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ORIGINAL ARTICLE

What is the crux of successful living-donor liver transplantation for recipients aged 70 and beyond?

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Abstract

Aim: There is limited evidence regarding the feasibility of living-donor liver transplantation (LDLT) for patients aged over 70. The aims of this study were to assess postoperative outcomes in elderly recipients and to ascertain the potential feasibility and acceptability of LDLT.

Methods: Data were collected from 762 recipients, including 26 in the elderly group (aged ≥70) and 736 in the younger group (aged <70), and reviewed even by propensity score matching (PSM).

Results: No significant differences were observed in the frequency of postoperative complications between the two groups. Additionally, both groups exhibited a comparable 30-day mortality rate after LDLT (3.9% in both) and similar hospital stays (36 days vs. 40 days). The 1-, 3-, and 5-year graft survival rates in the elderly group were 92.0%, which was comparable to those in the younger group ($p = 0.517$), as confirmed by PSM. Notably, all donors for elderly patients were the children of the recipients, with an average age of 41.6 years, and grafts from donors aged ≥50 years were not utilized, signifying the use of high-quality grafts. Our inclusion criterion for elderly recipients was strictly defined as an ECOG-PS score of 0–2, which played a pivotal role in achieving favorable postoperative outcomes.

Conclusion: LDLT can be performed safely for elderly patients aged 70 years or older, provided they have a preserved PS and receive high-quality grafts from younger donors, inevitably all children of elderly recipients. This approach yields acceptable long-term outcomes. Consequently, age alone should not serve as an absolute contraindication for LDLT.

KEYWORDS
elderly patient, indication for liver transplantation, liver transplantation, living-donor liver transplantation, performance status

1 | INTRODUCTION

The proportion of the world's population over 60 years will increase 1.5 times from about 14.0% to 21.4% between 2022 and 2050, especially in Japan, where it was already 34.9% in 2022.[1] The absolute number of individuals aged 60 years and older is expected to increase from 1.1 billion to 2.1 billion over the same period. In addition, an increase in the number of elderly patients who are possibly eligible for liver transplantation (LT) has been reported.[2] In the early years of LT, the upper limit of age for its indication was 45–55 years.[3,4] In recent times, advancements in postoperative outcomes following LT have prompted a reevaluation of the upper age limits. Notably, progress in surgical techniques, coupled with the availability of intensive care at a heightened level, and the evolution of immunosuppressive medications, have collectively facilitated the safe execution of LT in elderly patients.[5]

So far, we have reported good postoperative results for patients over 60 years of age[6] and for those over 65 years of age.[7] We reported in 2010 that postoperative outcomes were favorable in recipients older than 60 years in good general health with low model for End-Stage Liver Disease (MELD) scores, and that age was not a sole factor for their prognosis.[6] Similarly, in 2014, we reported that 46 recipients older than 65 years also had good postoperative outcomes.[7] Several other publications[8,9] have concentrated on the post-transplantation outcomes of elderly recipients. Nevertheless, these reports offer only scant insights when it comes to recipients exceeding the age of 70. The criteria for recipient age selection and listing in the context of deceased-donor liver transplantation can be somewhat restricted due to the imbalance between donor organ availability and the extensive waiting lists of patients in need of LT. Conversely, the unique dynamic between living donors and recipients in the context of living-donor liver transplantation (LDLT) creates opportunities for even those aged 70 years or older to potentially undergo this procedure.

In Japan, out of the 9760 cases of LDLT conducted between 1989 and 2020, a mere 41 cases (0.42%) comprised recipients aged 70 years or older.[10] Contrasting this statistical backdrop, it is noteworthy that we have carried out the majority of LDLTs in the elderly population, specifically individuals aged 70 years and above, constituting 63.4% (26 out of 41 cases) of all such cases in Japan. Hence, our comprehensive analysis of postoperative outcomes in recipients over the age of 70 serves as a highly pertinent microcosm for a nationwide evaluation.

Consequently, the aims of this study were twofold: to scrutinize the results of LDLT in recipients of advanced age, specifically those aged 70 years or older, and to assess the feasibility of LDLT with outcomes deemed as acceptable. This assessment was made in conjunction with a comprehensive review of relevant literature reports. In addition, to overcome possible selection bias, one-to-one matching using propensity score matching (PSM) was applied, which enabled us to override the different distribution of covariates among individuals allocated to specific interventions in the present study.

2 | METHODS

2.1 | Patient characteristics

This study enrolled a consecutive cohort of adult recipients who underwent LDLT at Kyushu University Hospital in Fukuoka, Japan, spanning the period from May 1997 to April 2022. The indications for LDLT ($n=762$) were liver cirrhosis resulting from hepatitis C (HCV, $n=240$), cholestatic cirrhosis ($n=152$), acute liver failure (ALF, $n=86$), alcohol abuse ($n=81$), hepatitis B (HBV, $n=63$), non-alcoholic steatohepatitis (NASH, $n=53$), autoimmune hepatitis ($n=21$), and other conditions ($n=66$).

LDLTs were performed after obtaining informed consent from all patients and approval from the Liver Transplantation Committee of Kyushu University. The study protocol was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and the Kyushu University Hospital Institutional Review Board (No. 2019-186).

2.2 | Indications for LDLT

LDLT is indicated for chronic liver diseases and ALF, with or without hepatic malignancies.[11] A recipient eligible for LDLT must satisfy the following criteria: (1) a high likelihood of having a healthy daily life after successful LDLT; (2) LDLT is the only treatment option to save the patient's life; (3) the patient's vital organs, other than the liver, showing well-preserved function; (4) no uncontrollable malignancy or active infection is present in any organ other than the liver; (5) the patient is not dependent on drugs or alcohol; and (6) the patient and the supporting family members are expected to show good compliance with medical management. There has never been a criterion excluding elderly recipients from LDLT since the inception of LT based on age. The cardiovascular workup for an LDLT candidate included evaluation of the patient's medical history, physical examination, electrocardiography, and echocardiography. Pulmonary function was assessed using a spirometer, and if abnormalities were detected on chest CT, further investigations such as bronchoscopy were conducted. Cerebrovascular workup included magnetic resonance imaging angiography and Doppler ultrasonography. Pre-transplant cancer screening for all recipient candidates included whole-body computed tomography with intravenous contrast medium, upper gastrointestinal endoscopy, and colonoscopy. Similar to the criteria for young recipients eligible for LDLT, in elderly recipients, if abnormalities were identified through comprehensive examinations, consultations with relevant medical specialties were initiated. Detailed discussions were held to assess whether each recipient possessed sufficient perioperative resilience for LT and to determine the necessary interventions during the perioperative period. It was deemed feasible to proceed with LT even for recipients with multiple lifestyle-related diseases, as long as these conditions were well-controlled without a worsening trend and responded well to pharmacological therapy.

A modified version of the Eastern Cooperative Oncology Group (ECOG) was used to measure recipients' performance status (PS).[12,13] ECOG scores were stratified into five groups: PS 0 (normal), PS 1 (minimally restricted level of activity), PS 2 (able to self-care, waking hours ≥50%), PS 3 (confined to bed or chair ≥50% of waking hours), and PS 4 (completely disabled and totally confined to bed or chair). ECOG scores were assessed by clinicians either at the time of transplantation or at the most recent clinic before surgery. Currently, we have not set a formal upper age limit for recipients; however, recipients who are 70 years old or older must meet additional criteria, including a PS 0–2. The number of cases involving elderly recipients is still limited at 26, making it challenging to establish definitive criteria. However, we believe that LDLT should not be denied to elderly patients based solely on their age, and that eligibility for LDLT should instead be based on objective pre-LDLT assessments for the overall condition. Instead, eligibility for LDLT should be determined through objective pre-LDLT assessments, taking into account the functions of organs other than the liver, such as the heart, lungs, and kidneys, and the actual indications for the procedure should be fully discussed on a case-by-case basis.

2.3 | Graft selection

Donors were required to be spouses or within the third degree of consanguinity with the recipients as well as between the ages of 20 and 65 years. For donors who were not within the third degree of consanguinity, individual approval was obtained from the Kyushu University Hospital Ethics Committee.[14] Grafts were selected as previously described.[15,16] Briefly, left lobe grafts, with or without the caudate lobe, were procured if the estimated graft weight (GW)/standard liver weight (SLW) was ≥35%. Right lobe grafts were procured if the estimated GW/SLW using the left lobe graft was <35%, and the preoperatively predicted remnant liver volume of the donor was ≥35%. A right posterior sector graft was considered when the remnant liver volume after a right hepatectomy was <35%. The graft types included left lobe with or without caudate lobe graft ($n = 385$), right lobe graft ($n = 362$), and posterior segment graft ($n = 15$).

2.4 | Postoperative management

The graft harvesting technique, recipient surgery, and recipient perioperative management, including immunosuppression regimens, have been described previously.[17,18] Immunosuppression was initiated using a protocol based on tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) or cyclosporine A (Neoral; Novartis Pharma K.K., Tokyo, Japan), with a steroid and/or mycophenolate mofetil (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan).[19,20] The target trough concentration for tacrolimus was set at 10 ng/mL for 3 months after LDLT, followed by 5–10 ng/mL thereafter. The target trough concentration for cyclosporine A was set at 250 ng/mL for 3 months after LDLT, followed by 150–200 ng/mL thereafter. Methylprednisolone was initiated on the day of LDLT, tapered, and converted to prednisolone 7 days after LDLT. Prednisolone treatment was tapered and discontinued 6 months after LDLT. Mycophenolate mofetil was administered, starting at 2000 mg/day on the day after LDLT, and then tapered and discontinued until 6 months after LDLT. All recipients underwent monthly follow-ups. The median follow-up period was 2616 days; 711 and 4136 days corresponded to the 25th and 75th percentiles, respectively.

2.5 | Statistical analysis

All statistical analyses were performed using JMP statistical software, version 15 (SAS Institute Inc., Cary, NC, USA), and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

A propensity score method was applied to reduce selection bias for comparisons between the two groups (elderly group and younger group), and a logistic regression model was used to calculate propensity scores for patients. PSM was performed at a 1:1 ratio using a caliper width of 0.02. Continuous variables were expressed as the mean ± standard deviation and compared using the nonparametric Wilcoxon test for independent samples. The chi-squared test was used to compare categorical values. Logistic regression analysis was applied for multivariate analyses.[20,21] Survival was calculated using the Kaplan–Meier product-limited method, and differences in survival between the groups were compared using the log-rank test. p-values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Recipient and donor characteristics

Elderly recipients, in the context of this study, were defined as individuals aged 70 years or older. Within the cohort of 762 patients, the average age of recipients in the elderly group (≥70 years old, $n = 26$) stood at 71.2 ± 1.6 years, while the younger group (<70 years old, $n = 736$) exhibited an average age of 53.2 ± 11.3 years. The histogram (Figure 1A) reveals that individuals aged 70–74 constitute 3.3% of the cohort, while those aged 75 and above make up a frequency of 0.1%. This is indicative that the elderly group (≥70 y.o.) accounts for a total of 3.3% of the entire cohort. The first LDLT for a recipient older than 70 years was performed in 2002 at our institution (Figure 1B). Since then, 26 elderly patients have undergone LDLT under this criterion. Particularly noteworthy is the rise in the proportion of elderly recipients, reflecting the aging trend in our society. In the most recent 4 years, this figure has reached approximately 9%, signifying a growing trend among recipients aged 70 and above. A comparison of the clinical characteristics of the

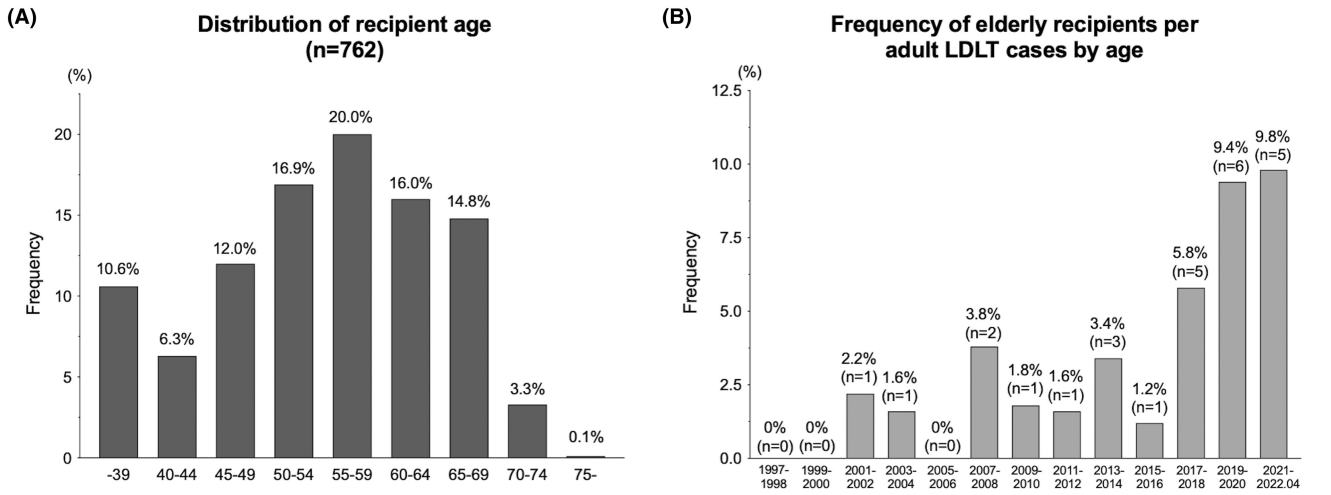

FIGURE 1 (A) Histogram illustrating the age distribution. This is indicative that the elderly group (≥70 y.o.) accounts for a total of 3.3% of the entire cohort; individuals aged 70–74 constitute 3.3% of the cohort, while those aged 75 and above make up a frequency of 0.1%. (B) Histogram illustrating the frequency of elderly recipients per adult LDLT cases by age. In the most recent 4 years, this figure has reached approximately 9%, signifying a growing trend among recipients aged 70 and above. LDLT, living-donor liver transplantation.

patients in the two groups is shown in Table 1. In comparison to the younger cohort, the elderly patients displayed several notable distinctions. They had a shorter height ($p = 0.001$, 155.1 cm vs. 160.7 cm) and a higher BMI ($p = 0.034$, 25.3 kg/m^2 vs. 23.7 kg/m^2). Additionally, they exhibited a higher prevalence of HCV and NASH with a lower incidence of HBV and PBC ($p = 0.004$). Moreover, the elderly group had a lower proportion of ALF as the primary diagnosis ($p = 0.012$, 0% vs. 11.7%) and a higher incidence of hepatocellular carcinoma ($p = 0.003$, 65.4% vs. 36.0%). They also had a higher prevalence of diabetes mellitus ($p = 0.044$, 34.6% vs. 18.8%) and hypertension ($p = 0.034$, 30.8% vs. 9.3%). Importantly, there were no significant differences between the groups in terms of preoperative general conditions, such as the frequency of Child–Pugh class C, MELD score, and prior hospitalization before LDLT. Furthermore, it's essential to note that the elderly group exclusively received grafts from donors under the age of 50, a marked contrast with the younger group ($p = 0.002$, 0% vs. 17.9%). They also less frequently received grafts from ABO-incompatible donors ($p = 0.004$, 0% vs. 15.1%). There were no significant disparities in graft type or factors related to GW, including the graft-to-standard liver weight (GW/SLW) ratio and graft-to-recipient weight ratio (GRWR).

Collectively, the elderly cohort exhibited diminished physical stature, reduced height, elevated frequencies of diabetes mellitus and hypertension, and received grafts from younger donors who were ABO-identical/compatible.

3.2 | Operative and postoperative outcomes

In terms of surgery-related variables (Table 1), it's noteworthy that the elderly group exhibited a higher incidence of undergoing splenectomy ($p = 0.042$, 84.6% vs. 66.7%) and experienced comparatively shorter operative times ($p = 0.028$, 685 min vs. 755 min) when compared to the younger group. Nevertheless, there were no significant disparities observed in portal vein pressure at laparotomy or during closure, ischemic time, portal flow, hepatic artery flow, or the volume of blood loss between these two groups. We compared the variables related to liver function between the two groups (Table S1). There were no significant differences in terms of T-Bil and PT-INR on POD 7 and POD 14. Among the elderly cohort, several notable postoperative complications were observed. Notably, 26.9% of this group experienced neuropsychiatric complications, 11.5% had bacterial sepsis, and 26.9% were affected by cytomegalovirus infection, with the incidence levels comparable to those observed in the younger group (Table 2). Furthermore, there were no statistically significant distinctions in the frequencies of various postoperative complications, including small-for-size graft syndrome, acute cellular rejection (ACR), hepatic artery or portal venous thrombosis, biliary stenosis, or the development of de novo malignancies. The 30-day mortality rates following LDLT were also comparable between the two groups ($p = 0.981$, 3.9% vs. 3.9%), as were the durations of hospitalization ($p = 0.511$, 36 days vs. 40 days). After discharge to their homes in the elderly group, two individuals experienced reversible kidney impairment due to dehydration, one patient required diuretic treatment for abdominal fluid retention, and another individual underwent steroid pulse therapy for ACR. However, all of these cases showed improvement, affirming that all older patients experienced favorable functional outcomes during this recovery period. This suggests that while regular outpatient follow-up remains essential, they managed to uphold an improved quality of life at home.

Taken together, our selection criteria for LDLT, which excluded elderly patients in poor general condition (such as those with PS 4), have led to similar rates of postoperative complications and a comparable short-term prognosis in elderly patients aged 70 years or older when compared to their younger counterparts.

TABLE 1 Recipient and donor characteristics between the younger group (<70 years old) and the older group (≥70 years old) ($n = 762$).

Variables ($n = 762$)	Younger group (<70 y.o; $n = 736$)	Elderly group (≥70 y.o; $n = 26$)	p value
Recipient			
Age (years, range)	53.2 ± 11.3	71.2 ± 1.6	**0.000**
Sex (male, %)	45.8%	30.8%	0.124
Height (cm)	160.7 ± 8.5	155.1 ± 8.6	**0.001**
Body weight	61.3 ± 11.4	60.9 ± 10.4	0.855
BMI (kg/m^2)	23.7 ± 3.6	25.3 ± 4.1	**0.034**
Etiology (%)			**0.004**
HCV/ HBV/ PBC/	31.2%/ 12.1%/ 15.6%/	42.3%/ 3.9%/ 7.7%/	
ETOH/NASH/Others	10.6%/ 6.3%/ 24.2%	11.5%/ 26.9%/ 7.7%	
Acute liver failure (%)	11.7%	0.0%	**0.012**
HCC (%)	36.0%	65.4%	**0.003**
Child–Pugh C (%)	65.2%	73.1%	0.398
MELD score (range)	16.4 ± 7.7	15.5 ± 4.9	0.522
MELD ≥20 (%)	27.2%	23.1%	0.639
Hospitalized (%)	40.5%	34.6%	0.545
Diabetes mellitus (%)	18.8%	34.6%	**0.044**
Hypertension (%)	9.3%	30.8%	**0.034**
Donor			
Age ≥ 50 y.o. (%)	17.9%	0.0%	**0.002**
Sex (male, %)	62.8%	69.2%	0.497
ABO incompatible (%)	15.1%	0.0%	**0.004**
Graft (right lobe, %)	47.6%	46.2%	0.888
Graft weight (g)	487.0 ± 115.1	472.0 ± 135.2	0.517
GW/SLW (%)	42.0 ± 9.2	41.9 ± 11.3	0.953
GRWR (%)	0.807 ± 0.193	0.784 ± 0.220	0.558
Operative outcomes			
PV pressure at laparotomy (mmHg)	24.5 ± 6.0	24.3 ± 6.9	0.892
PV pressure at closure (mmHg)	15.8 ± 3.9	14.1 ± 3.0	0.986
Cold ischemic time (min)	102.9 ± 58.7	107.8 ± 54.9	0.671
Warm ischemic time (min)	42.1 ± 13.0	37.4 ± 8.0	0.057
Portal vein flow (L/min)	1603.3 ± 655.9	1365.4 ± 520.7	0.068
Hepatic artery flow (L/min)	127.7 ± 95.4	107.4 ± 55.6	0.292
Splenectomy (%)	66.7%	84.6%	**0.042**
Portal venous thrombus (%)	16.7%	19.2%	0.740
Operative time (min)	755 ± 161	685 ± 94	**0.028**
Blood loss (mL)	6820 ± 473	5081 ± 2517	0.497

Note: Bold values indicate $p < 0.05$ with significant differences.

Abbreviations: BMI, body mass index; ETOH, ethyl alcohol abuse; GRWR, graft-to-recipient weight ratio; GW, graft weight; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Lier Disease; NASH, non-alcoholic steatohepatitis; SFSG, small-for-size graft syndrome; SLW, standard liver weight.

3.3 | Survival after LDLT in elderly patients

Figure 2A shows graft survival after LDLT; the graft survival rates at 1, 3, and 5 years for patients in the elderly group were all at 92.0%. Remarkably, these rates were similar to those observed in the younger group, which stood at 88.2%, 83.1%, and 80.1%, respectively ($p = 0.517$; hazard ratio [HR], 0.732; 95% confidence interval [CI], 0.272–1.973).

3.4 | Postoperative outcomes after LDLT after PSM

After PSM, each of the 22 patients were matched and included in each group. Tables 3 and 4 shows a comparison of variables between the two groups after PSM. Factors such as height, and the incidence of HCC, diabetes, and hypertension, which had been significantly different between the groups before PSM, were no longer significantly different, and there was no significant difference in

TABLE 2 Postoperative outcomes between the younger group (<70 years old) and the older group (≥70 years old) ($n=762$).

Variables ($n=762$)	Younger group (<70 y.o; $n=736$)	Elderly group (≥70 y.o; $n=26$)	p value
Postoperative outcomes			
Small-for-size graft syndrome (%)	11.4%	11.5%	0.984
Acute cellular rejection (%)	16.9%	11.5%	0.455
Hepatic artery thrombus (%)	1.8%	0.0%	0.340
Portal venous thrombus (%)	6.7%	0.0%	0.061
Cytomegalovirus infection (%)	18.9%	26.9%	0.327
Bacterial sepsis (%)	11.8%	11.5%	0.965
Neuropsychiatric complications (%)	20.9%	26.9%	0.474
Biliary stenosis (%)	15.4%	19.2%	0.602
De novo malignancy (%)	6.5%	3.9%	0.557
Postoperative 30-day mortality (%)	3.9%	3.9%	0.981
Hospital stays (day)	40.0 ± 30.3	36.0 ± 17.6	0.511

background variables of both recipients and donors between the two groups, as well as the postoperative outcomes (Tables 3 and 4).

Figure 2B shows graft survival after LDLT by PSM; the 1-, 3-, and 5-year graft survival rates of patients in the elderly group were 95.2%, and these survival rates were comparable to those in the younger group (86.4%, 71.7%, and 71.7%; $p=0.244$; hazard ratio [HR], 0.462; 95% confidence interval [CI], 0.119–1.790).

3.5 | Details of clinical characteristics in LDLT for Twenty-Six elderly patients

Table 5 presents the clinical profiles of the 26 LDLT cases in elderly patients. Among the elderly cohort, the highest recorded age was 76 years, the median MELD score was 15.5 (8 to 26), and the prevalence of Child–Pugh class C was 73.1%. Among the 26 recipients, 18 had some comorbidities. Nine of them had diabetes mellitus, with two managing them through insulin therapy. Seven patients had hypertension, and none had dyslipidemia. There was one recipient each who had experienced percutaneous coronary intervention for ischemic heart disease, had hepatopulmonary syndrome, or had asthma as a comorbidity. No recipients were on dialysis before LDLT, and none required post-LDLT dialysis (Table 5). From the perspective of the patient's general condition as measured by the ECOG-PS, it's worth noting that a 71-year-old woman (No. 26) with a PS 4 passed away due to bacterial sepsis following an operation for postoperative colonic perforation. Consequently, we afterward refined the criteria for selecting LDLT recipients, allowing those with PS scores between 0 and 2 while not imposing an upper age limit. Following these adjustments, there were no 30-day mortalities after LDLT, and only one patient (No. 9) experienced a fatality 36 days post-ascending aortic dissection (resulting in a 1-year overall survival of 92.3%).

In terms of graft quality, among the 26 cases, only three had a BMI of 25 kg/m^2 or higher. While microsteatosis was observed in four cases, none exhibited macrosteatosis pathologically. In six cases, there was minimal inflammation with very mild infiltration of inflammatory cells around the Glisson capsule (A1), however, all were pathologically diagnosed to have a high-quality graft (Table 5). In addition, it's noteworthy that the donors were exclusively the sons ($n=18$) or daughters ($n=8$) of the recipients, with an average age of 41.6 years and none of them were aged 50 or older (Figure 2C/D). An important consideration here is that elderly recipients did not receive grafts from donors over 50 years of age, as such grafts are generally considered to be of lower quality. This limitation is primarily due to the source of grafts for recipients aged 70 or above, which typically comes from their children rather than their spouses. The GW/SLW stood at 48.0%, with 84.6% of cases involving splenectomy. This high frequency of splenectomy was driven by the observation that the absence of splenectomy was associated with an increased mortality risk.[11]

4 | DISCUSSION

We evaluated the results of LDLT cases in patients over 70 years of age in our hospital; this accounted for 63.4% (26/41 cases) of the total number of cases in Japan. This is the first report showing that elderly patients, aged 70 years or older, with good PS and high-quality grafts from younger donors, have favorable postoperative outcomes.

Table 6 summarizes the outcomes of five studies involving LDLT patients aged over 65 and 70 years. Kwon et al.[2] investigated 15 LDLT cases in recipients aged ≥70, finding comparable outcomes between patients in their 60s and 70s, suggesting that age alone should not exclude older patients from LDLT. Their cohort exhibited relatively good liver function and health, using predominantly large grafts. While 13.3% had Child–Pugh C, the average MELD score was 13.4, and donor age was 39.8. Their cautious approach resulted in a 20.0% in-hospital mortality, utilizing mainly larger grafts. In contrast, our study's older patients faced a higher rate of Child–Pugh C at 73.1%, with younger donors and smaller grafts. Despite these

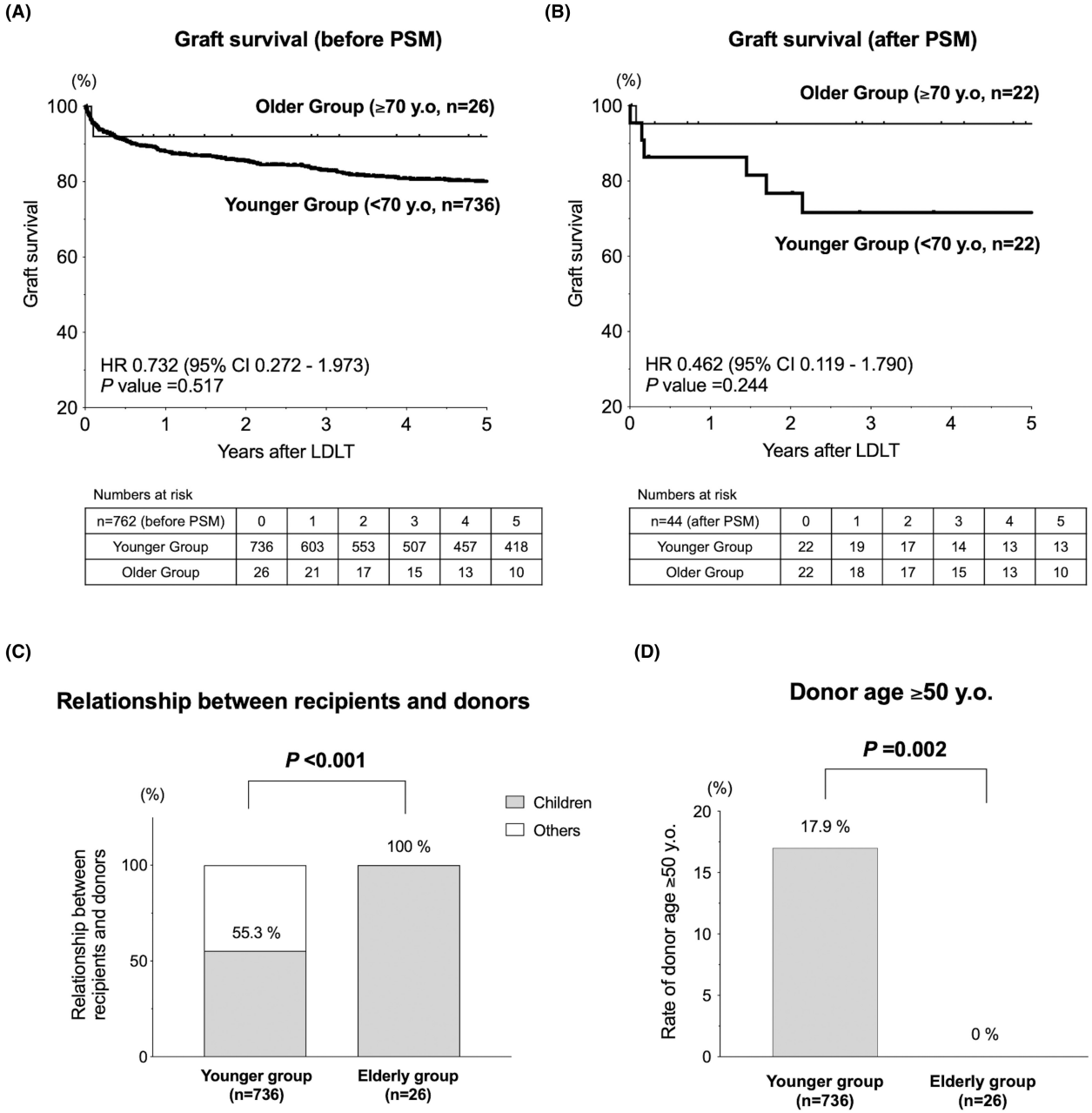

FIGURE 2 Comparison of graft survival after living-donor liver transplantation (LDLT) for the elderly group and the younger group, before and after propensity score matching (PSM) analysis. (A) Before PSM; The 1-, 3-, and 5-year graft survival rates of patients in the elderly group (≥70 years old, $n=26$) were all 92.0%, respectively, which was comparable to those in the younger group (<70 years old, $n=736$; 88.2%, 83.1%, and 80.1%; $p=0.517$; hazard ratio [HR], 0.732; 95% confidence interval [CI], 0.272–1.973). (B) After PSM; The 1-, 3-, and 5-year graft survival rates of patients in the elderly group (≥70 years old, $n=22$) were all 95.2%, respectively, which was comparable to those in the younger group (<70 years old, $n=22$; 86.4%, 71.7%, and 71.7%; $p=0.244$; HR, 0.462; 95% CI 0.119–1.790). (C) Relationship between recipients and donors. In the elderly group, the donors were all children: the sons ($n=18$) or daughters ($n=8$) of the recipients, in contrast, in the younger group, 55.3% were children of the recipients ($p<0.001$). (D) The rate of grafts from donors whose age ≥50 years old. The elderly group received no grafts from donors ≥50 years old, which is significantly fewer than the younger group ($p=0.002$, 0% vs. 17.9%). CI, confidence interval; HR, hazard ratio; LDLT, living-donor liver transplantation; PSM, propensity score matching.

differences, our in-hospital mortality was lower at 3.8%. The donors were exclusively adult children of recipients in their 70s, potentially contributing to better graft quality.[22] Notably, sepsis was a common cause of mortality in both studies, especially in patients with poor PS. All three patients with American Society of Anesthesiologists (ASA) III[23] or higher died postoperatively, making it clear that elderly patients with ASA ≥ III and poor general health conditions such as PS ≥4 were not appropriate as LDLT cases.

The Rela Center from India[9] was the only center to perform a PSM analysis with a cutoff age of 65 years for elderly patients. After

TABLE 3 Characteristics of recipient, donor, and operative outcomes between the younger group (<70 years old, $n=22$) and the older group (≥70 years old, $n=22$) after propensity score matching.

Variables ($n=44$)	Younger group (<70 y.o; $n=22$)	Elderly group (≥70 y.o; $n=22$)	p value
Recipient			
Age (years, range)	55.9 ± 12.2	71.4 ± 1.7	**0.001**
Sex (male, %)	45.5%	36.4%	0.539
Height (cm)	156.4 ± 7.1	156.3 ± 8.7	0.975
Body weight	59.7 ± 10.9	59.5 ± 10.3	0.940
BMI (kg/m^2)	24.4 ± 4.0	24.2 ± 2.9	0.901
Etiology (%)			0.530
HCV/ HBV/ PBC/	40.9%/ 4.5%/ 9.1%/	50.0%/ 4.6%/ 9.1%/	
ETOH/ NASH/ Others	27.3%/ 18.2%/ 0%	13.6%/ 13.6%/ 9.1%	
Acute liver failure (%)	0%	0%	1.000
HCC (%)	45.5%	65.463.6%	0.225
Child–Pugh C (%)	86.4%	68.2%	0.146
MELD score (range)	15.7 ± 5.7	15.4 ± 5.1	0.824
Hospitalized (%)	31.8%	31.8%	1.000
Diabetes mellitus (%)	27.3%	31.8%	0.741
Hypertension (%)	9.1%	13.6%	0.634
Donor			
Age ≥50 y.o. (%)	0%	0%	1.000
Sex (male, %)	77.3%	68.2%	0.498
ABO incompatible (%)	0%	0%	1.000
Graft (Right lobe, %)	36.4%	45.5%	0.539
Graft weight (g)	496.9 ± 109.6	464.0 ± 126.9	0.363
GW/SLW (%)	44.2 ± 8.9	41.4 ± 10.6	0.340
GRWR (%)	0.848 ± 0.189	0.792 ± 0.221	0.370
Operative outcomes			
PV pressure at laparotomy (mmHg)	27.7 ± 5.4	24.7 ± 6.1	0.152
PV pressure at closure (mmHg)	15.3 ± 2.3	14.4 ± 3.0	0.332
Cold ischemic time (min)	90.1 ± 60.1	97.5 ± 42.6	0.640
Warm ischemic time (min)	45.0 ± 15.7	37.3 ± 7.5	0.430
Portal vein flow (L/min)	1733.5 ± 583.1	1418.6 ± 542.6	0.077
Hepatic artery flow (L/min)	129.3 ± 106.9	98.0 ± 49.1	0.230
Splenectomy (%)	70.0%	89.5%	0.125
Portal venous thrombus (%)	4.6%	0%	0.235
Operative time (min)	757 ± 174	680 ± 93	0.073
Blood loss (mL)	8112 ± 1900	5255 ± 3687	0.294

Note: Bold values indicate $p < 0.05$ with significant differences.

Abbreviations: BMI, body mass index; ETOH, ethyl alcohol abuse; GRWR, graft-to-recipient weight ratio; GW, graft weight; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Lier Disease; NASH, non-alcoholic steatohepatitis; SFSG, small-for-size graft syndrome; SLW, standard liver weight.

PSM, older recipients ($n=46$) had longer durations of ventilation after LDLT (4.0 vs. 1.5 days) with a morbidity rate of 34.0%. They also concluded that the 30-day (13.0% vs. 2.4%) and overall mortality rates (21.7% vs. 7.1%) were significantly higher in older recipients than in younger recipients. All early mortality events in the older population in their cohort were attributed to sepsis and multiorgan failure. However, it is unclear if poor nutritional and functional status and overall frailty played a role in increasing the mortality in these patients. In this study, postoperative complications including sepsis were not more frequent in patients over 70 years of age. PSM analysis was performed with a cutoff age of 70 years; however, the fact that the preoperative status of most recipients was limited to ECOG-PS 0-2 as shown in Table 5 and that all grafts were good-quality grafts from donors under 50 years of age, children of elderly

TABLE 4 Postoperative outcomes between the younger group (<70 years old, $n=22$) and the older group (≥70 years old, $n=22$) after propensity score matching.

Variables ($n=44$)	Younger group (<70 y.o; $n=22$)	Elderly group (≥70 y.o; $n=22$)	p value
Postoperative outcomes			
Small-for-size graft syndrome (%)	18.2%	13.6%	0.680
Acute cellular rejection (%)	31.8%	13.6%	0.146
Hepatic artery thrombus (%)	0%	0%	1.000
Portal venous thrombus (%)	4.6%	0%	0.235
Cytomegalovirus infection (%)	13.6%	22.7%	0.432
Bacterial sepsis (%)	13.6%	13.6%	1.000
Neuropsychiatric complications (%)	27.3%	27.3%	1.000
Biliary stenosis (%)	22.7%	22.7%	1.000
De novo malignancy (%)	0%	4.6%	0.235
Postoperative 30-day mortality (%)	4.6%	4.6%	1.000
Hospital stays (day)	39.0 ± 25.0	35.0 ± 17.5	0.539

recipients, as shown in Figure 2 must have contributed to the good results. The limited physiological reserve of older patients provides them with a narrow window of ability to overcome perioperative complications, and so, they are best managed in the experienced units. This was also reflected in our study.

The age limit of the recipient is a commonly discussed topic.[7,19] In addition, it's the fact that the definition of "elderly recipients" has changed significantly in the world.[2,24] When we consider the serious risks associated with being a living donor, we believe that LDLT can only be ethically justified if the procedure increases the life expectancy and quality of life of the recipient. The life expectancy of a healthy 70-year-old patient was reported to be 10–12 years.[25] The life expectancy for patients aged ≥70 years with end-stage liver disease, even with a low MELD score, is, therefore, shorter than 10 years. Almost all of our patients had at least one complication of liver cirrhosis, such as intractable ascites, rupture-prone esophageal varices, mild encephalopathy, or spontaneous bacterial peritonitis. These complications lead to a significant decrease in the quality of life and expectancy. Although life expectancy after LDLT does not return to the same length as that of the average population, we believe that successful LDLT leads to an improvement in life expectancy and quality of life, even in elderly patients. In the present study, two of the 26 patients (7.7%) died within the first year after LDLT because of postoperative complications such as sepsis and arteriosclerosis-related aortic dissection. The main goal of the present study is to identify patients with a significant risk of perioperative mortality and exclude them from LDLT. The management of postoperative complications must be much more complex in elderly patients. And the precise calculation or prediction of comorbidity or mortality after LDLT must play an important role in the evaluation of elderly patients.

The present data indeed demonstrated a tendency towards enhanced 5-year survival within the elderly recipient group, albeit without achieving statistical significance. In line with our findings, we have identified several recipient and donor selection criteria that we deem of utmost importance in optimizing outcomes for LDLT among the elderly. These criteria are established based on our comprehensive analysis and clinical expertise, with a particular focus on the preoperative recipient status and the age of the donor. To begin, the careful selection of elderly recipients with favorable preoperative health statuses is of paramount significance. This involves a thorough evaluation of their overall physical well-being, existing comorbidities, and their capacity to endure the surgical procedure and subsequent recovery. In essence, prioritizing individuals with a PS of 0–2 and favorable health conditions is highly desirable. Additionally, while the age of the donor is not rigidly constrained, emphasizing donors with excellent liver function and overall health contributes substantially to improved graft functionality and post-transplant outcomes. Naturally, the selection of younger donors, typically under the age of 50, is advantageous, as it aligns well with the absence of spousal donors for elderly recipients. There are no specific restrictions on graft selection for elderly recipients, similar to that for younger recipients. We do not limit it to children's grafts. If siblings are suitable donors with appropriate graft volume and the ratio of remaining liver without concurrent conditions like graft steatosis, they qualify as LDLT donors. Besides, there is no reason to reject ABO-incompatible LDLT for the elderly recipients. While each criterion holds its own significance, we underscore the holistic evaluation of these factors, tailored to the distinct circumstances of each patient, as pivotal in attaining positive outcomes in LDLT for the elderly. It is imperative not to prioritize donor selection over recipient age, but rather to acknowledge the intricate interplay between donor and recipient factors. The intricate nature of the transplantation process underscores the necessity for a personalized approach that effectively balances the considerations of both recipients and donors.

Shortcomings of our study include the fact that it is a retrospective study. The small sample size, especially after PSM, was another limitation of the study, which reduces the validity of conclusions based on the lack of strong statistical significance or multivariate analyses. Although the number of these patients is small, the significance of this subject is based on the fact that the age of the patient

TABLE 5 Characteristics of LDLTs for the elderly patients ≥70 years old ($n = 26$).

Case No.	Recipient age (y.o)	PS	MELD	Child–Pugh C	Donor age (y.o)	Donor BMI (kg/m^2)	Relationship between reci and donor	Surgical past history	Pre-LDLT comorbidities	GW/SLW (%)	Spx	Steatosis by histology	Activity and fibrosis by histology	Post-LT complications	30-days mortality
1	70	0	11	NO	41	20.0	Son	Open-Spx	(–)	66.4	YES	No steatosis	A0, F0	(–)	Alive
2	70	0	14	YES	40	21.3	Son	Open-MCN	(–)	62.2	NO	5% microsteatosis	A0, F0	CMV antigenemia, SFSG, TMA	Alive
3	70	0	21	YES	45	23.5	daughter	(–)	(–)	61.1	YES	No steatosis	A1, F0	(–)	Alive
4	70	0	21	YES	45	23.0	daughter	(–)	DM (insulin)	61.7	YES	No steatosis	A0, F0	(–)	Alive
5	70	1	8	YES	47	18.7	daughter	(–)	DM, HT	36.1	YES	No steatosis	A1, F0	Sepsis	Alive
6	70	1	19	YES	41	24.4	Son	Exploratory laparotomy	HT	35.7	YES	No steatosis	A1, F0	(–)	Alive
7	70	1	21	YES	39	22.1	Son	PEIT	Hyperthyroidism	47.4	NO	N.A.	N.A.	(–)	Alive
8	70	1	22	YES	36	23.7	Son	Ovariectomy	(–)	47.9	YES	5% microsteatosis	A0, F0	CMV antigenemia	Alive
9	70	2	12	YES	45	24.2	Son	(–)	DM, HT	63.5	YES	No steatosis	A0, F0	Delirium, pancreatic fistula, CMV antigenemia	Alive
10	70	2	15	YES	44	25.9	Son	(–)	(–)	45.9	NO	N.A.	N.A.	Delirium	Alive
11	70	2	21	YES	47	24.7	Daughter	CBD lithotripsy	DM	52.3	YES	No steatosis	A0, F0	Re-operation for bleedings on Spx stump	Alive
12	70	3	12	NO	43	21.5	Daughter	Caesarotomy	HT	44.8	YES	No steatosis	A0, F0	CMV antigenemia	Alive
13	71	0	8	NO	29	20.7	Son	Colonectomy	DM, HT, IHD (PCI)	39.1	NO	No steatosis	A0, F0	(–)	Alive
14	71	0	9	NO	40	19.5	Daughter	(–)	Hypothyroidism	35.7	YES	N.A.	N.A.	(–)	Alive
15	71	0	18	YES	28	21.9	Son	(–)	DM, interstitial nephritis	39.9	YES	No steatosis	A0, F0	CMV antigenemia	Alive
16	71	1	14	YES	43	20.8	Son	(–)	HPS	71.2	YES	No steatosis	A0, F0	(–)	Alive
17	71	1	17	YES	42	29.6	Son	Lap-Hx	(–)	42.6	YES	No steatosis	A0, F0	CMV antigenemia	Alive
18	71	1	19	YES	44	19.0	Son	(–)	DM	56.7	YES	No steatosis	A0, F0	Delirium, CMV antigenemia	Alive
19	72	2	9	NO	43	27.7	Son	(–)	DM (insulin), HT	33.7	YES	10% microsteatosis	A1, F0	Delirium	Alive
20	73	0	10	NO	47	20.1	Son	(–)	(–)	49.3	YES	N.A.	N.A.	Delirium	Alive
21	73	0	14	NO	43	23.8	Daughter	Lap-Hx	HT	33.6	YES	No steatosis	A0, F0	(–)	Alive
22	73	0	15	YES	47	18.8	Son	Open-Cholecystectomy	Asthma	51.1	YES	3% microsteatosis	A0, F0	(–)	Alive
23	74	0	14	YES	40	21.0	Son	(–)	Prostatic hyperplasia	39.1	YES	No steatosis	A1, F0	(–)	Alive

(Continues)

TABLE 5 (Continued)

Case No.	Recipient age (y.o)	PS	MELD	Child–Pugh C	Donor age (y.o)	Donor BMI (kg/m^2)	Relationship between reci and donor	Surgical past history	Pre-LDLT comorbidities	GW/SLW (%)	Spx	Steatosis by histology	Activity and fibrosis by histology	Post-LT complications	30-days mortality
24	74	0	26	YES	37	20.5	Son	(–)	(–)	37.5	YES	No steatosis	A1, F0	(–)	Alive
25	76	0	18	YES	40	23.8	Son	(–)	DM	35.6	YES	No steatosis	A0, F0	Delirium, SFSG, Sepsis	Alive
26	71	4	14	YES	46	22.3	Daughter	(–)	Hypothyroidism	58.6	YES	No steatosis	A0, F0	Delirium, SFSG, Sepsis, Surgery for Colonic perforation	Dead on POD 28

Abbreviations: DM, diabetes mellitus; GW, graft weight; HT, hypertension; HPS, hepatopulmonary syndrome; IHD, ischemic heart disease; Lap-Hx, laparoscopic hepatectomy; MCN, microwave coagulo-necrotic therapy; MELD, Model for End-Stage Lier Disease; NA, not available; NASH, non-alcoholic steatohepatitis; PCI, percutaneous coronary intervention; PEIT, percutaneous ethanol injection therapy; PS, performance status; SFSG, small-for-size graft syndrome; Spx, splenectomy; SLW, standard liver weight; Spx, splenectomy; TMA, thrombotic microangiopathy.

TABLE 6 Literature review of LDLT for elderly patients ≥65 years old and ≥70 years old.

Author	Country	Age of cutoff	No. of older recipients	Study period	BMI (kg/m^2)	Etiology	Child–Pugh: C (%)	MELD	Donor age	Graft volume	Postoperative outcomes	Survival outcomes
Toshima T, et al. (present study)	Japan	70	26/ 762 (3.4%)	1997–2021	25.3	HCV 42.3% NASH 26.9% Others 50.8%	73.1%	15.5	41.6	GRWR 0.78 GW/SLW 41.9%	Morbidity[#3] 13.3%	1-year survival 92.0% 5-year survival 92.0%
Kwon JH, et al. (2017)	Korea	70	15/ 4356 (0.34%)	2000–2015	NA	HBV 40.0% HCV 33.3% Others 26.7%	13.3%	13.4	39.8	GRWR 1.22%[#4] GW/SLW 66.0%[#4]	Mobidity 40.0%	1-year survival 80.0% 5-year survival 66.7%
Oezcelik, et al. (2015)	Turkey	70	12/ 469 (2.5%)	2005–2013	NA	Viral hepatitis 58.4% ETOH 8.3% Others 33.3%	NA	13.0	40.0	GRWR 1.10	Morbidity 16.7%	1-year survival 84.0% 3-year survival 84.0%
Hakeem AR, et al. (2021)	India	65	50/ 801 (6.2%)	2009–2020	26.0	Viral hepatitis 40.0% NAFLD 36.0% Others 24.0%	NA	14.5	33.8	GRWR 1.01	Morbidity[#2] 34.0%	1-year survival 84.0% 5-year survival 78.0%
Abdelfattah MR, et al. (2015)	Egypt	65	25/ 55 (45.4%)	2001–2013	NA	Viral hepatitis 76.0% NASH 20.0% Others 4.0%	NA	14.1	NA	NA	Re-intubation 8.7% Re-operation 24.0%	1-year survival 95.8% 5-year survival 95.8%
Ikegami T, et al. (2014)	Japan	65	46/ 411 (11.1%)	1997–2013	23.2	HCV 71.7% Others 28.3%	50.0%	14.8	36.3	GRWR 0.79% GW/SLW 40.3%	Bacterial sepsis 4.3% CMV infection 21.7%	1-year survival 93.2% 5-year survival 82.8%

Note: #1 Total number of transplants during the study period was not available. #2 Total number of cases with Clavien–Dindo grade ≥ II. #3 Total number of cases with Clavien–Dindo grade ≥ IIIb. #4 Five cases had dual grafts.
Abbreviation: NA, not available.

population for LT is increasing significantly, and more data is needed for LDLT, as this is the only treatment option in some countries. In addition, the observed BMI range of 23 to 25 within the Japanese cohort underscores the demographic disparities that can exert an influence on study results. Recognizing the distinctive healthcare landscapes and patient profiles across different regions is imperative, as these factors may impact the interpretation and relevance of our findings within specific contexts. It is important to note that it's worth emphasizing that within the elderly subgroup of our Japanese cohort, we identified a prevalence of NASH at 26.9% along with an average BMI of 25.3 kg/m^2. These figures are notably lower than those typically seen in the US population. This discrepancy should be recognized as a limitation when attempting to generalize our study's findings to Western populations. However, the core message of our research underscores the paramount importance of a meticulous approach to donor and recipient selection. This fundamental aspect serves as the cornerstone for achieving positive outcomes in LDLT for elderly patients. Through conducting a comprehensive evaluation of both donor and recipient characteristics, we firmly believe that LDLT can be safely and effectively performed, even in the face of the intricate challenges posed by diverse patient demographics.

In conclusion, elderly LDLT recipients aged over 70, who maintain a good PS, exhibit comparable survival and morbidity rates when contrasted with their younger counterparts, as evidenced by the results of PSM analysis. This favorable outcome is likely attributable to the recipient's preoperative condition, including their favorable PS, as well as the high quality of grafts obtained from young donors. Consequently, age alone should not serve as an absolute contraindication for LDLT.

AUTHOR CONTRIBUTIONS

T. Toshima participated in the writing of the manuscript. T. Yoshizumi and T. Toshima participated in the conception and design of the study. Y. Bekki, T. Izumi, N. Iseda, Y. Tsutsui, and K. Toshida participated in the acquisition of the data. T. Toshima, S. Itoh, Y. Nagao, and S. Yoshiya participated in the statistical analysis and interpretation of the data. T. Yoshizumi participated in the review of the manuscript and final approval.

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CONFLICT OF INTEREST STATEMENT

Tomoharu Yoshizumi, one of the co-authors, is listed as Editorial Board Member of *AGS*.

DISCLOSURE AND ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board of ethics committee, national research committee, as well as with the 1964 Helsinki Declaration and its later amendments. The study protocol was approved by the Institutional Review Board (No. 2019-186).

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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