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Outcomes for Patients with Hepatitis C Virus after Liver Transplantation in Korea

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Hepatitis C virus (HCV)-related liver disease is the most common indication for liver transplantation (LT) in Western countries, whereas HCV LT is rare in Korea. We conducted a survey of HCV RNA-positive patients who underwent LT and investigated the prognostic factors for patient survival and the effects of immunosuppression. To accomplish this, we retrospectively reviewed the multicenter records of 192 HCV RNA-positive patients who underwent LT. The 1-, 3-, and 5-year overall survival rates were 78.8%, 75.3%, and 73.1%, respectively. Excluding cases of hospital mortality (n=23), 169 patients were evaluated. Most patients were genotype 1 (n=111, 65.7%) or genotype 2 (n=42, 24.9%). The proportion of living donors for LT (n=135, 79.9%) was higher than that of deceased donors (DDLT; n=34, 20.1%). The median donor and recipient ages were 32 and 56 years, respectively. Twenty-eight patients (16.6%) died during the observation period, while 75 underwent universal prophylaxis and 15 received preemptive therapy. HCV recurrence was detected in 97 patients. Recipients who were older than 60, received DDLT, used cyclosporine, or suffered acute rejection had lower rates of survival. Acute rejection was closely associated with a lack of induction therapy, cyclosporine use, and universal prophylaxis after transplantation. The careful avoidance of acute rejection in the post-transplant period through adequate use of tacrolimus is a preferable strategy that increases patient survival following liver transplantation.

Key Words: Hepacivirus, Hepatitis C, Immunosuppression, Tacrolimus, Graft rejection, Survival, Antiviral agents
중심 단어: C형 간염 바이러스, 면역억제, 타크로리무스, 간이식 급성 거부 반응, 생존, 항바이러스 치료

INTRODUCTION

An estimated 185 million individuals are chronically infected with hepatitis C virus (HCV) worldwide(1). Of all HCV-infected individuals, 20% to 30% develop liver cirrhosis and 1% to 4% of all patients with liver cirrhosis develop hepatocellular carcinomas(2). HCV infection is the most common indication for liver transplantation (LT) in Western countries. In Korea, 1% to 2% of the population is infected with HCV, and 15% to 20% of these infected individuals have chronic liver diseases related to HCV infection(3,4). As the prevalence has increased, HCV-related cirrhosis and HCV- related HCC will gradually become more common indications for LT in Korea(5).

Genetic variation in *interleukin-28B* (*IL28B*) predicts hepatitis C treatment-induced viral clearance. Single nucleotide polymorphisms in *IL28B* have varied distributions among ethnic groups. East Asian populations such as those in Korea, Japan, and China have the highest frequencies of single nucleotide polymorphisms in alleles associated with HCV clearance(6).

Although LT offers the optimal treatment for HCV-related end-stage liver disease and HCC, graft reinfection with HCV is not acute, but rather immediate and universal in all patients who are hepatitis C virus ribonucleic acid (HCV

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RNA)-positive at transplantation(7). HCV RNA levels increase when immunosuppression is the highest during the first few months after transplantation. The progression of fibrosis in LT patients is accelerated compared to that in non-transplanted patients because the virus is more aggressive after LT than it is in immunocompetent subjects(1). The relationship between HCV recurrence and immunosuppression severity or type remains unclear due to a lack of good evidence.

Recurrent HCV infection after LT is associated with reduced graft and patient survival(8). Progression to cirrhosis at 5 years occurs in 10% to 50% of LT patients(9), and the probability of liver graft failure is 42% within 12 months once cirrhosis is established(10). Immunosuppression for HCV patients requires a fine balance between suppressing immunity and maintaining an optimal host viral response(11). The effect of immunosuppression on recurrent HCV is difficult to assess.

Because there have been no reports of post-transplant HCV recurrence in HCV RNA-negative recipients, antiviral therapies based on PEGylated interferon-alpha (PEG-IFNα) and ribavirin (RBV) have been used to treat HCV in decompensated patients on the transplant waiting list until they are HCV RNA-negative(12). However, this therapy is limited due to poor tolerance, poor efficacy, and serious adverse events seen in those waiting for LT(8).

The cumulative number of HCV-related cirrhosis and HCV-related HCC cases in Korea is very small; therefore, we collected data of LT recipients with HCV from three major centers. We conducted a survey of HCV RNA-positive patients who underwent LT and investigated the prognostic factors for patient survival and the effects of immunosuppression.

MATERIALS AND METHODS

1. Patients

This was a multicenter study involving three LT centers in Korea: Samsung Medical Center (SMC), Asan Medical Center (AMC), and Seoul National University Hospital (SNUH). We retrospectively evaluated patients undergoing their first LT between 1994 and 2012. Data from all consecutive HCV RNA-positive cases were reviewed during this period. Each institution utilized a survey with study questionnaire items. Immunosuppression protocols, the treatment of rejection, and the treatment of recurrent HCV infection were not standardized across centers. The laboratory Model for End-stage Liver Disease (MELD) score was calculated at the time of transplantation.

Among the 255 cases with HCV-related cirrhosis who underwent LT during the study period, 63 cases were excluded due to re-transplantation (n=13) and HCV-RNA negativity (n=50). Among the remaining 192 included patients, we identified the causes for graft failure and mortality. We investigated the risk factors associated with patient survival, but did not include hospital mortality (n=23).

RESULTS

1. Patient survival and outcomes

The 1-, 3-, and 5-year cumulative patient survival rates were 78.8%, 75.3%, and 73.1%, respectively (Fig. 1). The causes of graft failure and mortality are summarized in Table 1. Thirty patients (15.6%) developed graft failure during the observation period and 13 patients underwent re-transplantation. Fifty patients (26.0%) died during the observation period. Most cases of mortality (38/50, 76%) occurred less than 1 year after transplantation. The patient survival curve showed an abrupt decrease, but then stable survival after 2 years after transplantation and onward. Recurrent HCV infection and hepatic failure (n=17) and

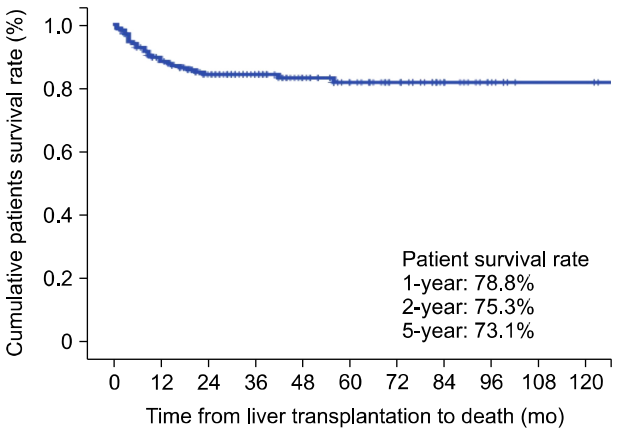

Fig. 1. Patient survival rates. The 1-, 3-, and 5-year patient survival rates are 78.8%, 75.3%, and 73.1%, respectively.

Table 1. The causes of graft failure and mortality

Variable	<1 Year	>1 Year
Graft failure	18	12
Chronic rejection	8	2
Graft dysfunction	2	0
HCC recurrence	1	0
HCV recurrence	4	6
Hepatic failure	3	4
Mortality (hospital mortality/ no hospital mortality)	38	12
Chronic rejection	2 (1/1)	1
Graft dysfunction	2 (2/0)	0
HCC recurrence	3 (0/3)	1
HCV recurrence	4 (0/4)	2
Hepatic failure	6 (5/1)	3
Infection	17 (10/7)	4
Cerebrovascular accident	1 (1/0)	1
Bronchial hemorrhage	1 (0/1)	0
Gastrointestinal bleeding	1 (1/0)	0
Stress-induced cardiomyopathy	1 (1/0)	0

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

chronic rejection (n=10) were the causes of graft failure. Chronic rejection was the main cause of graft failure in patients less than 1 year after transplantation. Infection (n=21) and recurrent HCV infection with hepatic failure (n=15) were the leading causes of recipient death. Infection was the main cause of hospital mortality in patients 1 year after transplantation.

2. Baseline characteristics

Among the 192 patients that were identified, we investigated the 169 patients, who represented all patients except those who died in the hospital (n=23). The characteristics of the 169 HCV RNA-positive LT recipients compared in this study are summarized in Table 2. There were 118 men and 51 women, with a median age of 56 years (range: 34～71 years). The median follow-up period was 38 months (range: 1～157 months), with a wide spectrum of follow-up duration due to death or shorter observation period from LT. The median MELD score and median HCV RNA levels were 16 (range: 6～50) and 133,568 IU/mL (range: 12～26,000,000 IU/mL), respectively. One hundred eleven patients (65.7%) had HCV genotype 1 and 42 patients (24.9%) had HCV genotype 2. The number of patients with coexisting HBV infection, HIV infection, and HCC was 21 (12.4%), 1 (0.6%), and 77 (45.6%), respectively. There were 135 living donor liver transplantations (LDLTs) (79.9%) and 34 deceased donor liver transplantations (DDLTs) (20.1%). The median age of the donors was 32 years (range: 16～70 years), and the graft type in the living donors was the right liver in 125 patients (74.0%). The median cold ischemic time and median warm ischemic time

Table 2. Baseline characteristics

Characteristic	Value
Gender	
Male	118 (69.8)
Female	51 (30.2)
Recipient age <60 years	117 (69.2)
HCV genotype	
Unknown	9 (5.3)
Type 1	111 (65.7)
Type 2	42 (24.9)
Type 3	4 (2.4)
Type 6	3 (1.8)
Coexistence of hepatitis B virus	21 (12.4)
Coexistence of hepatocellular carcinoma	77 (45.6)
HCV-RNA level at transplantation (IU/mL)	133,568 (12～26,000,000)
MELD score	16 (6～50)
Type of liver transplantation	
Deceased donor	34 (79.9)
Living donor	135 (20.1)
Donor age ≥30 years old	100 (59.2)
Donor gender	
Male	123 (72.8)
Female	46 (27.2)
Graft type	
Whole liver	33 (19.5)
Right Lobe	125 (74.0)
Left lobe	10 (5.9)
Split	1 (0.6)
Induction agent	
None	64 (37.9)
Basiliximab	105 (62.1)
Calcineurin inhibitor	
None	3 (1.8)
Cyclosporin	88 (52.1)
Tacrolimus	78 (46.2)
MMF	105 (62.1)

Data are presented as number (%) or median (range).
Abbreviations: HCV, hepatitis C virus; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil.

were 81 and 39 minutes, respectively.

3. Prognostic factors for patient survival

Recipient and donor factors were analyzed for their association with overall mortality. The results of the univariate and multivariate analyses are shown in Table 3. The univariate analysis revealed that recipient age ≥60 years (P=0.018), HCV RNA levels at pretransplant (P=0.023), DDLT (P=0.020), donor age ≥30 years (P=0.019), the use of cyclosporine (P=0.025), and biopsy-proven acute rejection (P<0.001) were significant predictors of poor outcome in HCV RNA-positive recipients. The duration of steroid use did not affect patient survival. The ROC curve (receiver operating characteristic curve) did not reveal a significant cut-off value for HCV-RNA levels in terms of patient survival. The multivariate analysis showed that recipient age ≥60 years (P=0.046), DDLT (P=0.040), the use of cyclosporine (P=0.029), and biopsy-proven acute rejection (P=0.001) were independent prognostic factors for mortality. The Kaplan-Meier survival curves stratified by these factors are presented in Fig. 2.

4. Antiviral treatments in pre- and post-transplant

A summary of the antiviral treatments is shown in Table 4. Of the 169 recipients, 129 did not receive antiviral treatment in the pre-transplant period and 30 underwent antiviral treatment. After LT, 75 patients received universal prophylaxis and 15 patients underwent preemptive treatment due to HCV reactivation. Most patients did not undergo a protocol biopsy, and HCV-RNA levels were monitored at every visit. HCV recurrence was detected in 97 patients (57.4%). Among the 97 patients with HCV recurrence, 48

Table 3. Risk factors for patient survival

Univariate	Odds ratio	95% Confidence interval	P-value
Recipient gender (female)	0.880	0.387~2.001	0.761
Recipient age ≥60 years	2.410	1.133~5.128	0.018
Genotype			
Type 1	1.392	0.185~10.486	0.748
Type 2	2.100	0.265~16.614	0.482
Pre-transplant antiviral treatment	2.048	0.897~4.680	0.089
HCV RNA level	1.000	1.000~1.000	0.023
Coexistence of hepatitis B virus	0.500	0.119~2.110	0.346
Coexistenceof Hepatocellular carcinoma	0.828	0.390~1.755	0.622
MELD score	0.990	0.941~1.042	0.703
Deceased donor liver transplantation	2.475	1.119~5.495	0.020
Donor age ≥30 years	3.214	1.216~8.493	0.019
Donor gender (female)	0.889	0.376~2.103	0.789
Cold ischemic time	1.000	0.997~1.002	0.858
Warm ischemic time	1.005	0.994~1.016	0.404
Induction agent (Basiliximab)	0.643	0.302~1.369	0.252
Use of cyclosporin	2.475	1.089~5.618	0.025
MMF	0.879	0.411~1.881	0.740
Universal prophylaxis	1.421	0.668~3.024	0.362
Preemptive treatment	0.663	0.154~2.862	0.582
HCV recurrence	1.113	0.529~2.344	0.778
Biopsy-proven acute rejection	4.013	1.909~8.436	<0.001
Multivariate			
Recipient age ≥60	2.277	1.014~5.113	0.046
Deceased donor liver transplantation	2.398	1.041~5.525	0.040
Use of cyclosporin	5.870	1.276~11.909	0.029
Biopsy-proven acute rejection	4.338	1.884~9.990	0.001

Abbreviations: HCV, hepatitis C virus; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil.

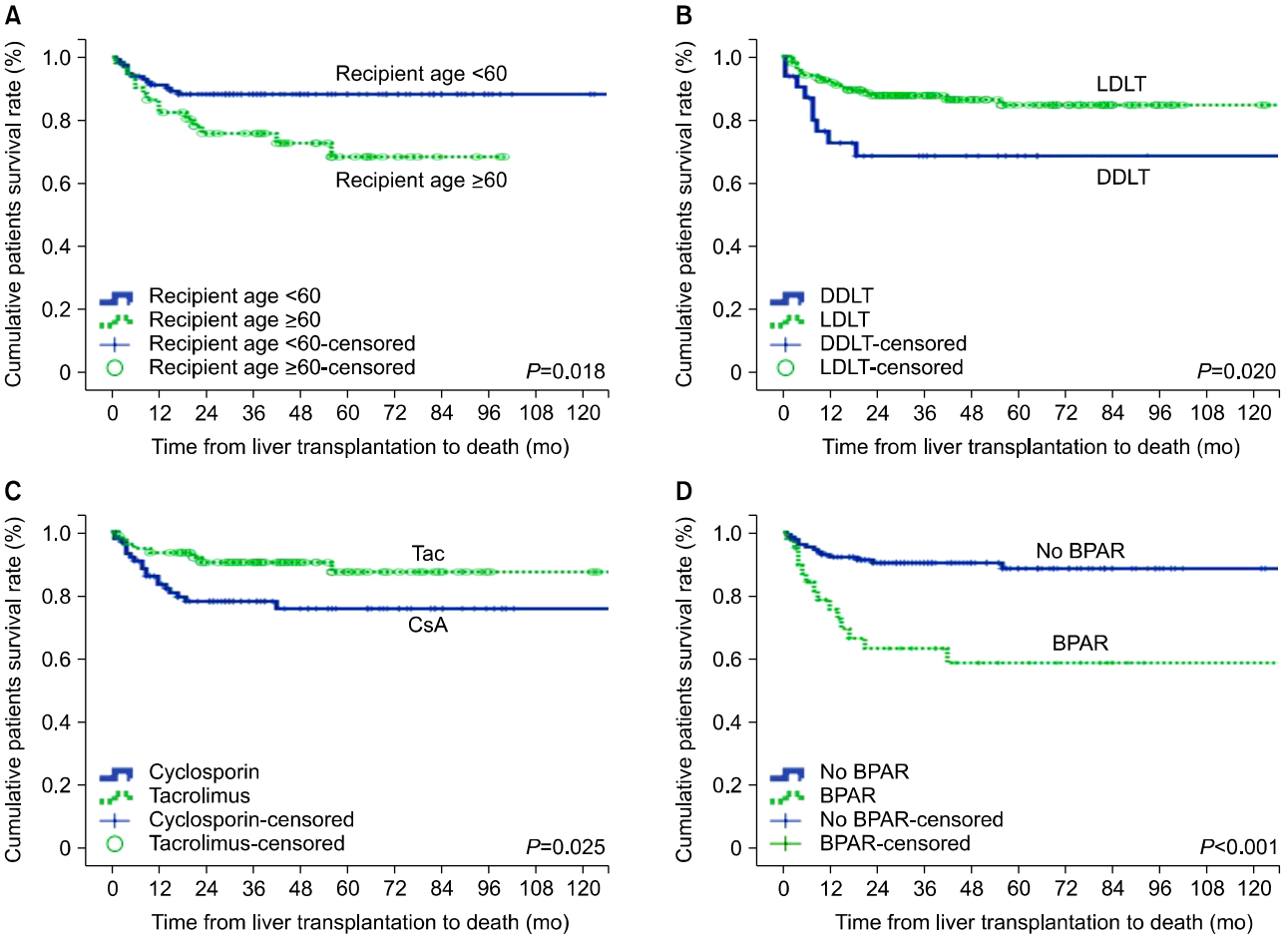

Fig. 2. Patient survival according to recipient age, donor type, calcineurin inhibitor, and biopsy-proven acute rejection. Abbreviations: LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; BPAR, biopsy-proven acute rejection.

patients were treated with antiviral therapy. The survival rates were higher in patients with sustained viral response (SVR) than in patients without SVR, but there was no statistically significant difference in patient survival between the two groups (P=0.062) (Fig. 3).

5. Biopsy-proven acute rejection

Biopsy-proven acute rejection occurred in 39 patients (23.1%). Most patients with acute rejection were treated with an increased immunosuppression dosage (n=9) or a calcineurin inhibitor change (n=23). Four patients were treated with steroid pulse therapy. Patients with biopsy-proven acute rejection were associated with a lower proportion receiving basiliximab, a higher proportion receiving cyclosporine, and a more universal prophylaxis than patients without biopsy-proven acute rejection (Table 5).

DISCUSSION

Literature from the United Network for Organ Sharing (UNOS) database reported a 5-year patient survival rate of 76%, and a study from the European Liver Transplant Registry (ELTR) reported a 5-year patient survival rate of 65%(13,14). Recently, nationwide survey in Japan of LDLT reported a 5-year patient survival rate of 72%(15). Our study here is the largest case series of LT for HCV RNA-positive recipients in Korea. A total of 192 recipients from three large institutions were reviewed and found to have a 5-year patient survival rate of 73.1%. Based on these studies, the outcomes of the present study may be superior to that of the ELTR and similar to that of the UNOS and Japanese survey. Comparisons of the survival rates of HCV recipients between studies should be interpreted with cau-

Table 4. Antiviral treatment in pre- and post-transplant

Variable	Value
Pre-transplant antiviral treatment	30 (17.8)
Regimen of pre-transplant antiviral treatments	
IFN	6
IFN and RBV	15
RBV	8
Unknown	2
Universal prophylaxis	75 (44.4)
Preemptive treatment	15 (8.9)
Post-transplant antiviral treatment	
No treatment	81 (47.9)
IFN	4 (2.4)
IFN and RBV	74 (43.8)
RBV	9 (5.3)
Unknown	1 (0.6)
First protocol biopsy	
None	138 (81.7)
<3 months	11 (6.5)
3~6 months	8 (4.7)
6~12 months	5 (3.0)
≥1 year	7 (4.1)
Interval of HCV RNA examination	
None	2 (1.2)
Every visits	103 (60.9)
<3 months	32 (18.9)
3~6 months	14 (8.3)
6~12 months	8 (4.7)
≥1 year	10 (5.9)
HCV recurrence	97 (57.4)
HCV recurrence based on pathology	37
HCV recurrence based on HCV RNA	52
HCV recurrence based on LFT	41
SVR	
Non-response	24
SVR achieved	64
Not assessed	9

Data are presented as number (%).
Abbreviations: IFN, interferon; RBV, ribavirin; HCV RNA, hepatitis C virus ribonucleic acid LFT, liver function test; SVR, sustained viral response.

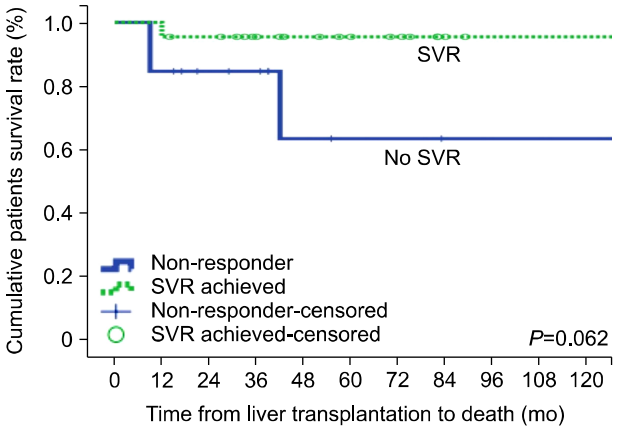

Fig. 3. Patient survival according to SVR. Patient survival in patients with SVR was higher than in patients without SVR, but there was no statistically significant difference in patient survival between the two groups. Abbreviations: SVR, sustained viral response.

tion because our study excluded patients with operative mortality, hospital mortality, and re-transplantation. The proportion of *IL28B* in Korea is higher than in European countries(6). The observation period of the databases used in Western countries was longer than the database used in Korea, which might reflect a bias from advances in surgical techniques and perioperative management in LT.

Post-transplant viral load is an important marker of disease severity, while pre-transplant viral load predicts more severe HCV recurrence after transplantation(16). Negative HCV viral load at the time of transplantation does not preclude HCV recurrence in the liver graft. A peak post-transplant HCV viral load $>10^7$ IU/mL was an independent predictor of graft loss and mortality(17). Our present study revealed that a high viral load was associated with mortality, but a cut-off value for the HCV RNA level was not drawn. Universal prophylaxis should be initiated soon after LT because the viral load is at its lowest level and fibrosis in the graft is absent(18). However, antiviral therapy may be less effective in the early post-transplant period secondary to strong immunosuppression, and tolerance is low because of the high risk of poor hematological tolerance, acute rejection, and sepsis(19,20). In the present study, the incidence of biopsy-proven acute rejection in patients with universal prophylaxis was higher than in patients without universal prophylaxis.

Post-transplant patients with HCV recurrence have significantly diminished survival compared to post-transplant patients with no recurrence. The progression of recurrent HCV is variable and the key risk factors remain unclear. Many factors have been reported to play a role prior to LT (genotype 1, viral load, and female gender) or after LT (time of cold or warm ischemia, blood transfusions, steatosis in the liver graft, age of the donor, the use of anti-lymphocytes, and co-infection with HIV)(8,21). The early detection of HCV recurrence is crucial because HCV-infected

Table 5. Comparison of patients with and without biopsy-proven acute rejection

	No BPAR (n=130)	BPAR (n=39)	*P*-value
Gender (male)	89 (68.5)	29 (74.4)	0.554
Recipient age ≥60	42 (32.3)	10 (25.6)	0.553
HCV genotype			0.585
Unknown	8 (6.2)	1 (2.6)	
Type 1	86 (66.2)	25 (64.1)	
Type 2	30 (23.1)	12 (30.8)	
Type 3	4 (3.1)	0 (0)	
Type 6	2 (1.5)	1 (2.6)	
Coexistence of HBV	17 (13.1)	4 (10.3)	0.786
Coexistence of HCC	62 (47.7)	15 (38.5)	0.362
LDLT	105 (80.8)	32 (82.1)	0.858
Donor age ≥30	77 (59.2)	23 (59.0)	0.977
Donor gender (male)	91 (70.0)	32 (82.1)	0.156
HCV RNA	156,885 (12～26,000,000)	63,493 (120～62,000,000)	0.077
MELD score	16 (6～50)	15 (9～40)	0.685
Cold ischemic time	81 (8～1437)	84 (27～463)	0.670
Basiliximab induction	92 (70.8)	13 (33.3)	<0.001
Main immunosuppression			<0.001
None	3 (2.3)	0 (0)	
Cyclosporin	55 (42.3)	33 (84.6)	
Tacrolimus	72 (55.4)	6 (15.4)	
MMF	84 (64.6)	21 (53.8)	0.260
Universal prophylaxis	47 (36.2)	28 (71.8)	<0.001
Preemptive treatment	11 (8.5)	4 (10.3)	0.751
Follow-up duration (mo)	38.5 (1～151)	27 (1～157)	0.019

Data are presented as number (%) or median (range).
Abbreviations: BPAR, biopsy-proven acute rejection; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil.

patients appear to respond better to early antiviral therapy(21). The current clinical standard for early detection is for protocol liver biopsies to be performed every 1 to 2 years after LT, as HCV-infected recipients are at increased risk of HCV-mediated graft cirrhosis(22). Antiviral treatment is delayed until there is histological evidence of recurrent hepatitis in many transplantation centers. However, none of the centers in the present study performed these protocol biopsies.

The successful treatment of recurrent HCV, which is demonstrated by sustained HCV clearance or an SVR, is associated with reduced liver-related mortality and improved overall survival. The combination of PEG-IFNα and RBV is the current standard of care(8,23). Our study also revealed this effect in the SVR group in recurrent HCV patients, but this did not reach statistical significance. However, the PHOENIX trial of PEG-IFNα and RBV given preemptively after the transplant for HCV found no clear benefits when considered in the context of side effects(20). In a very small study, donor or recipient *IL28B* genotypes were shown to predict SVR with PEG-IFNα and RBV therapy, and *IL28B* status was related to SVR after LT(24). However, this effect of the *IL28B* genotype was not identified in the present study, and our study did not reveal an association between *IL28B* and patient survival.

Prognostic factors, including recipient age >60 years, DDLT, the use of cyclosporin, and biopsy-proven acute rejection, were closely associated with patient mortality. HCV-related post-transplant cirrhosis has increased with the increasing use of stronger immunosuppression(8,10). However, data on the relative risk of different immunosuppressive agents are highly controversial. Cyclosporin has weak antiviral activity against HCV replication *in vitro*(25). Some studies have suggested that SVR rates are higher in patients

receiving cyclosporin compared with those receiving MMF or tacrolimus(26,27), and that the risk of HCV recurrence in the cyclosporine group has been shown to be lower than in the tacrolimus group(28). The effect of calcineurin inhibitors on HCV progression is highly controversial, with conflicting data exist regarding the relative risk of tacrolimus compared with cyclosporine. Most prospective studies suggest that there is no difference between cyclosporin-based regimens and tacrolimus-based regimens for liver histology, acute rejection, graft survival, or mortality(29,30). A recent analysis of the Scientific Registry of Transplant Recipients demonstrated that tacrolimus is associated with reduced mortality and graft cirrhosis in HCV patients(31). These studies comparing cyclosporine and tacrolimus supported the notion that tacrolimus might provide protection against graft cirrhosis in HCV recurrence. However, there is insufficient evidence to recommend the use of one calcineurin inhibitor over another because appropriately powered randomized controlled trials comparing antiviral therapies for recurrent HCV are lacking.

Acute rejection in conjunction with cyclosporine treatment is one of the most critical factors that influence patient survival. There are adverse effects of both early and repeated episodes of acute cellular rejection and its treatment on the progression of HCV graft fibrosis(32). Our study suggests that careful avoidance of acute rejection in the post-transplant period through adequate use of tacrolimus is a preferable strategy, because cyclosporin is associated with a greater incidence of acute rejection.

The findings of this retrospective, multicenter study are limited by several factors inherent to the study type, including variability in documentation, differences in the selection criteria and data collection, and missing data. To minimize variability, we sent a standardized collection form containing 56 questions to the transplant centers. The answers were either multiple-choice or involved providing a name or a specific value. However, the quality of the pre-transplant interviews from which the baseline data were derived, and the quality of the post-transplant follow-up data across the three centers may have varied. Furthermore, subjects had varying follow-up durations. We did not have data on the onset of biopsy-proven acute rejection or the date of graft failure. To address these limitations, a well-designed prospective study is needed.

CONCLUSION

This retrospective analysis of the largest three liver transplantation centers for HCV RNA-positive recipients in Korea revealed 1-, 3-, and 5-year survival rates of 78.8%, 75.3%, and 73.1%, respectively. The prognostic factors for patient survival except hospital mortality revealed that recipient age >60 years old, DDLT, the use of cyclosporin, and biopsy-proven acute rejection are closely associated with patient mortality. Based on the present results, calcineurin inhibitor selection for HCV RNA-positive recipients should be carefully reviewed to prevent biopsy-proven acute rejection and to improve patient survival.

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