**Table 1. Clinical Features of Recipients, Donors, and Grafts**

| | Group A ($n$ = 17) | Group B ($n$ = 17) | Group C ($n$ = 5) | $P$ (Group A + B vs C) | $P$ (Group A vs B) |
|---|---|---|---|---|---|
| Recipient age (y) | 51.2 ± 9.9 | 52.3 ± 11.1 | 40.3 ± 13.6 | .087 | .843 |
| Donor age (y) | 30.5 ± 9.5 | 39.9 ± 13.2 | 45.3 ± 10.7 | .068 | .009 |
| Preoperative | | | | | |
| Total bilirubin | 10.2 ± 12.1 | 9.6 ± 7.8 | 23.7 ± 16.1 | .026 | .273 |
| PT-INR | 1.80 ± 0.81 | 1.77 ± 0.67 | 3.16 ± 0.67 | .005 | .254 |
| Serum creatinine | 0.76 ± 0.33 | 1.39 ± 2.21 | 1.13 ± 0.71 | .644 | .594 |
| Serum albumin | 2.95 ± 0.67 | 2.90 ± 0.36 | 3.15 ± 0.74 | .957 | .874 |
| MELD score | 19.2 ± 7.6 | 20.8 ± 8.7 | 35.8 ± 5.6 | .004 | .117 |
| Type of graft | R: 12 L: 5 P: 0 | R: 11 L: 4 P: 2 | R: 3 L: 2 P: 0 | .735 | .787 |
| GLW (g) | 625 ± 118 | 583 ± 150 | 696 ± 211 | .600 | .573 |
| SLV (mL) | 1237 ± 135 | 1229 ± 73 | 1227 ± 40 | .334 | .522 |
| GLW/SLV (%) | 52.0 ± 9.5 | 48.0 ± 10.7 | 56.1 ± 17.4 | .585 | .503 |
| Operative time (min) | 776 ± 135 | 883 ± 232 | 1018 ± 260 | .227 | .106 |
| Blood loss | 6568 ± 5718 | 7525 ± 9117 | 14933 ± 1743 | .247 | .913 |
| CIT (min) | 65.6 ± 25.0 | 71.6 ± 32.9 | 72.5 ± 50.3 | .737 | .715 |
| WIT (min) | 42.2 ± 13.3 | 42.9 ± 12.1 | 51.3 ± 24.9 | .674 | .573 |
| Acute cellular rejection | 4 (23.5%) | 5 (31.2%) | 2 (40.0%) | .675 | .707 |

*Abbreviations:* CPT, Child–Turcotte–Pugh; MELD, model of end-stage liver disease; R, right lobe; L, left lobe; P, right posterior sector; GLV, graft liver volume; SLV, standard liver volume; CIT, cold ischemia time; WIT, warm ischemia time.

which the total bilirubin level did not decrease to less than 2.0 mg/dL, resulting in progressive deterioration leading to graft loss or death. The 39 cases were assigned to the three categories as follows: A, 17 cases; B, 17 cases; C, 5 cases. In four cases in group C, the grafts showed primary nonfunction.

The MELD score was calculated using the UNOS formula[7–9] based on data obtained within 3 days before LDLT. We compared recipient, donor and operative factors between the functioning graft groups (group A and group B combined) versus the failed graft group (group C), and between rapid functioning grafts (group A) versus those with prolonged hyperbilirubinemia (group B).

The statistical analysis utilized the Mann-Whitney $U$ test for nonparametric data, and Pearson correlation for correlations. A $P$-value of less than .05 was considered significant.

## RESULTS

The postoperative courses of the 39 cases were uneventful; there were no vascular or bile duct complications occurring in either the grafts that recovered or those that failed during the first month, except one group B case who developed a mild hepatic artery stenosis, which required intra-arterial balloon dilatation. Acute cellular rejection was diagnosed by liver biopsy during the recovery course in four group A cases (23.5%), five group B cases (31.2%) and two group C cases (40.0%), incidences which were not significantly different (Table 1).

The post-LDLT prothrombin time recovered earlier than the normalization of serum bilirubin (to a level of < 2.0 mg/dL) among group A and group B patients (PT, 14.5 ± 21.3 days versus bilirubin 34.6 ± 24.8 days). A significant correlation was observed between the postoperative periods characterized by an abnormal prothrombin time and a serum bilirubin level greater than 2.0 mg/dL after LDLT ($P$ < .001, Pearson correlation coefficient = 0.724). Therefore, a normal serum bilirubin level appears to represent normal graft function.

In all 39 cases histologic examinations were performed at the LDLT. All grafts were normal or had 5% or less fatty deposition, except two with 10% fatty deposition in group B, and one with 30% fatty deposition in group A.

### Comparison Between the Functioning Graft and Failed Grafts

Donor age, graft type, GLW, SLV, GLW/SLV ratio, preoperative albumin level, operative time, and cold and warm ischemia times were similar between the groups (Table 1). The preoperative MELD score was significantly higher among group C recipients than those in group A plus group B combined ($P$ = .004). The preoperative total bilirubin and PT-INR were significantly higher among group C than group A plus group B combined (0.026 and 0.005, respectively), whereas the serum creatinine levels were not

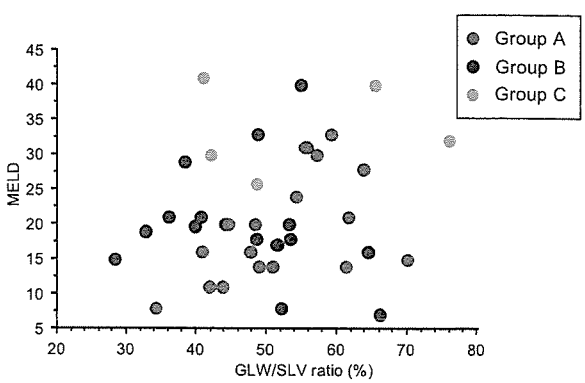


**Fig 1.** Correlation between MELD score and GLW/SLV ratio. This scatter gram of MELD score and GLW/SLV ratio shows that GLW/SLV ratio seemed independent of graft function, while cases with high MELD score tended to lose grafts.

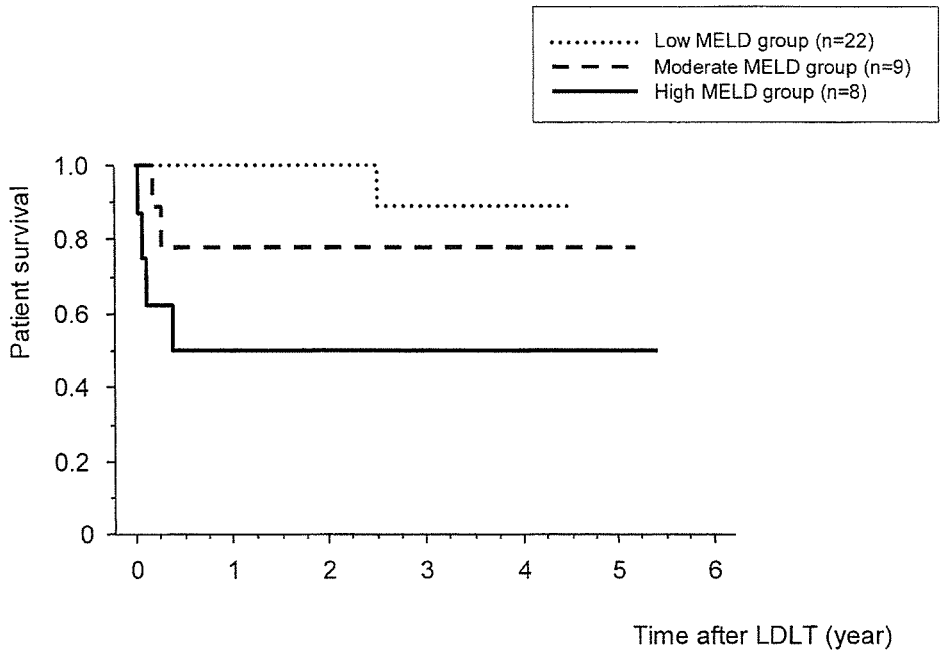


**Fig 2.** Patient survival stratified by MELD score. Patients were stratified by MELD score: low MELD score, ≤20, $n$ = 22; moderate MELD score, 21–30, $n$ = 9; high MELD score, ≥31, $n$ = 8. Prognosis was best in low MELD score group, and worst in high MELD score group. ($P$ = .006, Log-rank test.)

different ($P$ = .644). Recipient age was younger among group C and blood loss during the transplantation greater in group C than in group A plus group B combined, but they did not reach statistical significance.

To better understand the impact of the MELD score versus the GLW/SLV ratio on graft function after LDLT, we created a scatter gram of MELD score versus GLW/SLV ratio (Fig 1). The GLW/SLV ratio seemed to be independent of graft function, whereas cases with high MELD scores tended to lose their grafts.

### Comparison Between the Rapidly Functioning Grafts and the Prolonged Hyperbilirubinemia Grafts

All recipient, donor, and graft factors were similar between the groups except donor age was younger among group A

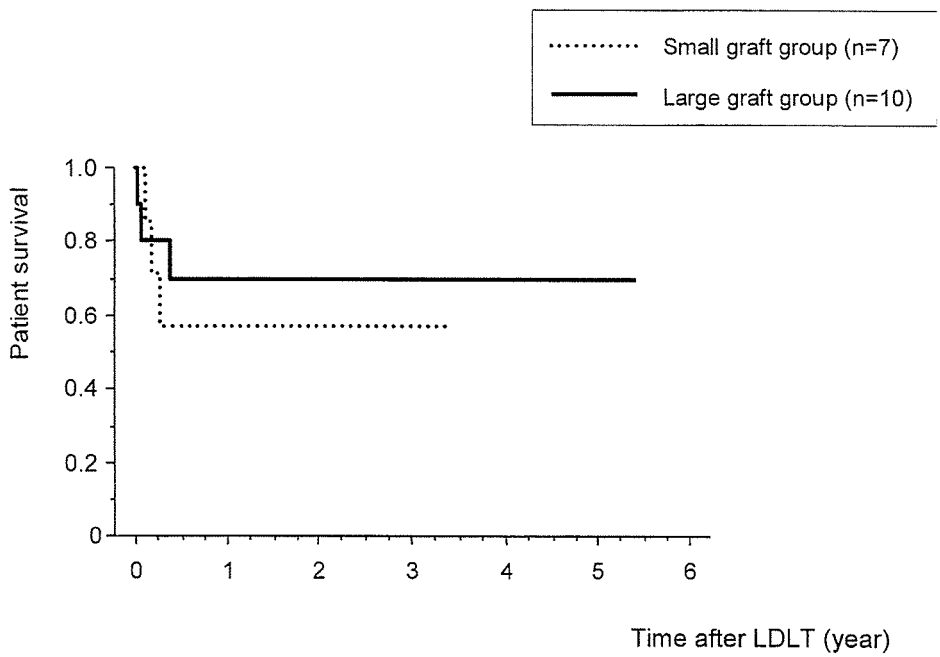


**Fig 3.** Patient survival divided by graft size in moderate or high MELD score patients. Patients with moderate or high MELD score ($n$ = 17) were divided into small graft group (<50% SLV) ($n$ = 7) and large graft group (≥50% SLV) ($n$ = 10). Patient survival curves were similar between them ($P$ = .654, Log-rank test).

than group B (Table 1). The MELD scores were not different ($P$ = .117), and the GLW/SLV ratio was also similar.

### Patient Survival Stratified by Preoperative MELD Score

Because the preoperative MELD score was the only factor associated with graft function in our cohort, we next verified the impact of MELD score on patient survival. Patients with low MELD scores (≤20) showed a better prognosis than those with moderate (21 to 30) or high MELD scores (≥31) (Fig 2). MELD score stratified patient prognosis well ($P$ = .006). The survivals of patients with moderate or high MELD scores (≥21), were similar whether the patient received a large (≥50% of SLV) or a small graft (<50% of SLV) (Fig 3).

## DISCUSSION

In contrast to cadaveric liver transplantation, living donor tissue can be selected with regard to fatty change, donor age can be limited, and the cold ischemia time can be easily controlled by the surgical team. Warm ischemia time can also be minimized. Although LDLT has these advantages over cadaveric liver transplantation, the size of the liver graft is often limited. In this context, it is relevant to determine the risk factor of greater importance to graft function. To date, graft size has been identified separate from other potential risk factors for graft failure, but not compared. The purpose of this report is to evaluate graft function comparing size mismatch with other risk factors.

In this study, the MELD score was significantly higher among group C than the other cohorts, suggesting that a high preoperative MELD score is a risk factor for graft failure in LDLT as it is in cadaveric donor whole liver transplantation.[3,4,10]

A GLW/SLV ratio more than 40% is considered to be a safe value.[11] Small-for-size grafts have been reported to be a risk factor for delayed function or graft failure.[5,6,12] The GLW/SLV ratio in our series ranged from 28.3% to 76.1%. The graft sizes among the failed graft group were not smaller than those in the well-functioning group, results suggesting that graft size has little impact on graft outcome after LDLT, unlike the preoperative MELD score. Therefore, it is not necessary to use larger LDLT, grafts even for sick patients with high preoperative MELD scores. Indeed they should be avoided if they do not leave an adequate remnant liver volume for the live donor, considering the higher morbidity of live donors of right lobes.[2]

We also observed that the donor age among group A was younger than that of group B. The other factors, including MELD score, incidence of acute cellular rejection episodes and GLW/SLV ratio, were similar. These findings suggest that hyperbilirubinemia after LDLT was associated with donor age rather than preoperative recipient condition or graft size.

This comparative study between the functioning and the failed graft groups demonstrated that preoperative MELD score but not graft size was different between them. We concluded that a high preoperative MELD score was associated with postoperative graft failure and that graft size had little impact on graft outcome. However, one should seek to use a larger LDLT, graft for patients with high preoperative MELD scores, only because larger grafts seem to be more suitable for sick recipients, but with the primary consideration being safety of the live donor.

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# Liver transplantation for hepatitis C

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**Abstract**
Hepatitis C virus (HCV) infection is the leading cause of endstage liver disease in Western and Asian countries. However, after liver transplantation, HCV recurs in virtually all patients, and estimated HCV-related graft cirrhosis at 5-year follow-up is 30%. Although immunosuppression accounts for a major part of the accelerated progression of HCV in the transplant population, the best immunosuppression for recipients with HCV that could avoid such complication remains unknown at present. Combination therapy of interferon and ribavirin is thought to be the most effective for the treatment or prophylaxis of HCV infection. However, who should be treated, when treatment should be initiated, and with what agent should patients with HCV infection be treated are still unknown. The current data on HCV recurrence in patients who have received either living- or deceased-donor liver transplantation are controversial, but they are, presumably, similar. Thus, to avoid HCV recurrence in living-donor liver transplantation, we have to take approaches similar to those used for patients receiving deceased-donor liver transplantation. Based on reports from major transplant centers around the world, we consider the best strategy for liver transplantation-related HCV infection is steroid-free immunosuppression and preemptive low-dose interferon and ribavirin combination therapy. Here we describe our experience with living-donor liver transplantion for patients with hepatitis C at Osaka University. There is a need for standardizing the treatment for HCV infection. This can only be achieved through collaborative work between various liver transplant centers worldwide.

**Key words** Liver transplantation · Hepatitis C · Immunosuppression · Antiviral therapy

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## Introduction

Hepatitis C virus (HCV) infection is a worldwide health problem, and is the leading cause of endstage liver disease in Western and Asian countries. In the United States, it is estimated that 3.9 million people are infected with HCV,[1] and 2.7 million people have detectable HCV RNA in their blood.[2] The number of HCV carriers in Japan is estimated to be 2 million people, and this number is expected to increase until around the year 2015.[3] The incidence of hepatocellular carcinoma (HCC) is also rising with the increase in HCV carriers. Of the HCC cases in Japan, about 80% are caused by HCV infection. Alongside these changes, the use of living-donor liver transplantation for adults has been rapidly growing in Japan, due to the development of technical skills and experience in right-lobe grafting. According to the Japanese Liver Transplantation Society, 2667 living-donor liver transplantations (1365 adult recipients) had been performed by December 2003, and 298 of them were for patients with HCV-liver cirrhosis.[4]

However, patient and graft survival rates in HCV-positive patients are relatively low after liver transplantation.[5,6] After liver transplantation, HCV infection recurs in virtually all patients.[7] HCV-induced allograft hepatitis occurs in 40%–50% of recipients within 1 year,[8] and in more than 90% by 5 years.[5,7] The incidence of HCV-related graft cirrhosis is estimated to reach 30% at 5-year follow-up.[9] After the development of HCV-related graft cirrhosis, decompensation develops, at a median of 7.8 months, with a significant drop in patient survival rate.[10] Thus, the survival of patients with clinically compensated HCV-graft cirrhosis is shorter compared with that of immunocompetent patients. Hence, there is a need to understand these disadvantages in HCV-positive patients, and to review current agents used for prevention or treatment of HCV re-infection after liver transplantation.

## Clinical outcome of liver transplantation for HCV cirrhosis

In patients with HCV before liver transplantation, HCV-induced allograft hepatitis occurs universally after the liver transplantation, and rapidly progresses to cirrhosis.[5-7] The leading cause of graft failure in patients with HCV is HCV recurrence, accounting for 35.9% of the cases of graft failure in the report of Neumann et al.[11]

The risk factors for HCV re-infection after liver transplantation have been discussed in several studies. Acute cellular rejection (ACR)[9,12] and the use of bolus corticosteroids[11] or OKT3 treatment[11] for ACR are associated with an increased risk of HCV recurrence. The dose of corticosteroids is also one of the risk factors.[12] The short-term use of corticosteroids,[13] and the induction with mycophenolate mofetil[13] and calcineurin inhibitors[14] are reported to be risk factors for HCV re-infection, though they remain controversial. Genotype 1b-infected recipients are at highest risk of chronic graft damage and cirrhosis.[5,9,15] Recently, donor age[16] age >40 years;[11] >50 years;[13,17] and >60 years[14] was reported as a risk factor for HCV recurrence, although Samonakis et al.[18] argued that donor age did not influence the progression of HCV recurrence. Interestingly, donor age is not a risk factor in patients with HBV, but it is the strongest predictor of graft loss and death of patients with HCV.[14] Cytomegalovirus infection occurred in 26.9% of recipients and was an independent risk factor for graft failure in these paients.[19]

Liver biopsy is essential for the diagnosis of HCV recurrence, but controversy exists about the usefulness of protocol biopsy. Histological findings are sometimes complex and hard to differentiate from those of various other conditions, such as ACR, obstruction, ischemia, and the effects of hepatotoxic drugs. Such differentiation may require serological, immunohistochemical, and radiological studies; drug discontinuation; and/or serial biopsies.[20] Nevertheless, Berenguer et al.[21] concluded that, because there was a high prevalence of abnormal histological findings in patients with HCV, protocol liver biopsy was recommended.[21]

Early histopathological findings seem to be useful in predicting clinical outcome. The degree of activity and the fibrosis score in the first-year biopsy specimens were higher in patients who ultimately progressed to cirrhosis,[9] and were correlated with disease progression at 5 years.[5] Furthermore, the degrees of steatosis, cholestasis, and hepatocyte ballooning were also reported to be useful predictors of outcome.[22]

The timing of HCV recurrence is also reported to be associated with progression to cirrhosis. Patients with histopathological recurrence within 6 or 12 months after liver transplantation are at increased risk for progression to cirrhosis, and their prognosis and graft survival rates are the worst.[12] In addition, preoperative HCV-RNA titers are associated with patient survival after liver transplantation.[23] Serum HCV-RNA levels correlate well with liver tissue HCV-RNA levels, and HCV-RNA levels pre- and early after liver transplantation correlate with HCV recurrence and fibrosis,[22] although the levels of viremia do not always correlate with histopathological findings.[7,24].

A recent multicenter trial reported that human hepatitis C immune globulin (HCIG; Civacir, Nabi Biopharmaceuticals, FL, USA) is safe for HCV-positive recipients,[25] although such treatment did not suppress serum HCV-RNA levels.

Against the background of these numerous reports on liver transplantation for hepatitis C, our current main concerns are immunosuppression and antiviral therapy for hepatitis C.

## Immunosuppression

Because the development of HCV hepatitis and cirrhosis in the transplanted population is very rapid compared with that in the nontransplant population, the immunosuppressive drugs used after liver transplantation are thought to be the main causative agents that reinforce HCV activity. Many studies have focused on the effects of immunosuppression on HCV recurrence. We can divide these drugs into three categories; (1) steroids, (2) calcineurin inhibitors, and (3) others.

### *Steroids*

Steroids accelerate the replication of HCV as well as that of HBV. In vitro, steroids accelerate the replication of both HBV[26] and HCV.[27] HCV-RNA in peripheral blood was increased 4- to 100-fold by methylprednisolone, used for the treatment of ACR after liver transplantation.[15] Other reports have also demonstrated that the cumulative steroid dose and steroid pulse therapy are associated with HCV recurrence and poor graft and patient survival rates.[23,28-33] These reports suggest that steroids accelerate HCV recurrence, as well as causing side effects such as post-transplant diabetes, obesity, hypertension, hyperlipidemia, and infection, Steroids can be avoided and other immunosuppressive agents can be used instead. Table 1 lists published steroid-free trials. Reding et al.[34] reported a pediatric steroid-free protocol with tacrolimus and basiliximab, versus tacrolimus and steroids and they demonstrated that the steroid-free treatment was feasible, without any side effects, with a similar incidence of ACR in both arms. We recently reported that it was safe to use steroid-free immunosuppression in adult-to-adult living-donor liver

**Table 1.** Steroid-free immunosuppression protocols

| Author | Year | Study design | No. of patients | Follow-up period (range) | Immunosuppression | Outcome | HCV recurrence |
|---|---|---|---|---|---|---|---|
| Tisone[68] | 1998 | RCT | 20 (10 vs 11) | 3 Months | CsA+AZA/CsA+AZA+St | ACR, 72% vs 72% | |
| Eason[69] | 2001 | RCT | 71 (36 vs 35) | 9 (3–18) Months | FK+MMF+RATG/FK+MMF+St | NS | |
| Filipponi[70] | 2001 | RCT | 140 (70 vs 70) | Not mentioned | FK+AZA+basiliximab/+St | Tolerated | |
| Eason[71] | 2001 | Pilot | 10 | 7 (1–13) Months | FK/MMF/RATG | Tolerated | |
| Ringe[72] | 2001 | Pilot | 30 | 597 (44–1224) Days | FK+MMF+RATG | Tolerated | |
| Figueras[73] | 2002 | Pilot | 71 | Not mentioned | FK+MMF+daclizumab | Tolerated | |
| Langrehr[74] | 2002 | RCT | 30 (15 vs 15) | 425 (47–774) Days | FK+MMF/FK+St | ACR; NS | |
| Pirenne[75] | 2003 | Pilot | 21 | 40 (34–45) Months | FK+AZA | ACR; 23.5% | |
| Reding[34] | 2003 | Pilot | 40 (20 vs 20) | >1 Year | FK+basiliximab/FK+ST | Less ACR; $P = 0.05$[a] | |
| Eason[36] | 2003 | RCT | 119 (PI, 71; PII, 48) | 18.5 Months | FK+MMF+RATG/FK+MMF+St | ACR; NS | 31/34; NS |

RCT, randomized controlled trial; FK, tacrolimus; CsA, cyclosporine A; AZA, azathioprine; St, steroid; PI, phase I; PII, phase II; MMF, mycophenolate mofetil; RATG, rabbit antithymocyte globulin; ACR, acute cellular rejection; NS, not significant

[a] In steroid-free arm

transplantation.[35] Thus, steroid-free immunosuppression after liver transplantation in either living-donor or deceased-donor liver transplantation has been established as a safe regimen. In this regard, the effect of steroid avoidance on HCV recurrence remains undetermined. However, Eason et al.[36] reported, in their randomized controlled trial, the lack of any difference in HCV recurrence between steroid-free recipients versus traditional immunosuppression recipients, although their sample size was small. Filipponi et al.[37] also reported the safety of steroid-free regimens, but the treatment had no effect on HCV recurrence. Rapid withdrawal of steroid after liver transplantation is recommended, although there is a paradoxical report that slow tapering off of steroids over 1 year may prevent the more aggressive forms of HCV recurrence.[38] Further studies are needed to evaluate the effects of steroid avoidance on HCV recurrence.

### *Calcineurin inhibitors*

Although both tacrolimus and cyclosporine act as calcineurin inhibitors, their behaviors are slightly different. Thus, tacrolimus binds to FK-506-binding proteins (FKBPs), while cyclosporine binds to cyclophilins (Cyps), which are distinct from FKBPs. Both the FKBP/tacrolimus complex and the Cyp/CsA complex can bind to calcineurin, thereby inhibiting its phosphatase activity. Many reports have focused on the relationship between tacrolimus/cyclosporine and HCV. Recently, Watashi et al.[39] reported that, in vitro, using an HCV subgenomic replicon cell culture system, cyclosporine inhibited HCV replication at both the HCV-RNA level and its protein expression, via cyclophilin, whereas tacrolimus did not have such effects. Watashi et al.[39] also showed that cyclosporine inhibited multiplication of the HCV genome in a cultured human hepatocyte cell line infected with HCV, when HCV-positive plasma was used. They[40] also demonstrated that a cellular peptidyl-prolyl cis-trans isomerase (PPIase), cyclophilin B (CyPB), was critical for the efficient replication of the HCV genome. However, clinical studies comparing tacrolimus to cyclosporine have not shown any difference in HCV activity after liver transplantation, except in one small retrospective study (Table 2). A multicenter randomized controlled trial study by Martin et al.[8] showed no significant differences between tacrolimus and cyclosporine in histologically diagnosed HCV recurrence or its severity. The current conclusion is that the use of calcineurin inhibitors does not have any impact on HCV activity after liver transplantation.

**Table 2.** Comparison between tacrolimus and cyclosporine A for liver transplant recipients with HCV

| Author | Year | Study design | NO. of patients | Follow-up period (range) | Immunosuppression | HCV recurrence | Difference in HCV activity between arms |
|---|---|---|---|---|---|---|---|
| Alikhan[76] | 1997 | Retrospective | Not mentioned | Not mentioned | CsA/FK | 33% vs 64% | Less in CsA arm; $P < 0.001$ |
| Zervos[77] | 1998 | RCT | 50 (25 vs 25) | 417 days (25–625) | CsA+St/FK+St | 20% vs 16% | NS |
| Martin[78] | 1998 | Retrospective | 85 (42 vs 43) | 292 days | CsA+AZA+St/FK+AZA+St | 25% vs 25% | NS |
| Smallwood[79] | 1999 | Retrospective | 105 (54 vs 51) | Not mentioned | CsA/FK | 47% vs 44% | NS |
| Edo[80] | 1999 | Retrospective | 26 (FK) | 1 year | CsA+St/FK+St | 35% vs 50% | NS |
| Bilbao[81] | 2001 | Retrospective | 59 (26 vs 33) | 1 year | CsA+St/FK+St | 61.5 vs 41.4 | NS |
| Rabkin[82] | 2001 | uncontrolled | 60 (31 vs 29) | Not mentioned | CsA+AZA+St/FK+AZA+St | 14% vs 23% | NS |
| Paik[83] | 2002 | Retrospective | 58 (22 vs 31) | Not mentioned | CsA/FK | 35.5% vs 45.5% | NS |
| Martin[8] | 2004 | RCT | 79 (38 vs 41) | 1 year | CsA+AZA+St/FK+AZA+St | 54% vs 38% | NS |

RCT, randomized controlled trial; FK, tacrolimus; CsA, cyclosporine A; AZA, azathioprine; St, steroid

*Mycophenolate mofetil (MMF)*

MMF has a structure analogous to that of ribavirin, and its potential antiviral effects have been mentioned.[41] Furthermore, the results of early clinical trials suggest synergism with interferon alpha. A prospective randomized trial by Jain et al.[42] showed that the incidence of HCV recurrence after liver transplantation was similar in a double-drug group and a triple-drug group using MMF (46.4% vs 46.0%). They concluded that MMF had no impact on patient survival, graft survival, rejection, hepatitis activity index score, or rate of HCV recurrence. A randomized double-blind comparative study between MMF and azathioprine, by Wiesner et al.,[43] showed that MMF was superior to azathioprine in perventing acute rejection in the first 6 months, but was similar with respective to graft loss and safety profiles. They added that MMF use improved long-term outcome after liver transplantation, regradless of HCV infection.[44] Thus, MMF appears to have no effect on HCV activity.

*Others*

OKT-3, the most commonly used antilymphocyte antibody for steroid-resistant ACR, has been reported to increase the incidence of HCV recurrence.[11] However, other reports have shown no or weak association between the severity of recurrent HCV and OKT3 use.[12,45] Anti-interlenkin (IL)-2 receptor antibodies have been used increasingly as induction immunosuppression therapy after liver transplantation. Nelson et al.[46] reported that the HCV-RNA level was higher at both 4 months and 1 year after liver transplantation, and that recurrent HCV hepatitis progressed more rapidly in recipients with anti-IL2 receptor antibodies. However, more recently, a steroid-free immunosuppressive regimen of anti-IL2 receptor antibodies was successfully applied and seemed effective in the eradication of HCV.[47]

## Prophylaxis and treatment of recurrent HCV infection in transplant recipients

We can divide antiviral therapy into three stages, (1) pretransplant therapy, (2) preemptive therapy after transplantation, and (3) treatment after HCV recurrence.

*Pretransplant therapy*

Because evidence suggests that the greater the viral load at the time of transplantation, the more rapidly the post-transplantation HCV disease recurs, it is hoped that HCV recurrence could be prevented by minimizing

the HCV viral load at transplantation. In the report of Thomas et al.,[48] 20 HCV-positive liver transplant recipients received aggressive treatment with interferon alpha-2b, at 5 MU daily for 14 ± 2.5 months before transplantation, and 12 (60%) showed a therapeutic response with serologic clearance of HCV before transplantation; 4 (20%) of them did not have evidence of HCV recurrence at 33.6 ± 11.3 months after transplantation. Interferon is effective for treating HCV, but its side effects, such as thrombocytopenia and depression, cannot be ignored and its applicability is limited to patients with platelet counts greater than 50000/μl. Everson et al.[49] reported the use of a low-grade accelerating-dosage regimen (LADR), which starts with interferon alpha-2b at 1.5 MU three times a week or pegylated interferon alpha-2b (Pegintron [Schering, NJ, USA], at 0.5 μg/kg, per week or Pegasys [Hottman-La Roche, NJ, USA], at 90 μg/week) and ribavirin at 600 mg/day, and is then adjusted to the maximum dose every 2 weeks. They employed LADR for pretransplant patients, even those with Child-Turcotte-Pugh (CTP) Class C. The pretransplant treatment course was successful in 46% of patients, who were HCV-RNA-negative at the end of the treatment. But, we should stress that there were clinically significant adverse effects, including 4 deaths, in 15 (12%) of their 122 patients.

*Preemptive therapy after transplantation*

The use of interferon early after transplantation was first reported by Singh et al.,[50] and subsequently by Sheiner et al.[51] In their randomized controlled trial studies, prophylactic interferon, starting 2 weeks after transplantation, demonstrated either an unchanged[50] or a reduced[51] incidence of HCV recurrence. Since the time of the controversy on interferon and ribavirin treatment for HCV recurrence after liver transplantation, low-dose interferon-based anti-HCV therapy combined with ribavirin, starting early after transplantation (preemptive therapy) was subsequently introduced.[52] In the latter therapy, reduced doses of interferon and ribavirin are used to minimize patient dropout, and the treatment is started as soon as possible after transplantation during the period when the HCV-RNA level is low, based on the hypothesis that eradication of HCV can be optimized if therapy is instituted in the early phase after liver transplantation, when the viral load in the recipient may be lower and the graft is uninjured. Sugawara et al.[53] reported the feasibility and effectiveness of such treatment in their pilot study. However, the randomized controlled trial conducted by Shergill et al.[54] showed a dropout rate of 85%, and the end-of-treatment response and sustained virological response (SVR) figures were low, at 13.6% and 9.1%, respectively. Thus, preemptive therapy is an attractive strategy, but it should be applied with caution; further evaluation studies are warranted.

*Interferon and ribavirin as treatment for HCV recurrence*

Treatment of HCV infection has dramatically improved during the past decade, with the advent of combination therapy with interferon and ribavirin; this is currently the most effective anti-HCV therapy and has been used for HCV recurrence after liver transplantation, as well as for treating the nontransplant population. This combination therapy has been reported to be highly effective in suppressing HCV-RNA in patients who tolerate the therapy; also, HCV eradication was reported to have a positive impact on graft survival.[55] However, the durability of the treatment effect and its effect on histopathological response remain controversial (Table 3). While Abdelmalek et al.[56] reported that the combination therapy for HCV recurrence was highly effective (SVR, 24.3%) and there was histological improvement of fibrosis in 27% of the patients, Samuel et al.[57] reported, in their randomized controlled trial study, that the dropout rate was 43% and the SVR was 21.4%. Stravitz et al.[58] reported that the same treatment did not consistently alleviate histological damage even after virological response, and that there was an increased risk of ACR. The safety of interferon-based therapy was also questioned by Saab et al.,[59] who described patients who had progressive cirrhosis despite achieving an SVR, and also patients with acute rejection and graft losses who had an SVR. In this regard, Stravitz et al.[58] reported that 8 (35%) of their 23 patients treated with interferon had evidence of acute or chronic rejection on posttreatment liver biopsy. On the other hand, Castells et al.[60] recently reported that a pegylated interferon alpha-plus-ribavirin combination was safe, and resulted in an end-of-treatment virological response of 62.5% and an SVR of 34.7%; however, they only studied 24 patients who were treated with pegylated interferon plus ribavirin versus 24 patients who did not receive any antiviral therapy. It seems that the percentages of early virological response and SVR are better in patients treated with pegylated interferon with ribavirin than in those not receiving antiviral therapy.[56,58,60,61] Care should be taken when using interferon-based treatment, and an appropriate strategy for recurrent HCV should be established.

## Living-donor liver transplantation vs deceased-donor liver transplantation

Several anecdotal reports have suggested that HCV recurred earlier and was more severe in recipients of

**Table 3.** Antiviral therapy for established HCV recurrence after liver transplantation

| Author | Year | Study design | Antiviral drugs | No. of patients | Dose IFN (MU)/ RBV (mg per day) | Duration (months) | ETR | SVR |
|---|---|---|---|---|---|---|---|---|
| Wright[84] | 1994 | Pilot | IFN | 18 | 3TPW | ≥4 | 28 | 0 |
| Vargas[85] | 1995 | Uncontrolled (IFN vs none) | IFN | 7 vs 7 | 3TPW | 6 | 0 | 0 |
| Feray[86] | 1995 | Uncontrolled (IFN vs none) | IFN | 14 vs 32 | 3TPW | 6 | 12 | 7 |
| Gane[87] | 1995 | Pilot | RBV | 7 | 1200 | 6 | 0 | 0 |
| Singh[88] | 1996 | Pilot | IFN | 18 | 3TPW | 6 | — | — |
| Cattral[89] | 1996 | Pilot | RBV | 9 | 800–1200 | 3 | 0 | 0 |
| Bizollon[90] | 1997 | Pilot | IFN+RBV | 21 | 3TPW/600–1200 | 6 | 48 | 24 |
| Kizilisik[91] | 1997 | Uncontrolled (RBV vs IFN/RBV vs none) | IFN+RBV | 3 vs 3 vs 13 | 600–1200 or 3TPW/600–1200, or none | 6 | 0 | 0 |
| Gane[92] | 1998 | RCT (IFN vs RBV) | IFN or RBV | 14 (IFN) vs 14 (RBV) | 3TPW vs up to 1200 | 6 | 0 vs 0 | 0 |
| Cattral[93] | 1999 | Pilot | RBV | 18 | 600–1200 | 12–44 | 0 | 0 |
| Cotler[94] | 2001 | RCT (IFN vs none) | IFN | 8 vs 4 | 3 Daily | 12 | 13 | 13 |
| Gopal[95] | 2001 | Pilot | IFN+RBV | 12 | 1–3TPW/600–1200 | Variable | 50 | 8.3 |
| Ahmad[96] | 2001 | Uncontrolled (IFN vs IFN/RBV) | IFN+RBV | 40 (IFN) vs 20 (IFN/RBV) | 3TPW vs 3TPW/1200 | 12 | 15 vs 40 | 2.5 vs 20 |
| Alberti[97] | 2001 | Pilot | IFN+RBV | 18 | 3TPW/600 | 12 | 44 | 27 |
| DeVera[98] | 2001 | Pilot | IFN+RBV | 3 | K 1.5–3TPW/600-1200 | ≥12 | 9 | 9 |
| Kornberg[99] | 2001 | Pilot | IFN+RBV | 15 | 3TPW/600 | 12 | 64 | — |
| Firpi[100] | 2002 | Pilot | IFN+RBV | 54 | 3TPW/800–1000 | 12 | 38 | 30 |
| Lavezzo[101] | 2002 | Uncontrolled (IFN 6 months vs IFN 12 months) | IFN+RBV | 27 vs 30 | 3TPW/800 | 6 vs 12 | 33 vs 23 | 22 vs 17 |
| Samuel[57] | 2003 | RCT (IFN/RBV vs none) | IFN+RBV | 28 vs 24 | 3 TPW/1000–1200 | 12 | 32 vs 0 | 21.4 vs 0 |
| Rodriguez-Luna[102] | 2004 | Pilot | PEGIFN+RBV | 37 | 0.5–1.5 μg/kg/per week (PEGIFN)/400–1000 | 12 after VR | 37 | 26 |
| Dumortier[103] | 2004 | Pilot | PEGIFN+RBV | 20 | 0.5–1 μg/kg/per week (PEGIFN)/ 400–1200 | 12 | 55 | 45 |
| Abdelmalek[56] | 2004 | Pilot | IFN or PEGIFN+RBV | 119 | 1.5–3TPW or 0.75–1.5 μg/kg/per week/400–1000 | 12 | 24.3 | 24.3 |
| Stravitz[58] | 2004 | Retrospective | IFN or PEGIFN+RBV | 23 | 1.5–3TPW or 1.0–1.5 μg/kg/per week/600–1000 | 12 | 48 | 35 |
| Castells[60] | 2005 | Uncontrolled (PEGIFN vs none) | PEGIFN+RBV | 24 vs 24 | 1–1.5 μg/kg/per week (PEGIFN)/ 600–800 | 12 | 62.5 | 34.7 |

ETR, end-of-treatment response; SVR, sustained viral response; RCT, randomized controlled trial; IFN, interferon; RBV, ribavirin; TPW, three times per week; PEGIFN, pegylated interferon

living-donor compared with deceased-donor liver transplantations.[62,63] The negative factors affecting HCV recurrence in recipients of living-donor transplants may be increased HLA donor-recipient matching, the type of immunosuppression, a high incidence of biliary complications following transplantation, and liver regeneration.[63,64] Gaglio et al.[62] reported, in their retrospective study, that the timing and incidence of HCV recurrence were not different between recipients of living-donor and recipients of deceased-donor liver transplantations, and that cholestatic hepatitis C, which was defined as total bilirubin greater than 10mg due to HCV recurrence, was more frequent in those who had received living-donor liver transplantation. Another retrospective study, by Van Vlierberghe et al.,[65] showed that the timing and incidence of HCV recurrence, and overall survival at 1 year after transplantation, were similar in recipients of living-donor and deceased-donor liver transplantations. The prospective study of Garcia-Retortillo and coworkers[66] showed that biopsy-proven HCV cirrhosis and clinical decompensation were increased in recipients of living-donor liver transplantations. On the other hand, another prospective case-control study, by Shiffman et al.,[67] showed that graft and patient survival rates were similar for recipients of living- and deceased-donor liver transplantations, and that HCV recurrence was not more severe in recipients of living-donor liver transplantations.[67] Thus, the current data on HCV recurrence in the recipients of living- and deceased-donor liver transplantations are controversial. Further studies of large numbers of patients should clarify these results in the future.

## Living-donor liver transplantation for patients with hepatitis C: Osaka University experience

We have performed 57 liver transplantations in adults (living donors, 56; cadaveric donor, 1) since 1999 at Osaka University Hospital. As mentioned above, adult-to-adult living-donor liver transplantations are increasing, and so are the numbers of HCV-positive recipients. Our records show 16 HCV-positive living-donor liver recipients so far at Osaka University.

### *What is the best strategy for living-donor liver recipients with HCV infection?*

To avoid HCV recurrence in recipients of living-donor liver transplantation, based on the results reported by transplant centers worldwide, we consider the best strategy for liver transplantation in HCV-positive patients is steroid-free immunosuppression and preemptive low-dose interferon and ribavirin combination therapy.

*Immunosuppression.* Pretransplantation, steroids should be avoided in HCV-positive recipients. Equally important is the avoidance of ACR and the use of steroids or antilymphocyte antibody to suppress HCV activity after liver transplantation. We have used the immunosuppressive regimen of a calcineurin inhibitor (either tacrolimus or cyclosporine) and mycophenolate mofetil, and anti-IL2 receptor antibodies without any steroids (steroid-free regimen). Our prospective pilot study comparing 9 recipients with a steroid-free regimen to 12 recipients with a standard steroid-containing immunosuppressive regimen showed that steroid-free immunosuppression was safe and feasible in adult-to-adult living-donor liver transplantation.[35] The incidence of ACR was similar in the two groups (steroid-free, 22.2%; steroid, 23.1%), and patient and graft survival rates were not different between the two groups. Furthermore, HCV-RNA levels tended to be suppressed in the steroid-free group, suggesting a possible suppressive effect on HCV activity.

*Antiviral therapy.* Interferon and ribavirin are strong and attractive tools for the control of HCV, as long as they are used safely and over a long period of time. Our strategy of antiviral therapy includes three points. First, we used a preemptive interferon and ribavirin combination as early as possible once clinical status was stabilized (total bilirubin <2mg/dl and normal transaminase level) after liver transplantation. Second, to minimize dropout, we started with a low dose of interferon (Intron A [Schering-Plough, Japan], 150MU three times per week; Pegasys, 90μg per week; Pegintron, 1μg/kg per week), with ribavirin at 400mg/day (low-dose interferon-ribavirin; LDIR) therapy. We then adjusted the regimen to the maximum dose of interferon (Intron A, 300MU three times per week; Pegasys, 180μg per week; Pegintron, 2μg/kg per week) and ribavirin 600–800mg per day. LDIR was discontinued at 6 months if HCV-RNA was negative on PCR assay, or the LDIR was continued when there was no response to therapy within a short period. Third, to maintain normal platelet counts, splenectomy was routinely performed during the surgery for living-donor liver transplantation with a left-lobe graft. In our retrospective analysis (data not shown), the platelet count in patients with preoperative thrombocytopenia of less than 50000/mm$^3$ returned to the same level without splenectomy, when a small graft, such as a left-lobe graft, was used.

By the end of 2004, 12 HCV-positive liver transplant recipients (7 male and 5 female) were enrolled in our LDIR study (Fig. 1). The median follow-up period was 20 months (range, 6–25 months). Genotype was 1b in all but one of the patients, who was genotype 2a. One patient developed graft failure and no LDIR therapy was provided. Also, 2 patients were not treated with

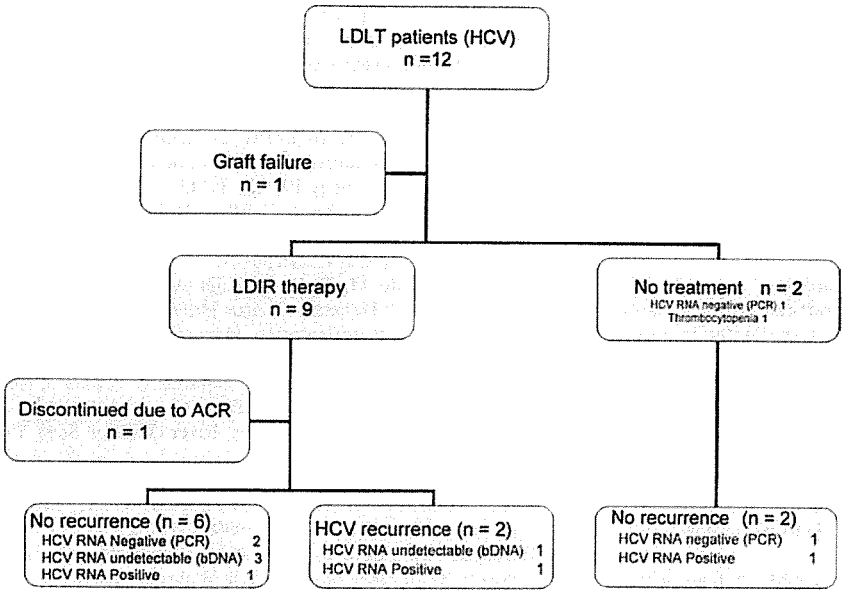


**Fig. 1.** Liver transplant recipients with hepatitis C virus (*HCV*) infection at Osaka University. *LDLT*, living-donor liver transplantation; *LDIR*, low-dose interferon-ribavirin; *ACR*, acute cellular rejection; *HCV RNA (PCR)*, HCV RNA quantitative assay by polymerase chain reaction (PCR) method; *HCV RNA (bDNA)*, HCV RNA quantitative assay by DNA-probe method

LDIR, due to thrombocytopenia ($n$ = 1) and due to PCR-confirmed spontaneous clearance of HCV-RNA in peripheral blood ($n$ = 1). LDIR therapy was thus initiated in 9 patients. One of the 9 patients developed ACR after 2 weeks of LDIR; the treatment was discontinued and the ACR was successfully treated with steroids. The remaining 8 patients continued LDIR therapy without any major clinical side effects. Of the 8 LDIR recipients, 6 showed no HCV recurrence (2 recipients showed clearance of HCV-RNA from peripheral blood, 3 had undetectable HCV-RNA in peripheral blood by the DNA probe method, and 1 was HCV-RNA-positive). The other 2 of the 9 LDIR recipients had HCV recurrence, but 1 of them finally showed HCV-RNA clearance 19 months after LDIR therapy, with biochemical and histopathological improvement. The two liver transplant recipients who could not be treated with LDIR have not yet developed HCV recurrence. These preliminary results should be confirmed with more cases and longer follow-up.

## Summary

HCV infection is the leading cause of liver transplantation in recipients of both deceased- and living-donor liver transplantations worldwide. However, liver transplantation is not a radical treatment for HCV. Unfortunately, HCV always recurs after liver transplantation unless antiviral treatment is successful. There is evidence to suggest that liver transplantation for HCV is associated with an inferior outcome compared with transplantation for other causes. The current data on HCV recurrence in recipients of living; and deceased-donor liver transplantations are controversial, but they are, presumably, similar, and we have to take similar approaches to avoid HCV recurrence recipients of both types of transplantation.

There have been numerous reports on liver transplantation and HCV infection, but the results are too confusing and controversial to yield a consensus between transplant centers. There is a need for further studies, with higher evidence levels and appropriate study designs, to establish a standard strategy for liver transplantation for patients with HCV infection. To solve this fundamental problem it is necessary to have maximum effort and collaboration between transplant centers.

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# Living-Donor Liver Transplantation with Renoportal Anastomosis for Patients with Large Spontaneous Splenorenal Shunts

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**Background.** End-stage liver disease is often accompanied by large spontaneous splenorenal shunts and thrombosed portal vein. Renoportal anastomosis for spontaneous splenorenal shunts in living-donor liver transplantations is one of the solutions for the treatment of these patients. However, the long-term outcome, portal venous hemodynamics after liver transplantation, and the effects of altering the renal venous drainage remained unknown.

**Methods.** We performed three living-donor liver transplantations with renoportal anastomosis for the treatment of spontaneous splenorenal shunts between 1999 and 2004. We then evaluated the outcome of this procedure using short- and long-term follow-ups in which the postoperative graft function, renal function, radiological images and portal hemodynamics were examined.

**Results.** All three patients who underwent a living-donor liver transplantation with renoportal anastomosis are alive with normal graft function and a patent renoportal anastomosis. The portal hemodynamics were similar to those in conventional living-donor liver transplantation recipients, and had no harmful effect on allograft function. Left renal function returned to normal after the temporal impairment in two cases, and remained slightly impaired in one, although it was negligible clinically.

**Conclusions.** Living-donor liver transplantation with renoportal anastomosis for the treatment of spontaneous splenorenal shunts in patients with end-stage liver disease is a life-saving and safe technique and should be discussed as a treatment option for patients with splenorenal shunts.

**Keywords:** Renoportal anastomosis, Portal vein thrombosis, Portal hemodynamics.

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End-stage liver disease is often accompanied by portal vein stenosis or thrombosis. Although various techniques, mainly low dissections, thrombectomy of the recipient portal vein, or interposition of venous graft between the donor portal vein and the recipient SMV, have made it feasible to perform liver transplantations in patients with portal vein thrombosis, these procedures are associated with a possibility of rethrombosis and a high mortality rate (*1–4*). Patients with a complete occlusion of the portal vein and large splenorenal collaterals, a special type of portal vein thrombosis, are not uncommon, but it is sometimes technically difficult to restore portal vein flow to the graft using conventional portal vein reconstruction techniques, a portal vein thrombectomy, or the ligation of collaterals with/without a splenectomy. As a novel technique to solve the underlying problem, we previously reported the successful use of a living-donor liver transplantation (LDLT) in combination with a renoportal anastomosis procedure (RP-LDLT) for the treatment of a patient with a phlebosclerotic portal vein and large splenorenal collaterals (*5*). However, the long-term outcome, portal venous hemodynamics after liver transplantation, and the effects of altering the left renal venous drainage remained unknown in this patient. We subsequently performed two more RP-LDLT procedures. In the present study, we evaluated the efficacy of this technique for the treatment of patients with large splenorenal collaterals based on the long-term outcomes of these three patients.

## PATIENTS AND METHODS

We performed 48 adult-to-adult LDLTs between March 1999 and December 2004 at our hospital. Among these patients, three adult patients had portal venous thrombosis with large splenorenal collaterals (Fig. 1A–C). Because our first attempt at performing a RP-LDLT appeared to be successful (*5*), we subsequently performed two additional RP-LDLTs using right lobe grafts. In the present study, we used prospectively collected data and evaluated the preoperative laboratory data, postoperative graft function, renal function, and short- and long-term outcomes of these three patients. We also compared portal venous flow and pressure and liver regeneration in the three RP-LDLT recipients with those of other conventional right-lobe LDLT recipients (n=23). Portal venous pressure during and after the operation were monitored in each case using a catheter inserted from a tributary of the gastroepiploic vein during the operation. Portal venous flow was also measured in each case during and after the operation using Doppler ultrasonography (SSD-6500, Aloka, Tokyo). An MD-CT scan was performed at 3, 6, and 12 months and annually thereafter; the 3D images of the vessels

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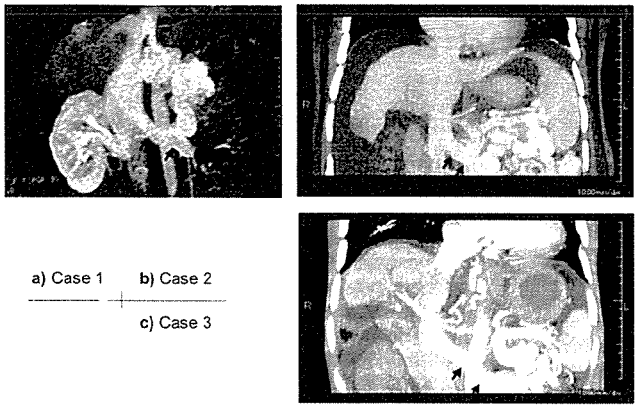


**FIGURE 1.** Reconstructed image of spontaneous splenorenal shunt. (A–C) Markedly dilated splenorenal shunts, pouring into the left renal shunt, are visible in all three cases. Other collaterals were small comparing with the splenorenal shunts. Left renal vein is indicated by the arrow.

were reconstructed and evaluated. A renogram using 99mTc-MAG3 was obtained to evaluate the effect of the renoportal anastomosis on renal function after the RP-LDLT procedure.

### Operative Technique

The operative procedure was described previously (*5*). Briefly, the hepatic hilum was dissected, and the portal vein was identified. An approximately 10-cm length of the left internal jugular vein was harvested for use as an interposition vein graft (Fig. 2A). The duodenum was mobilized using the Kocher maneuver. The left renal vein was then exposed and encircled with a vessel loop. The superior mesenteric venous (SMV) pressure was measured using a catheter placed in a tributary of the SMV. An extra-corporeal veno-venous bypass was not necessary. This procedure was used in the first case but was not used in the following cases because the SMV pressure did not increase during the procedure except a short period of time from the clamping of the left renal vein to the re-perfusion to the allograft. The native liver was removed using the piggyback technique. The left renal vein was cut on the IVC. After oversewing the stump of the renal vein, the internal jugular vein was anastomosed to the left renal vein using running sutures to prepare for the portal venous anastomosis.

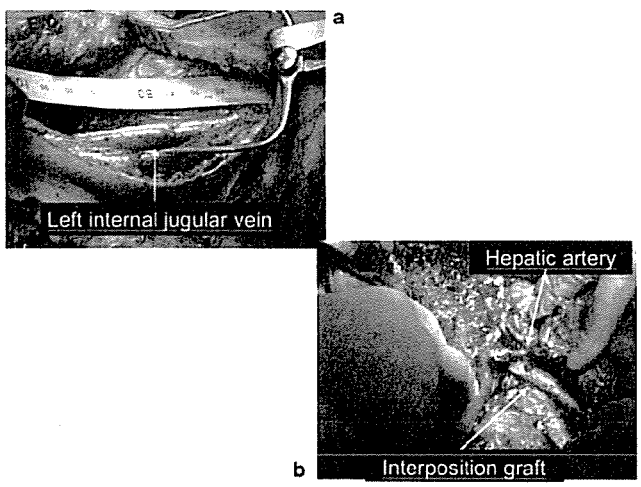


**FIGURE 2.** Left internal jugular vein and the reconstruction of renoportal anastomosis. (A) Left internal jugular vein of the recipient. The graft can be more than 10 cm in length. (B) Reconstructed view of the hepatic artery and portal vein anastomosed with an interposition graft during a LDLT. Sufficient blood flow was detected by an intraoperative Doppler sonography.

The right lobe of the donor was transferred to the recipient. The right hepatic vein of the graft was anastomosed to the newly created longitudinal cut on the IVC, and the right portal vein was anastomosed to the interposition vein graft using an appropriate length. After the reperfusion of the liver and the reconstruction of the anterior venous branches, the hepatic artery and biliary reconstructions were performed (Fig. 2B).

## RESULTS

Among the 48 adult recipients (28 males and 20 females), three patients (6.3%) (two males and one female) had as huge spontaneous splenorenal shunts as inferior vena cava prior to undergoing an LDLT (Table 2) The mean patient age was 46.6 years (range, 19–63 years). The causes of liver cirrhosis were Primary Sclerosing Cholangitis (PSC), Laënnec cirrhosis, and Wilson disease. The second patient also had six hepatocellular carcinomas, with a maximum tumor size of 45 mm; these findings exceeded the Milan criteria (*6*).

Esophageal varices were present in two cases, and one case required several endoscopic ligation procedures. All three patients received ABO-identical right-lobe liver grafts from living donors. The preoperative MELD scores of the patients were 31, 14, and 29.

The portal veins were phlebosclerotic, partially or completely thrombosed, and no signals or hepato-fugal blood flow were obtained during a preoperative sonogram (Table 1).

The operative time ranged from 15 hr 55 min to 19 hr 24 min. The median operative time for conventional right lobe LDLTs at our hospital is 13 hr 18 min (10 hr 5 min 23 hr 25 min). No significant difference in the durations of the RP-LDLT and conventional right lobe LDLT procedures was observed ($P=0.155$). The estimated blood loss ranged from 2,000 ml to 41,000 ml. The median blood loss for right lobe LDLTs at our hospital was 6,660 ml (1,525~24,050 ml). No significant difference in the blood losses associated with the RP-LDLT and conventional right lobe LDLT procedures was observed ($P=0.176$). The graft weight ranged from 476 g to 766 g, and the ratio of the graft and standard liver volume ranged from 38.3% to 55.6%. The cold ischemia time ranged from 46 min to 84 min, and the warm ischemia time ranged from 41 min to 59 min. The SMV pressure was monitored during and postoperatively in the last two cases. The SMV pressure, which is representative of the pressure in the portal system, did not differ from that of conventional right-lobe LDLT recipients (Fig. 3A). The portal venous flow volume after the RP-LDLT was also similar to that of conventional LDLT recipients (Fig. 3B).

Postoperative courses of these RP-LDLT recipients

**TABLE 1.** Demographic and clinical characteristics

| Patient no. | Age/ sex | Diagnosis | MELD | Portal vein flow | Operative time | Estimated blood loss | Type of graft | Graft liver weight | Graft liver weight: standard liver volume ratio | Interposition vein graft |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 29/F | PSC | 31 | Phlebosclerotic very small | 15 h 55 m | 2000 ml | Right lobe | 766 g | 56% | Left internal jugular vein |
| 2 | 61/M | Laennecs/HCC | 24 | PVT (complete) | 16 h 40 m | 9300 ml | Right lobe | 668 g | 49% | Left internal jugular vein |
| 3 | 61/M | Wilson | 29 | PVT (partial) Hepatofugal flow | 19 h 24 m | 41000 ml | Right lobe | 476 g | 38% | Left internal jugular vein |

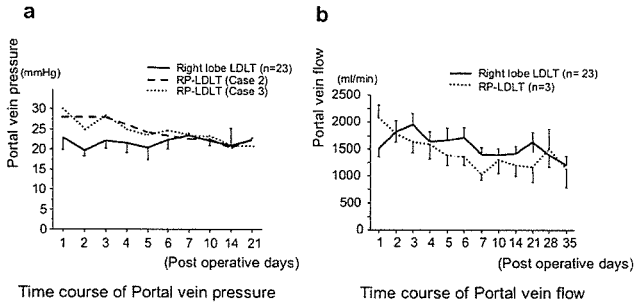


**FIGURE 3.** Time course of portal vein pressure and portal vein flow. (A) The portal venous pressure in the RP-LDLT recipient was slightly higher than in conventional right-lobe LDLT recipients until postoperative day 6, although the difference was not significant. (Line, right lobe LDLT (n=23), dotted line, RP-LDLT (n=3)). (B) Portal venous flow was measured using Doppler sonography and ranged from 1500 to 2000 ml/min on Day 1 and gradually decreased thereafter. The results of the two groups were similar.

were uneventful and satisfactory except pneumonia was developed and treated in Case 3 (Table 2). Liver function in the RP-LDLT recipients returned to normal, as determined by a mean total bilirubin value of less than 2.0 mg/dl on postoperative day (POD) 36, 13, and 74, respectively, whereas the average period for the other LDLT recipients was 34.7 POD (n=23, not significant). A small amount of ascites was present one month after the RP-LDLT in Cases 1 and 3. At three months after the RP-LDLT, however, CT scans showed the disappearance of the ascites in both cases. The need for diuretics was minimal, and diuretics were discontinued in all three cases within four weeks of the RP-LDLT. An MD-CT scan showed a patent renoportal anastomosis in all three cases at the time of the last follow-up (Fig. 4), which was also confirmed by the presence of hepato-petal flow on a Doppler sonography examination. The serum creatinine level was within the normal range at the 3-, 6-month, and annual follow up examinations in each case. Serial renograms after the RP-LDLT showed initial impairment of left kidney and full recovery of renal function with normal perfusion by a year after the RP-LDLT in Case 2 and 3 (Fig. 5). A slight impairment of left kidney function was shown in Case 1, although the patient was stable and the findings were clinically negligible.

## DISCUSSION

Spontaneous splenorenal shunt was first described in the 18th century as a type of portosystemic shunt. Although the incidence of splenorenal shunt has not been clearly identified, several authors have described its incidence to be between 5 to 12% in cirrhotic patients (*7*). We actually encountered three cases (6.3%) of splenorenal shunt among 48 adults with end-stage liver disease.

Patients with large splenorenal shunts form a special subgroup because of their hemodynamic characteristics that SMV venous return easily leaks to large collaterals, resulting in a reduced or reversed flow in the portal vein. It is often difficult to apply a conventional liver transplantation technique to such patients with splenorenal shunt as Cescon et al. described (*8*), because the portal venous flow is essential to the transplanted livers (*9*, *10*).

Large splenorenal shunts are often accompanied by portal vein thrombosis. Since the successful bypass of thrombotic segments using vein grafts (*11*) many authors have reported that liver transplantations are feasible even in the presence of portal vein thrombosis (*1–4*, *12*). Nevertheless, the incidence of re-thrombosis in the portal vein after liver transplantation has been reported to be as high as 6.6 % (30 cases of re-thrombosis out of 452 cases with portal vein thrombosis) with high mortality rate by a meta-analysis (*4*). Several authors have described the incidence of re-thrombosis depends on its severity (*1–4*). Manzanet et al. (*2*) reported that the incidence of re-thrombosis in patients with partial portal vein thrombosis was 2 %, whereas that in the patients with complete portal vein thrombosis was 14.7%. The incidence of re-thrombosis in patients with portal vein thrombosis and a large splenorenal shunt under the traditional technique may be much higher than previously reported incidences for patients with portal vein thrombosis due to its hemodynamic characteristics, although no report to date has focused on this relatively less familiar kind of portosystemic shunt.

To solve these underlying problems, renoportal anastomosis for patients with a surgical splenorenal shunt in deceased-donor liver transplantations was first described by Kato et al. in 2000 (*13*). We applied this technique to a LDLT recipient, as previously reported (*5*).

**TABLE 2.** Outcome of the renoportal anastomosis procedure

| Patient no. | Complication | Length of hospital stay | Status | Liver function | Renal function | Ascites at 3 months after transplantation | Duration of diuretics requirement | Renoportal anastomosis | Follow-up period |
|---|---|---|---|---|---|---|---|---|---|
| 1 | None | 64 days | Alive | Good | Good | None | 27 days | Patent | 4 years |
| 2 | None | 38 days | Alive | Good | Good | None | 3 days | Patent | 1 year, 8 months |
| 3 | Pneumonia (postoperative day 44) | 150 days | Alive | Good | Good | None | 14 days | Patent | 1 year, 4 months |

In our series of three RP-LDLTs, the postoperative courses of the patients were generally uneventful, and the long-term allograft and renal function were satisfactory. Although, the durations of the operations were rather long, and the blood loss in Case 3 was relatively large, these results do not mean that the RP-LDLT is a complicated and risky procedure. It is noted the operative time includes the waiting time for getting the donor graft ready and the back-table reconstruction of hepatic veins with or without interposition grafts after the hepatectomy. Sometimes, the donor liver took more than 2 hr to arrive. In fact, the duration of the RP-LDLTs was not significantly different from that of conventional LDLTs performed at our institution. As for the amount of blood loss, the preoperative condition of the third case was poor (MELD=29), the patient had a history of a prior partial hepatectomy for hepatocellular carcinoma, and a small-for-size graft was used (476 g, 38.3% of SLV). SMV pressure was around 24 to 27 mmHg during the hepatectomy and after reperfusion, which was not high enough for causing the bleeding. Furthermore, the bleeding was relatively controlled during the hepatectomy, and oozing from everywhere mainly after reperfusion of the allograft resulted in massive blood loss in this case, suggesting that the cause of the bleeding in Case 3 was coaglopathy and multifactorial, but not portal hypertension.

Renoportal anastomosis has several advantages for patients with a large splenorenal shunt. A splenectomy or ligation of the large collateral, which increases bleeding or other operative morbidity and the possibility of mortality, is not required in this technique to secure the portal venous flow to the liver. Adequate blood inflow to the portal vein of the liver graft is guaranteed, since all the blood flow in the left renal vein enters the portal vein. On the other hand, the technique also possesses some disadvantages. The large splenorenal collateral is preserved, therefore any collaterals, such as varices, will remain present and may deteriorate and bleed, causing portal hypertension after LDLT using a small graft; variceal bleeding in spontaneous splenorenal shunt patients is otherwise rare in patients who have not undergone an LDLT (*14*). Fortunately, we have not experienced any signs of postoperative growth of varices in our series. Other possible disadvantages are the injury of the liver graft from the elevated portal venous flow, renal dysfunction, anastomotic strictures or thrombosis of the interposition graft, and hypersplenism.

Renoportal anastomosis in LDLT recipients also requires an appropriate vein graft to connect the left renal vein to the portal vein of the graft liver. Since cadaveric vein grafts are rarely available in Japan, an internal jugular vein autograft, which can be 8–10 cm in length and is the same diameter as the portal vein, was removed from the recipient. The removal of the internal jugular vein does not have any harmful effects on the central nervous system (*15*). Another possible option for the vein graft would be an external iliac vein, which is usually 7–8 cm and shorter than the internal jugular vein.

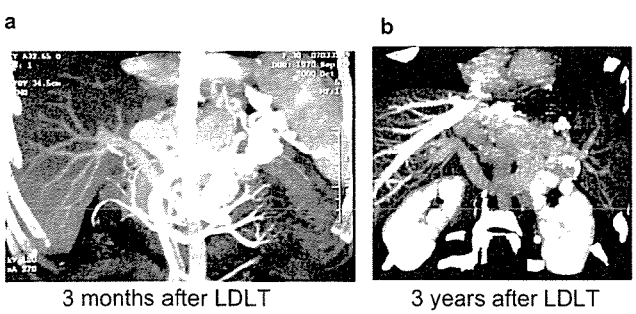


**FIGURE 4.** MD-CTscan after LDLT. Three months after LDLT (A) and 3 years after LDLT (B). The renoportal anastomosis is patent, and no signs of stenosis are visible in the portal system.

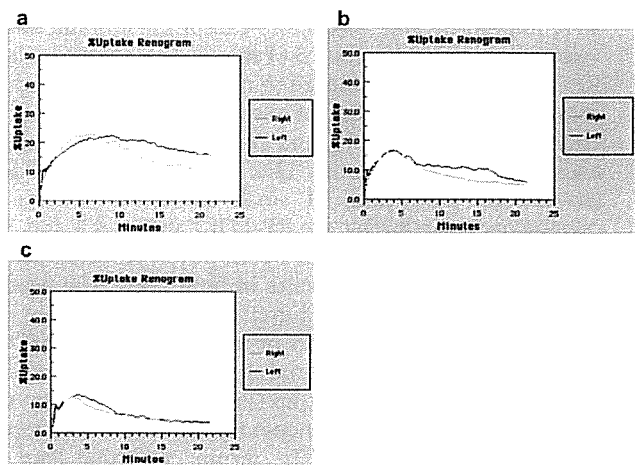


**FIGURE 5.** Renogram after the RP-LDLT. A renogram using 99mTc-MAG3 in Case 3 performed at 1 (A), 3 (B), and 12 (C) months after the RP-LDLT. A mild delay in accumulation and secretion in the left kidney was noted at 1 month after the RP-LDLT. Left renal function was then gradually recovered to normal by 12 months after the RP-LDLT.

The effect on portal hemodynamics was one of the major concerns in the RP-LDLT recipients. With partial liver graft LDLTs or split livers, the portal venous flow increases because of the reduced blood bed in the liver graft, resulting in the hyper-hemodynamics of the portal vein and possibly causing liver injury and impairment of the usual course of liver regeneration (known as small-for-size syndrome) (*16*). In our series, the portal venous flow was not elevated, compared to the average flow of well-functioning grafts, and the recovery of graft function did not differ from that of conventional right-lobe LDLT recipients.

The pressure of the left renal vein increases in subjects that undergo a renoportal anastomosis, possibly reducing the flow of the left renal vein. The function of the left kidney was slightly impaired in Case 1, but the findings were clinically negligible. The impairment of the left renal function may have started prior to the transplantation, since the venous pressure of the left renal vein was elevated because of the large splenorenal shunt in this particular case (*17*). In the remaining cases, left renal function was initially impaired slightly, but recovered fully by a year after the RP-LDLT, suggesting that the left renal dysfunction due to the alteration of drainage venous flow in this technique could be, if any, temporal and recovered.

Possible treatment alternatives for patients with large splenorenal shunts and insufficient portal venous flow, other than the renoportal anastomosis described here, include a portal vein thrombectomy or a thrombendovenectomy (*18*), an SMV-portal vein or collateral-portal vein anastomosis with or without an interposition vein graft, and a ligation of the splenorenal shunt with or without a splenectomy (*19*). These techniques are reportedly feasible in patients with portal vein thrombosis (*1–4*). However, the presence of large splenorenal shunts in the patients treated in these series was not noted. From the perspective of hemodynamic characteristics, simple anastomosis of the portal vein (without RP-LDLT), even if blood flow in the portal vein is present, may become inadequate and require a re-exploration to ligate the splenorenal shunt, increasing the risk of bleeding, infection, and mortality to the recipient, as described by Cescon et al. (*8*). Thus, an RP-LDLT may be the most appropriate treatment for patients with portal vein thrombus and a large splenorenal shunt, taking into account these advantages and disadvantages. Cavoportal hemitransposition is another option for these patients, but its morbidity and mortality cannot be ignored (*20*).

In conclusion, the present series of three patients suggests that hemodynamic changes in the portal venous system after the RP-LDLT were not significant and that the possible adverse effects of renoportal anastomosis, as discussed above, were clinically negligible, confirming the long-term effectiveness of the RP-LDLT. The RP-LDLT for spontaneous splenorenal shunt in end-stage liver disease patients appears to be a life-saving and safe technique and should be discussed as a treatment option for patients with splenorenal shunt.

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特集『ウイルス肝炎の肝移植』

# C型肝炎肝移植患者のT細胞性免疫応答の特性

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## はじめに

C型ウイルス（HCV）性肝硬変は肝移植の最も頻度の高い適応疾患のひとつであるが，移植後C型肝炎の再発が高率に起こり，また肝炎の進行も移植患者以外と比較すると急速であることが分かっている[1-3]。HCV陰性患者では術後急性拒絶反応は予後と関連しないのに対し，HCV陽性の移植患者における急性拒絶反応は予後不良因子とされている。HCV肝炎合併例では免疫抑制療法がウイルスの増勢を助長するためと理解されている[1-3]。従って，急性拒絶反応とC型肝炎再発，あるいはその他の原因とを的確に鑑別し，必要最低限の免疫抑制療法を行なうため，個々の患者の免疫状態を把握することが重要となる。信頼性のある免疫監視法の確立が求められるゆえんである。われわれは，carboxyfluorescein diacetate succimidyl ester（CFSE）細胞質染色とマルチパラメーターフローサイトメトリーを応用したmixed lymphocyte reaction assay（以後，CFSE-MLRと略す）を臨床導入している[4,5]。CFSE色素は細胞傷害性がなく細胞内蛋白を染色し，細胞分裂回数に比例して色素が半減化する性質を有し，反応性リンパ球の表面マーカーと同時にprecursor frequency, mitotic indexやstimulation indexの定量化が可能である（図1）[6,7]。CFSE-MLRによりHCV罹患肝移植患者のT細胞性免疫応答の特性を解析したので報告する。

## HCV肝硬変患者のT細胞アロ免疫応答

HCV患者では健常人に比べ樹状細胞の抗原提示能の低下が報告されている[8,9]。樹状細胞への直接的なHCV感染が起因する可能性やHCV感染が間接的に樹状細胞の成熟を抑制する可能性が指摘されているが，HCV患者におけるT細胞応答能の低下にかかわる機序はいまだ明らかではない。HCV肝硬変患者の抗原提示能の低下は，肝移植後に間接認識経路で惹起されるT細胞応答が他疾患による肝移植後に比べて弱い可能性を示唆する。しかし，肝移植後にグラフト由来の健常抗原提示細胞から直接認識経路で惹起されるT細胞応答について解析された報告は認められない。これを解析する目的でわれわれは，2004年8月～2006年2月の間に術前の末梢血リンパ球を用いたCFSE-MLRを施行した患者21名を対象に，その結果を解析した。T細胞のstimulation indexを原疾患別に比較したところ，ドナー由来の抗原提示細胞を認識したT細胞は，B型肝炎やアルコール性肝硬変などの他疾患で肝移植を要した患者と同等のアロ応答を示した（図2）。従ってHCV肝移植患者の拒絶予防には，他疾患による肝移植患者と同等の免疫抑制療法が必要であるものと考えられた。

## 肝移植後のアロ応答とHCVウイルス量の関係

当科においてCFSE-MLRで免疫監視を行ったC型肝炎患者に対する生体肝移植症例14例のうち，術後1年以内に血液生化学検査で肝機能異常を認め，急性拒絶反応を疑った症例は6例であった。このうち，CFSE-MLRによって抗ドナー応答の亢進を認め急性拒絶反応と診断し拒絶治療を要したのは3例であった。HCVウイルス量と急性拒絶反応および拒絶治療