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Outcomes of deceased donor liver transplantation from elderly donors

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Background: Favorable outcomes achieved after deceased donor liver transplantation (DDLT) suggest that use of elderly donors may be an effective way to expand donor pool.
Methods: This was a retrospective analysis of adult DDLT using elderly donors. It was a double-arm study that compared posttransplant outcomes to ascertain whether use of elderly donors (aged ≥76 years) has adverse effects on outcome of DDLT. Elderly donor study group included 14 donors aged ≥76 years and elderly donor control group comprised 39 donors aged 66–75 years.
Results: Mean donor age of the study and control groups was 78.2±3.1 years and 68.9±2.7 years, respectively (P<0.001). Other clinical parameters were comparable between these two donor groups. The 1-, 3-, and 5-year graft survival rates in the elderly study group were 83.6%, 59.7%, and 59.7%, respectively, and those in the elderly control group were 79.4%, 68.1%, and 59.6%, respectively (P=0.97). The overall 1-, 3-, and 5-year survival rates after donation from elderly study group were 83.6%, 59.7%, and 59.7%, respectively, and those after donation from control group were 79.3%, 72.1%, and 64.1%, respectively (P=0.74). Regarding overall patient survival, univariate analysis identified pretransplant requirement for ventilator support (P=0.021) and pretransplant renal replacement therapy (P=0.025) as statistically significant risk factors; however, neither was significant on multivariate analysis.
Conclusions: The results of this study suggest that using an elderly donor graft might not worsen the posttransplant outcomes significantly; thus, advanced age per se may not be an exclusion criterion for organ donation.

Keywords: Donor age; Elderly donor; Deceased donor liver transplantation; Octogenarian; Septuagenarian

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INTRODUCTION

Liver transplantation (LT) has become the treatment of choice for patients with end-stage liver disease because of improved results and broadening of indications. However, the shortage of organ donors and increased demand for LT have led to widening of concepts to increase the availability of grafts for LT. Acceptance of old and marginal liver donors, along with development of alternative techniques such as liver graft splitting, and the use of living donors and the domino procedure, have been proposed to reduce the mortality of patients on the waiting list. Although these

HIGHLIGHTS

- This was a retrospective double-arm analysis of adult deceased donor liver transplantation using elderly donors aged ≥76 years.
- The data suggest that organs from elderly donors do not worsen posttransplant outcomes.
- Advanced age should not be an exclusion criteria criterion; indeed, using such donors could be the key to increasing the supply of liver grafts.

procedures have increased the deceased donor organ pool, a profound shortage still remains.

Use of marginal donors, particularly older donors, is an important approach to expanding the donor pool [1,2]. Although favorable LT outcomes have been achieved with elderly donors [1-4], there is still a certain reluctance to use them due to concerns about early graft function and long-term graft survival. We present a retrospective analysis of our experience of adult deceased donor liver transplantation (DDLT) in a high-volume LT center using elderly donors aged ≥76 years.

METHODS

The study protocol was approved by the Institutional Review Board of Asan Medical Center, which waived the requirement for informed consent due to the retrospective nature of this study (IRB No. 2020-0857). This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013.

Patient Selection and Study Design

This study was a retrospective single-center analysis of DDLT data. Initially, the institutional LT database was searched to identify DDLT cases that used elderly donors ≥76 years of age during a 10-year period from January 2010 to December 2019. These LT cases were classified as the elderly donor study group. In addition, DDLT cases that received a graft from donors aged between 66 years and 75 years were used as an elderly donor control group. The study design was set to be a double-arm study comparing posttransplant outcomes between the study and control groups. The purpose was to ascertain whether using elderly donors had an adverse effect on the outcome of DDLT. Donor age was the only factor to classify the DDLT groups because detailed information on the donor condition and graft status was not available in the institutional medical record system. The patients in this study were followed up until April 2020.

Statistical Analysis

Numerical data are presented as the mean±standard deviation. Continuous variables were compared using Student t-test. Incidence variables were compared using the chi-square test and Fisher's exact test. Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS ver. 22 (IBM Corp., New York, NY, USA).

RESULTS

Patient Profiles

The age of the 430 adult DDLT donors during the 10-year study period is depicted in Fig. 1. The number of donors aged ≥76 years and 66–75 years was 14 (3.3%; elderly donor study group) and 39 (9.1%; elderly donor control group), respectively. The donor and recipient characteristics within these two groups are presented in Table 1.

The mean donor age of the elderly donor study group was 78.2±3.1 years (range, 76–86 years), which was sig-

Fig. 1. Distribution of ages of deceased donors for a 10-year study period in Korea.

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Table 1. Comparison of patient profiles

Variable	Elderly donor study group (≥76 yr)	Elderly donor control group (66–75 yr)	P-value
Patient no.	14	39	-
Recipient sex (male:female)	11:3	25:14	0.44
Recipient age (yr)	50.8±11.5	51.1±13.3	0.93
Primary disease			0.91[a]
HBV-LC	6 (42.9)	16 (41.0)	
HCV-LC	1 (7.1)	0	
ALD	5 (35.7)	11 (28.2)	
Others	2 (14.3)	12 (30.8)	
Recipient ABO blood group			0.09[b]
A	9 (64.3)	12 (30.8)	
B	4 (28.6)	13 (33.3)	
O	1 (7.1)	8 (20.5)	
AB	0	6 (15.4)	
Preoperative laboratory finding			
Total bilirubin (mg/dL)	20.7±11.9	23.2±14.7	0.54
Serum creatinine (mg/dL)	1.52±0.96	2.21±2.11	0.11
Prothrombin time (INR)	2.29±0.91	2.41±0.89	0.71
MELD score	31.0±9.3	32.2±9.9	0.72
Pretransplant ventilator support	4 (28.6)	11 (28.2)	0.98
Pretransplant renal replacement	3 (21.4)	16 (41.0)	0.19
HCC at explant liver	5 (35.7)	6 (15.4)	0.11
Donor sex (male:female)	7:7	27:12	0.20
Donor age (yr)	78.2±3.1	68.9±2.7	<0.001
Graft type			NA
Whole liver	14 (100)	39 (100)	
Split right liver	0	0	
Graft weight (g)	1181.9±239.5	1294.9±234.5	0.14
Graft-recipient weight ratio	1.59±0.53	1.98±0.84	0.42
Donor anti-HBc IgG	6 (42.9)	19 (48.7)	0.71
Ischemic time (min)			
Cold	285.6±136.9	299.1±89.7	0.81
Warm	56.3±56.4	59.4±58.4	0.78
Retransplantation			NA
Early (<3 mo)	0	1 (2.6)	
Late (>3 mo)	0	3 (7.7)	

Values are presented as mean±standard deviation or number (%).
HBV, hepatitis B virus; LC, liver cirrhosis; HCV, hepatitis C virus; ALD, alcoholic liver disease; INR, international normalization ratio; MELD, Model for End-Stage Liver Disease; HCC, hepatocellular carcinoma; NA, not available; anti-HBc IgG, hepatitis B virus core antibody immunoglobulin G.
[a]Comparison between HBV-LC and other groups; [b]Comparison between blood group A and B versus O and AB.

nificantly higher than that of the control group (68.9±2.7 years). Other parameters were comparable between the two groups. The Model for End-Stage Liver Disease (MELD) scores for the elderly donor study and control groups were 31.0±9.3 and 32.2±9.9, respectively (P=0.72).

Posttransplant Survival Results

None of the cases that received grafts from the elderly do-

nor study group required retransplantation; however, four cases (10.3%) that received grafts from the elderly donor control group did: one patient required early retransplantation due to graft dysfunction and three patients required late retransplantation due to chronic rejection. The graft survival rates at 1, 3, and 5 years were 83.6%, 59.7%, and

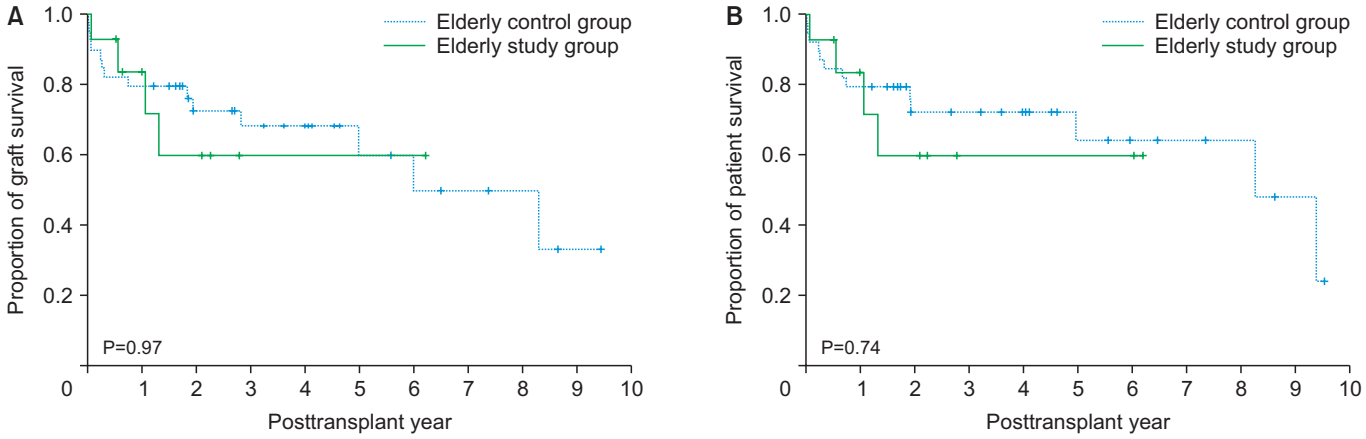

Fig. 2. Comparison of graft (A) and overall patient (B) survival outcomes according to donor age.

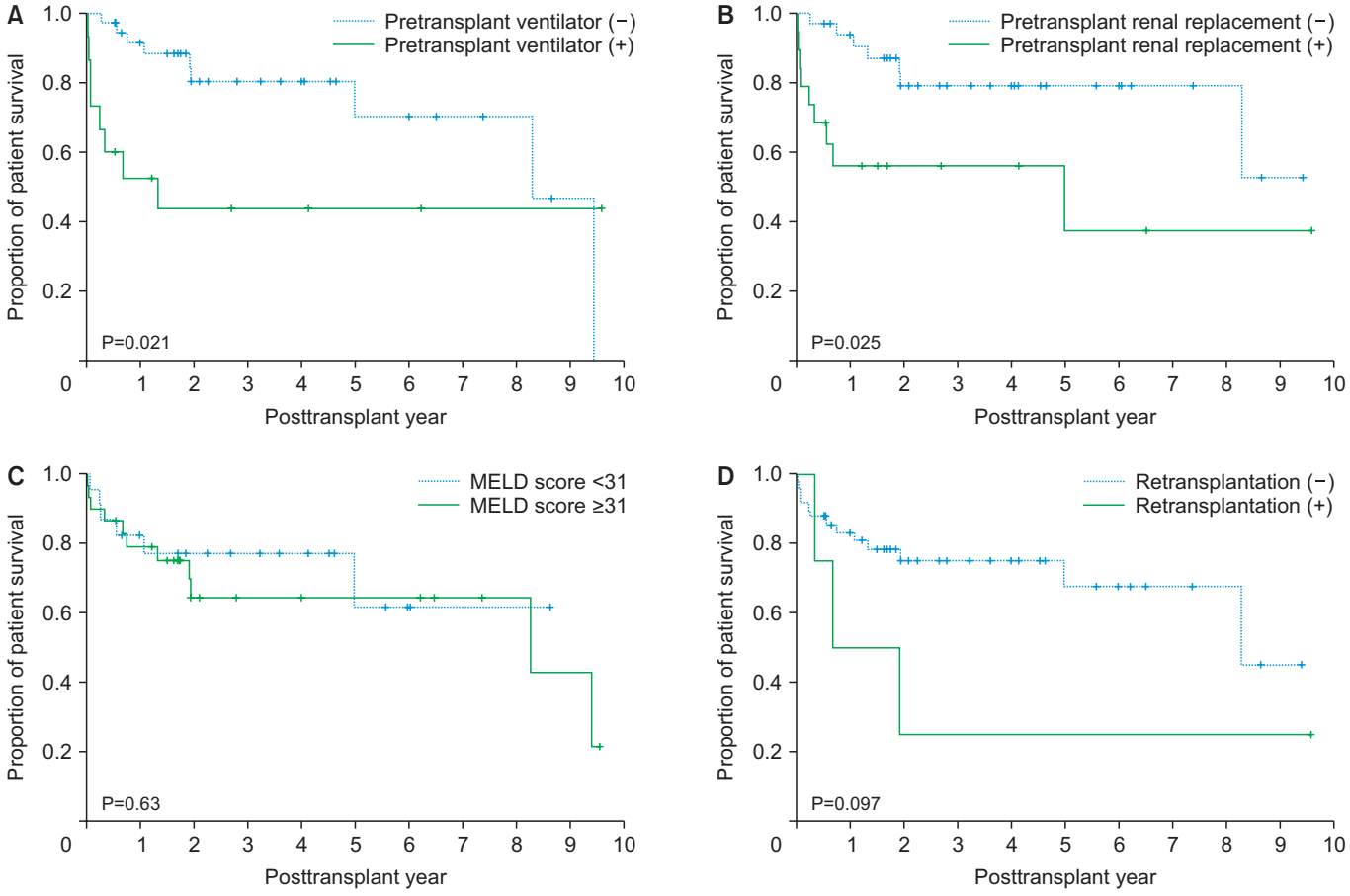

Fig. 3. Comparison of the overall patient survival outcomes according to pretransplant ventilator support (A), pretransplant renal replacement therapy (B), Model for End-Stage Liver Disease (MELD) score with a cutoff of 31 (C), and retransplantation (D).

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59.7%, respectively, for the elderly donor study group, and 79.4%, 68.1%, and 59.6%, respectively, for the elderly donor control group (P=0.97) (Fig. 2A).

The overall patient survival rates at 1, 3, and 5 years were 83.6%, 59.7%, and 59.7%, respectively, in the elderly donor study group and 79.3%, 72.1%, and 64.1%, respectively, in the elderly donor control group (P=0.74) (Fig. 2B). Four patients that received grafts from the elderly donor study group died due to posttransplant sepsis (n=1), late chronic rejection (n=1), and recurrence of hepatocellular carcinoma (n=2). Thus, peritransplant in-hospital mortality was one case (7.1%). By contrast, 13 patients (33.3%) that received grafts from the elderly donor control group died. Peritransplant in-hospital mortality occurred in six cases (15.4%), in which the underlying causes were graft dysfunction (n=2) and sepsis (n=4). Late mortality was caused by infection including pneumonia (n=3), chronic rejection (n=2), recurrence of hepatocellular carcinoma (n=1), and unknown causes (n=1).

Risk Factor Analysis for Patient Survival

Donor age was not a risk factor for patient survival; therefore, this parameter was excluded from the analysis. Univariate analysis revealed that pretransplant requirement for ventilator support (P=0.021) (Fig. 3A) and pretransplant requirement for renal replacement therapy were significant risk factors for overall survival (P=0.025) (Fig. 3B). A MELD score ≥31 was not a significant risk factor (P=0.63) (Fig. 3C). Retransplantation showed a noticeable prognostic contrast, but the significance was only marginal, primarily due to the small sample number (P=0.097) (Fig. 3D). Multivariate analysis did not identify pretransplant ventilator support, pretransplant renal replacement therapy, or retransplantation as independent risk factors (Table 2).

DISCUSSION

During the 10 years from January 2010 to December 2019, there were 4,395 deceased donors registered in the Korean Network for Organ Sharing (KONOS) database, which included 21 elderly donors aged between 76–79 years and 21 donors aged ≥80 years. The 42 elderly donors aged ≥76 years represent 0.96% of all deceased donors. Considering that deceased donors allocated for pediatric DDLT were excluded from our series, the proportion of elderly donors aged ≥76 years was approximately 3% of all deceased donors allocated to our patients. This proportion of elderly donors appears to be much lower than that in Western countries in which organ donation is common [1-4].

Reports on utilization and optimization of elderly donor grafts for DDLT are conflicting. Some studies advocate the use of elderly donor organs for less sick recipients [5-8]. However, other reports show that the recipient's MELD score has no effect on outcome after receiving a graft from an elderly donor [9,10]. These studies question the use of these "high-risk" donors in "low-risk" recipients. The results of our study show that a cutoff of MELD score of 31 is not a significant risk factor for patient survival. In real-world practice in Korea, such logical matching of high-risk donors to low-risk recipients is not possible due to a serious organ shortage [11]. By contrast, those in poor general condition and requiring pretransplant ventilator

Table 2. Results of univariate and multivariate analyses for overall patient survival

Variable	Case No.	Univariate analysis		Multivariate analysis	
		3-Year patient survival rate (%)	P-value	Hazard ratio (95% CI)	P-value
Pretransplant ventilatory support					
No	38	80.5		1	
Yes	15	43.8	0.021	2.41 (0.79–7.35)	0.12
Pretransplant renal replacement therapy					
No	34	79.2		1	
Yes	19	56.0	0.025	2.32 (0.76–6.94)	0.13
Retransplantation					
No	49	75.2		1	
Yes	4	25.0	0.097	1.53 (0.35–3.42)	0.32

CI, confidence interval.

support or renal replacement therapy are at significant risk of poor posttransplant outcomes, although multivariate analysis did not identify these as independent risk factors.

Some studies have examined the synergistic effects of donor age and cold ischemia time on graft survival after LT [12,13]. Prolonged cold ischemic time appears to be detrimental to the outcomes of elderly liver grafts; thus, we tried to shorten the cold and warm ischemic times as much as possible in such cases. However, we found no difference in the mean cold and warm ischemic times between the elderly study and control groups. Indeed, because the territory of South Korea is small, the cold ischemic time required for organ transportation is usually less than 4 hours. Thus, there is no need for time-saving donor-recipient matching in the current KONOS allocation system for DDLT.

Aging is characterized by a progressive decline in functions, which reduces the capacity of cells and organs to respond to intrinsic and extrinsic stimuli. Functional changes that develop with age should eventually lead to significant alterations in clinical practice. Synthetic, excretory, and metabolic changes in liver function may be affected by aging, and these effects may have clinical relevance [14]. The major age-related changes in the liver are reductions in tissue mass and blood flow. Here, we found that liver graft weight in the elderly study group was lower than that of the elderly control group. Indeed, there is an approximately 30% loss of liver volume and hepatic blood flow between the ages of 30 and 100 years [15].

Many studies show that using liver grafts from septuagenarian donors is not a contraindication to their utilization in DDLT per se [14]; however, some studies report significantly worse patient and graft survival when using liver grafts from donors older than 70 years [16-18]. Since the first reported case of successful graft from an 86-year-old donor [19], others have reported using liver grafts from octogenarian donors [2,14,20,21]; other studies have used grafts from nonagenarian donors [22-24].

Many studies of sexagenarian and septuagenarian donors demonstrate results that are similar to those obtained from younger donors. With respect to the use of octogenarian donors for DDLT, the general level of experience is less than that with grafts from younger donors. Therefore, to get good results using elderly liver grafts with no age limit, donors must be selected carefully according to strict criteria (normal liver function, good hemodynamic and pre-harvesting conditions, short intensive care unit stay, short cold and warm ischemic times, macrosteatosis <30%, absence of atherosclerosis in the hepatic artery, and absence of histological alterations in the biopsy) [14]. We think that the posttransplant results with elderly donors may improve if clinical factors are combined wisely with graft allocation. Because excellent outcomes can be achieved through strict donor selection, there may be no limit to the use of the octogenarian donors for stable patients [2].

This study has several limitations. It is a retrospective, single-center study with a relatively small number of patients. The choice as to whether to use an elderly liver graft was made on a case-by-case basis as there are no established guidelines. Further high-volume multicenter studies are necessary to validate the results of this study. In conclusion, the results of this study suggest that using an elderly donor graft might not worsen the posttransplant outcomes significantly; thus, advanced age per se may not be an absolute exclusion criterion for organ donation. Indeed, donor age factor has been considered for balancing the current supply and demand conundrum regarding liver grafts.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization: SH. Data curation: CSA, KHK, DBM, TYH, GWS, DHJ, GCP. Formal analysis: YIY, SGL. Methodology: WHK, HDC, BGN, SHK. Project administration: SH. Visualization: MK, SH. Writing–original draft: MK, SH. Writing–review & editing: SH.

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