Surgery Open Science 25 (2025) 8–13

Contents lists available at ScienceDirect

Surgery Open Science

journal homepage: www.journals.elsevier.com/surgery-open-science

Research Paper

Prolonged allograft survival in liver transplantation

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HIGHLIGHTS

- Certain liver allografts from older donors have exceptional survival with a cumulative liver age of >80 years
- Donors of prolonged cumulative survival allografts were less likely to have diabetes, history of infection, nor history of alcohol abuse
- Recipients were of prolonged cumulative survival allografts had lower MELD scores and rates of dialysis

ARTICLE INFO

Keywords:
Liver
Transplant
Donor age
Outcomes

ABSTRACT

Introduction: Donor age has traditionally been considered a factor associated with allograft failure in liver transplantation. We sought to examine the characteristics and outcomes of all liver allografts with a cumulative age of over 80 years within the US to better understand liver senescence.
Methods: Using the UNOS STARfile, allografts with a cumulative age (sum of age at transplant plus post-transplant survival) of octogenarian, 90–99 nonagenarian, and 100 years or greater (centurion) were identified from all adult transplant recipients between 1990 and 2022. Donor and recipient data as well as outcomes were analyzed.
Results: There were 3437 octogenarian, 622 nonagenarian, and 29 centurion allografts. Donors from allografts with prolonged cumulative age had less diabetes, less alcohol use, and fewer infections compared to all other donors. Recipients had significantly lower MELD scores at the time of transplant and dialysis rates.
Conclusions: Careful matching of older donors with lower MELD recipients results in excellent outcomes as evidenced by the presence of prolonged cumulative age livers, demonstrating the resilience of the liver to senescent events in appropriately matched recipients.

Introduction

Liver transplant is the only definitive treatment for patients with end-stage liver disease. Despite a 50 % increase in liver transplants from 2012 to 2022, 10,548 candidates remained on the waitlist as of December 31, 2022, and pre-transplant mortality remains >12.3 per 100 waiting-list years (1). To meet growing demands, there has been an increase in recovery of livers from donors >55 years of age who now comprise approximately 25 % of the donor pool (2).

Donor age has been extensively studied as a risk factor for post-transplant graft loss (3). There are several established models for predicting graft survival following deceased donor liver transplantation, all

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https://doi.org/10.1016/j.sopen.2025.03.006
Received 13 December 2024; Received in revised form 15 March 2025; Accepted 25 March 2025
Available online 28 March 2025

of which include donor age (4–7). Despite this, it is possible for carefully selected older donors (>70 years) with minimal cold ischemia time (CIT) to achieve acceptable post-transplant graft survival (8–14). Traditionally, these grafts are age-matched to older recipients who have lower post-transplant life expectancy but are medically optimized to tolerate transient allograft dysfunction.

Liver senescence is thought to be not as progressive as it is with other solid organs, thereby offering the potential for older transplanted allografts to survive for extended periods of time. Cumulative age, defined as donor age at transplantation plus post-transplant allograft survival, could provide a means to analyze and identify characteristics of donors with advanced age with favorable outcomes. In particular, allografts with a cumulative age of >80 years are known to exist but have not been formally studied (15). We hypothesized that such advanced cumulative age allografts would be from donors from lower health morbidities and would be placed into recipients with a lower MELD score and had lower rates of critical illness. We examined the characteristics and outcomes of all liver allografts with cumulative ages of 80–89 years (octogenarians), 90–99 years (nonagenarians), and >100 years (centurions). The aim of this study was to identify a subset of transplanted livers with the greatest cumulative survival and evaluate donor and recipient characteristics associated with prolonged cumulative allograft survival.

Methods

The UNOS Standard Transplant Analysis file (UNOS STARfile) is a national database of donor and recipient demographics and outcomes information reported to the Organ Procurement and Transplantation Network (OPTN) by all transplant centers in the United States. All deceased donor liver transplants from 1990 to 2022 were queried and included for analysis. Donor and recipient demographic data as well as outcomes were analyzed. Pediatric recipients, who were defined as under 18 years at the time of transplant, were excluded from the analysis.

Cumulative age was defined as the sum of deceased donor age plus post-transplant allograft survival in years. Donor livers with a cumulative age of at least 80–89 years (octogenarian), 90–99 years (nonagenarian), and 100 years or greater (Centurion) were identified and compared to all other livers (control).

Statistical analyses were performed using Stata 16/MP4 (StataCorp LP, College Station, TX). Donor and recipient characteristics were described using mean (standard deviation) for continuous variables and frequencies for categorical variables. Comparisons were made using a one-way analysis of variance (ANOVA) with the Sidak Test for multiple comparisons and $\chi 2$ test for continuous and categorical variables, respectively. *P*-values of <0.05 were considered statistically significant. Survival curves were generated using the Kaplan-Meier method. This study was exempt from IRB by the University of Texas Southwestern Medical Center Institutional Review Board.

Results

There were 169,373 livers transplanted during the study period. Of the 169,373 transplanted livers, 3414 (2.0 %) met criteria for octogenarian group, 622 (0.37 %) met criteria for the nonagenarian group, and 29 (0.017 %) met criteria for inclusion in the centurion group.

Donor demographic data

Average donor age and DRI were high across all three age groups and increased as cumulative liver survival increased (Table 1). When examining overall donor utilization, donors with ages 70–80 and 80+ had higher rates of allograft discards (17.5 %, 21.2 % respectively) compared to donors with age <70 (10.5 %, $p < 0.01$, Supplemental Table 1). Relative to transplanted livers with <80 years of cumulative survival, donors in all three groups were more likely to be female. Donor BMI and incidence of donor infection at time of death were lower in these groups and continued to decrease in incidence as cumulative liver age increased (Table 1). Donors with prolonged cumulative survival were less likely to have a history of significant alcohol use and infection at time of procurement but were more likely to have undergone a liver biopsy and have CVA as a cause of death (Table 1). All groups, including the control, had similar cold ischemia times (CIT), at slightly over 7 h.

Recipient demographic data

Recipients in all three older age groups were older with a lower MELD at the time of transplant but this only received statistical significance in the octogenarian and nonagenarian allograft groups (Table 2). Recipients were also less likely to be in the intensive care unit or be on dialysis prior to surgery. Recipients of prolonged cumulative survival livers were more likely to be female and this increased with cumulative age. There were no differences between the groups when comparing for presence of portal vein thrombosis, previous abdominal surgery, presence of TIPS, recipient diabetes, or previous liver transplant.

Table 1
Donor characteristics of allografts with prolonged cumulative survival.

Table 1. Donor Characteristics Of Prolonged Cumulative Allograft Survival	<80 Years (*n* = 165,310)	80–89 Years (*n* = 3414)	90–99 Years (*n* = 620)	≥100 Years (*n* = 29)	*P* value *Compared to age < 80
Age (years)	39.2 (SD = 16.0)	71.7 (SD = 7.1)*	76.8 (SD = 5.9)*	84.3 (SD = 5.2)*	*$p < 0.01$
Gender (% male)	60.7 %	45.2 %*	42.3 %*	37.9 %*	*p < 0.01
Mean BMI (kg/m^2)	27.0 (SD = 6.2)	26.6 (SD = 5.3)	25.5 (SD = 4.7)*	24.3 (SD 4.0)*	*$p < 0.01$
Cause of Death					
Anoxia	25.3 %	7.7 %	5.8 %	0 %	*p < 0.01
CVA	35.0 %	76.4 %	77.9 %	79.3 %	
Head trauma	35.1 %	14.1 %	15.0 %	20.7 %	
CNS tumor	0.6 %	0.4 %	0	0 %	
Other	4.0 %	1.4 %	1.3 %	0 %	
Diabetes (%)	9.5 %	19.2 %*	15.3 %*	*7.1 %	*p < 0.01
Donor risk index (DRI)	1.5 (SD = 0.47)	2.2 (SD = 0.37)*	2.3 (SD = 0.41)*	2.4 (SD = 0.4)*	*$p < 0.01$
Donor liver biopsy (%)	29.9 %	51.7 %*	48.4 %*	52.0 %*	*p < 0.01
Mean macrosteatosis content (%)	8.7 % (SD = 12.2)	6.4 % (9.1)*	5.6 % (7.6)*	2.6 % (SD = 5.5)	*p < 0.01
Mean terminal ALT (units/L)	75 (SD = 204)	36 (SD = 53)*	33 (SD = 37)*	29 (SD = 20)	*$p < 0.01$
Mean terminal AST (units/L)	81 (SD = 155)	51 (SD = 72)*	49 (SD = 43)*	42 (SD = 27)	*p < 0.01
Mean terminal Cr (mg/dL)	1.57 (SD = 1.80)	1.49 (SD = 1.42)	1.52 (SD = 1.67)	1.34 (SD = 0.61)	$p = 0.07$
Donor significant alcohol use (%)	15.6 %	11.2 %*	10.3 %*	0 %*	*p < 0.01
Donor infection (%)	52.7 %	35.5 %*	23.1 %*	3.6 %*	*p < 0.01
Cold ischemia time (hours)	7.2 (SD = 3.6)	7.3 (SD = 3.4)	7.3 (SD = 3.2)	7.3 (SD = 2.4)	$p = 0.98$
Distance from center (miles)	161 (SD = 255)	195 (SD = 294)*	220 (SD = 307)*	327 (SD = 422)	*$p < 0.01$

* Statistical signficance compared to age < 80.

Table 2
Recipient characteristics of allografts with prolonged cumulative survival.

Table 2. Recipient Characteristics	<80 Years (n = 165,310)	80–89 Years (n = 3414)	90–99 Years (n = 620)	≥100 Years (n = 29)	P value
Age (years)	53.1 (SD = 11.1)	55.1 (SD = 10.2)*	55.5 (SD = 10.0)*	55.1 (SD =12)	*p < 0.01
Gender (% male)	65.1 %	59.1 %*	55.3 %*	34.5 %*	*p < 0.01
Mean BMI (kg/mˆ2)	28.2 (SD = 5.8)	27.9 (SD = 5.6)*	27.1 (SD = 5.5)*	27.9 (SD = 6.0)	*p < 0.01
Diabetes (%)	24.9 %	25.7 %	22.3 %	14.3 %	p = 0.18
Time waiting (days)	227 (SD = 425)	273 (SD = 430)*	250 (SD = 430)	249 (SD = 568)	*p < 0.01
Final MELD	23.2 (SD = 10.7)	18.8 (SD = 8.7)*	18.2 (SD = 7.7)*	16.7 (SD = 8.3)*	*p < 0.01
Recipient on life support (%)	9.8 %	5.9 %*	7.3 %	8 %	*p < 0.01
Dialysis during week prior to transplant (%)	14.5 %	3.0 %*	3.0 %*	0 %*	*p < 0.01
Previous abdominal surgery (%)	41.7 %	40.4 %*	39.1 %*	28 %	p < 0.01
Previous TIPS procedure (%)	7.7 %	7.9 %	7.8 %	4 %	p = 0.10
Previous liver transplant (%)	7.2 %	2.7 %*	3.1 %*	0 %	*p < 0.01
Portal vein thrombosis (%)	8.7 %	6.7 %*	6.2 %*	0 %	*p < 0.01

* Statistical signficance compared to age < 80.

Recipient outcomes

Median post-transplant graft survival was 11.8 years (IQR 6.6–17.0 years) for octogenarian allografts, 16.2 years (13.0–20.0 years) for nonagenarian allografts, and 17.2 years (IQR 15.9–21 years) for the centurion allografts (Table 3). Overall, prolonged cumulative survival allografts had lower rates of retransplantation (6 % for <80 years, vs 2–5 % for prolonged cumulative survival allografts). Increased cumulative liver age was associated with increased post-transplant allograft and patient survival (Fig. 1, Fig. 2). Remarkably, >50 % of livers octogenarian and nonagenarian allografts remain alive with the potential to become centurion allografts. As expected, the rates of allograft failure were lower in the prolonged cumulative survival groups (Table 3). There were no significant differences in the incidence of rejection at twelve-months post-transplant in livers with octogenarian (14.4 %), nonagenarian (17.6 %) and centurion (23.8 %) allografts when compared to the control group (14.4 %, $p = 0.18$).

Centurions

The first centurion transplant occurred in 1993 and the rate of centurion transplants has gradually risen over time (Fig. 2). Geographically, 76 % of centurion allografts were transplanted in three OPTN regions. Region 9 had the highest rate of centurion transplants, followed by Region 3, and Region 11 (Fig. 3). While centurion allografts generally came from donors over 80 years of age, they were transplanted in recipients of a variety of ages, all having allograft survival of >10 years (Fig. 4). Analysis of centurion transplant by center showed that 16 centers had at least one centurion transplant with 2 centers responsible for having >10 % of the centurion population at each respective center (Fig. 5A). Likewise, allografts with cumulative survival between 90 and 100 years occurred at 77 centers with 3+ centers having >10 % each (Fig. 5B). Allografts with 80–90 years of cumulative survival occurred at 111 centers with no center having >7 % of the total population 80–90 cumulative survival allografts (Fig. 5C). This data suggests that there is some clustering of centers with the centurion and 90–100 population but not with the 80–90 population.

Discussion

In this study, we examined liver allografts with a minimum combined age of 80 years and demonstrated that these allografts exist and have excellent outcomes. Allografts with prolonged cumulative survival were more likely to be from older donors with lower BMI, lower rates of significant alcohol use, and fewer infections. Recipients of allografts with prolonged cumulative survival had lower MELD scores and were less likely to be on dialysis prior to transplant. Outcomes from centurion allografts, those with cumulative survival over 100 years, are particularly interesting as the average donor age was 85 years and the mean graft survival was >18 years. Taken together, these results suggest that utilization of older allografts with careful matching and management of donor and recipient risk factors can lead to excellent outcomes.

Transplantation of allografts from donors older than 70 occur, however their use is controversial. Several studies have shown acceptable outcomes (8–11,16). However, with use of older allografts, concerns of primary non-function and delayed graft function exist (11). In addition, allografts from octogenarians have been shown to be more likely to have biliary complications (17,18). Indeed, rates of allograft discard are higher donors in their 70s and 80s. The donor and recipient characteristics of allografts with prolonged cumulative survival identified in this study allow for direct comparison of these allografts against

Table 3
Recipient outcomes of allografts with prolonged cumulative survival.

Table 3. Recipient Outcomes	<80 Years (n = 165,310)	80–89 Years (n = 3414)	90–99 Years (n = 620)	≥100 Years (n = 29)	P value
Allograft Survival (years) [IQR]	4.8 [1.3–9.9]	11.8 [6.6–17.0]*	16.2 [13.0–20.0]*	17.2 [15.9–21.0]*	*p < 0.01
Patient Survival (years) [IQR]	4.9 [1.3–10.1]	11.9 [6.7–17.0]*	16.2 [13.0–20.1]*	17.3 [16.1–21.0]*	*p < 0.01
Retransplanted (%)	6.0 %	4.3 %*	2.3 %*	3.5 %*	*p < 0.01
Allograft Failure (%)	14.7 %	9.7 %*	5.0 %*	3.5 %*	*p < 0.01
Primary Non-Function	3.2 %	2.0 %*	0.8 %	0 %	*p < 0.01
Hepatic Artery Thrombosis	0.3 %	0.1 %*	0.3 %	0 %	*p < 0.01
Other Thrombosis	1.5 %	0.5 %*	0 %	0 %	*p < 0.01
Cholangiopathy	1.0 %	1.0 %	0.2 %	0 %	*p < 0.01
Infection	2.0 %	1.1 %*	0.5 %	0 %	*p < 0.01
Acute Rejection	0.8 %	0.4 %*	0 %	0 %	*p < 0.01
Chronic Rejection	1.4 %	1.0 %*	1.0 %	0 %	*p < 0.01
Recurrence of Hepatitis	2.7 %	2.0 %	0.3 %	3.5 %	p = 0.48
Recurrence of Disease	1.8 %	1.8 %	1.8 %	0 %	p = 0.30
Treated for rejection at 6 months	14.3 %	14.0 %	18.6 %	19.1 %	p = 0.09
Treated for rejection at 12 months	14.4 %	14.4 %	17.7 %	23.8 %	p = 0.18

* Statistical signficance compared to age < 80.

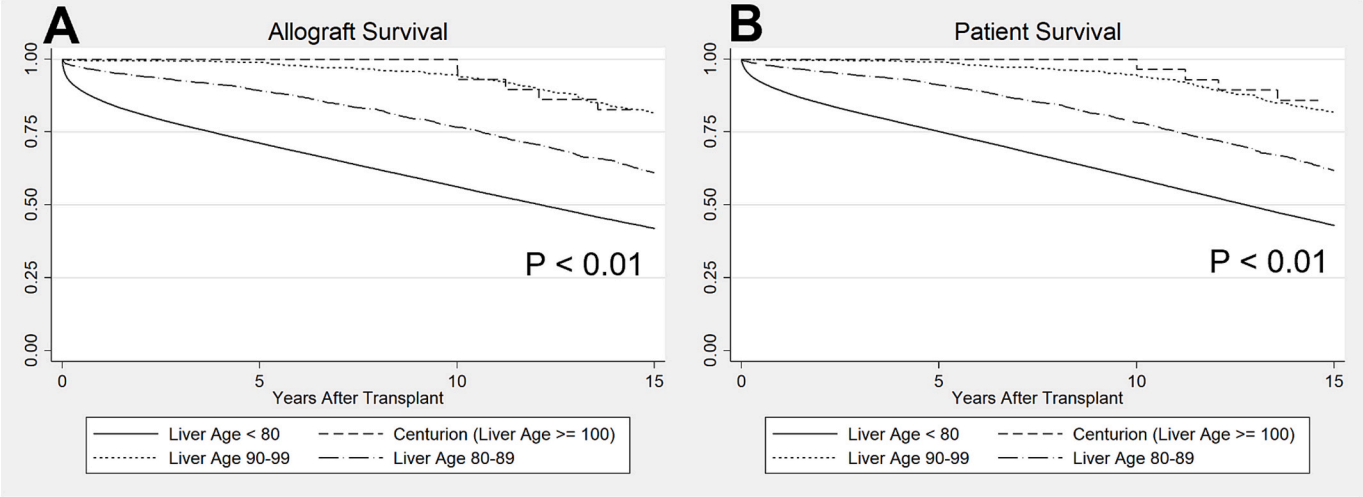

Fig. 1. Allograft and patient survival.
(A) Allograft Survival of Groups with Prolonged Cumulative Survival.
(B) Patient Survival of Groups with Prolonged Cumulative Survival.

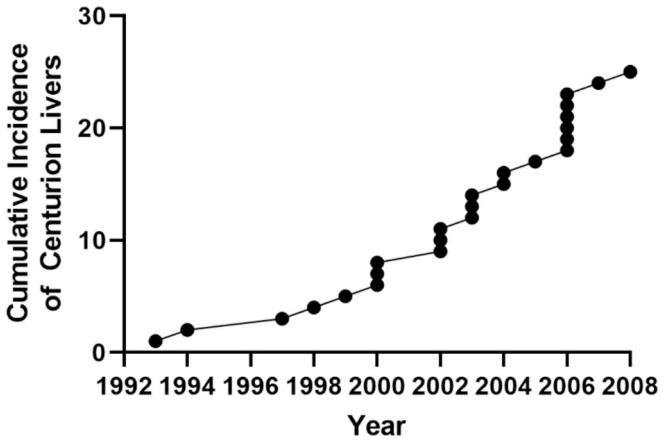

Fig. 2. Cumulative incidence of centurion livers.

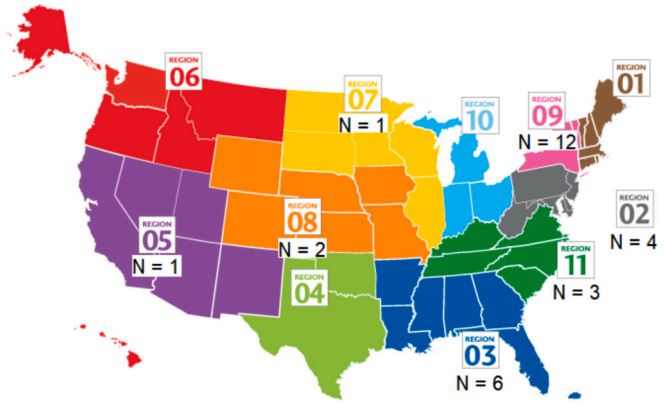

Fig. 3. Geographic distribution of centurion livers. Map adapted from UNOS.org

other transplanted livers with a similar risk profile. The donor risk index (DRI) utilizes seven donor factors and two procurement factors to quantitatively predict the risk of graft failure in the pre-transplant setting (19). Centurion, nonagenarian, and octogenarian allografts outperformed DRI-based expectations with 100 %, 98 %, and 75 %

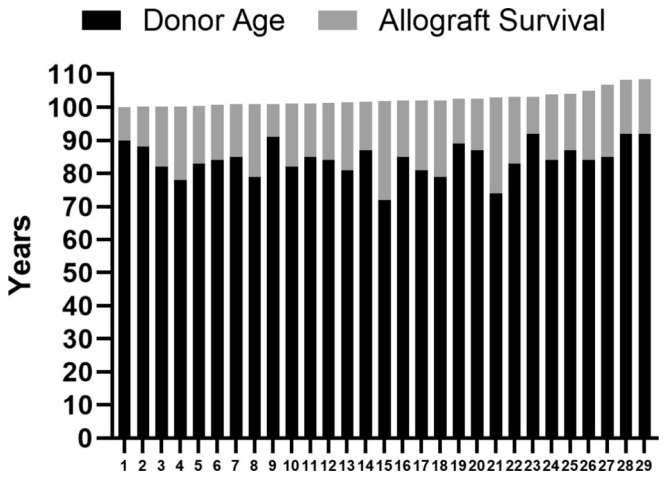

Fig. 4. Donor age, recipient age, and posttransplant survival among centurion livers.

survival at 10 years respectively. The fact that these allografts significantly outperform livers with similar risk stratification suggests that appropriate matching of donor and recipients can result in excellent outcomes using older allografts. All three groups were notable to have the following: donors who were older with lower BMI, lower incidence of significant alcohol use, lower incidence of donor infection. On the recipient end, recipients who were female with lower MELD scores who were less critically ill. This suggests that preferential transplantation of older donors to lower MELD recipients could result in overall longer allograft survival. These findings are aligned with studies from other institutions which show favorable outcomes using elderly donors in selected recipients (20–24), and our work adds to the literature by demonstrating similar findings using a national database to show greater generalizability of these findings. Interestingly, there was no difference in CIT between octogenarian, nonagenarian, and centurion groups compared to the control group. There is some evidence of clustering of the centurion and 90–100 cumulative population by center suggesting that some centers are perhaps better equipped to utilize older donors, however due to de-identification of center data we cannot verify if the location of the centers and whether they are high volume or not. Further exploration of differences across livers with the three cohorts of extended allograft age compared to the control may yield insight into

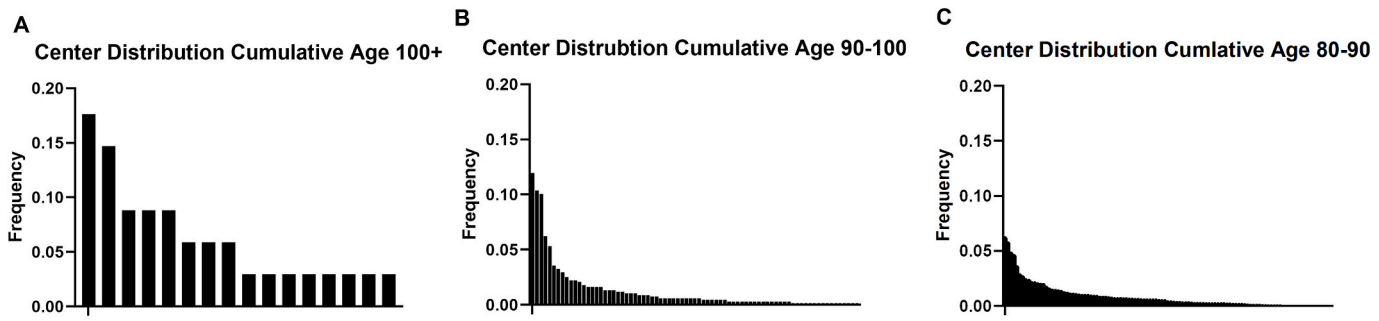

Fig. 5. Center distribution for cumulative age 100 + (Centurion, A), 90–100 (B) and (80–90).

protective factors contributing to allograft resilience.

This study is the first major of using cumulative liver age to identify recipient and donor factors that promote prolonged allograft survival with older allografts. The results suggest that older donors can be increasingly utilized for transplantation with proper donor/recipient selection. Indeed older patients have historically consisted of a significant portion of donor pool in Europe with ~30 % of European liver donors being older than 60 (25). In the US outcomes have with older donors have improved substantially since the 1990s with recipients of older donors only having nearly equivalent one year survival compared to recipients of younger donors in the 2010s (14). The number of octogenarian, nonagenarian, and centurion transplants will increase due to continued use of older donors and aging of those of have received advanced-age allografts. In addition, machine perfusion and normothermic regional perfusion have been explored as a means to evaluate allograft function from older donors and potentially reduce post-reperfusion syndrome (26–32). Furthermore, perfusion technologies could be utilized to address current concerns with storage of advanced age donors as the current OPTN policy promotes a 150 nautical mile range for older donors instead of the conventional 250 nautical mile range. The first reported transplant from a 100-year old donor was performed with machine perfusion (33), and this novel technology presents further opportunities to utilize grafts from donors with advanced age.

Limitations of this study include its retrospective design, and data having been obtained from a national registry, where the fidelity depends on the quality of data entered by the transplanting center. Subjects in the octogenarian, nonagenarian, and centurion group were selected in part based upon prolonged post-transplant survival which bias and confounds any analysis of allograft failure. For the centurion group small sample size ($n = 29$) could lead to type II error especially for rare events such as allograft failure. Additionally, the histologic analysis of allografts was limited with only the minority of allografts (~20–50 %) having a biopsy and data before 2014 lacking any data on fibrosis and portal infiltrates. Further studies improving understanding of liver allograft resilience to senescence may be needed. It will also be important to evaluate if and how recipient factors can modify senescence in the transplanted liver and if anti-aging properties in allografts can be augmented.

Conclusions

The existence of liver allografts from septuagenarians, octogenarians, and nonagenarians that function for over a decade, especially including those with over 100 years of cumulative age, reveals the dramatic resilience of the liver to senescent events and represents an ideal outcome from the use of advanced age donors. Further clinical studies to increase understanding and promote the use of older donors should be encouraged, as this will help to both characterize the ideal older donor, increase allograft utilization and increase allograft survival. Targeted studies of donor livers with proven longevity may also offer new insight into genetic and biological factors inherent in these allografts.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2025.03.006.

CRediT authorship contribution statement

Yash Kadakia: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Andrew D. Shubin:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation. **Malcolm MacConmara:** Conceptualization. **Madhukar S. Patel:** Writing – review & editing, Supervision, Investigation, Funding acquisition. **Jorge A. Sanchez-Vivaldi:** Writing – review & editing, Supervision, Conceptualization. **Lauren E. Matevish:** Writing – review & editing, Supervision. **Steven I. Hanish:** Writing – review & editing. **Parsia A. Vagefi:** Writing – review & editing. **Christine S. Hwang:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

Ethics statement

This study was exempt from an IRB by the UT-Southwestern ethics committee. All data from the UNOS Standard Transplant Analysis file (UNOS STARfile)was from the scientific registry of transplant recipients (SRTR) managed by the Hennepin Healthcare Research Institute.

Funding sources

Madhukar S. Patel is supported as the Dedman Scholar of Clinical Care at UT Southwestern Medical center. This work was supported by the 2019 American Society of Transplant Surgery Collaborative Scientist Grant.

Declaration of competing interest

Malcolm MacConmara is employed by TransMedics and Parsia Vagefi is a consultant for TransMedics OCS National Steering Committee. All other authors have no disclosures.

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