

## Retrospective Cohort Study

# Predictive factors for survival and score application in liver retransplantation for hepatitis C recurrence

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## Abstract

**AIM:** To identify risk factors associated with survival in patients retransplanted for hepatitis C virus (HCV) recurrence and to apply a survival score to this population.

**METHODS:** We retrospectively identified 108 patients retransplanted for HCV recurrence in eight European liver transplantation centers (seven in France, one in Spain). Data collection comprised clinical and laboratory variables, including virological and antiviral treatment data. We then analyzed the factors associated with survival in this population. A recently published score that predicts survival in retransplantation in patients with hepatitis C was applied. Because there are currently no uniform recommendations regarding selection of the best candidates for retransplantation in this setting, we also described the clinical characteristics of 164 patients not retransplanted, with F3, F4, or fibrosing cholestatic hepatitis (FCH) post-first graft presenting with hepatic decompensation.

**RESULTS:** Overall retransplantation patient survival rates were 55%, 47%, and 43% at 3, 5, and 10 years, respectively. Patients who were retransplanted for advanced cirrhosis had survival rates of 59%, 52%, and 49% at 3, 5, and 10 years, while those retransplanted for FCH had survival rates of 34%, 29%, and 11%, respectively. Under multivariate analysis, and adjusting for the center effect and the occurrence of FCH, factors associated with better survival after retransplantation were: negative HCV viremia before retransplantation, antiviral therapy after retransplantation, non-genotype 1, a Model for End-stage Liver Disease (MELD) score < 25 when replaced on the waiting list, and a retransplantation donor age < 60 years. Although the numbers were small, in the context of the new antivirals era, we showed that outcomes in patients

who underwent retransplantation with undetectable HCV viremia did not depend on donor age and MELD score. The Andrés score was applied to 102 patients for whom all score variables were available, producing a mean score of 43.4 (SD = 6.6). Survival rates after the date of the first decompensation post-first liver transplantation (LT1) in the liver retransplantation (reLT) group (94 patients decompensated) at 3, 5, and 10 years were 62%, 59%, and 51%, respectively, among 78 retransplanted individuals with advanced cirrhosis, and 42%, 32%, and 16% among 16 retransplanted individuals with FCH. In the non-reLT group with hepatic decompensation, survival rates were 27%, 18%, and 9% at 3, 5, and 10 years, respectively ( $P < 0.0001$ ). Compared with non-retransplanted patients, retransplanted patients were younger at LT1 (mean age  $48 \pm 8$  years compared to  $53 \pm 9$  years in the no reLT group,  $P < 0.0001$ ), less likely to have human immunodeficiency virus (HIV) co-infection (4% *vs* 14% among no reLT patients,  $P = 0.005$ ), more likely to have received corticosteroid bolus therapy after LT1 (25% in reLT *vs* 12% in the no reLT group,  $P = 0.01$ ), and more likely to have presented with sustained virological response (SVR) after the first transplantation (20% in the reLT group *vs* 7% in the no reLT group,  $P = 0.028$ ).

**CONCLUSION:** Antiviral therapy before and after retransplantation had a substantial impact on survival in the context of retransplantation for HCV recurrence, and with the new direct-acting antivirals now available, outcomes should be even better in the future.

**Key words:** Antivirals; Hepatitis C; Mortality; Prognosis; Retransplantation; Risk factors

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**Core tip:** Liver retransplantation for hepatitis C recurrence may be a subject of debate. This study was performed in order to assist patient selection for retransplantation in a context of donor scarcity. This retrospective multicenter study analyzed predictive factors for survival in a population of patients retransplanted for hepatitis C virus recurrence, including virological and antiviral treatment data. We also applied a previously published score to this population.

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## INTRODUCTION

Advanced liver disease caused by hepatitis C virus (HCV) is the leading cause of liver transplantation (LT) in Western countries<sup>[1,2]</sup>. The post-transplant detection of HCV ribonucleic acid (RNA) in the serum or graft is universal in pre-LT viremic patients<sup>[3,4]</sup>. Histologically documented chronic hepatitis C develops in approximately 70% of patients during the first year after LT<sup>[5]</sup>. Progression of this disease is particularly aggressive in transplanted patients, with a rapid evolution towards fibrosis (cirrhosis within approximately 9 to 12 years) when compared to immunocompetent individuals (cirrhosis within approximately 20-30 years)<sup>[4]</sup>, resulting in graft loss due to recurrent disease<sup>[6]</sup>. A previous study showed that patients with clinically compensated graft cirrhosis achieved a 1-year survival rate of 74%, but this rate fell to 41% in those with clinical decompensation<sup>[7]</sup>. In patients with established cirrhosis and graft failure, retransplantation (reLT) is the only therapeutic option<sup>[8]</sup>. However, because of organ shortages, cost issues, and poorer survival, the indications for reLT must be appropriate<sup>[9]</sup>. In previous studies, HCV-related disease did not indicate a poorer prognosis following reLT<sup>[9-21]</sup>, while other studies identified HCV recurrence as an independent predictive factor of mortality<sup>[22-24]</sup>. Few studies have evaluated risk factors for mortality among patients retransplanted for HCV recurrence<sup>[25-29]</sup>.

### **Predictive models for retransplantation**

In order to predict post-reLT survival and, therefore, aid in patient selection, several scores have been developed<sup>[30,31]</sup>. That most widely employed is the Rosen score<sup>[32]</sup>. However, like many others, this model was based on reLT cases in general and not just on cases of HCV recurrence.

The first score specifically designed for HCV-positive patients was published recently by Andres *et al.*<sup>[29]</sup>. This study analyzed registry data from the Scientific Registry of Transplant Recipients on 1422 individuals transplanted for HCV and retransplanted at least 30 d after the first transplant. In order to design a score that could predict survival after reLT, they identified six predictive variables associated with survival: recipient age at the time of the first transplant, interval elapsing between the two transplants, donor age, creatinine levels, international normalized ratio (INR), and serum albumin values before the second transplant.

Several factors currently influence the decision to retransplant patients who have experienced a recurrence of HCV after transplantation. These include factors related to the individual patient, the physician's judgement, transplant center policies and experience, and geographic donor organ availability. There are no uniform guidelines to indicate which patients with HCV recurrence should undergo reLT. A survey in 2003 showed that nearly all transplant centers in the United States were likely to offer reLT to patients experiencing

an HCV recurrence<sup>[33]</sup>. The scenario is likely to change radically with the development of new direct-acting antivirals (DAA). However, these drugs may not be available in some countries in the short- or medium-term.

The present study was performed in order to identify predictive survival factors in patients with HCV-related graft failure undergoing liver reLT before the era of new antivirals and to apply a previously published score<sup>[29]</sup> that predicts survival after reLT in recipients with HCV recurrence. Secondary objectives were to describe the natural history of HCV in retransplanted patients compared to their first transplantation and to describe a group of patients experiencing graft failure due to HCV recurrence who were not retransplanted in order to clarify which patients were selected for reLT, as there are no uniform criteria for reLT in the setting of HCV recurrence.

## MATERIALS AND METHODS

### **Study design and population**

This was a retrospective and multicenter study involving seven liver transplantation centers in France (Paul Brousse, Edouard Herriot, Beaujon, Saint Antoine, Pitié-Salpêtrière, Rennes and Henri Mondor Hospitals), and one center in Spain (La Fe Hospital). There were no specific recommendations regarding reLT criteria for HCV-related recurrence, and the indication for reLT depended on each center's policies. However, all centers generally indicated reLT in patients with graft failure, using the same criteria as those applied for the first transplantation. Protocol biopsies were performed yearly in all French centers, but not in the Spanish center. Immunosuppression protocols were similar, with the use of cyclosporine or tacrolimus, corticosteroids during the first 6-12 mo, and/or mycophenolate mofetil. Antiviral treatment policies were also similar; treatment was initiated with any degree of fibrosis or fibrosing cholestatic hepatitis, given that the clinical conditions were sufficient to undergo antiviral therapy.

We included patients aged 18 or older who had undergone LT for HCV-related disease and then reLT with HCV recurrence as the main indication between January 1994 and June 2012 (reLT group). HCV recurrence was confirmed histologically as the principal reason for reLT by prior biopsies or an explant displaying cirrhosis or fibrosing cholestatic hepatitis. Patients with hepatitis B (HBV) co-infection with positive HBV DNA after the first LT (LT1) were excluded.

In order to describe which patients were selected for reLT in the absence of uniform criteria for reLT in the setting of HCV recurrence, we also identified those transplanted for HCV-related disease and presenting with graft failure but who were not retransplanted (no reLT group). This group represented the population in whom reLT may have been indicated, as opposed to those with cirrhosis and no clinical decompensation, in whom reLT would not have been indicated. The

inclusion criteria were: patients aged 18 or older receiving LT between January 1994 and June 2012 for HCV-related disease and experiencing HCV recurrence in the form of Metavir F3, F4, or fibrosing cholestatic hepatitis (FCH) (confirmed histologically), presenting with clinical hepatic decompensation (defined as the presence of ascites, encephalopathy, variceal hemorrhage, or jaundice), who had not undergone reLT, and with positive serum HCV RNA after the first transplantation. Exclusion criteria were patients with HBV co-infection with positive HBV DNA after transplantation.

### Case identification

Retransplanted patients were identified by consulting prospectively maintained databases in the Spanish center and in five of the French centers or the database operated by the French Biomedicine Agency (Agence de la Biomédecine), which covered the two other French centers. This agency is a public organization under the supervision of the French Ministry of Health, whose responsibilities include organizing the procurement and transplantation of organs, tissues, and cells. All transplant centers in France are required to report all their cases to this agency.

To identify cases of non-retransplanted patients with advanced liver disease/FCH and graft failure in all centers, all patients transplanted for HCV-related disease were identified first. Subsequently, all post-LT biopsies revealing F3, F4, or FCH were included, and a chart review was performed in order to identify those patients presenting with hepatic decompensation (defined as the presence of ascites, encephalopathy, variceal hemorrhage, or jaundice).

### Data collection and definitions

After case identification, data were collected by consulting the prospectively maintained databases when available, which included several variables. Variables not available in the databases were collected through chart review in all centers.

### Regarding the first and second transplantations:

Donor age and gender, living or deceased donor, donor HCV serology, recipient age and gender, concomitant kidney transplantation, acute rejection episodes after LT, receipt of corticosteroid bolus, receipt of OKT3, maintenance immunosuppressive regimen, HCV treatment (medication and duration), reason for treatment discontinuation, HCV treatment response (as previously defined<sup>[34]</sup>), presence of hepatocellular carcinoma (HCC) prior to LT1, presence of alcoholic disease prior to LT1, human immunodeficiency virus (HIV) co-infection, diabetes mellitus pre or post-LT, Metavir fibrosis score on biopsies post-transplant, presence and timing of FCH, HCV viremia levels before LT1 and before reLT, HCV genotype, date and type

of hepatic decompensation, biochemical data 20-30 d after decompensation, fibrosis progression rate<sup>[35]</sup>, date and cause of death, reason for no reLT, and patient and graft survival (the latter being defined as the interval between the date of transplant and the date of hepatic decompensation or death).

### Regarding the second transplantation:

MELD score prior to transplant, pre-reLT bilirubin, pre-reLT creatinine, pre-reLT INR, pre-reLT albumin, date and type of decompensation, number of days of intensive care unit (ICU) hospitalization prior to reLT, date of graft failure (defined as clinical hepatic decompensation), and date and cause of death.

### Survival score

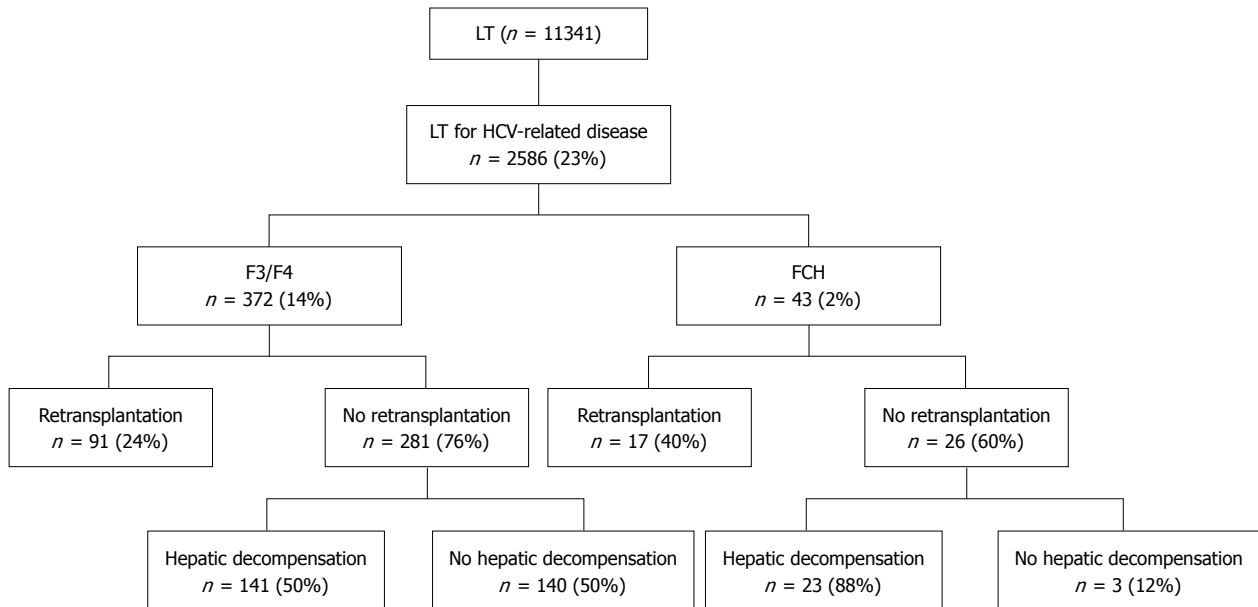
The survival score published previously by Andres *et al.*<sup>[29]</sup> was applied to all reLT cases for which such score variables were available. This score was calculated as follows:

$$(0.23 \times \text{donor age}) + (4.86 \times \text{creatinine log}) - (2.45 \times \text{interval between the first and second transplant log}) + (2.69 \times \text{INR}) - (0.10 \times \text{recipient age}) + (3.27 \times \text{albumin} + 40).$$

### Statistical analysis

The primary endpoint was to determine predictive factors for survival after reLT for a recurrence of hepatitis C. Graft and patient survival probabilities were determined using the Kaplan-Meier method and compared using the log-rank test. A Cox model with a likelihood ratio test was used to compare the difference in survival for continuous variables. Variables with a *P* value below 0.15 under univariate analysis were included in order to enable a stepwise multivariate evaluation using the Cox multivariate model, with the calculation of hazard ratios and corresponding 95%CI. Under multivariate analysis, a *P* value of 0.05 or lower was considered to be significant. A predictive model was constructed with the aim of predicting survival in individual patients retransplanted for hepatitis C recurrence according to the presence of prognostic factors<sup>[36]</sup>. For this, donor age was categorized as more or less than 60 years considering the scarcity of young donors, and MELD score superior or inferior to 25<sup>[37]</sup>. Data were compared between retransplanted and non-retransplanted patients using the  $\chi^2$  test for categorical data and the independent samples *t*-test for continuous data. Survival comparisons between the two groups were performed by taking account of the date of the first decompensation, considering that this could be the moment at which re-listing would be discussed. Differences between fibrosis progression rates were calculated using a paired *t* test. A *P* value of 0.05 or lower was considered to be significant. Statistical analyses were performed using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, United States).





**Figure 1** One hundred and eight retransplanted cases for hepatitis C virus recurrence and 164 not retransplanted F3/F4/ fibrosing cholestatic hepatitis cases presenting hepatic decompensation (in italics) after inclusion and exclusion criteria were applied. HCV: Hepatitis C virus; F3/F4: Metavir fibrosis score 3/4; FCH: Fibrosing cholestatic hepatitis.

## RESULTS

Between January 1994 and June 2012, 11341 LTs were performed in the eight study centers, and in 2586 (23%) patients, the main indication was HCV-related disease. Of these, 372 (14%) patients progressed to F3 or F4, and 91 patients were retransplanted. Forty-three patients (2%) presented FCH, and 17 of these were retransplanted, totaling 108 retransplanted patients. Figure 1 shows all cases that led to the final case selection. We also identified 164 patients with hepatic decompensation who did not undergo reLT (141 with F3 or F4 and 23 with FCH) prior to the data collection period. The center-based distribution of advanced fibrosis and FCH cases with and without reLT is described in Table 1. The mean interval elapsing between reLT re-listing and actual reLT was 151 d (1-1393), with no statistical difference between the groups ( $P = 0.22$ ). Explants revealed concomitant chronic rejection in three cases, non-alcoholic steatohepatitis in one case, and hepatocarcinoma in one case. In all other cases, HCV recurrence was the only diagnosis that led to reLT.

### Demographic and clinical characteristics

The principal clinical and demographic characteristics of the reLT patients were: mean age at LT1 of  $48 \pm 8$  years; mean age at reLT of  $54 \pm 8$  years; 81 (75%) were men; mean donor age at LT1 of  $51 \pm 15$  years; mean donor age at reLT of  $44 \pm 16$  years; none of the donors were seropositive for HCV; concomitant alcoholic disease in 20 patients (18%); HIV co-infection in four (4%); HCC at LT1 in 40 (37%); 84 patients (78%) presented with F4 after LT1, 18 (17%)

presented with FCH, and six (5%) presented with F3 and clinical hepatic decompensation; and 26 patients (25%) received corticosteroid bolus after LT1. The mean interval between LT1 and decompensation was 4.4 years (0.1-16.0). The mean interval between LT1 and reLT was 5.5 years (0.1-17.8). The mean MELD score 20-30 d after decompensation was  $21 \pm 7$ , and the mean MELD score before reLT was  $24.5 \pm 8.4$ . The first decompensation presented as ascites in 68 patients (68%), encephalopathy in 12 (12%), jaundice in 10 (10%), and variceal hemorrhage in 9 (9%).

### Survival and prognostic factors

Patient survival rates in the reLT group were 55%, 47%, and 43% at 3, 5, and 10 years, respectively, after the date of reLT. Patients who were retransplanted for advanced cirrhosis had survival rates of 59%, 52%, and 49% at 3, 5, and 10 years, while those retransplanted for FCH had survival rates of 34%, 29%, and 11%, respectively.

There were 28 cases of reLT before 2003, and 80 cases between 2003 and 2012. There was no statistical difference when survival was compared between these two periods ( $P = 0.26$ ).

Fourteen patients presented with a sustained virological response (SVR) after LT1. The survival rate in this group of patients was 86% at 5 years (12/14 patients), with a median reLT donor age of 44 years (14-62) and a median MELD score of 24 (14-38) (Table 2).

The risk factors associated with better survival under univariate analysis are shown in Tables 3 and 4. An Andrés score lower than 40 was significantly associated with better survival under univariate

**Table 1** Distribution of hepatitis C virus-related cases of advanced fibrosis/fibrosing cholestatic hepatitis cases after liver transplantation with and without liver retransplantation according to center *n* (%)

Center	<i>n</i> (LT)	LT related to HCV (percent of total LT)	F3/F4/FCH after LT (percent of LT for HCV)	F3/F4/FCH reLT (percent of LT for HCV)	F3/F4/FCH without reLT (percent of LT for HCV)
1	1933	770 (40)	174 (23)	31 (4)	143 (19)
2	2001	420 (21)	108 (26)	26 (6)	82 (20)
3	2124	412 (19)	20 (5)	12 (3)	8 (2)
4	1477	321 (22)	40 (12)	11 (3)	29 (9)
5	920	247 (27)	33 (13)	10 (4)	23 (9)
6	1576	141 (9)	16 (11)	8 (6)	8 (6)
7	450	143 (32)	16 (11)	8 (6)	8 (6)
8	860	132 (15)	8 (6)	2 (2)	6 (5)
Total	11341	2586 (23)	415 (16)	108 (4)	307 (12)

LT: Liver transplantation; reLT: Liver retransplantation; HCV: Hepatitis C virus; F3: Metavir score F3; F4: Metavir score F4; FCH: Fibrosing cholestatic hepatitis.

**Table 2** Donor age, MELD score, and outcomes in patients undergoing liver retransplantation for hepatitis C virus recurrence with undetectable hepatitis C virus viremia before liver retransplantation

reLT donor age (yr)	reLT MELD score	Outcome
14	35	Alive
19	22	Deceased
20	24	Alive
23	16	Alive
24	25	Alive
31	17	Alive
35	23	Alive
46	33	Deceased
47	38	Alive
52	26	Alive
58	21	Alive
60	28	Alive
62	14	Alive

reLT: Liver retransplantation; MELD: Model for End-stage Liver Disease.

analysis but not under multivariate analysis. Factors associated with survival under multivariate analysis are shown in Table 5, which concerns the 83 patients for whom all variables found to be significant under univariate analysis were available. Data were adjusted for the center effect and for the occurrence of FCH after LT1.

The causes of death among the 55/108 patients (51%) in the reLT group were as follows: septic shock of bacterial origin in 17 (31%), liver failure due to HCV recurrence in nine (16%), surgical complications during the perioperative period in seven (13%), hemorrhage in five (9%), multiorgan failure in four (7%), heart failure in two (4%), septic shock of fungal origin in two (4%), and other causes in eight (16%) (one case each of lymphoproliferative disorder, pulmonary embolism, renal insufficiency, septic shock of mycobacterial origin, non-liver solid cancer, and four unknown).

### Estimation of survival

An estimate of survival was calculated, based on the

presence of the five independent predictors of survival (Table 6). This table highlights two situations that underline the importance of HCV therapy after reLT. If modifiable factors were taken into account and a donor younger than 60 years was used, with the patient receiving antiviral treatment after reLT, estimated survival at 3 years was 73%. In contrast, the same situation but with no treatment after reLT generated a survival rate of only 18% at 3 years.

### Application of the score

The Andrés score was applied to the 102 patients for whom all score variables were available (in six patients, pre-reLT albumin values were not available), and this produced a mean score of 43.4 (SD = 6.6).

### Natural history

In the reLT group, 18/108 patients (17%) presented with FCH after the first LT. Of these, 5/18 (28%) progressed to FCH after reLT ( $P = 0.11$ ). Of the remaining 90/108 (83%) who did not present with FCH after LT1, six (7%) progressed to FCH after reLT.

In 52 patients with available pre and post-reLT biopsies, the mean fibrosis progression rate was 2.28 (0.27-16) Metavir units/year after LT1, compared to 1.49 (0-6.0) Metavir units/year after reLT ( $P = 0.051$ ). Of these, 13 (25%) received antiviral therapy before reLT (four patients presented with an SVR), and 11 (21%) received antiviral therapy after reLT (seven presented with an SVR).

Fifty-six of the remaining patients were not included in the analysis for the fibrosis progression rate for the following reasons: five did not undergo biopsies before reLT (so that the precise timing of fibrosis was not determined), 51 did not present biopsies with fibrosis after reLT (23 died within 90 d of reLT, six underwent biopsies that revealed lobular hepatitis, five had biopsies showing FCH, five had undetectable levels of HCV viremia before reLT, two presented with a sustained virological response after antiviral therapy following reLT, and ten for unknown reasons).

**Table 3** Univariate analysis of qualitative variables associated with survival in retransplanted patients for hepatitis C virus recurrence

Risk factor	n	Survival estimation			Log-rank P value
		3 yr	5 yr	10 yr	
HIV serology					
Negative	104	57%	49%	45%	0.006
Positive	4	0%			
IS after LT1					
Without MMF	82	58%	51%	47%	0.060
With MMF	26	45%	33%	0%	
Genotype 1					
No	23	69%	69%	69%	0.110
Yes	69	55%	45%	41%	
HCV viremia pre-reLT					
Negative	14	86%	86%	86%	0.005
Positive	94	50%	41%	36%	
Dialysis pre-reLT					
Yes	19	74%	67%	67%	0.060
No	89	51%	43%	37%	
Split graft at reLT					
No	101	57%	48%	44%	0.060
Yes	7	29%	29%	0%	
IS after reLT					
With tacrolimus	62	67%	57%	53%	0.038
Without tacrolimus	41	43%	37%	30%	
Antiviral therapy post-reLT					
Yes	35	85%	75%	64%	0.0003
No	63	44%	36%	36%	
Antiviral response post-reLT					
SVR	14	93%	93%	93%	0.039
Partial or NR	18	77%	59%	43%	
FCH post-LT1					
No	90	59%	52%	49%	0.018
Yes	18	34%	23%	0%	
Arterial complications post-reLT					
No	90	62%	53%	48%	0.030
Yes	11	27%	27%	27%	
Andres score > 40					
No	35	71%	64%	64%	0.019
Yes	67	49%	40%	37%	
Reinscription MELD < 25					
No	30	39%	34%	34%	0.026
Yes	72	66%	58%	51%	

HIV: Human immunodeficiency virus; IS: Immunosuppression; LT1: First liver transplantation; MMF: Mycophenolate mophetil; HCV: Hepatitis C virus; reLT: Liver retransplantation; SVR: Sustained virological response; NR: Non-responder; FCH: Fibrosing cholestatic hepatitis; MELD: Model for End-stage Liver Disease.

### No reLT group

Survival rates after the date of the first decompensation post-LT1 in the reLT group (94 patients decompensated) at 3, 5, and 10 years, were 59%, 55%, and 46%, respectively. In the non-reLT group with hepatic decompensation, survival rates were 27%, 18%, and 9% at 3, 5, and 10 years, respectively ( $P < 0.0001$ ).

Compared to non-retransplanted patients, retransplanted patients were younger at LT1 (mean age  $48 \pm 8$  years compared to  $53 \pm 9$  in the no reLT group,  $P < 0.0001$ ), less likely to have HIV co-infection (4% compared to 14% in the no reLT group,  $P = 0.005$ ), more likely to have received corticosteroid bolus after

**Table 4** Univariate analysis of quantitative variables associated with survival in retransplanted patients for hepatitis C virus recurrence

Risk factor	Hazard ratio	95%CI	P value
Less days under MV pre-reLT	1.25	1.02-1.52	0.031
Lower reLT donor age	1.02	1.00-1.04	0.017
Lower recipient age at LT1	1.04	1.00-1.08	0.027
Greater interval between LT1 and reLT	0.88	0.82-0.96	0.002

MV: Mechanical ventilation; reLT: Liver retransplantation; LT1: First liver transplantation.

**Table 5** Factors associated with survival according to multivariate analysis in patients undergoing liver retransplantation for hepatitis C virus recurrence, adjusted for center effect and fibrosing cholestatic hepatitis occurrence

Risk factor	Hazard ratio	95%CI	P value
Undetectable HCV viremia pre-reLT	8.80	1.96-39.39	0.004
Receipt of antiviral treatment after reLT	4.98	2.23-11.15	< 0.0001
ReLT donor age < 60 yr	3.54	1.42-8.82	0.007
Non-genotype 1	3.94	1.35-11.57	0.010
Reinscription MELD $\leq 25$	2.45	1.23-4.88	0.010

HCV: Hepatitis C virus; reLT: Liver retransplantation; MELD: Model for End-stage Liver Disease.

LT1 (25% in the reLT vs 12% in the no reLT group,  $P = 0.01$ ), and more likely to have presented with an SVR after the first transplantation (20% in reLT group vs 7% in no reLT group,  $P = 0.028$ ) (the data refer to 71 treatments in reLT group and 87 treatments in the no reLT group). Variables found to be similar in both groups included: acute rejection episodes after LT1, use of OKT3 after LT1, number of antiviral treatments, results of biochemical and hematological investigations up to 30 d after hepatic decompensation following LT1 (bilirubin, creatinine, INR, hemoglobin, platelets, sodium and albumin), genotype distribution, type of antiviral treatment, treatment duration, and rate of treatment discontinuation.

In the non-reLT group with hepatic decompensation, 20 (12.1%) of the 164 patients were re-listed or were undergoing a pre-reLT work-up for relisting at the time of data collection. The reasons for not replacing the remaining 144 patients on the waiting list were: death due to hepatic decompensation before relisting (30.6%), clinically considered as unsuitable because of hepatic, cardiac, renal, neurological, psychiatric or other systemic diseases (22.9%), advanced age (over 70 years) (11.8%), *de novo* cancer or HCC recurrence (6.9%), alcohol consumption (4.9%), stable without further decompensation (4.2%), under antiviral therapy at the time of data collection and would be considered for reLT depending on outcome (2.4%), poor compliance (2.8%), stabilized after a SVR (1.4%),

**Table 6** Survival estimation according to the presence of each of the independent mortality risk factors

RT inscription MELD > 25	Genotype 1	RT donor age > 60 yr	No antiviral treatment post-RT	HCV viremia pre-RT	Number of factors	Survival		
						1 yr	3 yr	5 yr
-	-	-	-	-	0	99.7%	99.5%	99.3%
+	-	-	-	-	1	99.1%	98.7%	98.3%
-	+	-	-	-		98.8%	98.1%	97.2%
-	-	+	-	-		99.0%	97.9%	97.0%
-	-	-	+	-		98.6%	97.7%	96.8%
-	-	-	-	+		98.0%	96.2%	94.8%
+	+	-	-	-	2	97.4%	95.3%	94.6%
+	-	+	-	-		97.7%	95.9%	94.3%
+	-	-	+	-		96.9%	95.1%	93.2%
-	+	+	-	-		96.0%	93.4%	90.8%
+	-	-	-	+		95.3%	91.7%	88.3%
-	+	-	+	-		94.8%	91.3%	87.9%
-	-	+	+	-		94.8%	90.7%	87.3%
-	+	-	-	+		91.3%	85.9%	81.0%
-	-	+	-	+		91.3%	85.7%	79.6%
-	-	-	+	+		87.0%	79.4%	71.2%
+	+	+	-	-	3	92.3%	87.8%	83.2%
+	+	-	+	-		89.4%	82.5%	76.4%
+	+	-	-	+		83.2%	73.1% <sup>1</sup>	63.9%
+	-	+	-	+		82.5%	72.1%	63.1%
-	+	+	+	-		82.0%	71.2%	61.9%
+	-	-	+	+		75.2%	61.4%	50.3%
+	-	+	+	-		72.5%	58.1%	47.0%
-	+	+	-	+		71.1%	56.3%	44.5%
-	+	-	+	+		61.2%	42.7%	30.2%
-	-	+	+	+		59.9%	41.6%	28.5%
+	+	+	+	-	4	67.2%	50.5%	37.9%
+	+	+	-	+		52.0%	32.4%	20.1%
+	+	-	+	+		36.9%	18.1% <sup>1</sup>	8.9%
+	-	+	+	+		35.7%	17.1%	8.3%
-	+	+	+	+		17.0%	4.5%	1.5%
+	+	+	+	+	5	2.8%	0.3%	0.0%

<sup>1</sup>Two situations that underline the importance of HCV therapy after reLT. HCV: Hepatitis C virus; MELD: Model for End-stage Liver Disease.

patient refused reLT (0.7%), reLT not possible due to surgical impediments (0.7%), and unknown (10.8%). The mean follow-up period was of 5796 d (62-9541).

## DISCUSSION

Because of the large number of patients with HCV recurrence seen at our transplantation centers, this multicenter and retrospective study is the first non-registry study to have been performed on reLT. Furthermore, it is also the first to have analyzed detailed virological data and antiviral therapies in this population, giving great importance to this factor when selecting patients with HCV recurrence for reLT, especially in the current era of direct-acting antivirals. In this context, the principal prognostic factors associated with the survival in our cohort were: negative HCV viremia before reLT, antiviral therapy after reLT, non-genotype 1, re-listing at MELD below 25, and a reLT donor age < 60 years. The non-retransplanted group was helpful in trying to explain the selection bias for and against an indication for reLT, as the decision to retransplant a patient with HCV recurrence depended on each center's policies.

The most important contribution of our study is

the evidence concerning the considerable influence of antiviral therapy before and after reLT. Previous studies had demonstrated the importance of treating HCV before and after LT<sup>1</sup><sup>[38-47]</sup>. During the period of our study, the new drugs that became available were protease inhibitors, and we included only one patient under sofosbuvir, one of the newer direct-acting antivirals. In the modern era of direct-acting antivirals, encouraging results have been achieved using interferon-free HCV regimens in the population of patients with advanced cirrhosis on the waiting list, with high SVR rates and low rates of serious adverse events requiring treatment discontinuation<sup>[48,49]</sup>. Studies of post-LT treatment with the new DAAs studies have demonstrated SVR rates ranging from 70%-94%<sup>[49-53]</sup>. Although the numbers in our study were small, we were also able to show that in the 14 patients undergoing reLT with undetectable HCV viremia, the reLT donor age and MELD score did not influence outcome. In the long-term, early antiviral treatment post-LT may become the standard-of-care and reduce the occurrence of advanced graft cirrhosis. However, the subpopulations of individuals presenting with genotype 3, end-stage renal disease, and resistance to DAAs remain a concern.



Several early studies had described high mortality rates in individuals retransplanted for HCV recurrence<sup>[25,26]</sup>, with more recent studies producing survival rates similar to ours<sup>[27,54]</sup>. Our reLT survival rates of 55%, 47%, and 43% at 3, 5, and 10 years, respectively, were not excessively disappointing given the LT survival rates for HCV cirrhosis alone reported in the literature, which average 75%, 65%, and 52% at 1, 3, and 5 years<sup>[55]</sup>. A minimum acceptable threshold for graft survival is difficult to define<sup>[56]</sup>. Previous meetings have suggested a minimum 5-year survival of 50% for reLT<sup>[57]</sup>. At 5 years, the patients in our cohort achieved a 47% survival rate, but no defined criteria for re-listing were applied. Better patient selection should, therefore, improve survival. Although the survival of the four HIV co-infected patients after reLT was extremely poor (no patient was alive at 3 years), in the context of new DAA, the response rates are promising in the non-transplanted population<sup>[58,59]</sup>. In a recent multicenter study on reLT in HIV-infected individuals, only four patients experienced an HCV recurrence requiring reLT, even though DAAs were not yet available<sup>[60]</sup>. Regarding the disappointing survival rates seen in non retransplanted patients compared to those undergoing reLT, many factors may have influenced this result, such as higher rates of SVR in the reLT group and possibly higher rates of comorbidities leading to contraindications for reLT.

In McCashland's study<sup>[27]</sup>, although the MELD score was not predictive of survival, higher MELD scores pre-reLT (> 25) were associated with mortality rates. However, that study was not designed to analyze predictive factors for survival. Our data analyses found that relisting with a MELD > 25 was associated with a poor prognosis but not the MELD score before reLT. In their no-reLT group with decompensated HCV recurrence, survival reached 47% at 3 years, compared to 27% in our study. The percentage of relisted patients in their study was similar to our findings (15% vs 12%).

One known factor to improve survival in the setting of HCV-related diseases is donor age<sup>[61]</sup>, and our data confirmed this finding in the context of reLT. Our estimation of survival not only demonstrated the importance of antiviral therapy but also the impact of donor age. This finding triggers another discussion regarding the futility of the procedure in an era of young donor shortages<sup>[62]</sup>. Although the numbers are small, we also showed that outcomes in patients who underwent reLT with undetectable HCV viremia did not depend on donor age. This issue warrants future evaluation in the context of the availability of new antivirals.

In the registry study by Andres *et al.*<sup>[29]</sup>, which proposed the score applied to our patients, several variables were not available from this registry, such as HCV genotype, level of viremia, type of anti-HCV treatment, and biopsy scores, all of which could have

markedly affected survival. In our study, patients with an Andres score over 40 had a 5-year survival rate of 40%, compared to an estimated survival of 27% in their cohort. One possible explanation for these discrepant results may have been their inclusion criteria (more than 30 d after reLT for all HCV-positive retransplanted cases), so that they did not solely include patients with HCV recurrence. In addition, our cohort may have included more severely ill patients. Our study was not designed to validate the score, as statistically the number of cases was still too small to offer new thresholds. Other previously published scores had either not been designed specifically for reLT in the event of HCV recurrence<sup>[12,32]</sup> or were derived from LT1 cases and then extended to reLT and, therefore, did not focus on this population<sup>[14]</sup>.

Our study did have some limitations. Considering that surgical techniques, immunosuppression regimens, antiviral treatment, anesthesiology, and intensive care have changed over the years, the long period we covered could have influenced survival. Notably, the survival rates were similar when our analysis compared reLT before and after 2003. Although our study included data from eight different liver transplantation centers, two of them contributed more than half of the reLT cases (57/108; 53%). As these two centers could be considered more experienced in this technique, an analysis was performed after adjusting for the center effect. No uniform criteria exist for reLT indication in HCV recurrence, and each center adopted its own policies. This analysis also applied to antiviral therapy before and after reLT. Another limitation was that the identification of cases for the non-reLT group was based on histological biopsies post-LT1, but because one center did not perform protocol biopsies, this group may have been under-represented. Furthermore, FCH was defined according to the pathologist's report, and, hence, may not have strictly followed previously accepted definitions of FCH<sup>[63-65]</sup>.

In conclusion, reLT in the context of HCV recurrence requires careful patient selection. From this present study, the first to analyze such detailed virological and treatment data, we can conclude that antiviral therapy both before and after reLT can play an important role when deciding whether to retransplant or not. In an era of new direct-acting antivirals agents, the scenario of retransplantation for HCV recurrence will most likely change dramatically in the future. The findings of our study could nevertheless be useful in the medium term while HCV recurrence is still prevalent, especially in limited-resource settings where direct-acting antivirals are not yet available.

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## COMMENTS

## Background

Advanced liver disease caused by hepatitis C virus (HCV) is the leading cause of liver transplantation (LT) in Western countries. Histologically documented chronic hepatitis C develops in approximately 70% of patients during the first year after LT. Progression of this disease is particularly aggressive in transplanted patients, with a rapid evolution towards fibrosis when compared to immunocompetent individuals, resulting in graft loss due to recurrent disease. In patients with established cirrhosis and graft failure, retransplantation (reLT) is the only therapeutic option. Because of organ shortages, cost issues, and poor survival, the indications for reLT must be appropriate. In previous studies, HCV-related disease did not indicate a poorer prognosis following reLT, while other studies have identified HCV recurrence as an independent predictive factor for mortality. Few studies, however, have evaluated risk factors for mortality among patients retransplanted for HCV recurrence.

## Research frontiers

Retransplantation for HCV recurrence has been a controversial issue because of the possibility of poorer survival compared to other indications. The published literature is scarce on this topic, as there are currently no formal recommendations as to which patients should undergo retransplantation in this context. A multicenter study was performed in order to analyze survival factors in this population.

## Innovations and breakthroughs

This is the first published study with a fair number of retransplantations for HCV recurrence to analyze, in terms of virological findings and HCV antiviral therapy, risk factors for improving better prognosis. In view of the new era of direct-acting antivirals and donor scarcity, the results of this study should aid in decision-making in the context of indications for retransplantation.

## Applications

In this new era of direct-acting antivirals and donor scarcity, the results of this study should aid with decision-making in the context of indications for retransplantation.

## Terminology

The recurrence of hepatitis C is universal among individuals transplanted for HCV-related cirrhosis and with a positive viral load prior to transplantation. Retransplantation may be indicated in those patients who progress to cirrhosis after HCV recurrence on the graft.

## Peer-review

This article addresses a very important topic in the era of chronic organ shortage. The authors have very nicely written a review of 108 patients retransplanted for HCV recurrence in eight European liver transplantation centers and analyzed the factors associated with survival in this population.

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