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Virological response for recurrent hepatitis C improves long-term survival in liver transplant recipients

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Summary

Recurrent hepatitis C virus (HCV) infection occurs universally and is regarded as a major cause of mortality after liver transplantation (LT) for HCV-related end-stage liver disease. We conducted this large, single-center, retrospective study to ascertain the long-term impact of virological response to treatment of recurrent hepatitis C on survival of LT recipients. From August 1987 to October 2011, 285 patients have received interferon-based antiviral therapy for recurrent hepatitis C. Of these 285, 245 patients were enrolled in this study. One hundred and twenty-six patients (51.4%) achieved sustained virological response (SVR). Relapsers (undetectable HCV-RNA at end of treatment, becoming positive afterward) comprised 9.0% (22/245), and nonresponse (NR; never achieving undetectable HCV-RNA) 39.6% (97/245). The median follow-up after completion of antiviral treatment was 2081 days. Using Kaplan–Meier method, patients who achieved SVR were shown to have significantly better 5-year patient survival (95.2%) than the NR group (49.9%) ($P < 0.001$), and a trend toward better 5-year survival than relapsers (87.5%) ($P = 0.14$); relapsers had a significantly longer survival than NR group ($P = 0.005$). When compared with NR, SVR and relapse appeared to be significant predictors of better survival, independent of underlying characteristics. In conclusion, virological response, especially SVR, translates into markedly improved long-term patient outcomes in patients transplanted for hepatitis C.

Introduction

End-stage liver disease secondary to chronic hepatitis C virus (HCV) infection is still the leading indication for liver transplantation (LT) [1]. HCV re-infection of the graft occurs universally. Recurrence progressing to graft cirrhosis in 10–30% of recipients within 3–5 years is reported [2,3], and graft failure secondary to recurrent hepatitis C is the most common cause of patient death and retransplantation within 5 years of LT [4].

Current standard therapy for HCV recurrence post-LT is pegylated interferon (PEG-IFN)-α in combination with ribavirin (RBV). Progression of fibrosis demonstrated on serial liver biopsies typically prompts the introduction of antiviral therapy [5]. Although the use of antiviral therapy is widespread in recurrent hepatitis C, sustained virological response (SVR) rates are generally poorer than in the nontransplant setting [6–13]. However, importantly, several reports have indicated improved long-term survival of recipients achieving SVR when treated for recurrent hepatitis C [14–16].

We have previously published preliminary data on the outcomes of virological response for recurrent hepatitis C in LT recipients [17]. In this current report, we conducted a retrospective study afresh to ensure the extended long-term efficacy of any virological response in LT recipients with HCV recurrence, involving the largest number of patients ever published as a single-center experience, to our best knowledge.

Patients and methods

The study was approved by the Research Ethics Board of the University Health Network (Toronto, Canada).

Patients

This is a single center, retrospective study of all consecutive patients who underwent LT for HCV-related end-stage liver disease from August 1987 to October 2011, and were then treated for recurrent hepatitis C. A total of 677 adult patients underwent LT for this indication in our center during this period. All patients were followed until October 2011 or until their death. Graft failure was defined as occurring at the time of retransplantation or death. Pretransplant characteristics were collected retrospectively via the Organ Transplant Tracking Registry software (OTTR; HKS Medical Information Systems, Omaha, NE, USA), an internal Web-based transplantation database linked to the electronic medical record of all patients evaluated for a solid organ transplant at the University Health Network. All the liver grafts were from brain dead donors or living donors.

Immunosuppression

Patients received immunosuppressive agents according to previously published internal protocols [18]. Steroids were given preoperatively (methylprednisolone, 500 mg intravenously), with a rapid taper to prednisone (20 mg daily by mouth) after 6 days and a more gradual taper over the ensuing 3–6 months. In living donor liver transplantation recipients, antithymocyte globulin (1.5 mg/kg of body weight intravenously and daily for 5 days) was in routine use until December 2005; basiliximab (20mg intravenously on postoperative day 0 and 4) was introduced from January 2006 onward. Some of the deceased donor liver transplant recipients received induction therapy, including OKT-3, basiliximab or antithymocyte globulin for reasons, including renal or neurological sparing, mainly to delay the introduction of calcineurin inhibitors. Maintenance immunosuppression consisted of a double or triple-drug regimen that included tacrolimus or cyclosporine and prednisone, with or without mycophenolate mofetil (MMF) added for those patients who required cyclosporine or tacrolimus dose reduction. The tacrolimus was monitored by the trough level, and cyclosporine was monitored by the blood concentration level at 2 h postdose (C2).

Histological analysis

Recipients undergoing LT for hepatitis C in our program had liver biopsies as clinically indicated until 2000; since 2001, recipients have been protocolized for liver biopsies at 6 and 12 months post-LT and yearly thereafter. Additional biopsies were performed only when clinically indicated. All liver biopsies were read by one of three experienced liver pathologists (SF, MG and OA), and HCV recurrence was diagnosed based on the typical appearance of mononuclear portal infiltrate with lobular necroinflammation [19]. Activity grade and fibrosis stage were scored according to Metavir [20]. All the histopathologic results in this current study were based on the original reports at the time of the corresponding biopsies.

Protocol for treatment of HCV recurrence post-LT

All serum HCV RNA-positive patients with histopathologic recurrence and Metavir fibrosis stage greater than or equal to 1 (mostly more than 2) and/or Metavir activity grade more than or equal to 2 were considered for antiviral therapy. The usual contraindications to an antiviral treatment were applied (pretreatment neutrophils $<1.0 \times 10^9$/l, platelets $<40 \times 10^9$/l, hemoglobin <100g/l, decompensated liver disease, evidence of acute cellular rejection (ACR) within 3 months prior to starting therapy, evidence of chronic ductopenic rejection, serum creatinine >150 umol/l, history of or ongoing severe psychiatric disorders).

Of 677 consecutive patients undergoing LT for end-stage liver disease related to HCV from August 1987 to October 2011, 361 (54%) fulfilled the aforementioned criteria for antiviral treatment as of October 2011; the first commencing treatment was in June 1998. Of these 361 eligible patients, 70 (19%) had one or more of the aforementioned contraindications for IFN/PEG-IFN and RBV, and six (2%) patients declined to receive antiviral treatment. The remaining 285 patients (79%), including nine who have been treated on the basis of activity grade ≥2 without histopathological fibrosis (based on the findings of more progression of fibrosis in the patients with significant histological activity early post-LT [21]), and seven who have been treated for the fibrosing cholestatic variant of HCV recurrence, have received antiviral therapy for recurrent hepatitis C. Antiviral treatment was mostly started immediately once the result of the corresponding biopsy was reviewed.

Patients received antiviral treatment for recurrent hepatitis C according to previously published internal protocols [17].

Statistical analysis

We used the SPSS 17.0 statistical software (SPSS Inc., Chicago, IL) to analyze the relevant data. Continuous variables were summarized with mean (SD) or median (range), whereas categorical variables were presented with

proportions, and Student's *t*-test, Fisher's exact test, or ANOVA were used for group comparisons as appropriate. Patient and graft survival since the completion of antiviral treatment for recurrent hepatitis C was calculated using the Kaplan–Meier method and compared using the log-rank test.

Cox–regression hazard model was conducted assessing risk factors for patient death after the completion of antiviral treatment for recurrent hepatitis C. On the basis of clinical importance, univariate model included the following variables; virological response (NR/SVR/relapse), recipient age (by every 1 year), male gender (versus female), BMI at LT (by every 1 kg/m^2), donor age (by every 1 year), MELD at LT (by every 1 point), LDLT (versus DDLT), presence of hepatocellular carcinoma (HCC) at LT, HCV genotype 2 or 3 (versus others), antiviral treatment since Aug 2003 when Peg-IFN + RVB became available in Canada (versus prior to July 2003), cyclosporine-based immunosupression (versus tacrolimus-based), interval between LT and antiviral treatment (per year), pretreatment activity grade 3 (versus 0/1/2, as per Metavir), pretreatment fibrosis stage 3/4 (versus 0/1/2, as per Metavir), pretreatment platelet count (by every 10^9/l), duration of antiviral treatment (by every 1 month). To optimize the number of covariates [22], only variables both with clinical validity and statistical significance of at least 0.10 on the univariate analysis were then applied for the multivariate Cox–hazards model; virological response, donor age, retransplantation before antiviral treatment, HCV genotype, and pretreatment fibrosis stage 3/4 were chosen. The results of Cox–hazard model were shown using hazard ratio (HR) estimates, together with corresponding 95% confidence intervals (CIs) and Wald's test *P*-values. The *P*-values of < 0.05 were considered significant.

Results

Of all the 285 patients undergoing antiviral therapy for recurrent hepatitis C, 40 patients were excluded from this current study; 33 were on treatment at the most immediate follow-up before study entry (October 2011), one had achieved end-of-treatment response (ETR, undetectable HCV RNA at the end of the antiviral therapy), but died of sepsis while awaiting sustained virological response (SVR, defined as HCV-RNA negativity, determined using reverse transcription polymerase chain reaction, 6 months after cessation of antiviral therapy), three had ETR, but were awaiting SVR, and three died while on antiviral treatment (all caused by severe HCV recurrence). The remaining 245 patients were included in the analysis and were categorized as SVR, relapse (achieving ETR, but becoming positive afterward), and nonresponse (NR; never achieving undetectable HCV-RNA). The median follow-up period of these 245 patients from the time of LT was 2720 (range, 96–8841) days.

Of the 245 patients included in the study, 126 (51.4%) achieved SVR; 40.0% (64/161) in genotype 1, 80.1% (46/

Table 1. Characteristics of the patients according to virological response (*n* = 245).

	SVR (*n* = 126)	Relapse (*n* = 22)	NR (*n* = 97)	*P* value
Male gender, *n* (%)	98 (78)	15 (68)	75 (77)	0.61
Recipient age (years)	52 ± 7.4	56 ± 7.6	52 ± 9.3	0.12
BMI (kg/m^2)	27 ± 5.6	27 ± 8.4	27 ± 4.8	0.88
LDLT, *n* (%)	26 (21)	2 (9)	28 (29)	0.10
Donor age (years)	45 ± 14	48 ± 18	49 ± 15	0.14
HCC at LT, *n* (%)	52 (41)	10 (45)	46 (47)	0.43
HCV genotype 2/3, *n* (%)	46 (37)	2 (9)	9 (9)	<0.001
Cyclosporine A-based IS, *n* (%)	73 (58)	8 (36)	56 (58)	0.14
Pretreatment activity grade ≤2*, *n* (%)	108 (86)	16 (72)	86 (89)	0.53
Pretreatment fibrosis stage ≤2*, *n* (%)	103 (82)	17 (61)	67 (69)	0.09
Pretreatment platelet count (10^9/l)	127 (46–275)	131 (61–269)	124 (38–291)	0.71
Fibrosing cholestatic hepatitis, *n* (%)	1 (1)	1 (5)	5 (5)	0.14
Interval between LT and start of therapy (years)	2.9 ± 3.1	2.8 ± 2.5	2.9 ± 3.3	0.40
Antiviral treatment since Aug 2003 (versus prior to July 2003), *n* (%)	110 (88)	20 (91)	85 (88)	0.51
PEG-IFN/RBV, *n* (%)†	117 (93)	22 (100)	89 (91)	0.33
Duration of antiviral treatment (months)	10 +/– 6.3	12 +/– 5.6	11 +/– 8.6	0.22
Retransplantation before AVT	2 (2)	1 (5)	4 (4)	0.46

SVR, sustained virological response; NR, nonresponse; BMI, body mass index; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LT, liver transplantation; IS, immunosupression; IFN, interferon; PEG-IFN, pegylated interferon; RBV, ribavirin; AVT, antiviral treatment.

Unless otherwise indicated, data are given as the mean ± SD. HCV genotype was not available in 11 patients.

*As per Metavir.

†Others received IFN monotherapy or in combination with ribavirin.

57) in genotype 2/3, 61.5% (8/13) in genotype 4, and 57.1% (8/14) in other genotypes. Relapsers comprised 9.0% (22/245), and NR group 39.6% (97/245). The proportion of patients infected by HCV genotype 2/3 was significantly lower in relapsers and NR than SVR group. The other characteristics showed no significant differences among three groups (Table 1).

Graft failure

The causes of graft failure are summarized in Table 2. Of the 245 patients, 62 patients died during the follow-up period; 45 of liver related disease (37 of recurrent HCV, four of recurrent HCC, one of hepatic artery thrombosis, and three of chronic rejection), and 17 died of nonliver related causes (six of cardiac disease, one of renal disease, one of bladder cancer, one of pancreatic cancer, seven of sepsis and one of intracranial hemorrhage). None of the SVR group lost their graft because of recurrent hepatitis C. There were no significant differences in deaths owing to nonliver causes or recurrent HCC among each category of virological response. All the patients who died because of HCC had been diagnosed with HCC prior to LT. Twelve patients underwent retransplantation. Only one patient, a relapser, underwent retransplantation for recurrent hepatitis C. The remaining eleven patients underwent retransplantation for non-HCV liver diseases; seven patients before the introduction of antiviral treatment (five for hepatic artery thrombosis, one for chronic rejection, and one for bile duct problem), and four patients post-antiviral treatment (one for hepatic artery thrombosis, one for chronic rejection, and two for bile duct problems). Graft failure because of rejection post-antiviral treatment occurred in four patients (all proven to be chronic rejection by liver biopsy or histopathology of explanted graft, one death and one retransplantation in SVR group, and two deaths in NR group, $P = 0.87$; none of the patients lost their graft because of acute cellular rejection during or after antiviral treatment).

The Kaplan–Meier analysis for patient and graft survival

The patient survival categorized by virological response are shown in Fig. 1 (the median follow-up period, as the end of antiviral treatment was 2081 [range, 42–4350) days]. Patients who achieved SVR had significantly better overall survival (95.2% at 5 years) than the NR group (49.9% at 5 years) (log rank test, $P < 0.001$), and a trend toward better overall survival than relapsers (87.5% at 5 years) (log-rank test, $P = 0.14$); relapsers had a significantly better survival rate than NR (log-rank test, $P = 0.005$). The 5-year graft survival of SVR group and relapsers (92.3% and 81.3% respectively) was significantly greater than NR group (48.5%), as shown in Fig. 2(log-rank test, $P < 0.001$).

Impact of virological response on patient survival using cox regression hazard model

On univariate Cox–hazard model, SVR [HR = 0.10 (0.05–0.19), $P < 0.001$, versus NR], relapse [HR = 0.20

Table 2. Cause of graft failure (retransplantation and death, $n = 245$).

Cause	Total ($n = 245$)	SVR ($n = 126$)	Relapse ($n = 22$)	NR ($n = 97$)
Liver related (overall) (%)	57 (23)	7 (6)	4 (18)	46 (47)
Death (%)	45 (18)	2 (2)	2 (9)	41 (42)
Recurrent HCV	37	0	1	36
Recurrent HCC*	4	1	1	2
Other causes†	4	1	0	3
Re-LT (%)	12 (5)	5 (4)	2 (9)	5 (5)
Recurrent HCV (pre/post-antivirals)	1 (0/1)	0 (0/0)	1 (0/1)	0 (0/0)
Other causes (%) (pre-/post-antivirals)†	11 (7/4)	5 (2/3)	1 (1/0)	5 (4/1)
Nonliver related (all death) (%)**	17 (8)	6 (5)	1 (5)	10 (10)
Cardiac	6	4	0	2
Renal	1	1	0	0
Nonliver malignancies	2	0	0	2
Sepsis	7	1	1	5
Intracranial hemorrhage	1	0	0	1

SVR, sustained virological response; NR, nonresponse; HCV, hepatitis C virus; LT, liver transplantation; HCC, hepatocellular carcinoma.

*$P = 0.41$.

**$P = 0.25$

†Includes chronic rejection, hepatic artery thrombosis, and bile duct problem.

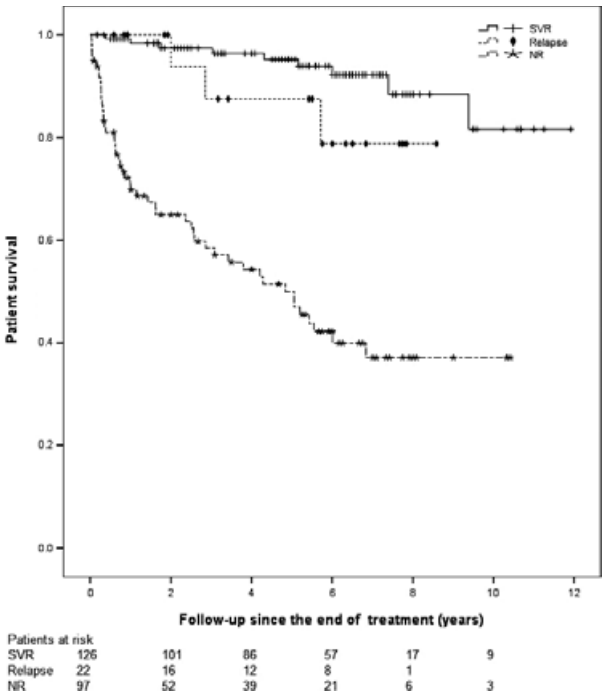

Figure 1 Patient survival starting at the end of antiviral treatment. Patients with sustained virological response (SVR, $n = 126$) and relapse ($n = 22$) showed a significantly lower mortality than those with nonresponse (NR, $n = 97$; log-rank test: $P < 0.001$).

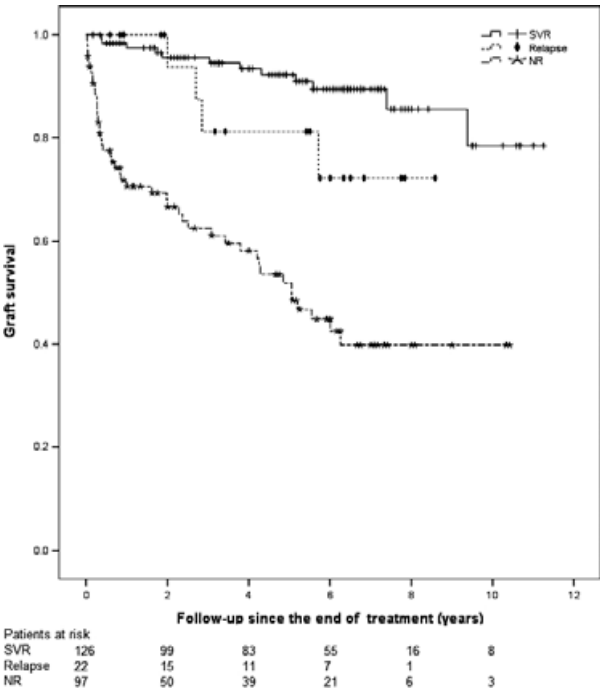

Figure 2 Graft survival starting at the end of antiviral treatment. Patients with sustained virological response (SVR, $n = 126$) and relapse ($n = 22$) showed a significantly lower rate of graft loss than those with nonresponse (NR, $n = 97$; log-rank test: $P < 0.001$).

(0.06–0.64), $P = 0.007$, versus NR], and pretreatment fibrosis stage 3/4 (versus 0/1/2) [HR = 1.80 (1.06–3.05), $P = 0.029$] were the only variables significantly associated with a decreased probability of overall patient death. On multivariate Cox–hazard model, SVR [HR = 0.091 (0.04–0.21), $P < 0.001$] and, to a lesser extent, relapse [HR = 0.19 (0.06–0.63), $P = 0.006$], when compared with NR, independently reduced the risk of overall death. None of the other factors showed statistically significant impact on patient survival in this multivariate analysis. The results of the Cox–hazard model are shown in Table 3.

Discussion

SVR following antiviral therapy in the nontransplant setting has been convincingly shown to improve the clinical outcome, including histopathological fibrosis stage [23,24] and patient survival [25,26]. ETR has also been suggested to be associated with improved histopathological activity and fibrosis [23], which might contribute to improved patient survival, although this has not been determined. In contrast, information about the impact of virological response on patient survival post-LT for end-stage liver disease related to hepatitis C has been scarce until recently. In addition, it has been reported that antiviral treatment in this setting has lower efficacy than in the nontransplant setting (the mean SVR rate in the literature is 30.2% (range, 8–50%) [7], and higher (approximately 50%) in this current study and our previous publication as well [17]), and could cause significant side effects, such as cytopathic or immune mediated graft damage as well as the common complications, described in nontransplant patients [27]. Of note, several studies have reported the favorable impact of SVR in recurrent hepatitis C on patient survival using Kaplan–Meier analysis [14–16]. It has been also reported in some studies that SVR stabilized the progression of histopathological fibrosis caused by recurrent hepatitis C [10,28–30], which may contribute to the impact of SVR on patient or graft survival, whereas others failed to do so [31,32].

In this current study, we showed the results of a retrospective single-centered, long-term follow-up study in LT recipients for end-stage liver disease caused by hepatitis C, to corroborate the impact of virological response with IFN-based antiviral treatment on patient survival. In our current large cohort, importantly, we report that patients who achieved SVR or at least ETR with antiviral treatment enjoyed an independently significant benefit on survival, when compared with NR group. The authors recognize that survival rate should optimally be evaluated from 6 months after the completion of treatment, considering the accurate definition of responses to antiviral

Table 3. Risk of patient death since the end of antiviral treatment by Cox–hazard model.

	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Virological response						
NR	1			1		
SVR	0.095	0.05–0.19	<0.001	0.091	0.04–0.21	<0.001
Relapse	0.20	0.06–0.64	0.007	0.19	0.06–0.63	0.006
Age (by every 1 year)	1.01	0.98–1.04	0.61			
Male gender (versus female)	0.80	0.45–1.42	0.45			
BMI at LT (by every 1 kg/m^2)	1.05	0.97–1.06	0.58			
Donor age (by every 1 year)	1.02	0.99–1.03	0.10	1.01	0.99–1.03	0.40
MELD at LT (by every 1 point)	1.01	0.98–1.04	0.49			
LDLT (versus DDLT)	1.25	0.69–2.27	0.47			
Presence of HCC at LT	1.45	0.91–2.39	0.14			
HCV genotype 2 or 3 (versus others)	0.62	0.38–1.02	0.061	0.88	0.48–2.37	0.86
Antiviral treatment since Aug 2003 (versus prior to July 2003)	1.35	0.63–2.88	0.44			
Cyclosporine-based immunosupression (versus Tacrolimus)	0.93	0.57–1.55	0.79			
Interval between LT and AVT (by every 1 year)	0.99	0.91–1.08	0.86			
Pretreatment activity grade 3 (versus 0/1/2)*	1.02	0.5–2.06	0.96			
Pretreatment fibrosis stage 3/4 (versus 0/1/2)*	1.80	1.06–3.05	0.029	1.13	0.61–2.11	0.70
Pretreatment platelet count (by every 10^9/l)	0.98	0.92–1.06	0.69			
Duration of AVT	0.99	0.95–1.03	0.49			
Retransplantation before AVT	2.63	0.95–7.23	0.064	2.76	0.64–11.2	0.19

HR, hazard ratio; CI, confidential interval; NR, nonresponse; SVR, sustained virological response; BMI, body mass index; LT, liver transplantation; MELD, Model of End stage Liver Disease score; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; AVT, antiviral treatment.

*As per Metavir.

treatment. However, in the NR group, whose antivirological responses are defined at the end of treatment, patients who died before 6 months post-treatment would be eliminated from the analysis, and their survival rate would be overestimated. In addition, previous studies in this topic performed the survival analysis starting at heterogeneous time points (at the end of treatment [14], at LT [15], and at treatment initiation [16]). Thus, we finally chose to evaluate patient and graft survival starting at the end of the antiviral treatment. We have also tested the Kaplan–Meier analysis of patient survival starting at LT, at treatment initiation, and 6 months post-treatment in our patient cohort, all of which showed similar results indicating SVR and relapse showed significant survival benefit when compared with NR (data not shown). Some of the patients in this current study died soon after the completion of treatment (mostly in NR group), although we usually avoid antiviral treatment for patients with decompensated liver disease. Additional study is warranted to identify patients who would not benefit from anti-viral treatment before starting it.

Twelve patients received retransplantation, as their LT, however, seven of all 12 retransplanted patients underwent retransplantation before they received antiviral treatment for recurrent hepatitis C, and the indication for retransplantation performed post-antiviral treatment was recurrent hepatitis C in only one of five patients. Four patients (1.8%) developed graft failure because of chronic rejection post-antiviral treatment, an occurrence rate similar to that seen in liver transplant recipients overall [33].

A unique observation of the current study is relapsers in addition to SVR patients showed significantly higher survival rates than the NR group, although the underlying mechanism to support this finding remains unclear. In the nontransplant setting, a meta-analysis of three large randomized trials demonstrated that PEG-IFN reduced histopathological inflammation and fibrosis in patients with both an SVR and a relapse, but not in nonresponders [23]. However, the role of relapse on patient outcome after antiviral treatment for recurrent hepatitis C remains still unclear. We have reported that the necroinflamation improved, but fibrosis stage did not, in relapsers at mean of 12 months from completion of antiviral treatment for recurrent hepatitis C [17]. In addition, patients with NR often experienced discontinuation of treatment before the completion of therapy (usually within 3–6 months)

because of the detectable HCV-RNA during antiviral treatment, and they received antiviral treatment for less duration than virological responders (relapsers and SVR patients) who receive the treatment mostly for 12 months in this setting. Thus, virological responders should enjoy the longer time period with lower necroinflamation (or at least with lower viral load) than NR group. This could be potentially associated with survival benefit regardless of the long-standing virological effect. Previous reports, which indicated the survival benefit of antiviral treatment itself for recurrent hepatitis C compared with nontreated group might also support this hypothesis [16,34], although longer antiviral treatment itself did not show significant survival benefit in our current study. However, as the number of the relapsers in our current study is only 22, larger and prospective studies to evaluate the impact of ETR without SVR on graft fibrosis and patient/graft survival are clearly required.

Importantly, recent approval of direct-acting antiviral agents, such as boceprevir and telaprevir, combined with PEG-IFN and RBV offers a major advance in the management of HCV infection in nontransplant chronic hepatitis C [35], although these agents have not been recommended for use in the transplant setting owing to lack of reliable information about toxicities and potential drug interactions with calcineurin inhibitors [36]. Nevertheless, these regimens have the potential of also improving virological response in LT recipients with recurrent hepatitis C. The findings shown in our current study, demonstrating the survival benefit of both SVR and ETR, set the stage for these new regimens to also contribute significantly to improved patient survival. Additional studies of these agents in transplant setting are strongly warranted.

Our current study is limited by its retrospective and nonrandomized nature. The study group does not have a control arm (patients not receiving antiviral treatment for recurrent hepatitis C), and is heterogeneous regarding immunosuppressive regimen, type of antiviral treatment and its duration. NR group included more patients receiving LDLT and undergoing antiviral treatment with advanced fibrosis stage (≥3) than other groups, which might have been related to the poorer patient outcome, although neither of those reached statistical significance. We also could not acquire detailed data on the pretransplant IFN-based antiviral treatment for hepatitis C, as most of the patients undergoing LT in our center were referred from other hospitals; however, the majority was treatment naive. In addition, as we have previously published the article regarding the characteristics of a subset of this patient cohort with different virological response to antiviral treatment for recurrent hepatitis C [17], those aspects were not the actual focus of this current study. Nevertheless, this analysis is powered by the largest patient cohort enabling us to evaluate multivariate Cox–hazard regression analysis adjusted for underlining conditions and by the longest median follow-up period ever published, to our best knowledge.

In conclusion, LT recipients with recurrent hepatitis C achieving SVR, and to lesser extent relapsers, enjoy markedly improved long-term patient survival. Although prospective and randomized studies are needed to fully evaluate the impact of virological response (not only SVR, but ETR) on post-transplant patient survival, the findings in our current study should also be valid in the coming era of direct-acting antiviral agents.

Authorship

TT, NS and LL: participated in research design and data analysis. TT and LL: participated in the writing of the paper. GT, NS, ER and LL: participated in following up and data collection.

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