who underwent steroid pulse treatment for BPAR, with infectious complications being the most common causes of mortality (8).

Therapy for recurrent HCV continues to be a formidable challenge in LDLT (24-26). In our study, the viral load 3 months after transplant was significantly lower in the St− group, raising hope for better response to antiviral therapy early after transplantation. However, the therapy had to be discontinued in 5/11 (45%) recipients whose medications were initiated within 12 months from transplantation and overall sustained virological response rates were marginal. Novel strategies for treating HCV in liver transplantation are on the horizon and are expected to improve outcomes (27-29).

A subtle renal protective effect of the St+ protocol disappeared when the ABO incompatible cases were excluded from the analysis. Intraportal infusion of steroids and prostaglandin E1 administered for ABO incompatible cases during the first 2 weeks after transplantation (13) could have played a role; however, the sample size was very small to draw a definite conclusion. Prostaglandin E1 is a potent vasodilator and may potentially protect the kidney; however, the positive effect of steroids on kidney function has been shown in only animal studies at the time of writing (30,31).

The limitations of our study include its non-randomized study design, small number of patients, and absences of protocol liver biopsies.

In conclusion, our steroid minimization protocol using basiliximab as a replacement agent is safe and provides equivalent acute rejection rates. However, when compared to standard immunosuppression, no statistically significant differences were observed in progression to recurrent HCV, patient survival, or other adverse events. Steroid pulse therapy is associated with grave prognosis and should be used only as a last resort.

ACKNOWLEDGEMENTS

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Table 1. Patient demographics.

	St− ($N = 14$)	St+ ($N = 13$)	P
Recipient age, yr	54 (50–61)	55 (49–59)	0.69
Male: female	10:4	8:5	0.70
MELD	16 (11–18)	14 (12–17)	0.79
Genotype 1B	14 (100%)	7 (78%)	0.14
HCV-RNA, $\log_{10}$ IU/ml	5.3 (4.5–6.0)	5.7 (5.3–6.1)	0.31
Diabetes mellitus	3 (21%)	5 (37%)	0.42
Total cholesterol, mg/dl	108 (78–153)	123 (108–138)	0.49
Triglyceride, mg/dl	66 (48–78)	64 (49–117)	0.83
Hypertension	4 (29%)	2 (15%)	0.65
eGFR, ml/min/1.73 m^2	87 (50–115)	104 (54–130)	0.36
Donor age, yr	43 (33–51)	38 (30–53)	0.94
Donor male: female	8:6	6:7	0.57
ABO incompatible	0 (0%)	5 (39%)	0.02
GRWR	0.86 (0.67–1.02)	0.84 (0.80–1.10)	0.91
Warm ischemia time, min	82 (48–114)	77 (47–141)	0.46
Cold ischemia time, min	57 (54–63)	54 (45–64)	0.61
Splenectomy	6 (43%)	7 (54%)	0.57
Hepatocellular carcinoma	10 (71%)	6 (46%)	0.25
CyA: Tac	10:4	6:7	0.25

MELD, Model for End-stage Liver Disease; HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate; GRWR, graft/recipient weight ratio; CyA, cyclosporine A; Tac, tacrolimus.

Table 2. Immunosuppression agents.

	St− ($N = 14$)	St+ ($N = 13$)	P
CyA trough level, ng/ml			
Month 1	181 (103–240)	244 (200–285)	0.10
Month 3	135 (95–207)	180 (135–229)	0.37
Month 6	130 (100–185)	150 (79–215)	0.90
Month 12	120 (100–145)	200 (86–215)	0.44
Month 24	100 (90–117)	100 (85–109)	0.86
Tac trough level, ng/ml			
Month 1	8.0 (7.0–9.0)	7.0 (7.0–8.5)	0.67
Month 3	5.5 (4.8–6.8)	6.0 (5.7–7.0)	0.41
Month 6	7.0 (4.5–9.5)	5.0 (5.0–7.1)	0.53
Month 12	4.0 (3.6–6.5)	5.0 (4.0–5.0)	0.79
Month 24	6.1 (6.0–6.2)	4.1 (3.1–5.0)	0.33
Steroid dose, mg/day			
Month 0–3	0	10 (9–18)	<0.001
Month 3–6	0†	5 (3–9)	<0.001
Month 6–12	0‡	1 (0–2)	0.04
Month 12–24	0	0	1.00

CyA, cyclosporine A; Tac, tacrolimus.

†,‡One patient in the St− group required steroid pulse therapy for acute cellular rejection (average dose, 8 mg/day between 3–6 months and 2 mg/day between 6–10 months).

Table 3. Postoperative outcomes.

	St− ($N = 14$)	St+ ($N = 13$)	P	St+ without ABO-I ($N = 8$)	P†
BPAR	2 (14%)	3 (23%)	0.65	2 (25%)	0.60
Steroid pulse	1 (7%)	2 (15%)	0.60	1 (13%)	1.00
Recurrent hepatitis C	9 (64%)	7 (54%)	0.58	5 (63%)	0.38
SVR	3/9 (33%)	2/7 (29%)	1.00	1/3 (33%)	1.00
Fibrosis stage ≥2	3 (21%)	2 (15%)	1.00	2 (25%)	1.00
NODM	0/11 (0%)	2/8 (25%)	0.16	2/5 (40%)	0.08
Total cholesterol, mg/dl					
Month 3	193 (120–216)	157 (148–169)	0.570	154 (129–165)	0.52
Month 6	195 (139–208)	160 (124–178)	0.11	153 (116–176)	0.045
Month 12	192 (138–258)	141 (116–189)	0.13	145 (91–171)	0.17
Month 24	207 (127–267)	162 (119–182)	0.22	135 (102–154)	0.22
Triglyceride, mg/dl					
Month 3	111 (84–138)	119 (84–218)	0.53	120 (119–186)	0.18
Month 6	158 (99–199)	136 (93–168)	0.59	145 (83–186)	0.66
Month 12	106 (73–158)	78 (73–103)	0.60	NA	–
Month 24	110 (73–140)	91 (61–137)	0.79	108 (70–145)	1.00
eGFR, ml/min/1.73 m^2					
Month 3	49 (34–68)	52 (45–87)	0.40	45 (35–63)	0.92
Month 6	57 (39–65)	70 (45–91)	0.12	59 (33–75)	0.94
Month 12	52 (44–61)	71 (59–81)	0.03	59 (31–78)	0.44
Month 24	43 (32–58)	80 (57–88)	0.08	57 (33–75)	0.73

Infection	4 (29%)	6 (46%)	0.44	3 (38%)	1.00

ABO-I, ABO incompatible; BPAR, biopsy-proven acute rejection; SVR, sustained virological response; NODM, new-onset diabetes mellitus; NA, not available; eGFR, estimated glomerular filtration rate.

†Comparison between the St– group and the St+ group without ABO incompatible cases.

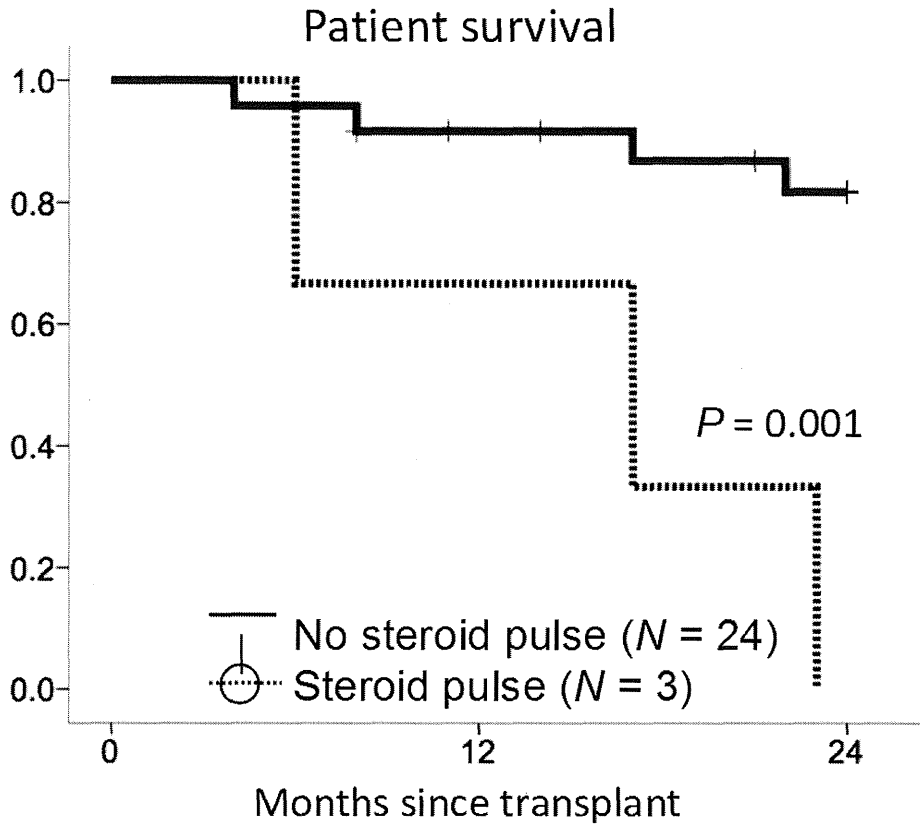

Figure 1. Two-year overall patient survival of patients who received steroid pulse therapy ($N = 3$: dotted line) and of those who did not ($N = 24$: solid line).

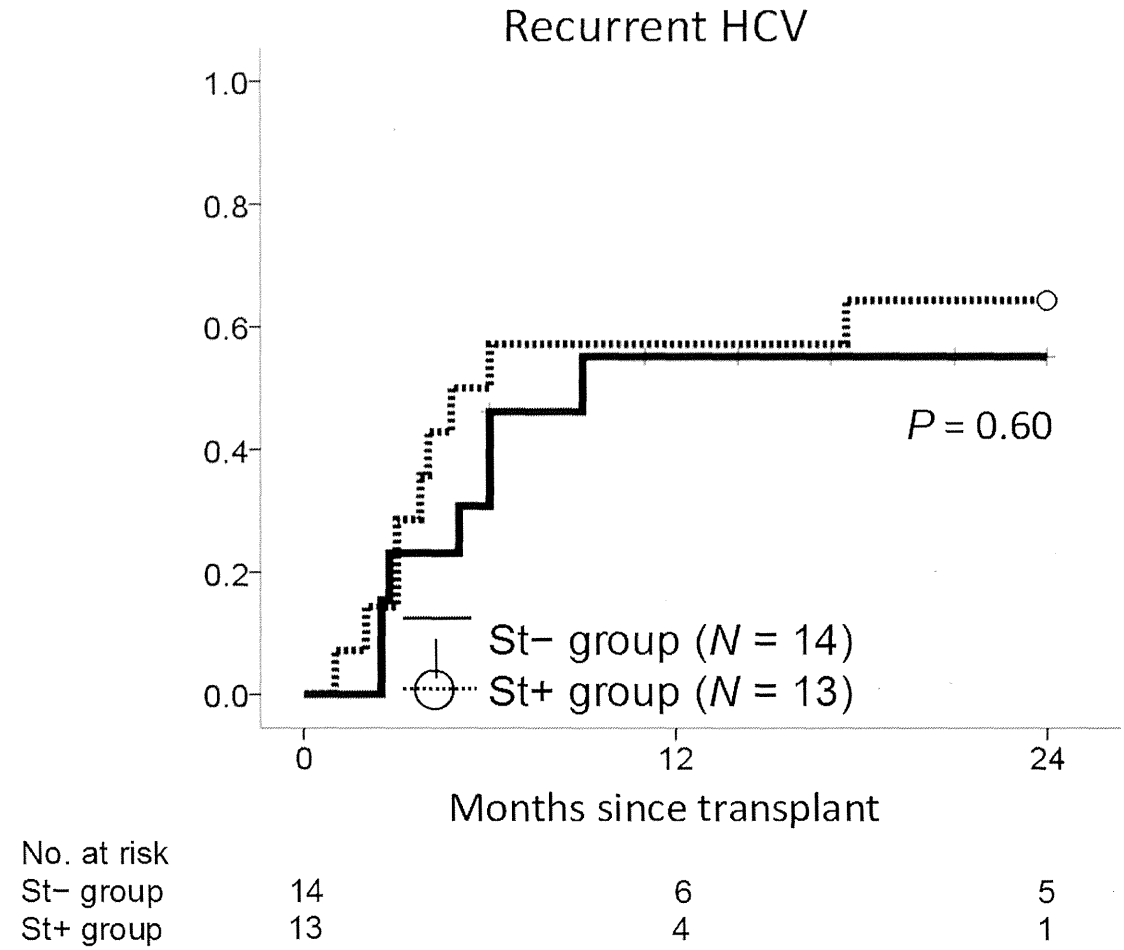

Figure 2. Two-year HCV recurrence rate in the St− (N = 14: solid line) and St+ (N = 13: dotted line) groups.

HCV, hepatitis C virus; St−, steroid minimization protocol; St+, standard immunosuppression protocol.

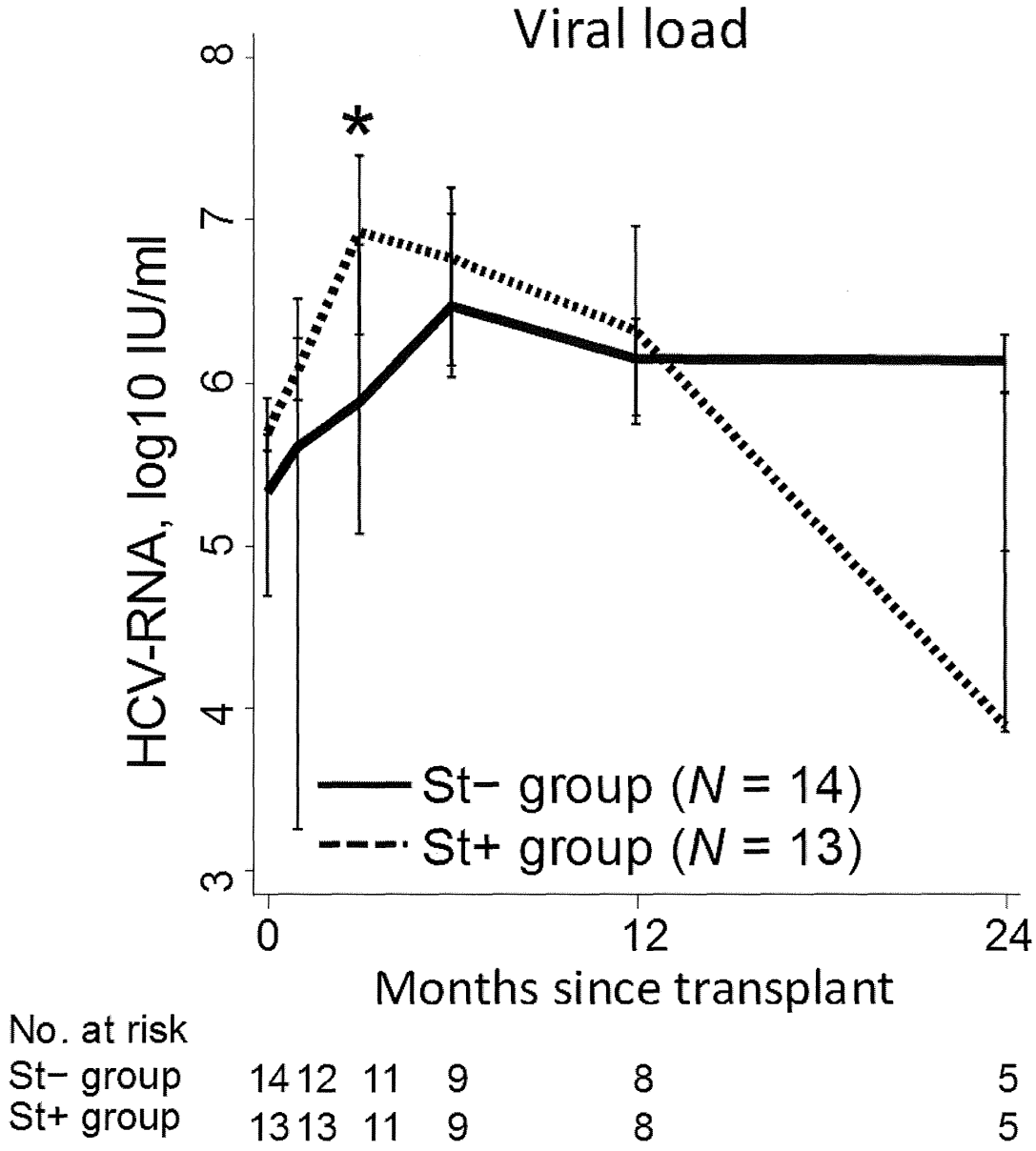

Figure 3. Hepatitis C virus (HCV)-RNA levels pre-transplant and at 1, 3, 6, 12, and 24 months after transplantation in the St− ($N = 14$: solid line) and St+ ($N = 13$: dotted line) groups. The patients who received anti-HCV therapy within 2 years post-transplant were removed from the analysis at each time point of the initiation of therapy.

St−, steroid minimization protocol; St+, standard immunosuppression protocol. *, $P = 0.04$.

ELSEVIER

Clinical Efficacy of Simultaneous Splenectomy in Liver Transplant Recipients With Hepatitis C Virus

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ABSTRACT

Background. Interferon (IFN) therapy is a well-established antiviral treatment for hepatitis C virus (HCV) – infected patients. However, susceptibility to thrombocytopenia is a major obstacle in its initiation or continuation, particularly in patients with HCV who underwent liver transplantation (LT). We previously showed that the coexistence of splenomegaly and thrombocytopenia could result in persistent thrombocytopenia after LT. Here we retrospectively evaluated the validity of this criterion for simultaneous splenectomy in recipients with HCV.

Patients and Methods. Subjects included 36 recipients with HCV who received LT between January 2006 and February 2012 at Hiroshima University. We analyzed the spleen volume, body surface area, platelet (PLT) count, and rate of completion or continuation with IFN therapy in these recipients.

Result. Of these recipients, 30 did not require simultaneous splenectomy according to the criterion, and 24 actually did not receive simultaneous splenectomy. In this group, 21 (87.5%) started IFN therapy. Fifteen (71.4%) of these recipients completed or continued IFN therapy, whereas 13 (61.9%) achieved either a sustained virological response (SVR) or an end-of-treatment response. The PLT count increased to $>100{,}000/mm^3$ 1 month after LT in 16 (66.7%) recipients from this group.

Conclusion. Our criterion detected the PLT count outcome after LT in recipients with HCV and achieved a better SVR result after IFN therapy.

LIVER disease caused by chronic hepatitis C virus (HCV) infection is the most common indication for liver transplantation (LT) [1]. However, almost all recipients with HCV infection experience graft reinfection after LT [2]. HCV recurrence is the most frequent cause of death and graft loss in these recipients [3]. The combination therapy of interferon (IFN) and ribavirin (RBV) is well established as a standard antiviral treatment for HCV recurrence after LT [4]. However, susceptibility to both thrombocytopenia and anemia is a major obstacle in the initiation or continuation of this therapy [5]. Postoperative thrombocytopenia is a common feature in liver transplant recipients with splenomegaly. Therefore, splenectomy is usually performed to improve thrombocytopenia after LT [6–8].

We previously showed that the coexistence of splenomegaly and thrombocytopenia (spleen volume [SV]/body surface area [BSA] ≥ 400 mL/m^2, platelet [PLT] count $\leq 5 \times 10^4/mm^3$) could result in persistent thrombocytopenia after LT [9], and we consider this condition the criterion for

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simultaneous splenectomy in recipients who require subsequent IFN therapy. In this study, we retrospectively evaluate the validity of this criterion for simultaneous splenectomy in recipients with HCV in our institution.

PATIENTS AND METHODS

Between January 2006 and February 2012, 53 LTs in 52 patients with HCV were performed at Hiroshima University. Of these, 16 recipients were excluded from the study because of sustained virological response (SVR) at the time of LT (n = 6), splenectomy that had already been performed at the time of LT (n = 4), re-transplantation (n = 1), or insufficient clinical examinations (n = 5). The remaining 36 recipients with HCV who received LT due to liver cirrhosis were enrolled in this study.

We analyzed the SV, BSA, PLT count, and rate of completion or continuation with IFN therapy in these recipients. The SV was measured from computed tomographic images obtained with a workstation (Virtual Place Advance 300; AZE, Tokyo, Japan). The BSA was calculated with the mathematical equation previously reported by Whitington et al [10]. The PLT counts and rate of completion or continuation with IFN therapy were obtained from the recipients' medical charts.

RESULTS

As shown in Fig 1, 30 (83.3%) of 36 recipients belonged to the group that did not require simultaneous splenectomy according to the criterion. However, 6 recipients in this group received simultaneous splenectomy due to portal hypertension (≥20 mm Hg) after reflow (n = 4), ABO blood type incompatibility (n = 1), or idiopathic thrombocytopenic purpura (n = 1). The remaining 24 recipients did not receive simultaneous splenectomy according to the criterion. Fifteen (71.4%) of these recipients could complete (n = 13) or continue (n = 2) IFN therapy, but two recipients required metachronous splenectomy for continuing IFN therapy due to thrombocytopenia. However, the other 9 (37.5%) recipients could not start or continue IFN therapy for the following reasons except for cytopenia, such as liver failure, purulent spondylitis, spontaneous remission, rejection, interstitial pneumonia, depression, myelodysplastic syndrome, cerebral infarction, and myopathy. Of the recipients who could start or continue IFN therapy, 13 (61.9%) achieved SVR or end-of-treatment response, and two recipients could complete IFN therapy and achieve SVR after metachronous splenectomy. However, 6 (16.7%) of 36 recipients who were enrolled in this study also belonged to the group that required simultaneous splenectomy according to the criterion. Four recipients in this group actually received splenectomy and completed IFN therapy. Regardless of using the criterion, the remaining 2 recipients did not receive splenectomy to maintain immunity due to a pre-LT infection.

The kinetics of PLT count in each group with or without simultaneous splenectomy according to the criterion are shown in Fig 2. The PLT count of both groups immediately increased 1 month after LT; however, alternation of the PLT count became stable after that time. The PLT count of the recipients who required simultaneous splenectomy according to the criterion remarkably increased after splenectomy. The PLT count of the recipients who did not require simultaneous splenectomy also increased to the

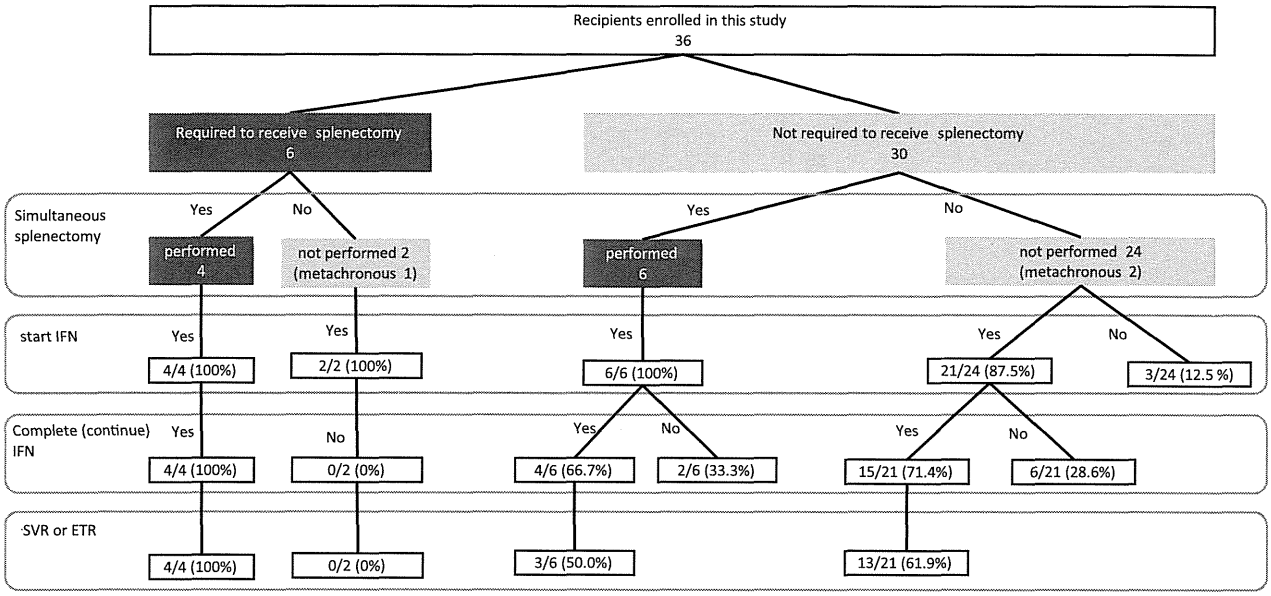

Fig 1. Algorithm according to the criterion for simultaneous splenectomy. Of the 36 recipients enrolled in this study, 6 belonged to the group that required simultaneous splenectomy. Among them, 4 recipients received simultaneous splenectomy and the other 2 did not. The remaining 30 recipients belonged to the group that did not require simultaneous splenectomy. Of them, 24 recipients did not receive simultaneous splenectomy, while the other 6 did. The number of recipients who could start, complete, or continue interferon therapy and achieved sustained virological response or end-of-therapy response in each group is listed.

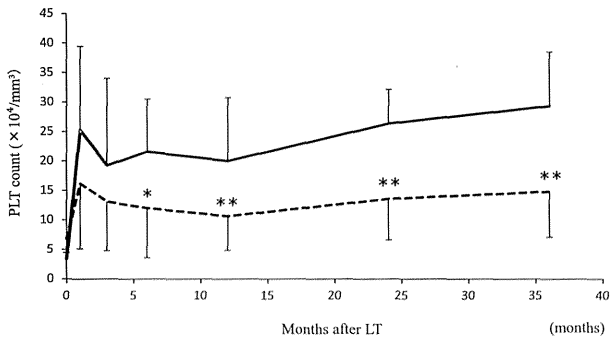

Fig 2. The kinetics of platelet count in each group with or without simultaneous splenectomy according to the criterion. The solid line indicates the kinetics of mean platelet count of the recipients who required receiving simultaneous splenectomy (n = 6). The dotted line indicates the kinetics of mean platelet count of the recipients who did not require receiving simultaneous splenectomy (n = 30) (mean ± standard deviation, $^{*}P < .05$, $^{**}P < .01$).

enough level for initiating IFN therapy at the early time of after LT, and subsequently maintained enough level for continuing IFN therapy. Furthermore, the kinetics of the PLT count after LT, in the individual recipient who did not require simultaneous splenectomy, is shown in Fig 3. In 16 (66.7%) recipients from this group, the PLT count increased to >100,000/mm^3 1 month after LT. The average PLT counts pre-LT and 1 month after LT were 7.0 ± 2.2/mm^3 and 11.7 ± 5.2/mm^3, respectively. Twenty-one (87.5%) recipients could start IFN therapy and the other 3 recipients could not because of liver failure, purulent spondylitis, or spontaneous remission.

DISCUSSION

In LT recipients, splenectomy is mainly performed for the purpose of improving thrombocytopenia due to hypersplenism, controlling portal vein pressure in small-for-size syndrome, and/or immunotherapy for ABO incompatibility [11–16]. Splenectomy itself potentially has disadvantages associated with multiple complications, such as portal vein thrombosis, pancreatic leaks, and infection [15,17–20]. Among them, the most serious complication is considered to be infections such as overwhelming post-splenectomy infection (OPSI), especially in immunosuppressed recipients after LT [17]. Immunizing recipients before splenectomy to decrease the risk of OPSI is recommended [21], although the response rate of vaccinations is reportedly only 40% to 80% in LT recipients [22,23]. Therefore, we established the criterion for simultaneous splenectomy to avoid unnecessary splenectomy in the LT recipients with HCV infection and evaluated the validity of this criterion in this study.

In the present study, the PLT counts of the recipients who received splenectomy according to the criterion increased immediately, and all of them completed the IFN therapy. However, one of them suffered from a bloodstream infection caused by diplococcus pneumonia that was considered an OPSI. On the other hand, the recipients who did not require simultaneous splenectomy according to the criterion also reached the appropriate level of PLT count and achieved reasonable outcomes. However, 8.3% of these patients required subsequent metachronous splenectomy to continue IFN therapy.

To improve the accuracy of our criterion, we investigated the functional variant in the inosine triphosphatase (*ITPA*) gene of the recipients. The functional single-nucleotide

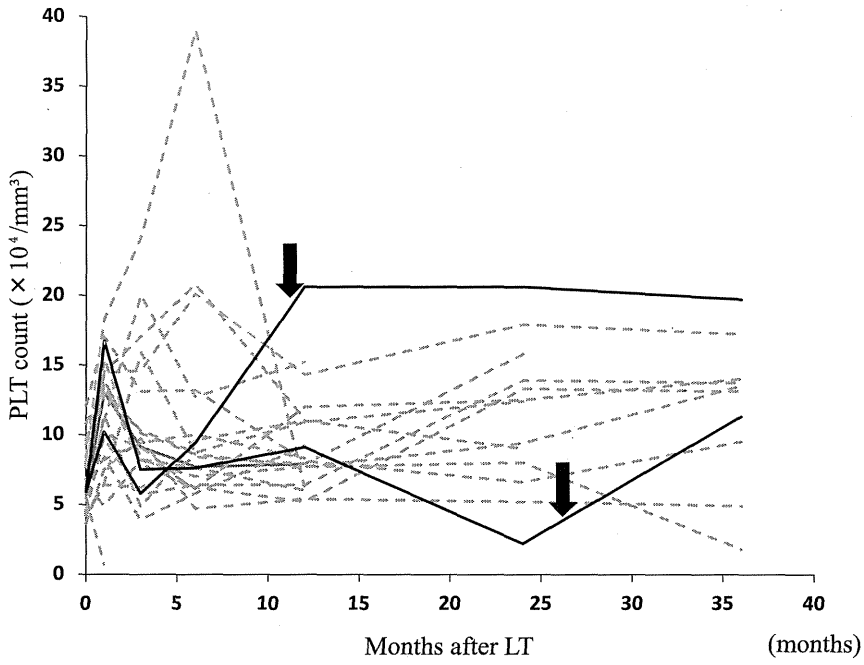

Fig 3. The kinetics of platelet count in the recipients who did not require simultaneous splenectomy according to the criterion. The black solid and gray dotted lines indicate the kinetics of platelet (PLT) count after liver transplantation in the recipients who did not require receiving simultaneous splenectomy. The black solid lines indicate the PLT count in the recipients who required metachronous splenectomy for continuing interferon therapy. The black arrows indicate the timing of metachronous splenectomy.

polymorphism (SNP) of the *ITPA* gene is associated with RBV-induced anemia and IFN-induced thrombocytopenia in Japanese genetic populations [24]. Severe anemia induced by RBV, which is mainly found in patients with *ITPA-CC* (major variant), was inversely correlated with thrombocytopenia. The functional variant in the *ITPA* gene was identified in the 13 recipients who belonged to the group that did not require simultaneous splenectomy. Twelve of the 13 recipients had *ITPA-CC* variants that are protective against IFN-induced thrombocytopenia, although 2 recipients who required metachronous splenectomy for continuing IFN therapy had the CC variants. However, the small number of recipients investigated here did not allow us to analyze whether this SNP could predict the outcome.

In conclusion, our criterion detected the outcome of PLT count after LT in recipients with HCV and achieved better result of SVR after IFN therapy. However, further factors may need to be identified to improve the prediction of thrombocytopenia in HCV recipients after LT.

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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.

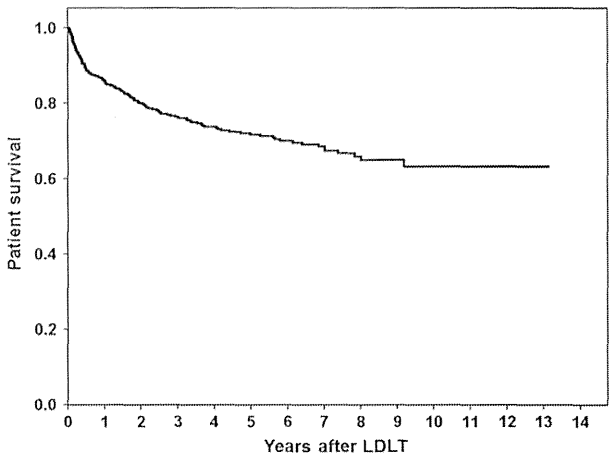

Figure 1 Kaplan–Meier survival curve of the cohort. LDLT, living donor liver transplantation.

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