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A Donor Age-Based and Graft Volume–Based Analysis for Living Donor Liver Transplantation in Elderly Recipients

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Background. Given the expected increase in the number of elderly recipients, details regarding how clinical factors influence the outcome in living donor liver transplantation (LDLT) for the elderly remain unclear. We examined the survival outcomes according to the results of donor age-based and graft volume–based analyses and assessed the impact of prognostic factors on the survival after LDLT for elderly recipients. **Methods.** The 198 adult recipients were classified into 2 groups: an elderly group (n = 70, E group; ≥ 60 years of age) and a younger group (n = 128, Y group; <60 years of age). We analyzed the prognostic factors for the survival in the E group and the survival rate for both groups at several follow-up points and conducted subgroup analyses in the E group by combining the donor age (≥50 vs <50 years) and graft weight (GW)/standard liver volume (SLV) (≥40% vs <40%). **Results.** Donor age (hazard ratio [HR], 2.17; $P = 0.062$) and GW/SLV (HR, 1.80; $P = 0.23$) tended to have a high HR in the E group. The overall patient survival rates at 1, 3, and 5 years were 78.3%, 73.0%, and 61.0% in the E group, and 82.0%, 75.1%, and 69.2% in the Y group, respectively ($P = 0.459$). However, the outcomes tended to be worse in recipients of grafts from donors ≥50 years of age than in those with grafts from younger donors with GW/SLV < 40% ($P = 0.048$). **Conclusions.** A worse outcome might be associated with aging of the donor, which leads to impairment of the graft function and liver regeneration. Both the graft volume and donor age should be considered when choosing grafts for LDLT in elderly patients.

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Liver transplantation (LT) is the treatment of choice for patients with end-stage chronic liver disease, acute liver failure, and certain metabolic liver diseases. Living donor LT (LDLT), an alternative to deceased donor LT (DDLT), has become the mainstream treatment in Asia due to a shortage of deceased liver grafts. A further increase in the number of elderly recipients is expected, due to the rapidly aging Asian population. In general, older patients are seen as higher-risk recipients than younger ones, due to the presence of comorbidities and increased mortality related to both hepatic and nonhepatic causes.[1] However, the findings have thus far been controversial. For example, Yoshizumi et al[2] reported that recipient age did not affect the outcome of LDLT when patients with low Model for End-Stage Liver Disease (MELD) scores (<20) received grafts from living donors. Similarly, Cross et al[3] found the 5-year survival in patients 60 years or older undergoing LT to be comparable to that in patients younger than 60 years. As such, LT should not be ruled out in aged recipients on the basis of age alone. However, other groups have reported relatively poor outcomes in aged recipients of LT.[4-6] Therefore, how clinical factors influence the outcome of LDLT among elderly patients remains unclear.

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In orthotopic liver transplant patients, Chapman et al[7] reported comparable outcomes in both the graft and patient survivals using donors older than 60 years, regardless of the recipient age, in their donor age-based analysis. Unlike DDLT, LDLT depends on liver regeneration of the partial liver graft, and securing a sufficient graft volume (GV) for the recipient is important. We therefore hypothesized that the donor age and GV, which are essential points in LDLT, influence the survival of LDLT for elderly recipients.

The aim of this study was to clarify the survival outcomes after LDLT for elderly recipients based on the results of a donor age- and GV-based analysis and the impact of prognostic factors on the survival of LDLT for elderly recipients.

MATERIALS AND METHODS

This was a retrospective study conducted at the Department of Surgery, Nagasaki University Hospital. The study design and protocol were approved by the institutional review board at our institute.

Between August 1997 and March 2016, a total of 228 LDLTs were performed at our institute. In the present study, we examined the 198 adult recipients (≥15 years of age) whose follow-up duration exceeded 1 year. We classified the recipients into 2 groups: an elderly group (E group; ≥60 years of age) and a younger group (Y group; <60 years of age), with age 60 years established as the cutoff due to its usage in similar studies.[8-10] Recipient variables, including the characteristics, patient survival, and cause of death, were collected and used for the analysis. To assess the impact of recipient factors on the survival, a Cox proportional analysis was performed in all recipients as well as in the Y and E groups.

We analyzed the overall patient survival in both the Y and E groups as well as among recipients with a MELD score of 20 or higher, which was established as the cutoff of high-risk recipients.[2] We also conducted a subgroup analysis of the patient survival in the E group based on the combination of donor age (≥50 vs <50 years of age) and graft weight (GW)/standard liver volume (SLV) (≥40% vs <40%). We used a cutoff of 50 years for the donor age because recipients of grafts from donors 50 years or older have a higher mortality rate and a lower 1-year survival rate than recipients of grafts from younger donors.[11]

Operative Procedure and Algorithm for Decision Making Regarding Graft Use in LDLT

The management of LDLT recipients as well as criteria for donor and graft selection have been previously described.[12-14] In brief, liver grafts typically were implanted using a piggyback technique. Arterial reconstruction was carried out under a microscope using end-to-end anastomosis with interrupted sutures.[15] Duct-to-duct anastomosis was performed for biliary reconstruction, except in patients with primary sclerosing cholangitis and biliary atresia. A biliary splint (2 mm, chloride vinyl tube) was placed beyond the anastomosis, and the splint was externalized through the upper edge of the duodenum with a Witzel-type fistula. The splint was removed approximately 3 months after LDLT using a 2-step protocol.[16]

Graft selection was based on the findings of a volumetric study using a software program (From 1997 to 2010: Flexi Trace software; Tree Star, Inc., San Carlos, CA[17]; and from 2010 to present: SYNAPSE VINCENT; Fuji Film, Tokyo, Japan) and computed tomography to obtain the GV versus the recipient's SLV. We generally considered an extended left lobe to be the optimal graft if the desired GV/SLV ratio exceeded 30% in the recipient. A right lobe graft was also considered if the simulated GV/SLV ratio for the extended left lobe graft was less than 30%. If the simulated GV/SLV ratio for the remnant liver volume was less than 30%, we considered a posterior segment graft with a volume exceeding 35% (Figure 1).

Statistical Analyses

All data are expressed as the median values with ranges. The statistical analyses were performed using the χ^2 test for

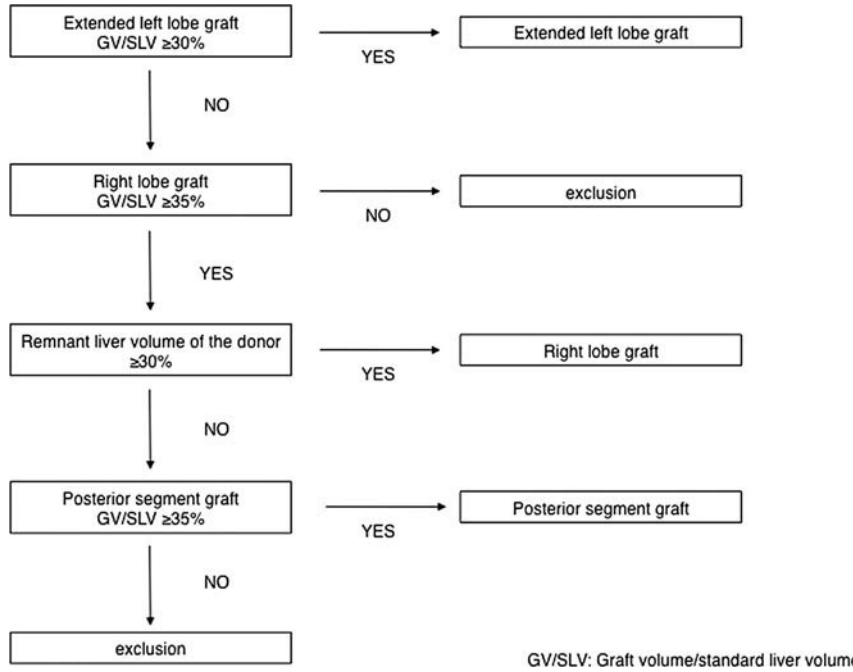

FIGURE 1. Algorithm for decision-making regarding the use of grafts in LDLT for elderly recipients.

TABLE 1.
Recipient characteristics

	Y group (n = 128)	E group (n = 70)	*P*
Donor age, y	39.5 (19-67)	39 (21-64)	0.864
MELD score	18 (4-47)	15 (7-36)	0.0033
Child-Pugh score	10 (5-15)	10 (5-14)	0.150
HCV	46 (35.9%)	30 (42.9%)	0.339
HCC	49 (38.3%)	38 (54.3%)	0.030
Diabetes mellitus	35 (27.3%)	28 (40.0%)	0.070
ABO incompatibility	23 (17.9%)	14 (20.0%)	0.726
Left lobe graft	66 (51.6%)	44 (62.9%)	0.124
GV/SLV, %	47.5 (27.8-79.8)	45.5 (25.9-80.0)	0.241
GW/SLV, %	40.5 (22.5-84.7)	40.1 (24.8-63.2)	0.666
Bleeding, mL	6815 (520-126 700)	5700 (1100-121 348)	0.916
Bacteremia	36 (28.1%)	22 (31.4%)	0.626
Cytomegalovirus infection	39 (30.5%)	27 (38.6%)	0.249

MELD, Model for End-stage Liver Disease; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

categorical variables and the Mann-Whitney *U* test for continuous variables. The patient survival was calculated via the Kaplan-Meier method and compared using the Log rank test. To assess the impact of recipient factors on the survival, 7 clinical variables of all recipients and 4 clinical variables of the Y and E groups were included in the multivariate analyses using the Cox proportional hazard model. *P* less than 0.05 was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University).[18]

RESULTS

Recipient Characteristics

There were 120 men and 78 women in the present study. The median (range) follow-up duration was 76.5 (12-187) months. The recipient characteristics are summarized in Table 1. A total of 70 recipients (35.4%) were classified into the E group. No significant differences between the Y and E groups were noted in the donor age, Child-Pugh score, the viral status, the presence of diabetes mellitus, ABO incompatibility, graft type, GV/SLV, GW/SLV, bleeding amount, or the presence of bacteremia or cytomegalovirus infection. However, significant differences were observed in the median MELD score and the presence of hepatocellular carcinoma between these 2 groups (*P* = 0.0030 and *P* = 0.030, respectively). The median MELD scores were 15 in the E group and 18 in the Y group, and 72 recipients had a MELD score of 20 or greater (17 in the E group and 55 the Y group).

Multivariate Analyses of the Clinical Factors for the Survival of Recipients After LDLT

A Cox proportional hazard model was performed to assess the clinical factors for the survival in all recipients and in the Y and E groups after LDLT. As variables, preoperative factors (donor age, GV/SLV, MELD, diabetes mellitus, hepatitis C virus, ABO incompatibility) and GW/SLV were chosen for the analysis in all recipients. Donor age (HR, 1.82; *P* = 0.017) was identified as significantly influencing the survival after LDLT in all recipients (Table 2). In the Y and E groups, the donor age, GV/SLV, GW/SLV, and MELD were chosen as the variables for the analysis, as we determined these factors to be mandatory to analyze the impact of these factors on the survival in this study. In the Y group, although no significant differences were noted in any factors, the donor age tended to have a high hazard ratio (HR, 1.83; *P* = 0.06) (Table 3). In addition, in the E group, although no significant differences were noted in any factors, the donor age (HR, 2.17; *P* = 0.062) and GW/SLV (HR, 1.80; *P* = 0.23), which reflected the actual volume size, tended to have high HRs (Table 4).

Patient Survival

The overall patient survival rates at 1, 3, and 5 years were 78.3%, 73.0%, and 61.0% in the E group, and 82.0%, 75.1%, and 69.2% in the Y group, respectively. No significant differences in the survival rate were noted between these groups (*P* = 0.548; Figure 2). Among recipients with a MELD score of 20 or greater, the survival rates at 1, 3, and 5 years were 76.5%, 69.5%, and 69.5% in the E group, and 74.6%, 65.4%, and 65.4% in the Y group, respectively. No significant differences in the survival rate were noted between these groups for recipients with a MELD score greater than 20 (*P* = 0.10).

In the E group, 37 recipients had GW/SLV of 40% or greater, and 33 had GW/SLV less than 40%. On further stratification of these 2 subgroups by donor age (≥50 or <50 years of age), the GW/SLV 40% or greater group included 10 recipients of grafts from donors 50 years or older and 27 from donors younger than 50 years. The GW/SLV less than 40% group included 10 recipients of grafts from donors 50 years or older and 23 from donors younger than 50 years. Although no significant differences were noted in the survival rate between the recipients of grafts from donors 50 years or older versus those from donors younger than 50 years in the GW/SLV 40% or greater group (*P* = 0.467; Figure 3A), the survival rate for those receiving grafts from donors 50 years or older was significantly lower than that of those with grafts from donors younger than 50 years in the GW/SLV less than 40% group (*P* = 0.048; Figure 3B).

Causes of Death in Elderly Recipients

The causes of death in the E group (n = 70) are summarized in Table 5. Thus far, 26 (37.1%) recipients have died in the follow-up period, with the most prevalent causes of death being graft failure (n = 13, 50.0%) and postoperative sepsis (n = 5, 19.2%). In addition, 10 recipients with grafts from donors 50 years or older (38.5%) have died, and liver graft failure accounted for 6 deaths (60.0%). Regarding small-for-size grafts (GW/SLV < 30%), which is a cause of graft failure, there were 11 (15.7%) recipients of such grafts in the E group. Among these 11 recipients, 5 (45.5%) have died, but none of

TABLE 2.
Multivariate analysis for patient survival in all recipients

Variables	Categories	HR	95% CI	*P*
Donor age, y	≥50	1.82	1.11-2.96	0.017
GV/SLV	<40%	1.38	0.71-2.69	0.35
GW/SLV	<40%	0.99	0.54-1.84	0.99
MELD	≥20	1.35	0.80-2.26	0.26
Diabetes mellitus	(+)	1.43	0.85-2.39	0.18
HCV	(+)	1.52	0.92-2.53	0.1
ABO incompatibility	(+)	1.13	0.62-2.09	0.69

TABLE 3.

Multivariate analysis for patient survival in younger recipient group

Variables	Categories	HR	95% CI	*P*
Donor age, y	≥50	1.83	0.98-3.41	0.06
GV/SLV	<40%	2.38	0.95-5.97	0.064
GW/SLV	<40%	0.65	0.28-1.52	0.32
MELD	≥20	1.56	0.82-2.97	0.18

their deaths have been related to graft failure due to a small-for-size graft (causes of death, infection after LDLT).

DISCUSSION

Advances in surgical procedures and immunosuppressive therapies have improved the patient survival for LT, even in aging societies.[19] Upper age limits on recipients have therefore been relaxed in recent years, and LT should no longer be ruled out in aged recipients due solely to their age.[3,20] Indeed, several groups have reported acceptable findings with regard to the outcomes of LT in elderly recipients.[3,7,21] We clarified the survival outcomes after LDLT for elderly recipients based on the results of combined analyses of independent risk factors (elderly donors and GV). A donor age- and GV-based analysis showed that the outcomes were worse in those receiving grafts from donors 50 years or older with GW/SLV less than 40 for LDLT than in those receiving grafts from donors 50 years or older with GW/SLV of 40 or greater. In addition, the donor age, but not GW/SLV, was detected as a significant prognostic factor in a multivariate analysis among all recipients. Furthermore, although no significant differences were noted in any factors in a multivariate analysis, donor age tended to have a high HR in both the Y and E groups, and GW/SLV, which reflected the actual volume size, tended to have a high HR in the E group. We believe that these 2 factors may be useful as limiting factors for LDLT in elderly recipients.

Unlike DDLT, where GV is relatively irrelevant as the graft is taken from the whole liver, securing a sufficient GV for the recipient is important in LDLT. In addition, living liver donors must retain a secure sufficient remnant liver volume. We described the algorithm used for graft selection in the Materials and Methods above. Briefly, the GV/SLV ratio was determined as follows: those with a ratio greater than 30% received an extended left lobe, and those with a ratio greater than 35% received a right lobe graft and a posterior segment graft (Figure 1). Regarding small-for-size grafts (GW/SLV < 30%), there were 11 (15.7%) recipients of such grafts in the E group, but none of the 5 deaths in these patients have been related to graft failure. The prevention of small-for size grafts is essential

TABLE 4.

Multivariate analysis for patient survival in elderly recipient group

Variables	Categories	HR	95% CI	*P*
Donor age, y	≥50	2.17	0.96-4.91	0.062
GV/SLV	<40%	0.75	0.27-2.10	0.58
GW/SLV	<40%	1.80	0.69-4.69	0.23
MELD	≥20	0.82	0.30-2.26	0.71

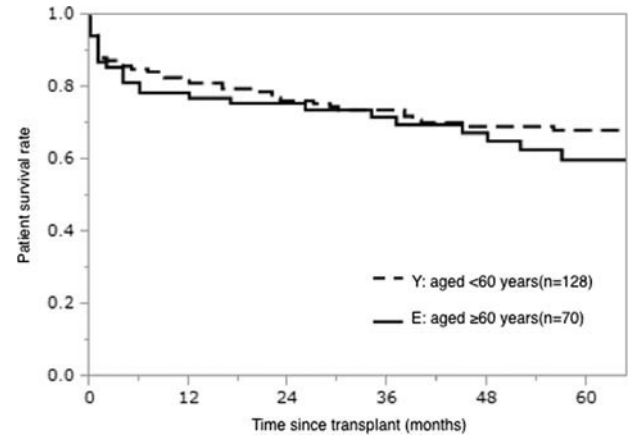

FIGURE 2. Overall patient survival rates divided based on a cutoff age of 60 years. E group (n = 128): elderly recipients (≥60 years), Y group (n = 70): younger recipients (aged <60 years); *P* = 0.548, Log rank test.

to eliminating small-for-size syndrome. However, especially in LDLT cases, we may have no choice but to select a small-for-size graft (actual volume around 30%) due to limitations on graft selection or the prioritization of donor safety. This is a dilemma in living donor liver donation, but we determined the GV needed to ensure a sufficient total volume of 40% or greater, regardless of the graft type, for grafts from donors 50 years or older based on the results of this study. Furthermore, we believe that left liver donation has no effect on the outcome of LDLT, because left lobe graft implantation is simpler than right lobe graft implantation due to the single orifice of the bile duct, the prevention of congestion by the wide orifice of the hepatic vein for anastomosis, and the safety of the surgical technique. In right liver donation, we took into consideration the stipulation that the simulated GV/SLV ratio for the remnant liver volume must exceed 30% for the safety of living donors. A small liver remnant is the best predictor of hepatic dysfunction after liver resection.[22] Dayangac et al[11] reported that liver donation resulting in a remnant liver volume less than 35% should be avoided in donors 50 years or older to ensure their safety. Despite the conflicts inherent in ensuring both a sufficient GV for the recipient and a sufficient remnant liver volume for the donor, the safety of living donors should take priority in LDLT for elderly recipients.

The proportion of aged donors in LDLT has gradually increased in recent years to meet a surging demand.[2,21] Because old donor age is generally considered a major risk factor negatively influencing the graft and patient survivals, aged donors have traditionally been excluded from donating or been regarded as "marginal donors."[23-25] However, to expand the availability of organs for LT, many transplant centers have begun accepting marginal or extended criteria donor organs, which includes allowing grafts from aged donors.[9,26-29] Several groups have reported comparable outcomes in the graft and recipient survivals, regardless of donor age.[7,30] Indeed, the recipient survival when using sexagenarian, septuagenarian, and even octogenarian donors for OLT has been shown to be comparable with that of younger donors.[31] However, conflicting data have also been reported, and a reduced capacity for protein synthesis and prolonged cholestasis have been reported in older liver graft donors from studies on both DDLT and LDLT.[25,32,33] Furthermore, the findings from both animal

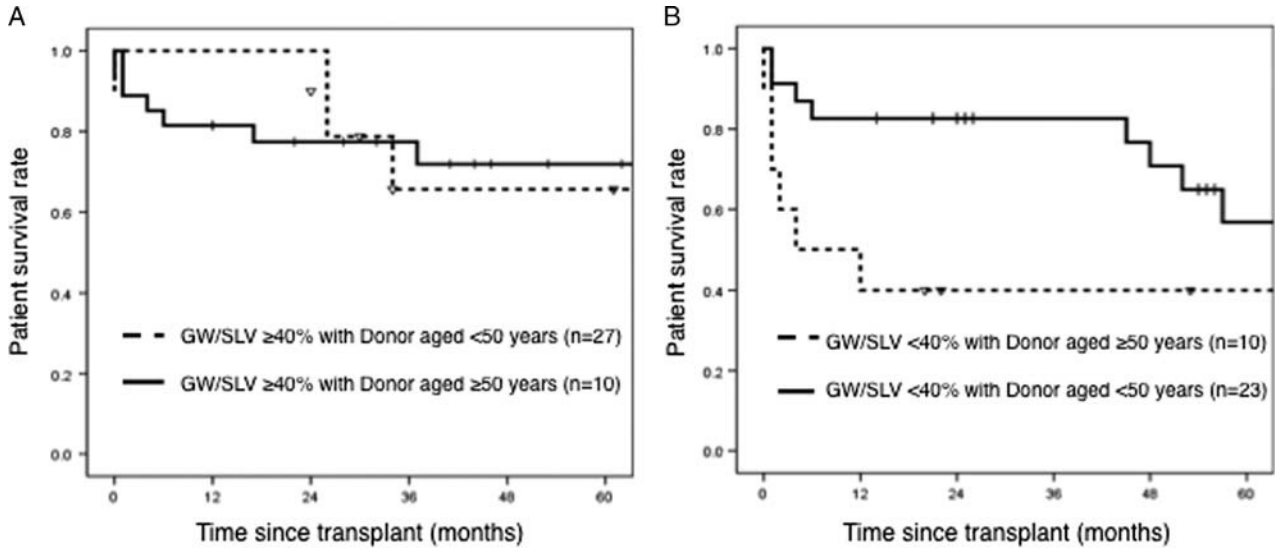

FIGURE 3. A, No significant differences were noted in the survival rate between the recipients of grafts from donors 50 years or older versus those from donors younger than 50 years of age in the GW/SLV 40% or greater group; $P = 0.467$, Log-rank test. B, The survival rate receiving grafts from donors 50 years or older was significantly lower than that of those with grafts from donors younger than 50 years in the GW/SLV less than 40% group; $P = 0.048$, Log-rank test.

TABLE 5.

Cause of death in elderly recipients

	Donor age, y		
	≥50	<50	n (%)
Graft failure	6	7	13 (50.0)
Postoperative sepsis	2	3	5 (19.2)
De novo malignancy	2	0	2 (7.7)
Recurrent malignancy	0	1	1 (3.8)
Phagocytic syndrome	0	1	1 (3.8)
Cardiovascular	0	1	1 (3.8)
Renal	0	1	1 (3.8)
Cerebral hemorrhage	0	1	1 (3.8)
Unknown	0	1	1 (3.8)

and human studies have shown a decreased and delayed capacity for regeneration in older donors.[34]

The key to the outcome is the liver regeneration and recovery of the liver function during the early period after LDLT. Regarding the evaluation of the quality of the graft liver, we previously reported on the correlation between hepatic compliance and the prognosis of LDLT recipients. The mortality rate was significantly higher among recipients with donors 60 years or older than in those with younger donors (5/7, 71.4%). In addition, hepatic compliance differed significantly between the deceased and surviving cases, with no hepatic compliance noted in the 5 deceased cases and favorable compliance observed in the 2 surviving cases.[35] Hidaka et al[14] reported that the lower number of Kupffer cells, indicated as CD68-positive cells, in the liver graft was related to the outcome of LDLT with elderly donors, leading to delayed liver regeneration and an increased risk of infectious disease after LDLT. Kupffer cells are tissue macrophages localized within the liver sinusoid and serve as mediators that promote homeostatic liver regeneration, as well as gatekeepers of this regeneration.[36,37] It can be said that the reduction in the hepatic compliance and the number of Kupffer cells in the graft might be due to the aging process and therefore distinctive in elderly donors. Aging leads to the impairment of liver regeneration and the graft function, as well as an increased risk of infectious disease, and these factors may contribute to liver graft failure. In the present study, liver graft failure was found as the main cause of death (Table 5) in elderly recipients (50.0%), especially in recipients with grafts from donors 50 years or older (60%). In addition, LDLT depends on liver regeneration of the partial liver graft, unlike DDLT, where the GV is relatively irrelevant because the graft is taken from the whole liver. Impaired liver regeneration due to the aging process in aged donors might be closely related to the outcome of LDLT in elderly recipients. We must take into consideration the quality of the donor in elderly recipients.

One limitation associated with the present study is the small number of elderly recipients. As such, further investigations will be needed.

In conclusion, the outcomes of LDLT in elderly recipients with grafts from donors 50 years or older with GW/SLV less than 40% were significantly worse than those with other combinations of age and GW/SLV. These results might be related to the aging process in donors, which leads to impairment of the graft function and liver regeneration. This is a problem to be resolved in LDLT, which depends on liver regeneration.In the clinical setting, we should consider not only the GV but also the donor age when choosing grafts for LDLT in elderly patients.

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