meta-analysis. *HPB (Oxford)*. 2019;21:14–25.
13. Ahmed O, Vachharajani N, Chang SH, et al. Access to liver transplantation for hepatocellular carcinoma: does candidate age matter? *J Am Coll Surg*. 2021;233:140–151.
14. Wilson GC, Quillin RC 3rd, Wima K, et al. Is liver transplantation safe and effective in elderly (≥70 years) recipients? A case-controlled analysis. *HPB (Oxford)*. 2014;16:1088–1094.
15. Eke PI, Wei L, Borgnakke WS, et al. Periodontitis prevalence in adults ≥ 65 years of age, in the USA. *Periodontol 2000*. 2016;72:76–95.
16. Remington PL. Trends in US life expectancy: falling behind and failing to act. *Am J Public Health*. 2023;113:956–958.
17. Arias E, Xu J. United States life tables, 2019. *Natl Vital Stat Rep*. 2022;70:1–59.
18. Zetterman RK, Belle SH, Hoofnagle JH, et al. Age and liver transplantation: a report of the Liver transplantation database. *Transplantation*. 1998;66:500–506.
19. Collins BH, Pirsch JD, Becker YT, et al. Long-term results of liver transplantation in older patients 60 years of age and older. *Transplantation*. 2000;70:780–783.
20. Goldaracena N, Cullen JM, Kim DS, et al. Expanding the donor pool for liver transplantation with marginal donors. *Int J Surg*. 2020;82:30–35.
21. Luo X, Leanza J, Massie AB, et al. MELD as a metric for survival benefit of liver transplantation. *Am J Transplant*. 2018;18:1231–1237.
22. Merion RM, Schaubel DE, Dykstra DM, et al. The survival benefit of liver transplantation. *Am J Transplant*. 2005;5:307–313.
23. Jackson WE, Malamon JS, Kaplan B, et al. Survival benefit of living-donor liver transplant. *JAMA Surg*. 2022;157:926–932.
24. Su F, Yu L, Berry K, et al. Aging of liver transplant registrants and recipients: trends and impact on waitlist outcomes, post-transplantation outcomes, and transplant-related survival benefit. *Gastroenterology*. 2016;150:441–53.e6; quiz e16.
25. Yang JD, Larson JJ, Watt KD, et al. Hepatocellular carcinoma is the most common indication for liver transplantation and placement on the waitlist in the United States. *Clin Gastroenterol Hepatol*. 2017;15:767–775.e3.
26. Lee E, Sarkar M, Dodge J, et al. Shorter height is associated with lower probability of liver transplantation in patients with hepatocellular carcinoma. *Transplantation*. 2020;104:988–995.
27. Durbach IN, Stewart TJ. Using expected values to simplify decision making under uncertainty. *Omega*. 2009;37:312–330.
28. Briceño J, Ciria R, de la Mata M. Donor-recipient matching: myths and realities. *J Hepatol*. 2013;58:811–820.
29. Bilbao I, Armadans L, Lazaro JL, et al. Predictive factors for early mortality following liver transplantation. *Clin Transplant*. 2003;17:401–411.
30. Desai NM, Mange KC, Crawford MD, et al. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function. *Transplantation*. 2004;77:99–106.
31. Gil E, Kim JM, Jeon K, et al. Recipient age and mortality after liver transplantation: a population-based cohort study. *Transplantation*. 2018;102:2025–2032.
32. Habka D, Mann D, Landes R, et al. Future economics of liver transplantation: a 20-year cost modeling forecast and the prospect of bioengineering autologous liver grafts. *PLoS One*. 2015;10:e0131764.
33. Salvalaggio PR, Dzebisashvili N, MacLeod KE, et al. The interaction among donor characteristics, severity of liver disease, and the cost of liver transplantation. *Liver Transpl*. 2011;17:233–242.
34. Snyder A, Kojima L, Imaoka Y, et al. Evaluating the outcomes of donor-recipient age differences in young adults undergoing liver transplantation. *Liver Transpl*. 2023;29:793–803.