Impact of Donor Age on Recipient Survival in Adult-to-Adult Living-donor Liver Transplantation

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Objective: To investigate the influence of donor age on recipient outcome after living-donor partial liver transplantation (LDLT).

Background: Donor age is a well-known prognostic factor in deceased donor liver transplantation; however, its role in LDLT remains unclear.

Methods: We retrospectively analyzed 315 consecutive cases of primary adult-to-adult LDLT in our center between April 2006 and March 2014. Recipients were divided into 5 groups according to the donor age: D-20s ($n = 60$); D-30s ($n = 72$); D-40s ($n = 57$); D-50s ($n = 94$); and D-60s ($n = 32$). The recipient survival and the association with various clinical factors were investigated.

Results: Recipient survival proportions were significantly higher in D-20s compared with all the other groups ($P = 0.008$, < 0.001, < 0.001, and $= 0.006$, vs D-30s, -40s, -50s, and -60s, respectively), whereas there was no association between recipient survival and their own age. There are 3 typical relationships between donors and recipients in adult-to-adult LDLT: from *child-to-parent*, between *spouses/siblings*, and from *parent-to-child*. The overall survival in *child-to-parent* was significantly higher than in *spouses/siblings* ($P = 0.002$) and in *parent-to-child* ($P = 0.005$), despite significantly higher recipient age in *child-to-parent* [59 (42–69) years, $P < 0.001$]. Contrastingly, *parent-to-child* exhibited the lowest survival, despite the youngest recipient age [26 (20–43) years, $P < 0.001$]. In addition, younger donor age exhibited significantly better recipient survival both in hepatitis C virus-related and in non-hepatitis C virus diseases. Univariate and multivariate analyses both demonstrated that donor age and graft-type (right-sided livers) are independent prognostic factors for recipient survival.

Conclusions: Donor age is an independent, strong prognostic factor in adult-to-adult LDLT.

Keywords: donor age, donor-recipient relationship, liver regeneration, living-donor liver transplantation

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Liver transplantation (LTx) has been widely spread all over the world, as the only curative treatment for end-stage liver diseases. Since the first human LTx in 1963,[1] more than half a century has already past, and a multitude of risk factors affecting recipient outcome in deceased-donor liver transplantation (DDLT) have been identified, such as elderly donors,[2–4] duration of donor hypotension,[5] use of vasoactive agents, type and degree of steatosis,[6,7] and comorbid hepatorenal syndrome.[8] Based on these, several formulae have been postulated to predict the recipient or graft prognosis, including Model for End-Stage Liver Disease (MELD) score.[9,10] Recently, this formula has been updated to taken into consideration donor age, and is referred to as D-MELD score.[11] This scoring system has been used to aid appropriate donor-recipient matching, which has recently been under active debate in DDLT.[12,13]

On the other hand, living-donor partial liver transplantation (LDLT) has also been increasing worldwide, particularly in Asian and Islamic countries mainly because of religious reasons. LDLT has also been recognized in Western countries as a therapeutic alternative to DDLT in the era of critical shortage of donor organs. In contrast to DDLT, however, a quarter of a century has just passed from the first successful LDLT in 1989.[14] Unlike DDLT, the concept of reasonable donor allocation is less relevant for LDLT, as this form of LTx relies mainly on altruistic donors, such as parents, children, spouses, and siblings. Therefore, the concept of appropriate donor-recipient matching is not always considered in LDLT.

LDLT has several inherent disadvantages compared with DDLT. For example, liver graft volume is inevitably small in adult-to-adult LDLT, which increases the risk for small-for-size syndrome.[15,16] Needless to say, donor safety should be the first priority in LDLT, therefore, there has been a recent transition towards the use of smaller grafts than before, to increase the future remnant volume of donor livers, and thus to maximize donor safety.[17,18] Considering such inevitable aspects in adult LDLT, regenerative

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potential of partial liver grafts after surgery should be of quite importance for restoring its function, and for surviving critically-sick postoperative period after LDLT.[19] It has recently been demonstrated that younger livers generally exhibit better regeneration after LTx[20–22] and hepatectomy.[23] Moreover, aged livers have a significant risk for reinfection and rapid progression of hepatitis C virus (HCV), resulting in lower rates of patient and graft survival in HCV-positive recipients.[24–26] Given that LDLT is more common in Asian countries, where HCV-related cirrhosis is the leading cause of adult LTx, investigating the prognostic impact of donor age on recipient outcome after LDLT should be a clinical priority.

In light of the available evidence summarized above, we hypothesized that the influence of donor age, especially younger donor age, might be more significant in LDLT rather than in DDLT. This study was thus designed to elucidate the impact of donor age on survival outcomes after primary adult-to-adult LDLT.

PATIENTS AND METHODS

Patients

We performed 518 cases of LTx in our single center between April 2006 and March 2014. Of these, DDLTs, pediatric cases, re- or re-re-transplants, and a case of LDLT from an uncle to a nephew, were all excluded. A total of 315 cases of primary adult-to-adult LDLT (recipient age $\geq$ 18 years) were included in the final study. To investigate the prognostic impact of donor age on recipient survival, the recipients were divided into 5 groups according to the donor age: D-20s (20–29 years, $n = 60$); D-30s (30–39 years, $n = 72$); D-40s (40–49 years, $n = 57$); D-50s (50–59 years, $n = 94$); and D-60's (60–69 years, $n = 32$). Recipients were also divided into 5 groups according to their own age: R-20s ($n = 20$); R-30s ($n = 28$); R-40s ($n = 46$); R-50s ($n = 138$); and R-60s ($n = 83$). Recipients' survival proportions and the association between survival and various clinical factors were investigated and compared among the 5 age-groups. In addition, recipient survival was compared among the following 3 groups according to the donor-recipient relationship: from *child-to-parent*, $n = 125$; between *spouses/siblings*, $n = 158$; and from *parent-to-child*, $n = 32$. The median follow-up period of the 315 patients was 49.5 (1–105) months. The majority of the recipients were carefully followed up by transplant surgeons in every 1 to 3 weekly intervals, as appropriate, for the first 3 postoperative months. Thereafter, most patients were followed by the surgeons in our hospital in every 1 to 3 months, or alternately followed by our team and by hepatologists in a nearby hospital every 3 months, if stable. All patients provided written informed consent. All clinical investigations were conducted in accordance with the institutional guidelines, and with the Declaration of Helsinki principles (2000) for medical research involving human subjects.

Variables

The demographic and preoperative clinical variables of interest were recipient sex and age, underlying liver etiologies, Child-Pugh-Turcotte (CPT) score, MELD score, donor sex and age, graft-type (right- or left-side), graft-versus-recipient weight ratio (GRWR), and ABO blood-type compatibility. The operative variables included intraoperative blood loss, operation time, cold ischemic time, warm ischemic time, and the portal venous pressure at the end of operation (final PVP). The postoperative variables were malignant or benign diseases, and recipient survival.

Selection Criteria for LDLT Donors

The selection criteria for donors and recipients, and the surgical procedures performed are described in detail elsewhere.[27] In brief, the donor age in LDLT ranged from 20 to 64 years, and donors aged 65 to 67 years were individually evaluated and approved by the Institutional Review Board, if appropriate. Both the liver graft and the remnant liver volume were preoperatively estimated by the MeVis software (MeVis Medical Solutions AG, Bremen, Germany) based on 3-dimensional images of vascular anatomy reconstructed from multidetector computed tomography of the donor liver. The inclusion criteria for LDLT donors in our institution are as follows: (i) expression of willingness to donate their partial liver, without influence by others; (ii) normal liver function and no systemic or other organ diseases requiring medical therapies; and (iii) $\geq$0.6% GRWR for recipients, and >30% future remnant liver volume in donors, assessed by preoperative CT volumetry. Needless to say, donor safety should be the first priority in living-donor organ transplantation. From this perspective, we have gradually decreased the lower limit of GRWR during the study period to increase the remnant volume of donor livers and guarantee donor safety, as follows: $\geq$0.8% until November 2007, $\geq$0.7% from December 2007 until March 2009, and $\geq$0.6% from April 2009, as described in detail elsewhere.[18,28]

Immunosuppression Protocols

The standard immunosuppression protocol with tacrolimus, mycophenolate mofetil, and steroids was employed and varied minimally over the study period.[29,30] In ABO blood-type incompatible cases, the recipients were preoperatively treated with anti-CD20 antibody (rituximab: 375 mg/m^2) to prevent antibody-mediated humoral rejection.[31]

Statistical Analysis

Continuous variables were summarized as means $\pm$ standard deviations (SD). Categorical variables were summarized as counts and proportions. Differences among the 5 groups according to donor age (D-20s [range: 20–29 years], D-30s [30–39 years], D-40s [40–49 years], D-50s [50–59 years], and D-60s [60–69 years]) or recipient age were compared by using one-way analysis of variance (ANOVA) for continuous variables, χ^2 test for categorical variables, and Kaplan-Meier method followed by log-rank test for recipient survival.

The clinical factors associated with 6-month mortality were evaluated by using Student t test, χ^2 test (univariate analysis), and logistic regression analysis (multivariate analysis). All $P < 0.05$ were considered statistically significant. All statistical analyses were performed by using Prism 5 (Graph Pad Software, Inc., La Jolla, CA) and SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Recipient Characteristics According to Donor Age

The recipient characteristics in the 5 age-groups are summarized in Table 1. The recipient age was significantly older in D-20s and -30s than in the other groups ($P < 0.001$), reflecting a higher proportion of *child-to-parent* relationship therein (95% in D-20s, 79% in D-30s, $P < 0.001$, Table 1). In addition, left-sided grafts were significantly more selected in D-30s compared with all the others ($P = 0.032$). There were no significant differences in the other factors, such as sex, HCV-related cirrhosis, acute liver failure (ALF), malignant or benign diseases, ABO compatibility, GRWR, CPT, and MELD scores.

Recipient Characteristics According to Recipient Age

The recipient characteristics in the 5 groups according to recipient age are summarized in Table 2. The donor age was

TABLE 1. Recipient Characteristics in the 5 Groups According to Donor Age

	D-20s ($n = 60$)	D-30s ($n = 72$)	D-40s ($n = 57$)	D-50s ($n = 94$)	D-60s ($n = 32$)	*P*
Recipient age	55 ± 8	57 ± 10	50 ± 11	51 ± 12	50 ± 13	<0.001
Sex (male/female)	36/24	27/45	27/30	53/41	17/15	0.071
HCV/not	17/43	29/43	20/37	42/52	7/25	0.096
ALF/not	5/55	7/65	4/53	2/92	5/27	0.103
Malignant/benign	16/44	20/52	15/42	33/61	11/21	0.680
ABO compatibility (incompatible/not)	13/47	15/57	20/30	22/72	9/23	0.355
GRWR	0.94 ± 0.22	0.90 ± 0.22	0.93 ± 0.19	0.92 ± 0.20	0.96 ± 0.23	0.642
Graft type (right-/left-side)	36/24	33/39	35/22	66/28	21/11	0.032
CPT score (A/B/C)	2/18/31	2/21/39	2/16/34	4/20/59	5/4/20	0.095
MELD score	21 ± 10	20 ± 8	20 ± 7	20 ± 8	21 ± 9	0.772
D/R relationship						
Child-to-parent	57	57	11	0	0	<0.001
Spouses/Siblings	3	15	44	77	19	
Parent-to-child	0	0	2	17	13	

*The data are presented as mean ± SD.

Differences among the 5 groups were compared by using one-way analysis of variance (ANOVA) for continuous variables, and χ^2 test for categorical variables. All $P < 0.05$ were considered statistically significant.

ALF indicates acute liver failure; CPT, child-Pugh-Turcotte; D, donor; D-, donor-; GRWR, graft-versus-recipient weight ratio; HCV, hepatitis-C virus; MELD, model for end-stage liver diseases; R, recipient.

significantly older in R-20s and -30s than in the others ($P < 0.001$, Table 2), reflecting a higher proportion of *parent-to-child* relationship (85% in D-20s, $P < 0.001$). Older recipients had higher rates of HCV-related cirrhosis (0, 4, 39, 41, and 48% in R-20s, -30s, -40s, -50s, and -60s, respectively, $P < 0.001$, Table 2) and malignancies (0, 7, 11, 33, and 52% in R-20s, -30s, -40s, -50s, and -60s, respectively, $P < 0.001$). R-30s showed the highest rate of ALF (6 out of 28 cases, 21%, $P = 0.008$). There were no significant differences in sex, ABO compatibility, GRWR, graft-type, CPT, and MELD scores.

Relationship Between Donor and Recipient

Figure 1 shows the relationship between donor and recipient age. As illustrated by 95% bivariate normal density ellipses, there are naturally separated 3 groups representing the 3 typical combinations in LDLT: from *child-to-parent*, from *parent-to-child*, and between *spouses/siblings*.

Background Etiologies in the Three Donor-recipient Relationships

The etiologies of recipient liver disease in the 3 donor-recipient relationships are summarized in Supplemental Table, http://links.lww.com/SLA/B197. The proportion of HCV-related cirrhosis and malignancies tended to be higher in *child-to-parent*, reflecting the high incidence of HCC in this group. On the other hand, biliary atresia (BA) and ALF tended to be more common in *parent-to-child*.

Overall Recipient Survival According to Donor and Recipient Age

Figure 2A shows the overall recipient survival in this series of 315 recipients after adult LDLT. As seen, LDLT recipients who survived for the first 6 months after surgery could survive longer thereafter. This relatively-lower decline with time in recipient

TABLE 2. Recipient Characteristics in the 5 Groups According to Recipient Age

	R-20s ($n = 20$)	R-30s ($n = 28$)	R-40s ($n = 46$)	R-50s ($n = 138$)	R-60s ($n = 83$)	*P*
Donor age	51 ± 10	48 ± 13	44 ± 10	42 ± 14	42 ± 12	0.001
Sex (male/female)	6/14	12/16	27/19	73/65	42/41	0.235
HCV/not	0/20	1/27	18/28	56/82	40/43	<0.001
ALF/not	1/19	6/22	3/43	4/134	9/74	0.008
Malignant/benign	0/20	2/26	5/41	45/93	43/40	<0.001
ABO compatibility (incompatible/not)	6/14	9/19	15/31	30/108	19/64	0.490
GRWR	0.91 ± 0.17	0.86 ± 0.19	0.94 ± 0.18	0.94 ± 0.21	0.93 ± 0.23	0.290
Graft type (right-/left-side)	10/10	16/12	30/16	85/53	50/33	0.817
CPT score (A/B/C)	2/6/9	4/5/13	0/11/29	5/36/86	4/21/46	0.148
MELD score	19 ± 8	21 ± 8	22 ± 8	20 ± 8	19 ± 8	0.285
D/R relationship						
Child-to-parent	0	0	5	64	56	<0.001
Spouses/siblings	3	15	39	74	27	
Parent-to-child	17	13	2	0	0	

*The data are presented as means ± SD.

Differences among the 5 groups were compared by using one-way analysis of variance (ANOVA) for continuous variables, and chi-square test for categorical variables. All P values <0.05 were considered statistically significant.

ALF indicates acute liver failure; CPT, child-Pugh-Turcotte; D, donor; GRWR, graft-versus-recipient weight ratio; HCV, hepatitis C virus; MELD, model for end-stage liver diseases; R, recipient; R-, recipient-.

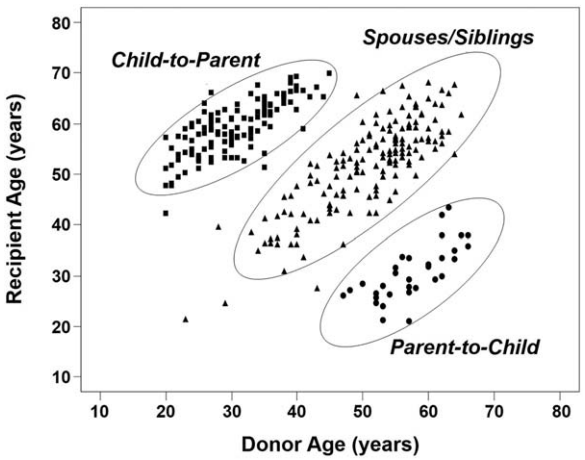

FIGURE 1. A. The relationships between donors and recipients in adult-to-adult LDLT. The scatter plot shows the relationships between donor and recipient age in our series of 315 primary adult-to-adult LDLT; 95% bivariate normal density ellipses display 3 naturally-separated combinations, reflecting the 3 typical relationships in LDLT: from *child-to-parent* (closed rectangles), from *parent-to-child* (closed circles), and between *spouses/siblings* (closed triangles).

survival is a characteristic feature in Japan. Conversely, identifying the factors affecting the perioperative (6-month) mortality in adult LDLT (red dotted circle in Fig. 2A) is an urgent issue that needs to be addressed. For this purpose, uni- and multivariate analyses were both performed, and presented afterward (Tables 3 and 4).

As shown in Fig. 2B, the cumulative recipient survival proportion was significantly higher in D-20s than in all the other groups (log-rank: $P = 0.008$, <0.001, <0.001, and $= 0.006$ vs D-30s, -40s, -50s, and -60s, respectively). In contrast to donor age, recipient age did not significantly affect their own survival, as shown in Fig. 2C. Though statistically not significant, recipient survival in R-20s [26 (20–29) years; the mean (range)] tended to be lower than in R-30s [36 (30–39) years], -50s [55 (50–59)], and -60s [63 (60–69)], and comparable with that of R-40s [45 (40–49)], despite their significantly younger age. Taken together, these results indicate that recipient survival after LDLT depends on donor age but not recipient age.

Overall Recipient Survival According to Donor-recipient Relationship

The overall recipient survival rates according to donor-recipient relationship are summarized in Figure 2D. Of interest, the proportion of surviving recipients in *child-to-parent* was significantly higher than in the other 2 subgroups (Log-rank: $P = 0.005$ vs *parent-to-child*, and $P = 0.002$ vs *spouses/siblings*), despite the highest recipient age in this combination [59 (42–69) years, $P < 0.001$]. It is also noteworthy that the *parent-to-child* group exhibited the lowest survival, though the recipient age was the youngest [26 (20–43) years, $P < 0.001$].

Overall Survival in Adult LDLT Recipients With or Without HCV

It is well-known that HCV-related disease is associated with lower rates of both recipient and graft survival in DDLT, and that donor age is an important prognostic factor in such cases.[32,33] In our series of LDLT, however, overall recipient survival was not different between the HCV and non-HCV subgroups. In fact, the survival curves of both groups approximated each other (Fig. 3A).

Among HCV-positive recipients, cumulative survival proportion in D-20s was significantly higher than in -40s, -50s, and -60s (Log-rank: $P = 0.006$, 0.006, and 0.024, respectively), whereas no significant difference was observed between D-20s and -30s (Fig. 3B). Figure 3C illustrates the cumulative recipient survival with HCV, separated by recipient age. Though statistically not significant, 5-year survival proportions in R-40s, -50s, and -60s were 60%, 75%, and 82%, respectively.

Interestingly, older the recipients, higher the survival rate. As an explanation for this seemingly-paradoxical result, the proportions of *child-to-parent* in R-40s, -50s, and -60s were 11%, 46%, and 67%, respectively ($P < 0.001$, Table 2 and Figure 2A).

Similarly, in non-HCV cirrhosis, the recipient survival proportion in D-20s was significantly higher than in all the others [Log-rank: $P = 0.020$, 0.006, 0.035 vs -30s, -40s, -50s, respectively (Fig. 3D)]. Unexpectedly, the recipient survival in R-50s was significantly higher than in R-40s [Log-rank: $P = 0.018$ (Fig. 3E)]. A possible reason for this incomprehensible result is that R-40s included only 3 donors in their 20s out of 28 (10.7%), whereas in R-50s, 30 out of 82 donors were in their 20s (36.6%, $P = 0.007$ by χ^2 test).

Univariate Analysis of Clinical Factors Affecting Recipient Survival After LDLT

As shown in Table 3, univariate analysis revealed that donor age ($P = 0.002$) and graft-type (left-sided graft, $P = 0.006$) were significant risk factors for 6-month mortality in adult LDLT recipients. Unexpectedly, no recipient factors, neither MELD, CPT scores nor even their own age, were related to recipient survival during critically ill postoperative days for the first 6 months (Table 3 and Fig. 2A).

Multivariate Logistic Regression Analysis of Clinical Factors Affecting Recipient Survival After LDLT

The variables included were determined based on the univariate analysis, in which the following 5 factors were left at the significance level of $P < 0.1$ (Table 3): Donor age ($P = 0.002$); graft type ($P = 0.006$); ABO blood-type incompatibility ($P = 0.067$); MELD score ($P = 0.080$); and CPT score ($P = 0.098$). The latter 2 are similar quantitative measures for the severity of liver failure, both of which include the same laboratory data: serum bilirubin level and prothrombin time. In terms of multicolinearity, more widely used MELD score was chosen.

Moreover, a linear relationship was not observed between recipient survival proportions and donor age (Fig. 2B and 2C). In particular, those in D-40s deviated greatly from linear relationship, suggesting that donor age could not be treated as a continuous variable in multivariate logistic regression analysis.

Thus, 4 categorical variables (D-20s vs -30s, -40s, -50s, and -60s) in donor age, graft type, ABO-compatibility, and MELD score, were included in the analysis, all of which are considered to be clinically important.

As a result, donor age and graft-type were identified as independent prognostic factors for recipient survival. As summarized in Table 4, D-20s ($P = 0.001$ and $P = 0.009$, vs D-40s and D-50s, respectively) and the use of right-sided graft (OR 2.19, $P = 0.014$) were statistically significant for 6-month recipient survival.

DISCUSSION

In the current study, we demonstrated that younger donor age was significantly associated with higher recipient survival

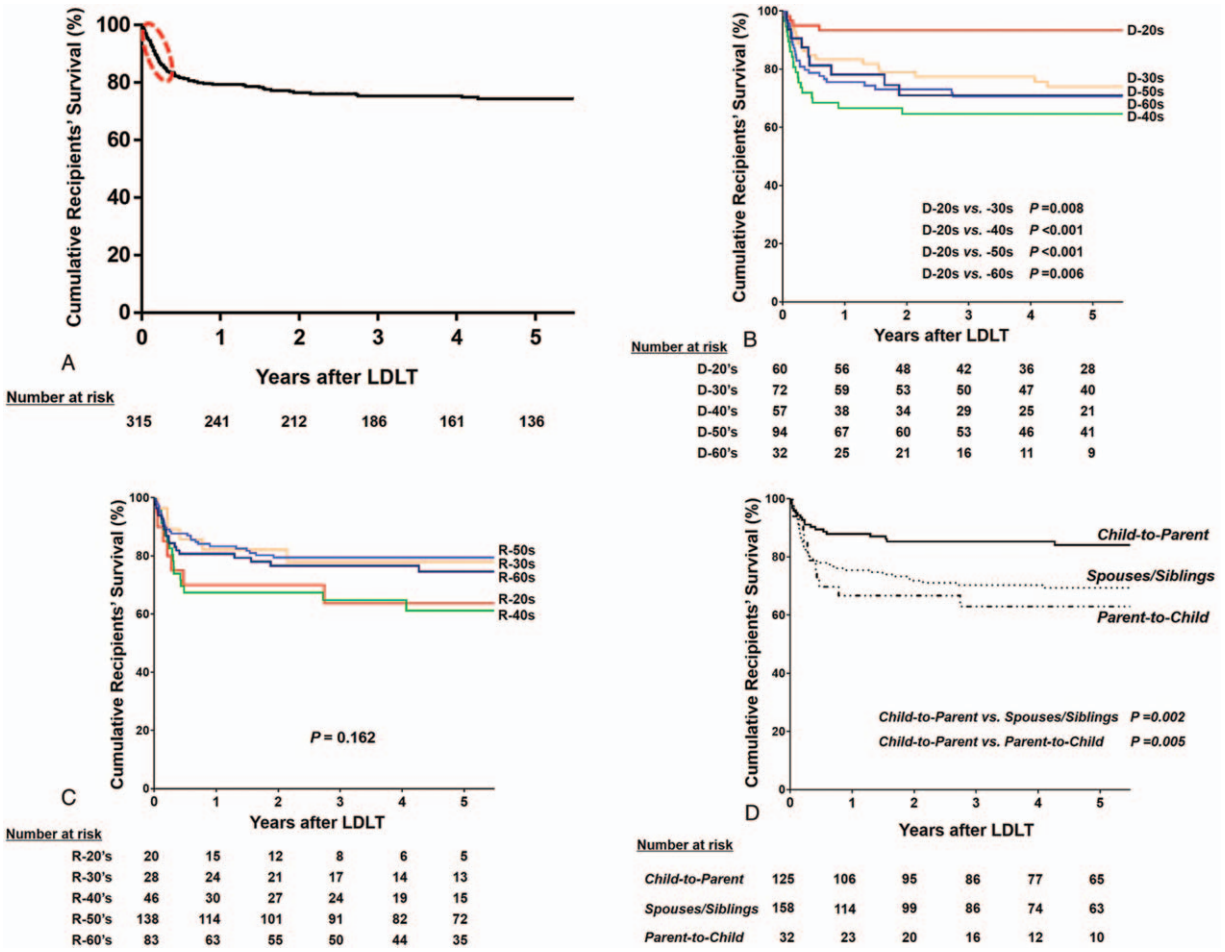

FIGURE 2. Recipient overall survival in adult-to-adult LDLT according to donor and recipient age. A, The overall recipient survival in the 315 recipients after primary adult-to-adult LDLT (between April 2006 and March 2014). As seen, LDLT recipients who survived for the first 6 months after surgery could survive longer thereafter. This relatively-lower decline with time in recipient survival is a characteristic feature in Japan. B, Recipient overall survival in adult-to-adult LDLT according to donor age. The recipient survival proportion in D-20s was significantly higher than in the other groups (Log-rank: $P = 0.008$, <0.001, <0.001, and 0.006 vs D-30s, -40s, -50s, and -60s, respectively). C, Recipient overall survival in adult-to-adult LDLT according to recipient age. No significant difference was observed as compared with recipient age. Survival proportions were estimated with the Kaplan-Meier method and were compared with the Log-rank test. *P* values less than 0.05 were regarded as statistically significant. D, Recipient overall survival in adult-to-adult LDLT according to donor-recipient relationships. The recipient survival proportion in *child-to-parent* was significantly higher than in the other 2 groups (Log-rank: $P = 0.005$ vs *parent-to-child*, $P = 0.002$ vs *spouses/siblings*), despite the oldest recipient age in this group [59 (42–69) years, $P < 0.001$ by 1-way ANOVA]. It is also noteworthy that the survival proportion in *parent-to-child* exhibited the lowest, though the recipients' age in this group was the youngest [26 (20–43) years, $P < 0.001$ by 1-way ANOVA].

proportions in adult-to-adult LDLT. Although several studies have reported that use of elderly donors led to worse recipient prognosis after LDLT,[34,35,36] the majority of these were limited to comparisons between 2 groups: ≥50 years or younger in some studies, ≥40 or ≥60 in others. In the current study, we divided our 315 patient cohort into 5 groups based on donor age: D-20s, -30s, -40s, -50s, and -60s. Of interest, younger donor age, especially D-20s, and the use of right-sided graft were identified as independent prognostic factors improving recipient survival, whereas any recipients' factors including MELD scores, CPT scores or even their own age were not significant. Surprisingly, the odds ratios of D-20s to the other groups were quite high (3.37 to 9.26, Table 4), directly indicating several times higher risk in recipient perioperative mortality in D-30s to -60s than in D-20s in adult-to-adult LDLT.

All living-donors should be, even in emergent cases, proven to be healthy, and all liver grafts must be, both in their volume and functions, strictly evaluated preoperatively. Consequently, all the liver grafts in LDLT should have good condition and function homogeneously, neither with steatosis nor with long CIT. This is the characteristic difference between DDLT and LDLT, that is, ''bigger but with some damage'' in the former, and ''smaller but healthy condition'' in the latter. Assuming that the parenchymal conditions and functions are homogeneously good in LDLT, the differences in liver graft quality in LDLT might be theoretically attributed to the following 3 factors: age, graft-type (generally, left- or right-side), and the volume (GRWR). Of these, uni- and multivariate analyses both demonstrated that the former 2 factors were significant.

TABLE 3. Clinical Factors Affecting Postoperative Mortality (Univariate Analysis)

	Survival ≥ 6 Months ($n = 257$)	Survival < 6 Months ($n = 58$)	*P*
Sex (male/female)	135/122	25/33	0.195
Donor age, y	42 ± 13	48 ± 10	0.002
Recipient age, y	53 ± 11	51 ± 12	0.215
ABO compatibility (incompatible/not)	59/198	20 /38	0.067
GRWR, %	0.93 ± 0.21	0.91 ± 0.21	0.473
Graft type (right-/left-side)	165/92	26/32	0.006
MELD score	20 ± 8	22 ± 9	0.080
Operation time, h	13.6 ± 2.7	13.5 ± 3.0	0.694
Blood loss, mL	8622 ± 9818	10923 ± 12859	0.250
CIT, min	114 ± 93	126 ± 155	0.645
WIT, min	44 ± 12	42 ± 12	0.149
final PVP (>15 mmHg or not)	39/162	11/36	0.540
CPT score (A/B/C)	15/64/141	0/15/42	0.098
ALF/not	17/240	6/52	0.324
HCV/non-HCV	96/161	19/39	0.511
Malignant/benign	82/175	13/45	0.155

*The data are presented as mean ± SD.

ALF indicates acute liver failure; CIT, cold ischemic time; CPT, child-Pugh-Turcotte; GRWR, graft-versus-recipient weight ratio; HCV, hepatitis C virus; MELD, model for end-stage liver diseases; PVP, portal vein pressure; WIT, warm ischemic time.

One advantage of younger liver grafts is presumed to be in their higher regenerative potential. Accumulating evidence indicated that regeneration of liver allografts from younger donors is superior to that observed in elderly counterparts.[20,21,22] Conversely, the most distinctive and well-documented effect of aged livers is impaired liver regeneration.[37] Yoshizumi et al[38] reported that partial liver grafts from younger donors (<50 years) significantly reduced post-operative ascites discharge in adult LDLT recipients than those in elderly donors (≥50 years). This was probably because of better regeneration, and lower vascular resistance (higher compliance) of hepatic parenchyma in younger livers.

Another advantage of young livers is the increased resistance to recurrent hepatitis C after LTx. Decompensated liver cirrhosis and/or HCCs attributed to HCV infection are the leading indication for adult LTx worldwide.[39] Posttransplant HCV recurrence has long been a major problem because of its extremely high rate of re-infection to naïve liver grafts,[40] 10- to 20-fold higher viral load under immunosuppressed conditions,[41] and resultant rapid progression leading to cirrhosis within 5 to 10 years, unless properly treated.[42] Thus HCV-related disease is a well-known etiology associated with worse recipient outcome in DDLT.[24–26]. In our series of adult LDLT, however, the recipient prognosis with HCV was comparable to that of non-HCV recipients. As shown in Fig. 3A, recipient survival with HCV rivals or surpasses that of non-HCV recipients. As a possible reason for this seemingly contradictory result, the difference in donor age between DDLT and LDLT might be involved. In our 114 cases of HCV-related LDLT, 46 recipients (40.4%) received young livers from donors in their 20s or 30s, despite 96 recipients (84.2%) were in their 50s or 60s. Such a combination of younger donors and elderly HCV-positive recipients is relatively uncommon in DDLT, but not in LDLT, where the *child-to-parent* donor-recipient relationship is quite common. Thus, it is reasonable to suppose that younger liver age contributed at least partly to the better recipient outcome with HCV in LDLT.[43]

TABLE 4. Clinical Factors Affecting Postoperative Mortality (Multivariate Logistic Regression Analysis)

	OR	95% CI	*P*
D-30s vs D-20s	3.37	0.87–13.09	0.079
D-40s vs D-20s	9.26	2.46–34.77	0.001
D-50s vs D-20s	5.63	1.54–20.61	0.009
D-60s vs D-20s	4.31	0.96–19.30	0.056
Graft type (right-/left-side)	2.19	1.18–4.08	0.014
ABO compatibility (incompatible/not)	0.68	0.35–1.31	0.250
MELD score	1.04	1.00–1.07	0.069

CI indicates confidence interval; D, donor; OR, odds ratio MELD, model for end-stage liver diseases.

In addition, recent advancement in anti-HCV therapies during the last 2 years of study conduction is also noteworthy. In November 2011 and December 2013, we introduced telaprevir and simeprevir, respectively, in addition to peginterferon and ribavirin (PEG-IFN + RBV). Simeprevir- and telaprevir-based triple therapies improved the sustained virological response rate from 30% with PEG-IFN + RBV up to 69%.[44] Even though the number of HCV-positive recipients who could have benefits from such direct-acting antivirals (DAAs) was rather small (just 8 cases with telaprevir and 19 cases with simeprevir, out of 114 cases), the introduction of these DAAs might have contributed in part to the current results. From now on, interferon-free DAA combination therapies will likely improve the worse prognosis of HCV-positive recipients than before, thereby opening a new era in the management of HCV before and after LTx.[45]

This study has several limitations. First, this was a retrospective cohort study, and therefore we could not control for differences in the distribution of donor/recipient age or in underlying etiology among groups. In LDLT, however, relationships between the donor and the recipient are naturally divided into 3 typical combinations: *child-to-parent*, *parent-to-child*, and *spouses/siblings*. In such relationships, donor/recipients age must naturally show heterogeneous distribution, as manifested in Figure 1. Such typical relationships are the characteristic feature in LDLT, which is thought to be an universal and everlasting standard in LDLT. Moreover, in these 3 groups, younger livers tend to be transplanted to elderly recipients (*child-to-parent*, Fig. 1). From these points of view, heterogeneous age distribution never detracted from the significance of younger donor age in LDLT but rather enhanced its impact on partial liver transplants, in which liver regeneration is of significant importance for recipient survival.

In conclusion, we demonstrated that younger donor age and the use of a right-sided graft were independent prognostic factors for improving recipient survival in adult-to-adult LDLT. Although

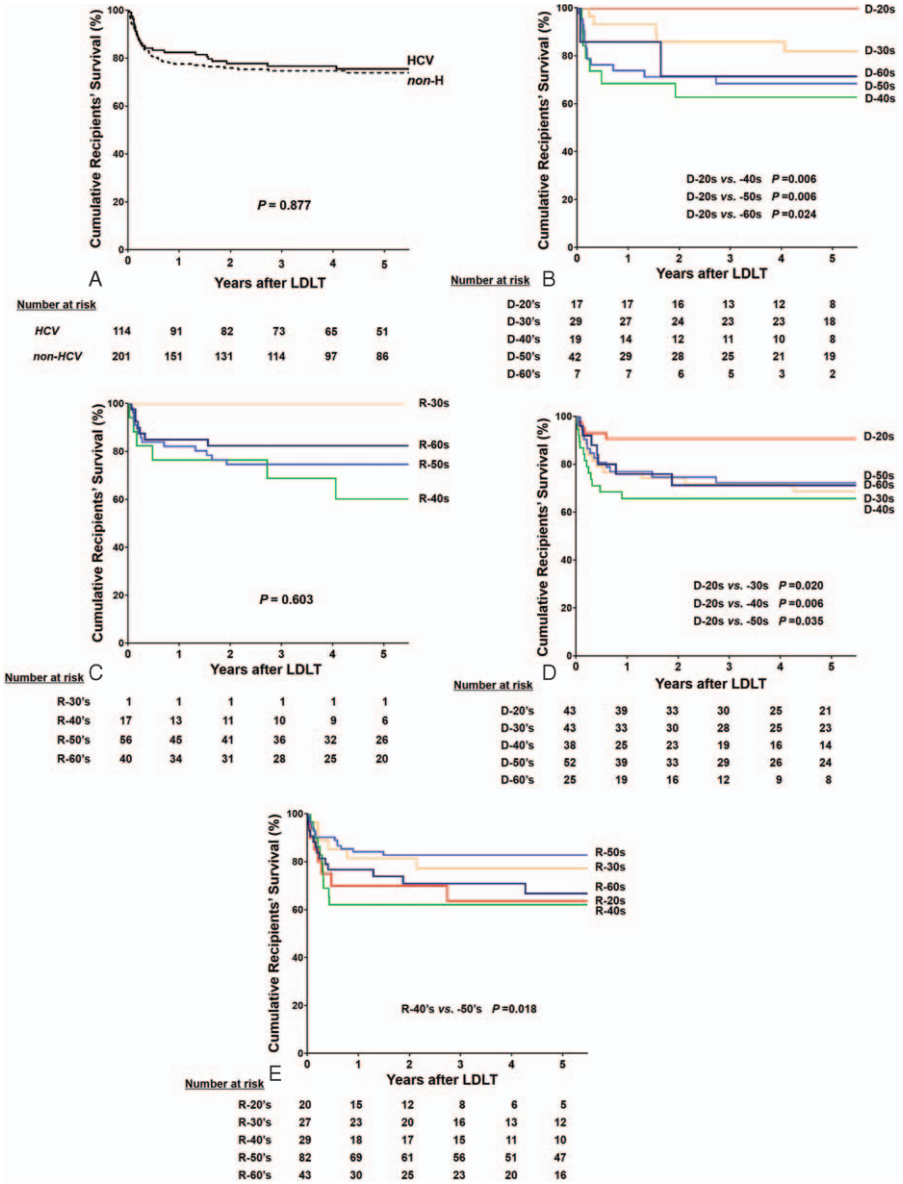

FIGURE 3. Recipient survival with or without HCV in adult-to-adult LDLT according to donor and recipient age. A, Cumulative recipient survival in adult-to-adult LDLT with or without hepatitis-C. As seen, the recipient survival with HCV rivals or surpasses that in non-HCV, indicating that HCV did not deteriorate the recipient survival in this series of adult-to-adult LDLT. B, Cumulative survival rates of HCV recipients according to the donor age. As shown, the recipient survival in D-20s was significantly higher than in D-40s, -50s, and -60s (Log-rank: $P = 0.006$, 0.006, and 0.024, respectively). The recipients' survival proportion in D-30s was the second best, but could not reach the statistical significance against all the others (Log-rank: $P = 0.08$, 0.08, 0.06, and 0.6 vs D-20s, -40s, -50s, and -60s, respectively). C, Cumulative recipient survival with HCV separated by their own age. No significant difference was observed among the subgroups. Though statistically not significant, 5-year survival proportions in R-40s, -50s, and -60s were 60%, 75%, and 82%, respectively. Interestingly, older the recipients, higher the survival rate. D, Cumulative recipient survival with non-HCV according to the donor age. As with all the other analyses, D-20s resulted in significantly higher recipient survival proportion than in D-30s, -40s, and -50s (Log-rank: $P = 0.020$, 0.006, and 0.035, respectively). E, Cumulative recipient survival with non-HCV according to the recipient age. Unexpectedly, the recipient survival in R-50s was significantly higher than in R-40s (Log-rank: $P = 0.018$).

further large-scale studies are required to validate the results of this study, our results highlight the significance of liver age on partial LT outcome, and will be clinically valuable in cases of adult LDLT and split LT.

Postscript

Apart from the scientific facts presented in this study, we would like to mention that the first priority in our donor selection criteria in LDLT has been, and will be in the voluntary will from close relatives, who really desire to cure their invaluable person with irreversible liver failure.

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