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ORIGINAL ARTICLE

Outcomes of living donor liver transplantation for hepatitis C virus-positive recipients in Japan: results of a nationwide survey

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Summary

A nationwide survey of living donor liver transplantation (LDLT) for hepatitis C virus (HCV)-positive recipients was performed in Japan. A total of 514 recipients are reported and included in the study. The cumulative patient survival rate at 5 and 10 years was 72% and 63%, respectively. Of the 514 recipients, 142 patients (28%) died until the end of the observation, among which the leading cause was recurrent hepatitis C (42 cases). According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, acute rejection episode, and absence of a sustained virologic response were independent prognostic factors. Of the 514 recipients, 361 underwent antiviral treatment mainly with pegylated-interferon and ribavirin (preemptive treatment in 150 patients and treatment for confirmed recurrent hepatitis in 211). The dose reduction rate and discontinuation rate were 40% and 42%, respectively, with a sustained virologic response rate of 43%. In conclusion, patient survival of HCV-positive recipients after LDLT was good, with a 10-year survival of 63%. Right liver graft might be preferable for HCV-positive recipients in an LDLT setting.

Introduction

End-stage liver disease caused by chronic hepatitis C virus (HCV) infection is the leading cause of liver transplantation in Western countries [1,2] and Japan [3]. Liver transplantation, including deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT), is an established treatment for these patients, although it unfortunately does not cure HCV-infected recipients. Reinfection by HCV occurs universally and the progression of recurrent hepatitis C in the graft is accelerated compared with chronic hepatitis C infection in the nontransplant population, resulting in the impaired outcome of HCV-positive recipients compared with those with other indications [4–6]. Recently, effective antiviral therapies with new protease inhibitors have been aggressively investigated [7]; however, post-transplant antiviral treatment with pegylated-interferon (PEG-INF) and ribavirin (RBV) has been the main strategy to improve the outcome in both DDLT and LDLT [8] in our study period. While patient survival is significantly improved by achieving a sustained virologic response (SVR) with antiviral treatment among patients with chronic hepatitis C [9], the efficacy of antiviral treatment varies among HCV-positive liver transplant recipients [10].

Here, we conducted a nationwide survey of LDLT for HCV-positive patients and investigated the outcome and prognostic factors for patient survival to further improve the LDLT outcome. We also provide an overview of the antiviral treatment for LDLT recipients in Japan.

Patients and methods

Liver transplantations performed between 1998 and 2012 were collected and reviewed, and the initial LDLT was the subject of this study. The survey was conducted by the Research Group on Hepatitis under the aegis of the Japanese Ministry of Health, Welfare, and Labor. The indication of LDLT for HCV-positive recipients in Japan is similar to that for deceased donor liver transplantation (DDLT) in Western countries [11]. As for cases with hepatocellular carcinoma (HCC), Milan criteria are basically used; however, all institutions apply center-specific extended criteria for those beyond Milan provided that they are without extrahepatic lesions and macroscopic vascular invasions [12]. Data of all consecutive HCV-positive cases were enrolled in the study during this period, completing questionnaire items on computerized database by each institution. A total of 514 HCV-positive recipients from 12 institutions were enrolled in the present retrospective analysis. We first analyzed patient outcome and investigated the factors associated with poor survival among the collected variables. Next, we administered a survey regarding antiviral treatment after LDLT in Japan.

Evaluated variables

The following variables were obtained from the nationwide survey. As for recipient factors, patient age, sex, the existence of pretransplant antiviral treatment, HCV genotype, model for end-stage liver disease (MELD) score, the coexistence of hepatocellular carcinoma, the type of calcineurin inhibitor, use of mycophenolate mofetil (MMF), existence of steroid withdrawal, existence of steroid bolus treatment, splenectomized or not, episodes of acute rejection, existence of the post-transplant antiviral treatment, and achievement of SVR were collected. The diagnosis of acute rejection was based on internationally accepted histologic criteria (Banff guidelines) based on liver biopsies, which was treated with steroid bolus injection initially in the majority of center. The second-line treatments were center dependent, such as 1500–3000 mg of MMF or basiliximab, an interleukin-2 receptor antagonist. Additionally, donor age and the type of partial liver graft were added as variables. The number of LDLT cases per year at each center was also incorporated as a variable, with a cutoff value of 20 cases per year. All these factors were completely fulfilled by each center and assessed for their association with patient outcome. Other incomplete variables which may have a possible association with patient survival, such as IL-28 gene polymorphisms, histological findings, biliary complications, and cytomegalovirus infection, were not incorporated into the analysis.

We then surveyed post-LDLT antiviral treatment. The timing of the antiviral treatment (preemptive or after confirmation of recurrent disease), the antiviral treatment regimen used, time from LDLT to starting antiviral therapy, duration of antiviral therapy, adherence to the treatment, dose reduction rate, and finally the SVR rate were summarized.

Statistical analysis

Continuous variables are reported as medians and ranges, and categorical variables are reported as numbers (proportions). Cumulative survival is presented with Kaplan–Meier curves, and differences in survival between the groups were analyzed with a log-rank test. Factors associated with survival in the log-rank test were then analyzed using a Cox regression analysis. Five patients were lost to follow up during the observation period, and they were censored in the survival analysis. The cutoff value for the continuous variables was basically set according to each mean value, except for the recipient age for which it was set at 60 (mean value of 57) based on literatures. All statistical tests were two-sided, and a P-value of <0.05 was considered significant. The statistical analyses were performed with SPSS statistical software (Chicago, IL, USA) 18.0 for Windows.

Table 1. Characteristics of living donor liver transplantations for HCV-positive recipients in Japan.

	Total n = 514 (%)
Age (years)	57 (19–73)
Gender: male/female	320 (62)/194 (38)
Body mass index	25 (16–41)
Pretransplant antiviral treatment: yes/no	230 (45)/284 (55)
HCV genotype: 1b/other types	404 (79)/110 (21)
Co-existence of HCC: yes/no	330 (64)/184 (36)
MELD score	15 (4–47)
Transplant at the center with LDLT cases over 20 per year: yes/no	259 (50)/255 (50)
Calcineurin inhibitor: Tac/CsA	324 (63)/198 (37)
Mycophenolate mofetil yes/no	251 (49)/ 263 (51)
Steroid withdrawal: yes/no	144 (28)/370 (72)
Splenectomy: yes/no	284 (55)/230 (45)
Episode of acute rejection: yes/no	127 (25)/387 (75)
Steroid bolus injection: yes/no	414 (81)/100 (19)
Post-transplant antiviral treatment: yes/no	361 (71)/153 (29)
Achievement of SVR: yes/no	154 (30)/360 (70)
Donor age (years)	35 (17–66)
Type of graft: right/non-right	259 (50)/255 (50)

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

Results

Patient characteristics

The characteristics of 514 HCV-positive recipients are summarized in Table 1. There were 320 men and 194 women, with a median age of 57 years (range = 19–73). The median follow-up period was 3.5 years (range = 0.4–13), with a wide spectrum of follow-up duration due to death or shorter observation period from LDLT. The median MELD score was 14.7 (range = 4–47). HCV genotype was 1b in 405 patients (79%). The median age of the living donors was 35 years (range = 17–66), and the graft type was right liver in 259 cases (50%), left liver in 239 cases (46%), and the right lateral sector in 16 cases (4%).

Patient survival

The cumulative patient survival rate at 1, 3, 5, and 10 years was 86%, 76%, 72%, and 63%, respectively (Fig. 1). The causes of patient loss are summarized in Table 2. A total of 142 patients died until the end of the observation. Patient loss due to recurrent hepatitis, which was the leading cause of recipient death in this cohort, occurred in 42 cases, corresponding to 3% of all cases and 30% of lost cases, respectively. Hepatocellular carcinoma recurrence and sepsis were second, with 22 cases each. Additionally, the number of patient death was presented among two groups stratified by the achievement of SVR.

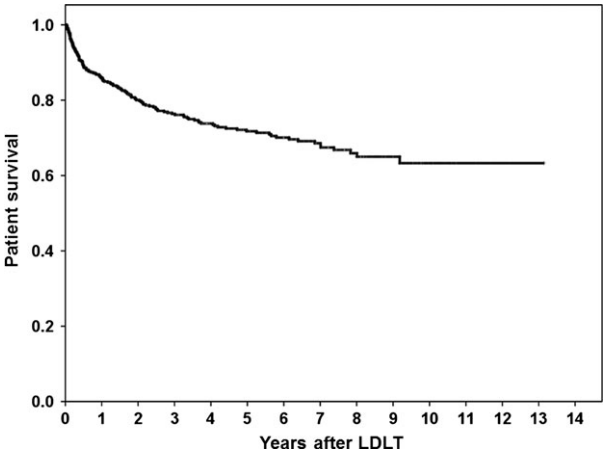

Figure 1 Kaplan–Meier survival curve of the cohort. LDLT, living donor liver transplantation.

Prognostic factors associated with patient survival after LDLT

Recipient and donor factors were analyzed for overall mortality. The results of univariate and multivariate analyses are shown in Table 3. Univariate analysis by the log-rank test revealed that donor age (>40 years; $P < 0.001$), non-right liver graft ($P = 0.036$), an episode of acute rejection ($P < 0.001$), steroid bolus injection ($P < 0.001$), and the absence of SVR ($P < 0.001$) were significant predictors of a poorer outcome of HCV-positive recipients. The Kaplan–Meier survival curves stratified by these factors are presented in Fig. 2. According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, an acute rejection episode, and the absence of SVR were independent prognostic factors (Table 3).

Additionally, we did the same analysis among those achieved SVR after antiviral treatment ($n = 154$), in which no factor was revealed to be associated with the patient survival (Table 4).

Antiviral treatment after LDLT

Of the 514 recipients, while 153 patients have never undergone antiviral treatment including five patients achieving preoperative SVR, 361 underwent antiviral treatment. Of those, 211 patients (58%) received antiviral treatment after confirmation of recurrent hepatitis C, while the remaining 150 recipients received antiviral treatment preemptively. The summary of the antiviral treatment is shown in Table 5. Time from LDLT to beginning treatment was

Table 2. Causes of patient death.

Patient group	All patients (n = 514) n (%)	With SVR (n = 154) n (%)	Without SVR (n = 360) n (%)
Recurrent HCV	42 (30)	0	42 (37)
Recurrent HCC	22 (15)	8 (30)	14 (12)
Infection	22 (15)	4 (15)	18 (16)
Cerebrovascular diseases	12 (8)	4 (15)	8 (7)
Rejection	8 (6)	0	8 (7)
Graft thrombosis	7 (5)	0	7 (6)
Small for size syndrome	6 (4)	0	6 (5)
Other causes	23 (17)	11 (40)	12 (10)
Total	142	27	115

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

rather short (median: 3 months), whereas the treatment duration was long (median: 17 months), the rate of dose reduction (40%) and discontinuation (42%) were high, and the SVR rate was 43%.

Discussion

This is the largest series of LDLT for HCV-positive recipients reported to date. A total of 514 recipients from 12 Japanese institutions were enrolled and reviewed, with 5- and 10-year cumulative patient survival rates of 72% and 63%, respectively. A recent article from the United Network for Organ Sharing (UNOS) database in the United States of America (USA) reported patient survival rates of 76% and 71% at 5 and 10 years, respectively, among 15 147 HCV-positive DDLT recipients [1]. Similarly, the European Liver Transplant Registry reported 5- and 10-year patient survival rates of 65% and 53%, respectively, among 10 753 HCV-positive DDLT recipients [2]. Based on these reports, the present outcomes of the Japanese nationwide survey of LDLT for HCV-positive recipients are comparable with those of deceased donor whole liver transplantation (DDLT) in both the USA and Europe. However, caution should be paid in comparing the survival results of HCV-positive recipients between LDLT and DDLT. As shown in previous reports [13,14], laboratory MELD score of HCV-positive recipients was higher in DDLT recipients than that in LDLT recipients. Actually, our result, mean MELD score of 15 (median: 14.7, range: 4–47) was lower than that reported in DDLT recipients in Western countries (around 20), which might have a positive impact on patient survival in our study. Another point which should be noted is that the observation period of database of USA and Europe was longer than that of Japan, which might result in the bias of the improvement in techniques and managements in liver transplant.

Table 3. Factors associated with patient survival after living donor liver transplantation for HCV-positive recipients.

Univariate analysis	Hazard ratio (95% confidence interval)	P-value
Recipient age: ≥60 years vs. <60 years	1.322 (0.915–1.876)	0.122
Recipient gender: male versus female	1.072 (0.765–1.432)	0.682
Body mass index: ≥25 vs. <25	0.999 (0.64–1.559)	0.995
Pretransplant antiviral treatment: yes versus no	0.921 (0.721–1.387)	0.912
HCV genotype: 1b versus other types	1.211 (0.781–1.901)	0.723
Co-existence of HCC: yes versus no	0.893 (0.612–1.223)	0.754
MELD score: ≥15 vs. <15	1.125 (0.878–1.389)	0.801
LDLT cases per year: ≥20 vs. <20	1.122 (0.669–1.881)	0.663
Calcineurin inhibitor: Tac versus CyA	0.887 (0.643–1.511)	0.789
Mycophenolate mofetil: yes versus no	0.963 (0.642–1.446)	0.857
Steroid withdrawal: yes versus no	1.003 (0.761–1.621)	0.932
Splenectomy: yes versus no	0.961 (0.623–1.367)	0.889
Episode of acute rejection: yes versus no	3.101 (2.013–5.871)	<0.001
Steroid bolus injection: yes versus no	2.512 (1.541–3.512)	0.003
Achievement of SVR: yes versus no	0.167 (0.121–0.254)	<0.001
Donor age: ≥40 years vs. <40 years	2.231 (1.401–3.331)	<0.001
Type of graft: right liver versus non-right liver	0.422 (0.311–0.711)	0.029
Multivariate analysis		
Episode of acute rejection: yes versus no	3.241 (1.789–5.329)	<0.001
Achievement of SVR: yes versus no	0.181 (0.124–0.301)	<0.001
Donor age: ≥40 years vs. <40 years	2.311 (1.498–3.311)	<0.001
Type of graft: right liver versus non-right liver	0.467 (0.331–0.621)	0.001

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

The present analysis of prognostic factors for impaired patient survival revealed four variables as independent predictors: donor age over 40 years, an acute rejection episode, absence of SVR, and a non-right liver graft. In contrast to the report from USA [13], the center experience did not affect the outcome of patient outcome.

The impact of donor age on outcome has gained increased attention in the DDLT setting due to the

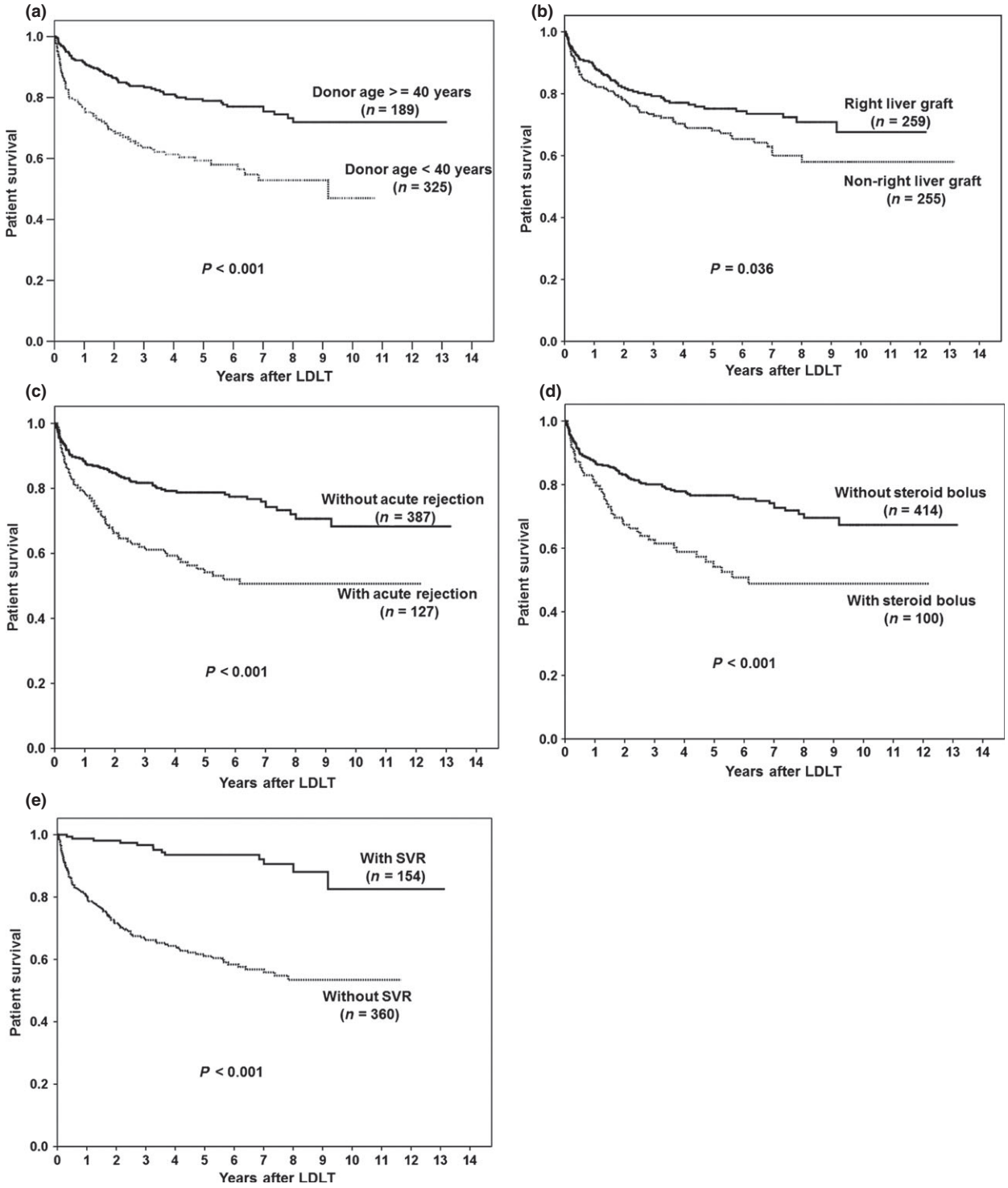

Figure 2 Kaplan–Meier curves stratified by each variable: (a) donor age, (b) graft type, (c) acute rejection, (d) steroid bolus, and (e) sustained virologic response. LDLT, living donor liver transplantation; SVR, sustained virologic response.

increased use of liver grafts from older donors. For HCV-positive recipients, two large retrospective reports from the Scientific Registry of Transplant Recipients and UNOS databases reported that donor age over 40 is an independent predictor of patient death [15,16]. Other accumulating reports [14,17,18] indicate that the grafts from older

Table 4. Factors associated with patient survival among those achieved SVR (n = 154).

Cox regression analysis	Hazard ratio (95% confidence interval)	*P*-value
Recipient age: ≥60 years (n = 43) vs. <60 years (n = 111)	1.424 (0.318–2.385)	0.644
Recipient gender: male (n = 100) versus female (n = 54)	4.709 (0.918–24.161)	0.063
Pretransplant antiviral treatment: yes (n = 66) versus no (n = 88)	1.666 (0.350–7.931)	0.522
HCV genotype: 1b (n = 112) versus other types (n = 42)	0.873 (0.203–3.747)	0.855
Co-existence of HCC: yes (n = 54) versus no (n = 100)	0.728 (0.179–2.694)	0.635
MELD score: ≥15 (n = 54) vs. <15 (n = 98)	1.354 (0.578–3.204)	0.785
LDLT cases per year: ≥20 (n = 82) vs. <20 (n = 72)	1.054 (0.458–1.254)	0.854
Calcineurin inhibitor: Tac (n = 94) versus CyA (n = 60)	3.580 (0.736–17.421)	0.114
Mycophenolate mofetil: yes (n = 78) versus no (n = 76)	0.932 (0.456–1.884)	0.781
Steroid withdrawal: yes (n = 40) versus no (n = 114)	0.449 (0.096–2.102)	0.31
Splenectomy: yes (n = 59) versus no (n = 95)	1.402 (0.335–5.873)	0.644
Episode of acute rejection: yes (n = 34) versus no (n = 120)	1.854 (0.216–15.914)	0.574
Steroid bolus injection: yes (n = 26) versus no (n = 128)	0.16 (0.019–1.386)	0.096
Donor age: ≥40 years (n = 43) vs. <40 years (n = 111)	1.18 (0.296–4.698)	0.815
Type of graft: right liver (n = 80) versus non-right liver (n = 74)	2.799 (0.818–9.573)	0.101

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

donors are at greater risk for disease progression and impaired graft/patient survival compared with those from younger donors. Our results are definitely consistent with these reports.

Acute rejection in conjunction with treatment with a steroid bolus is one of the most critical factors to address with respect to HCV recurrence. Historical studies [19,20] have demonstrated that steroid bolus for acute rejection in HCV-positive recipients accelerates the recurrence of hepatitis and decreases patient survival. A recent study reported that HCV-positive recipients who receive high-dose steroid treatment for acute rejection are at increased risk of severe recurrent hepatitis, in which older donor age and an episode of rejection are the two most important predictors of developing fibrosing cholestatic hepatitis [21]. Similarly, our study also revealed that both older donor age and acute rejection are independent predictors for impaired patient outcome among LDLT recipients.

Table 5. Summary of antiviral treatment.

	Total (n = 361)	Treatment for established recurrent hepatitis C (n = 211)	Preemptive treatment (n = 150)
Time since LDLT (months)	3 (0–102)	4 (0.5–102)	1 (0–68)
Treatment duration (months)	15 (0.3–99)	14 (0.3–99)	17 (0.3–55)
Regimen: PEG-INF alfa-2a/RBV	45 (12%)	33 (16%)	12 (8%)
PEG-INF alfa-2b/ RBV	223 (62%)	146 (69%)	77 (51%)
INF alfa-2b	93 (26%)	32 (15%)	61 (41%)
Dose reduction	143 (40%)	85 (40%)	58 (39%)
Discontinuation	150 (42%)	66 (31%)	84 (56%)
Sustained virologic response	154 (43%)	89 (42%)	65 (43%)

LDLT, living donor liver transplantation; PEG-INF, pegylated-interferon; RBV, ribavirin; INF, interferon.

The association between achieving SVR and graft/patient survival after liver transplantation for HCV-positive recipients is a matter of debate [10]. Many studies with standard dual treatment of PEG-INF/RBV for 12 months in a DDLT setting have implied a survival benefit of achieving SVR [8,22], but there has been no evidence to support the recommendation of antiviral treatment for recurrent graft hepatitis C due to the lack of clinical benefit with sufficient long-term observation and the existence of frequent severe adverse effects, as concluded by a recent Cochrane meta-analysis [10]. Recent retrospective cohort studies with a long follow-up duration reported improved patient/graft survival in patients who obtained an SVR after antiviral treatment [23–25]. In accordance with those reports, our retrospective analysis indicated a positive effect of achieving SVR on patient survival. Caution should be taken in interpreting our results; however, as SVR was assessed among the whole cohort, including patients who were not indicated for antiviral treatment, the follow-up period after achieving SVR was rather short, and most importantly, a large variety of antiviral treatment regimens were used in Japan, which will be described later.

A noteworthy finding in the present retrospective analysis is the impaired patient survival in recipients who received a non-right liver graft (left liver in 239 cases and right lateral sector in 16 cases). Recent studies comparing outcomes between LDLT and DDLT in HCV-positive recipients have reported equal or even improved outcomes both in patient/graft survival and in fibrosis progression in the LDLT setting, which could be attributed to the younger donor age and shorter ischemic time of LDLT grafts [13,14,26–29].

Based on these findings, LDLT for HCV-positive recipients is now widely accepted as an established alternative to DDLT, even in Western countries. On the contrary, however, the present finding may raise an alarm for reduced size grafts, as a left or posterior graft is clearly smaller than a right liver graft. Another point to be emphasized here is that all LDLTs investigated in the aforementioned studies comparing LDLT and DDLT were universally performed with right liver grafts. One possible explanation for the inferior outcome of the smaller graft is that the intense hepatocyte proliferation that occurs in smaller partial liver grafts may lead to increased viral translation and replication, as advocated by previous authors [30–32]. However, there are several limitations among these speculations. First, the data of the viral load, which is reported to reach a maximum level between the first and third post-transplant months [33], were not available in this study to demonstrate the higher viral replication in the smaller grafts during this period. Another is that the graft type selection is based on the ratio of the volume of the graft to recipient body weight or standard liver volume in our society, which will lead to the bias in the comparison of the right liver versus non-right liver graft. Despite these limitations, considering that comparable outcomes between left liver graft and right liver graft have been reported by us [34] and others [35] in LDLT recipients as a whole, caution should be taken in selecting the type of graft (left versus right) for HCV-positive recipients. Thus, future LDLT studies are required to investigate whether a smaller partial liver graft (left liver) is potentially inferior compared with a larger graft (right liver) in terms of graft/patient survival and recurrent hepatitis severity among HCV-positive recipients.

The antiviral treatment for recurrent hepatitis C after LDLT in Japan was also reviewed in the present study. As described elsewhere in detail [11], the antiviral treatment regimen in Japan differs widely from center to center; preemptive treatment versus treatment after confirmation of recurrent disease, starting dose and method of escalation, and the duration of treatment (usually longer than 12 months). Consequently, our data only present an overview of antiviral treatment in Japan, and no definite conclusion can be drawn regarding the actual efficacy of antiviral treatment after LDLT. Moreover, based on the recent prospective, multicenter, randomized study by Bzowej *et al.* [36], European and USA transplant societies do not support the routine use of preemptive antiviral therapy. A review of Western literature regarding the standard 12-month PEG-INF/RBV treatment for established recurrent hepatitis C after DDLT reveals that the median SVR rate is 33% (0–56%) with a dose reduction rate of 70% and a discontinuation rate of 30% [37]. The present result of an SVR rate of 43% with a dose reduction rate of 40% and a discontinuation rate of 42% seems not so different from those of previous literatures; however, as discussed above, the diversity in the methods, the doses, and the duration of treatment in Japan preclude the direct comparison with Western findings.

Conclusion

This retrospective analysis of the largest series of LDLT for HCV-positive recipients in Japan revealed 5- and 10-year survival rates of 72% and 63%, respectively, and that donor age (>40), non-right liver graft, an acute rejection episode, and the absence of SVR are independent predictors of patient survival. Based on the present result, caution should be made in the selection of the left liver graft for HCV-positive recipients; however, the development of more effective antiviral treatment in the near future may facilitate the application of the left liver graft.

Authorship

YM: designed the study. TI: collected data. NA, YS, NK, SE, TF, HO, HN, AT, YK, MS, YK, KY, KS, MM and MT: performed the study. NA and YS: analyzed and wrote the paper.

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