ORIGINAL ARTICLE

Simple prediction of long-term clinical outcomes in patients with mild hepatitis C recurrence after liver transplantation

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SUMMARY

Little is known about the long-term outcomes of mild hepatitis C recurrence after liver transplantation (LT). In an era where most patients request treatment with direct acting antivirals (DAAs), data on the natural history in these patients are relevant. We have prospectively assessed the clinical outcomes of 173 patients with mild hepatitis C recurrence 1 year after LT. The endpoints were cirrhosis development ($F = 4$, HVPG ≥10 mmHg, liver stiffness measurement ≥14 kPa) and HCV-related graft loss. After a median follow-up of 80 months, the cumulative probability (CP) of HCV-related graft loss 5 and 10 years after LT were only 3% and 10%, respectively. Graft cirrhosis developed in 26 (15%) patients over time, with a CP of 13% and 30% at 5 and 10 years after LT, respectively. The CP of cirrhosis 5 years after LT was only 8% in patients with a donor <50 years and AST <60 IU/l 1 year after LT ($n = 67$), compared with 46% in those 24 individuals with both risk factors. Our data support an excellent long-term outcome of patients with mild hepatitis C recurrence 1 year after LT. There are, however, some patients progressing to cirrhosis who can be easily identified and who should receive prompt antiviral therapy.

Transplant International 2016; 29: 698–706

Key words
direct acting antivirals, graft survival, mild hepatitis C, outcomes

Received: 18 May 2015; Revision requested: 20 August 2015; Accepted: 1 December 2015

Introduction

HCV infection induces an accelerated fibrosis progression in the graft after liver transplantation (LT); 30% of patients develop graft cirrhosis during the first years following transplantation [1–3]. Fortunately, the use of interferon-free (IFN-free) regimens will prevent HCV graft infection in a significant proportion of patients treated while awaiting LT [4] or eradicate HCV after LT [5–8]. Despite the American and European Guidelines for the management of hepatitis C recommend IFN-free treatments for all HCV-infected liver transplant recipients [9,10], the economic burden will limit their general use in the next few years. In most countries, patients with more advanced fibrosis undergo antiviral therapy with direct acting antivirals (DAAs), whereas patients with mild hepatitis C (even in the transplant setting) are told to wait. Nevertheless, most patients with mild hepatitis C recurrence after transplantation request information on the availability of DAAs and on their disease outcome if treatment is delayed.

doi:10.1111/tri.12730

Very few studies in this field have evaluated the long-term outcomes of patients with mild hepatitis C recurrence following a liver transplant, as the great majority of them aimed to identify variables related to graft loss and treatment efficacy in patients with severe hepatitis C recurrence. In this study, we prospectively assessed the clinical outcomes of a large cohort of patients classified as mild hepatitis C recurrence in a single transplant center.

Patients and methods

Patient population and collected data

All patients with end-stage liver disease or hepatocellular carcinoma (HCC) secondary to chronic hepatitis C infection who underwent LT at Hospital Clínic of Barcelona between May 1999 and March 2012 were considered in this study. Exclusion criteria were as follows: sustained virological response (SVR) to antiviral therapy while on the waiting list, HIV coinfection, kidney–liver simultaneous transplant, and death or retransplantation due to non-HCV-related causes during the first 6 months after LT.

To compare graft survival in patients with mild hepatitis C recurrence with a control group, we also evaluated the outcome of patients who underwent LT for reasons different than hepatitis C during the same time period (n = 425). We used identical exclusion criteria for this group.

Patients were followed by a standard protocol [3], and relevant variables were collected prospectively and included in a database, after approval by the Ethical Committee of the Hospital Clínic of Barcelona. All patients signed an inform consent to this purpose. Regarding transplant-related variables, we considered cold ischemia time and type of transplant (living donor LT, domino-amyloidosis, split, non-heart-beating donor). Donor age and gender were also registered. Among medical complications, the following variables were prospectively registered: biliary complications requiring interventional therapy, diabetes mellitus, acute graft rejection (including episodes requiring prednisone-based treatment), and cytomegalovirus infection [3].

Histological and noninvasive evaluation of HCV-related disease progression after LT

Until 2007, in all HCV-infected liver recipients' per-protocol percutaneous or transjugular graft biopsies (in most cases with HVPG measurements) were obtained at yearly intervals after transplantation. During the following 2 years, both liver biopsy and liver stiffness measurement (LSM) were performed annually; from 2009 on, liver biopsy was performed only if LSM was 8.7 kPa or greater and in case of suspected graft dysfunction. One expert pathologist (R.M.) scored all biopsies according to the METAVIR system. Liver stiffness measurement was determined on the right lobe of the liver by an expert nurse.

Severe hepatitis C recurrence was defined by the presence of one of the following criteria within the first year after LT: significant fibrosis (F ≥2), portal hypertension (HVPG ≥6 mmHg), cholestatic hepatitis C (bilirubin >6 mg/dl, GGT and ALP ≥5 ULN, very high serum HCV-RNA, and typical histology in the absence of biliary/arterial complications) [11], and severe acute hepatitis (presence of moderate/severe necroinflammatory changes and/or portal hypertension in the acute hepatitis phase) [3]. Mild hepatitis C recurrence was defined by absent or minimal fibrosis (F0–F1) or LSM below 8.7 kPa, 1 year after LT.

Definition of clinical outcomes

The main aim of the study was to assess the progression to HCV-related graft cirrhosis and graft loss during a long-term follow-up in patients with mild hepatitis C recurrence. Cirrhosis was defined by at least one of the following criteria: biopsy-proven fibrosis stage F4, HVPG ≥10 mmHg, LSM ≥14 kPa in at least two determinations, clinical decompensation (ascites or hepatic encephalopathy due to HCV-related disease progression).

Antiviral treatment

Antiviral treatment consisted of Peg-interferon alpha-2b and ribavirin. Sustained virological response was defined as undetectable serum HCV-RNA at the end of therapy that persisted for 24 weeks after treatment completion. Criteria for treatment included: (i) HCV recurrence with a fibrosis stage ≥2 and/or a HVPG ≥6 mmHg, and (ii) cholestatic hepatitis, fibrosing cholestatic hepatitis, or severe acute hepatitis. Some patients underwent antiviral therapy outside these criteria as part of a clinical trial [12].

Statistical analysis

Continuous variables are depicted using median and interquartile ranges, and categorical variables are expressed as absolute numbers and percentages. HCV-

related graft survival and disease progression rates to cirrhosis in patients with mild hepatitis C recurrence were calculated using Kaplan–Meier curves and comparisons according to relevant variables were performed using log-rank test. Patients were censored at their last follow-up or at the time of graft loss (death or retransplantation). Patients who underwent antiviral therapy and achieved SVR were censored at the beginning of antiviral treatment. Univariate and multivariable Cox hazard regressions (including clinically meaningful variables) were performed to define the predictive factors for cirrhosis development in patients with mild hepatitis C recurrence. Data from multivariable analysis were reported using p values and hazard ratios with 95% confidence interval (CI). The median [95% CI] follow-up was calculated using the reverse Kaplan–Meier estimate [13].

We estimated the linear slope of LSM for patients with mild hepatitis C recurrence categorized according to progression to cirrhosis using a longitudinal mixed model for repeated measurements (MMRM) setting the (co)variance matrix to unstructured. Statistical analyses were performed with SPSS version 18 (SPSS, Chicago, IL, USA) and SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

Results

Study population

During the study period, 515 adult patients with end-stage liver disease related to HCV infection underwent LT. Among them, 109 patients were excluded for different reasons: SVR during the waiting list ($n = 30$), HIV coinfection ($n = 15$), simultaneous kidney–liver transplant ($n = 19$), and retransplantation or death during the first 6 postoperative months due to non-HCV-related causes ($n = 45$). Thirty-three patients were further excluded because liver biopsy or LSMs were not available during the first year after LT due to medical complications (i.e., biliary tree dilation) or technical reasons (i.e., obesity). Thus, the final cohort consisted in 373 HCV-infected liver recipients (Table 1).

During the first year after LT, 200 patients (53%) were classified as severe hepatitis C recurrence, either by the presence of significant fibrosis or portal hypertension during the first 12 months following LT or by the occurrence of a cholestatic hepatitis C or severe acute hepatitis. The remaining 173 (46%) patients were classified mild hepatitis C recurrence. The median (95% CI) follow-up time for the entire cohort was 92 months (81.1–98.3). Cumulative HCV-related graft survival rates 5 and 10 years after LT were 64% and 51% in patients with severe hepatitis C recurrence versus 97% and 90% in patients with mild hepatitis C recurrence, respectively ($P < 0.001$) (Fig. 1).

Clinical outcomes of patients with mild hepatitis C recurrence

The baseline characteristics of the 173 patients with mild hepatitis C recurrence are illustrated in Table 1. Two-thirds of patients underwent a liver biopsy ($n = 130$ with $F = 0$–1), in 85 of them also with HVPG measurement (HVPG <6 mmHg). The remaining patients were classified as mild hepatitis C recurrence by LSM below 8.7 kPa ($n = 45$), 1 year after LT.

After a median follow-up of 80 months (95% CI 69.1–87.8), the cumulative incidence of HCV-related graft loss was only 3.3% (95% CI 1.2–8.6%) at 5 years and 13.5% (95% CI 6.5–27%) at 10 years. Due to the small number of patients who lost their graft ($n = 9$), it was not possible to determine which variables were associated with this outcome.

Interestingly, cumulative all-cause graft survival rates at 5 and 10 years after transplantation were 85% and 65%, respectively, in patients with mild hepatitis C recurrence ($n = 173$), and 87% and 77% in the HCV-negative cohort ($n = 425$), with no statistically significant differences between both groups (log-rank $P = 0.2$). In control patients, non-liver-related events accounted for most graft losses (69%), with *de novo* neoplasia, infections, and cardiovascular disease being the most frequent causes of graft loss. In recipients with mild hepatitis C recurrence, non-liver-related events were responsible for 57% of graft losses, and *de novo* neoplasia and infections were also the most frequent causes of graft loss.

Twenty-six (15%) of the 173 patients with mild hepatitis C recurrence developed cirrhosis overtime: the diagnosis of liver cirrhosis was performed by liver biopsy in 13 patients, by the presence of HVPG ≥10 mmHg in 7, by the occurrence of clinical decompensation in 3, and by a LSM ≥14 kPa in 3. The cumulative risk of cirrhosis was 13% (95% CI 8.2–21.6%) and 30% (95% CI 19.8–43.4%) at 5 and 10 years after LT, respectively (Fig. 2a). When the analysis was performed excluding all patients who underwent antiviral therapy, the figures were very similar (8% and 34% at 5 and 10 years after LT, respectively). One of the 26 patients who developed cirrhosis during follow-up had a BMI >30 and histological evidences of NASH; the

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remaining patients did not have other potential causes that could justify fibrosis progression (alcohol intake >30 g/day, NASH, BMI >30). Donor, recipient, and transplant-related characteristics were investigated to identify those patients at risk of cirrhosis development, as shown in Table 2. By univariate analysis, only donor age, considered as continuous or categorized variable (≥50 years), and AST ≥60 IU/l 1 year after LT were associated with a higher risk of cirrhosis. Early markers of hepatitis C recurrence (such as HCV viral load or AST and GGT values during the first months after LT) were not associated with the risk of cirrhosis development. Similarly, donor/recipient sex and/or IL28B mismatch did not influence outcomes in our cohort. In the multivariable analysis, donor age and AST 1 year after transplantation were confirmed as independent predictive risk factors for the development of cirrhosis (Table 2). Using Kaplan–Meier analysis, the risk of cirrhosis was significantly higher in patients who received a graft from a donor ≥50 years compared with a donor <50 years (27% vs. 7% 5 years after LT) ($P = 0.044$) (Fig. 2b). Similarly, patients with AST ≥60 IU/l 1 year after LT had a higher risk of developing cirrhosis than patients with AST <60 IU/l (20% vs. 9% 5 years after LT) ($P = 0.013$) (Fig. 2c). As expected, those recipients ($n = 24$, 26%) who had both risk factors (AST ≥60 IU/l and donor age ≥50 years) were at highest risk of developing liver cirrhosis over time (46% 5-years after LT). The figures for those individuals with only one risk factor or without any risk factor (AST <60 IU/l and donor age <50 years) were much favorable, with a CP of cirrhosis 5 years after LT ranging from 6% to 12% ($P < 0.001$) (Fig. 2d). Importantly, the negative predictive value to exclude the development of cirrhosis in patients without the two risk factors was very high (89%) (Table S1).

Table 1. Baseline characteristics of whole population of HCV-infected liver recipients ($n = 373$), including patients with mild ($n = 173$) and severe ($n = 200$) hepatitis C recurrence after LT.

Median, IQR *N* (%)	Overall population $n = 373$	Mild recurrence $n = 173$	Severe recurrence $n = 200$
Recipient age (year)	58 (52–63)	57 (51–63)	59 (52–65)
Recipient gender (male)	270 (66.5)	122 (70%)	125 (62)
HCV Genotype (genotype 1)	349 (91%)	145 (88%)	179 (94)
HCV viral load before LT (log)	5.1 (4–5.7)	5.07 (3.8–5.6)	5.3 (4.4–5.8)
HCC as indication for LT	222 (54.7)	99 (57%)	110 (55)
Transplant type			
Deceased donor	321 (79%)	128 (74%)	168 (84%)
Living donor	44 (10.8%)	23 (13%)	16 (8%)
Domino-amyloidosis	16 (3.9%)	11 (6.4%)	5 (2.5%)
Split	2 (0.5%)	1 (0.6%)	1 (0.5%)
HCV-positive donor	5 (1.2%)	3 (1.7%)	2 (1%)
NHBD	18 (4.4%)	7 (4%)	8 (4%)
Recipient IL28-60 CC	81 (26.9%)	37 (28%)	33 (23%)
Donor IL28-60 CC	93 (38%)	29 (28%)	57 (46%)
Donor age (year)*,†	49 (34–63)	42 (31–56)	60 (45–69)
Donor gender (female)	155 (39%)	66 (39%)	80 (40%)
Donor/recipient gender mismatch	159 (40%)	65 (39%)	83 (42%)
MELD at LT	12.85 (6–39)	12.8 (6–34)	12.9 (6–39)
Cold ischemia time (min)	370 (284–460)	407 (281–495)	370 (300–465)
Immunosuppression (TAC)	254 (62%)	109 (66%)	129 (67%)
Basiliximab	77 (19%)	39 (22%)	33 (16%)
MMF therapy in the first month after LT	162 (40%)	74 (43%)	77 (38%)
Diabetes within 1 year after LT*,†	233 (59%)	83 (48%)	132 (68%)
Biliary complications	85 (21%)	41 (24%)	37 (18%)
Acute graft rejection	99 (24%)	41 (24%)	48 (24%)
Prednisone boluses	60 (14%)	24 (14%)	29 (14%)
CMV infection*,†	46 (11.3%)	8 (5%)	34 (17%)

HCC, hepatocellular carcinoma; MMF, mycophenolate mofetil; NHBD, non-heart-beating donor.

Those variables which showed significantly differences between patients with mild versus patients with severe hepatitis C recurrence are depicted with * for univariate analysis, and † for multivariable analysis.

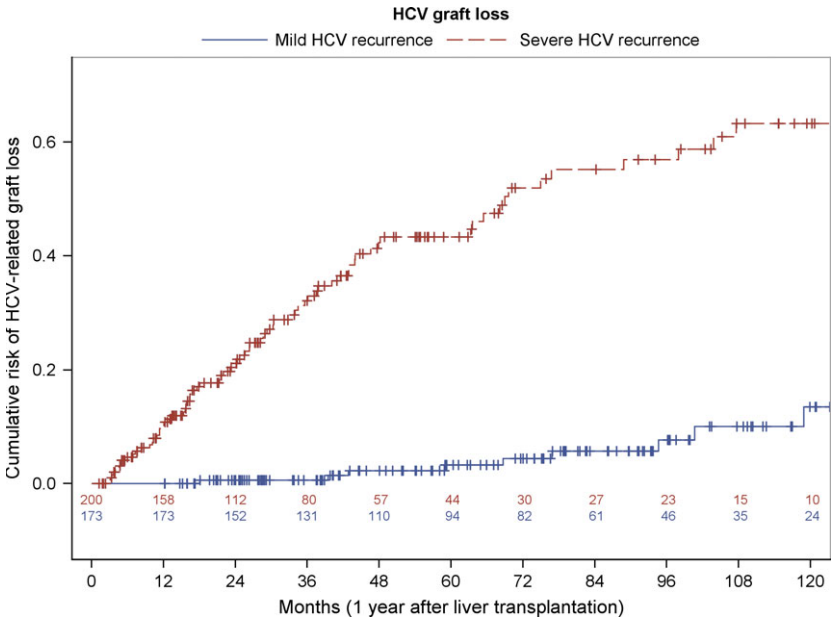

Figure 1 Kaplan–Meier analysis showing cumulative probabilities of HCV-related graft survival in patients with mild hepatitis C recurrence versus severe hepatitis C recurrence.

Slope of liver stiffness within the first 2 years after LT

We were interested to see whether early changes in LSM over time were able to predict clinical outcomes. LSM were available in 98, 69, and 84 patients at 12, 18, and 24 months after LT, respectively. One year after LT, median liver stiffness values did not differ significantly in patients who did and did not developed cirrhosis overtime [7.3 vs. 6.49 kPa ($P = 0.059$)]. As expected, at the two following time points, 18 and 24 months after LT, patients who developed cirrhosis had a median liver stiffness value significantly higher than those who did not [9.3 vs. 7.04 kPa at 18 months ($P = 0.021$); 11.2 vs. 7.59 kPa at 24 months ($P = 0.005$)]. Indeed, none of the patients with a LSM <7.8 kPa 18 months after LT progressed to liver cirrhosis.

Using the MMRM of liver stiffness determinations at 12, 18, and 24 months after LT, the slope of liver stiffness progression in patients who developed cirrhosis was significantly greater (0.331 kPa/month) compared with patients who did not develop cirrhosis (0.091 kPa/month) (0.240 kPa/year difference, $P = 0.038$). In the latter group, liver stiffness remained stable within the first 2 years after LT (Fig. 3).

Discussion

Due to high efficacy and safety profile of all-oral regimens in liver transplant recipients, the US and European Guidelines on the management of hepatitis C [9,10] recommend treatment of all HCV-infected liver transplant recipients. This strategy will not only improve HCV-related outcomes of LT recipients, but might also impact in some HCV-related morbidities (such as diabetes). It is true that liver transplant recipients compromise a small proportion of the total HCV-infected population, but in centers performing LT the number of patients may be very high. Additionally, in most countries limitation of healthcare resources will make it necessary to prioritize treatment in patients with more advance disease, at least during the next few years. Meanwhile, many HCV-infected liver transplant recipients with a mild HCV recurrence will request information on the new antiviral regimens; having solid data on their natural history becomes relevant.

We selected a large cohort of patients with mild hepatitis C recurrence in a single referral center and investigated the long-term graft and patient survival, the rate of cirrhosis development, and the related risk factors. The definition of mild hepatitis C recurrence was based on widely accepted criteria [3]: the majority of patients showed absent or mild fibrosis in a liver biopsy or an HVPG below 6 mmHg 1 year after LT, a small proportion were diagnosed by a LSM <8.7 kPa. Our results show that HCV-related graft loss is exceptional in patients who are classified as having a mild hepatitis C (only 9 of 173 patients lost their graft due to hepatitis C during a long-term follow-up). Our results confirm the usefulness of the

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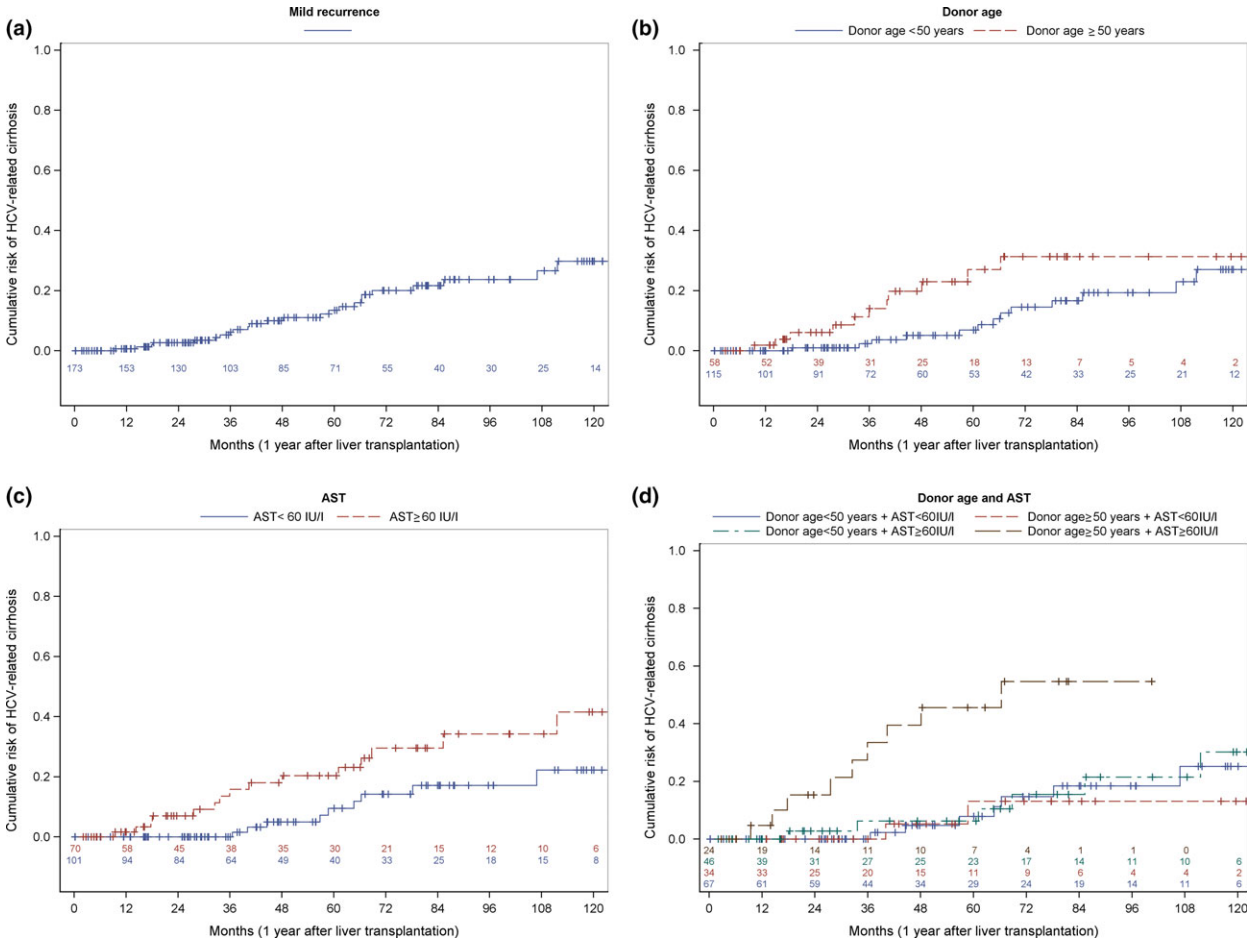

Figure 2 Kaplan–Meier analysis showing cumulative probabilities of HCV-related graft cirrhosis development in all patients with mild hepatitis C recurrence (a), or in patients with mild hepatitis C recurrence stratified by donor age (b), by AST 1 year after LT (c) and by combination of both variables (d).

classification of patients as mild hepatitis C recurrence based on the assessment of graft fibrosis 1 year after LT [2,3] and are in concordance with those published by Neumann *et al.* [14]. In our study, and due to the impact of antiviral therapy on clinical outcomes [12,15], we censored all patients who achieved SVR at the beginning of treatment. When excluding all patients who underwent antiviral therapy, we obtained the same results.

Despite these excellent outcomes, a subset of patients (15%) developed cirrhosis due to hepatitis C progression. Similar results were reported by Firpi *et al.* [16] in a smaller series including 57 patients with mild recurrence 12 months after LT: 11% of them progressed to cirrhosis within the first 5 years after transplantation. We have shown that donor age ≥50 years and AST ≥60 IU/l 1 year after LT were independently associated with the risk of progression to cirrhosis. The proportion of patients with both risk factors was low, due to the fact that this is a selected population. Nevertheless, patients with a donor ≥50 years and AST ≥60 IU/l had a remarkable risk of disease progression (46% at 5 after LT). Several studies have implicated an increased donor age as a risk factor for graft failure in HCV-infected recipients following LT [17]. However, the age that defines an 'old' donor varies considerably among studies. In our study, the cutoff was quite low (50 years), due to the fact that patients with mild disease recurrence typically receive a graft from younger donors. The other variable related to progression to cirrhosis was AST ≥60 IU/l, likely reflecting a higher necroinflammation in the graft, which is an established risk factor for disease progression [18]. As expected, in patients with mild hepatitis C, recurrence LSM 1 year after LT was low, but its progressive increase (slope) throughout the first 2 years after transplantation proved very helpful to identify individuals at risk of cirrhosis.

Table 2. Risk factors associated with cirrhosis development during the follow-up in patients with mild hepatitis C recurrence using Cox uni- and multivariate analysis. Continuous variables are presented as median (interquartile range), categorical variables as *n* (%). Cutoff values were selected according to median value in the entire population.

Variable mild hepatitis C recurrence (*N* = 173)	No cirrhosis *N* = 147	Cirrhosis *N* = 26	Univariate		Multivariate	
			*P**	HR (IC 95%)	*P*†	HR (IC 95%)
Recipient age (year)	58 (49–63)	58 (50–65)	0.126			
Recipient gender (male)	105 (71%)	17 (65%)	0.763			
Genotype 1	122 (87%)	23 (96%)	0.369			
Donor age (year)	44 (28–56)	55 (40–64)	0.012	1.03 (1.01–1.06)		
Donor age ≥50 (year)	46 (31%)	12 (46%)	0.047	2.23 (1.01–4.91)	0.033	2.42 (1.07–5.48)
IL28 CC recipient	31 (28%)	6 (27%)	0.662			
IL28 CC donor	23 (26%)	6 (38%)	0.435			
Donor gender (female)	57 (39%)	9 (36%)	0.643			
Gender mismatch	55 (39%)	10 (40%)	0.791			
Cold ischemia time (min)	452 (347–517)	435 (400–545)	0.770			
Immunosuppression (CsA)	51 (37%)	5 (19%)	0.171			
Diabetes 1 year after LT	68 (46%)	15 (58%)	0.583			
Biliary complications	37 (25%)	4 (15%)	0.413			
Acute graft rejection	32 (22%)	9 (37%)	0.760			
Prednisone boluses	19 (13%)	5 (19%)	0.791			
CMV infection	5 (3%)	3 (11%)	0.167			
AST (IU/l) 12 month	47 (28–68)	70 (41–144)	0.412			
AST 12 month ≥60 (IU/l)	54 (37%)	16 (61%)	0.017	2.71 (1.20–6.14)	0.011	2.89 (1.27–6.58)
ALT (IU/l) 12 month	61 (35–105)	130 (44–204)	0.525			
ALT >70 (IU/l) 12 month	70 (48%)	15 (57%)	0.226			
GGT (IU/l) 12 month	63 (30–143)	108 (53–262)	0.956			
Bilirubin (mg/dl) 12 month	0.7 (0.5–1)	0.5 (0.4–0.7)	0.249			
HCV-RNA log (IU/ml) 12 month	6.2 (5.6–6.4)	6.4 (6–6.4)	0.118			

*Univariate.

†Multivariate.

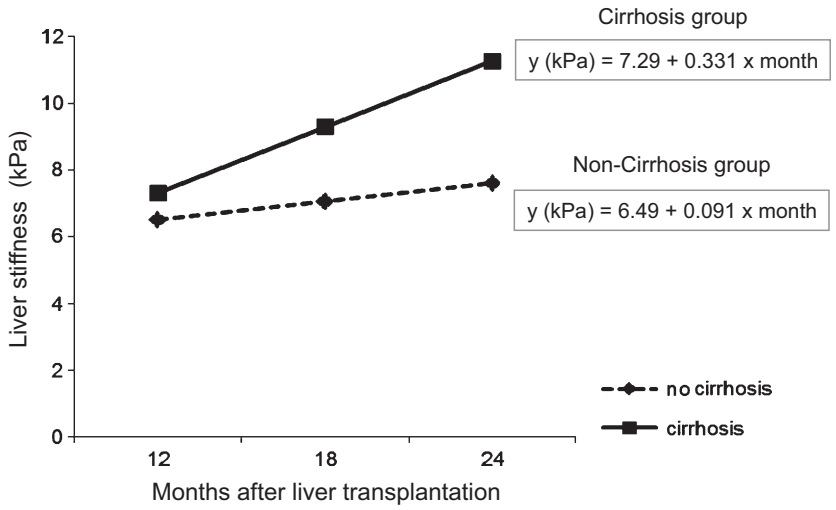

Figure 3 Liver stiffness progression using a mixed model for repeated-measurements (MMRM) approach. The slope (kPa per month) in patients who developed graft cirrhosis (0.331) was significantly higher than the slope in those who did not develop graft cirrhosis (0.091), $P = 0.038$.

From a practical point of view, the presence of mild recurrence 1 year after LT in patients is a guarantee for an excellent clinical outcome as only 3% of them lost their graft and only 5% of them developed cirrhosis, 5 years after LT. This is particularly true for patients who received a liver from a young donor and had low

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AST values 1 year after LT; the negative predictive value for progression to cirrhosis is very high. For this reason, it seems reasonable to delay the use of DAAs in areas where prioritization is necessary due to an economical burden. Our data may be reassuring for patients who ask for IFN-free therapy and are told to wait. On the other hand, there is a subgroup of patients who, despite being classified as mild hepatitis C recurrence, have a relatively high risk of fibrosis progression over time; in them, early antiviral treatment with DAAs should be considered.

The strongest point of our study is the fact that all patients have been followed using the same protocol (follow-up visits, liver biopsies, LSM) and that disease progression has been assessed prospectively during a long-term follow-up. Importantly, diagnosis of liver cirrhosis was based on liver histology or HVPG measurement in most cases. Our study has also some limitations. First, 43 of the 173 patients were classified as mild hepatitis C recurrence by LSM (and not by liver biopsy). There are, however, several studies showing the excellent negative predictive value of LSM to exclude significant fibrosis [19,20]. Moreover, when we assessed clinical outcomes in these 43 patients, only 2 (4,6%) developed cirrhosis (5-year CP of cirrhosis of 9%). Another limitation is that LSM was only available in a subset of patients, due to the fact that the technique was implemented after 2007. Finally, our cohort included a large proportion of patients with preserved liver function in whom the indication of LT was HCC. Nevertheless, the impact of pre-LT liver dysfunction on post-LT outcome is controversial, and in our cohort, we did not find differences in pre-LT MELD score between patients with mild and severe recurrence. Although our results cannot be generalized to other cohorts, we believe that HCC with preserved liver function will be an increasing indication of LT worldwide.

In summary, our study supports an excellent long-term outcome of mild hepatitis C recurrence after LT. There are, however, some patients progressing to cirrhosis who can be easily identified and who should not wait for antiviral therapy.

Authorship

MG, XF, MN and GC: designed the study and analyzed and discussed the data. MG and XF wrote the manuscript. FT: contributed to the statistical analyses. JC, LLL, ML, SL, ZM and RM: analyzed and reviewed the data and contributed to the study design and discussion; in addition. RM: reviewed all histological samples. CB: contributed to data analysis and performed all liver stiffness measurements.

Financial support

X. Forns and M Navasa received support in part by grants from Instituto de Salud Carlos III (PI11/01907 and PI14/01055, respectively), Ministerio de Economía y Competitividad, co-funded by Fondo Europeo de Desarrollo Regional, Unión Europea, Una manera de hacer Europa and by the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (grant 2014_SGR_605). CIBEREHD is funded by the Instituto de Salud Carlos III. M. Gambato has been awarded with the EASL Entry Level Research Fellowship 2014 (Dame Sheila Sherlock EASL Fellowship Programme).

Conflicts of interest

XF has acted as advisor for Janssen, Gilead and Abbvie and has received unrestricted grant support from Janssen. SL has acted as advisor for Gilead, MSD and Janssen. MCL has acted as advisor for Janssen and BMS. ZM has acted as advisor for BMS. MN has acted as advisor for Astellas and Novartis.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of AST 1 year after LT and donor age, for the prediction of cirrhosis development in patients with mild recurrence 1 year after LT.

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