Retransplantation in patients with hepatitis C recurrence after liver transplantation

José A. Carrió, Miquel Navasa, Xavier Forns*

Liver Unit, Institut de Malalties Digestives, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Barcelona, Spain

Hepatitis C virus (HCV) infection recurs universally after liver transplantation (LT) and fibrosis progression is accelerated in the graft. Retransplantation (RT) is the only therapeutic option to achieve long-term survival in patients with decompensated cirrhosis after LT. Patient and graft survival rates after RT are inferior to those after primary LT. It is generally accepted that severe hepatitis C recurrence (cholestatic hepatitis) and forms with rapid fibrosis progression have a poor survival after RT. However, it is not clear whether rapid fibrosis progression in the first graft will be followed by the same rate of fibrosis progression in the second graft. The use of prognostic scores as screening tools has shown an improvement in survival in HCV-infected patients after RT, reaching similar survival rates as those obtained in non-HCV-infected patients. Moreover, these scores can identify candidates with a high risk of mortality in whom the use of a new organ would be unreasonable. Prevention of severe hepatitis C recurrence could be the first step to avoid RT. Thus, antiviral treatment on the waiting list (if possible) and early identification and treatment of patients with severe hepatitis C recurrence may be a good strategy to avoid RT. In addition, active management of factors which can accelerate fibrosis progression (donor age, post-transplant diabetes, high dose of corticosteroids) might reduce the incidence of severe forms of hepatitis C recurrence.

© 2010 Published by Elsevier B.V. on behalf of the European Association for the Study of the Liver.

Retransplantation in HCV-infected patients: general considerations

Hepatitis C virus (HCV) infection has become the most common cause of cirrhosis and hepatocellular carcinoma in the Western world. End-stage liver disease due to HCV-infection is the leading indication for liver transplantation (LT). Unfortunately, HCV infection recurs universally after LT in patients with detectable HCV RNA at the time of transplantation [1]. Fibrosis progression, cirrhosis development, and clinical decompensation occur more rapidly in HCV-infected liver transplant recipients than in immunocompetent patients [2]: whereas the median interval from infection to cirrhosis is around 9.5 years in LT recipients, the same interval is around 30 years in immunocompetent patients. Cirrhosis develops in around one-third of HCV-infected patients during the first 5 years after LT [3]. In addition, a small number of individuals (2–5%) develop fibrosing cholestatic hepatitis (FCH), a severe form of hepatitis C recurrence characterized by cholestatic hepatitis, hepatocyte ballooning, and perisinusoidal fibrosis leading to graft failure within a few months after LT [4]. As a consequence, hepatitis C recurrence is the primary cause of graft loss and reduction in patient survival in transplant programs in which HCV-infection is the main indication for LT [5]. The prognosis of patients once graft cirrhosis is established is poor and when graft failure occurs, retransplantation (RT) is the only therapeutic option offering a chance for long-term survival. Berenguer et al. [2] found that patients with clinically compensated cirrhosis achieved a 1-year survival rate of 74%. However, once patients developed clinical decompensation, survival decreased to 41% at 1 year and approximately 10% at 3 years.

It is generally accepted that progression to cirrhosis is faster after RT than after primary LT, particularly in patients with severe hepatitis C recurrence (cholestatic hepatitis and graft failure within the first year). Patient and graft survival rates after RT are inferior to those after primary LT and are associated with a greater cost. Pelletier et al. [6] demonstrated a 30% increase in mortality for HCV-infected LT recipients (20% for HCV-infected primary LT [7]). Table 1 shows the liver graft survival rate after LT and after RT between 1984 and 2008 in Spain. Most deaths after RT are, however, not related to hepatitis C recurrence but to post-operative complications such as bacterial infections. Patients with a more severe liver disease and poor preoperative clinical conditions have the highest mortality following RT [8]. Despite liver fibrosis progression after primary LT has been well characterized [9], studies assessing this subject after RT are insufficient to draw any solid conclusions [10,11]. Moreover, other facts may influence the evolution of HCV-infection after RT. Recent studies have suggested that the grafting of a new liver may produce significant changes in the HCV quasispecies and may thereby change the severity of the disease and the susceptibility to antiviral treatment [12,13].
Among patients with multiple RTs, a recent analysis of the Spanish Transplant Organization showed a worse outcome in individuals with more than one RT [14] (Table 1). Multivariate analysis demonstrated a significantly higher risk of mortality in patients who received a second [HR: 1.53 (95% CI: 1.38–1.7) \( p < 0.01 \)] or third graft [HR: 1.85 (95% CI: 1.4–2.4) \( p < 0.01 \)] as compared to the first transplant [15]. However, Akpinar et al. [16], evaluated 2527 LT between 1987 and 2008. Two hundred and thirty-five (9%) patients received two grafts; 32 (1.2%) three; five (0.2%) four; and two (0.01%) five grafts. Patients who underwent more than one RT had a survival rate of 72%, 56%, and 50% at 1, 5, and 10 years, respectively. There were no statistically significant differences in survival between these patients and those who underwent one RT, concluding that multiple RT can be safely performed.

**Is HCV-infection an independent risk factor for mortality after retransplantation?**

The main causes of liver graft failure are primary non-function (PNF), hepatic artery thrombosis (HAT), chronic rejection, and recurrence of viral or autoimmune disease. RT is performed at different times depending on the etiology of graft failure: PNF requires RT during the first days, whereas HAT may result in urgent or delayed RT (the latter when secondary ischemic cholangitis is the main complication). Chronic rejection and recurrence of viral or autoimmune disease are indications of elective RT. In general, there are no concerns regarding the use of a liver graft for RT in emergency situations (such as PNF or HAT) but elective RT (particularly for HCV recurrence) is much more controversial. Whereas some studies do not clearly identify HCV recurrence as an independent predictive factor of mortality after RT [17–22], other recent studies [6,23–26] seem to indicate a poorer prognosis in RT of HCV-infected patients (Tables 2 and 3).

Studies evaluating early post-transplant variables did not find HCV-infection to be an independent predictor of mortality after RT [17–22]. The University of Pittsburgh [17] analyzed 418 (17.6%) patients who underwent RT out of 2376 LT performed from 1987 to 1993. The 1- and 5-year graft survival after RT was significantly lower than that of primary LT (50% and 35%, respectively). The leading causes of graft failure after RT were sepsis (44%) and ischemic injury-PNF (12%). The variables associated with graft failure after RT were donor and recipient age, female donor sex, the need for mechanical ventilation, renal failure, high levels of bilirubin and immunosuppression with cyclosporine.

Some studies have suggested HCV-infection as a risk factor of mortality [25–28]. Rosen et al. [27] analyzed 1356 patients who underwent RT from the United Network for Organ Sharing (UNOS) from 1990 to 1996. Recipient age, bilirubin and creatinine levels, etiology of graft failure and UNOS status (intensive care, hospitalization, medical care or stable at home) were independent predictors of poor outcome after RT. Hepatitis C and donor age were associated with a poor prognosis on univariate analysis, but neither had enough power to be included in a predictive model. Similarly, Ghabril et al. [28] have recently evaluated 1034 HCV-infected patients and 1249 non-HCV-infected patients who underwent RT between 1994 and 2005. Patient and graft survival were significantly lower for HCV-infected compared to non-HCV-infected patients who underwent RT at least 90 days after primary LT. However, based on multivariate analysis, the only independent predictors of mortality were recipient age, model for end-stage liver disease (MELD) >25, RT during the first year after LT, donor age >60 and, a warm ischemia time \( \geqslant 75 \) min.

Other studies, have clearly identified HCV-infection as a risk factor of mortality not only after primary LT but also after RT [6,23,24]. One of the largest clinical UNOS series with more than 4000 patients who underwent RT from 1988 to 2001 [23] showed seven risk factors for death after RT: PNF, HCV-infection, donor, and recipient age, creatinine -serum levels before RT, African-American race, and UNOS status. Patients with HCV recurrence were 20% and 30% more likely to lose their graft between 1 and 3 years compared with non-HCV-infected patients. Roayaie et al. [24] showed that HCV-infected patients undergoing RT had a significantly shorter median survival than those undergoing RT for other chronic reasons of graft loss. However, most deaths occurred during the first 6 months after RT and were due to sepsis by peritonitis or pneumonia. Similarly, Pelletier et al. [6] analyzed 1718 RT patients (27% with HCV-infection) from 1997 to 2002 in the Scientific Registry of Transplant Recipients database. HCV-infected recipients had a 30% higher risk of mortality than those without HCV-infection (HR: 1.30; CI 95%: 1.10–1.54; \( p = 0.002 \)). Most deaths occurred between 3 and 12 months after RT and variables associated with a worse outcome were donor and recipient age, serum-creatinine level, presence in the intensive care unit, and HCV-infection.

---

**Table 1. Graft survival of transplanted (LT) and retransplanted (RT) patients from 1984 to 2008 in Spain. Database from “Organización Nacional de Trasplante” (ONT) [14]**

<table>
<thead>
<tr>
<th>All etiologies</th>
<th>1-month survival</th>
<th>3-month survival</th>
<th>1-year survival</th>
<th>3-year survival</th>
<th>5-year survival</th>
<th>10-year survival</th>
<th>15-year survival</th>
<th>20-year survival</th>
<th>Mortality risk: HR (95%CI), ( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT (n = 14,223)</td>
<td>90.3%</td>
<td>86%</td>
<td>78.5%</td>
<td>69.7%</td>
<td>64.1%</td>
<td>52.7%</td>
<td>44.2%</td>
<td>35.6%</td>
<td></td>
</tr>
<tr>
<td>2º graft (n = 1,239)</td>
<td>76.3%</td>
<td>67.1%</td>
<td>58.1%</td>
<td>50.9%</td>
<td>44.5%</td>
<td>35%</td>
<td>30.2%</td>
<td>24%</td>
<td>2nd vs. 1st graft: 1.53 (1.38 - 1.7), ( &lt;0.01 )</td>
</tr>
<tr>
<td>3º graft (n = 127)</td>
<td>66.1%</td>
<td>58.3%</td>
<td>49.6%</td>
<td>44.2%</td>
<td>38.3%</td>
<td>27%</td>
<td>27%</td>
<td>-</td>
<td>3rd vs. 1st graft: 1.85 (1.4 - 2.4), ( &lt;0.01 )</td>
</tr>
<tr>
<td>LT (n = 4,925)</td>
<td>91.9%</td>
<td>87.5%</td>
<td>77.7%</td>
<td>65.8%</td>
<td>57.7%</td>
<td>43.8%</td>
<td>34.3%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2º graft (n = 273)</td>
<td>83.5%</td>
<td>73.4%</td>
<td>63.4%</td>
<td>53%</td>
<td>42.4%</td>
<td>32.6%</td>
<td>20%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3º graft (n = 13)</td>
<td>100%</td>
<td>92.3%</td>
<td>69.2%</td>
<td>43.3%</td>
<td>34.6%</td>
<td>34.6%</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

LT, liver transplantation; RT, retransplantation; HR, hazard ratio; 95% CI, 95% confidence interval.
Table 2. Studies and predictive models in urgent and elective RT.

<table>
<thead>
<tr>
<th>Author et al. (year), reference</th>
<th>Period and population</th>
<th>LT (n)</th>
<th>RT (n)</th>
<th>Variables associated with worse outcome after RT</th>
<th>Predictive model</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doyle et al. (1999), [17]</td>
<td>1987-1993 (Univ. of Pittsburgh)</td>
<td>2,376*</td>
<td>418*</td>
<td>Donor age and sex, recipient age, HCV infection</td>
<td>R = -2.019 + 0.089 × donor age - 0.52 × donor sex + 0.05 × recipient age + 0.08 × HCV + 0.21 × creatinine + 0.633 × bilirubin + 1.17 × cyclosporine (male donor, non-transplanted and tacrolimus as 0; female donor, MV and cyclosporine as 1).</td>
<td>5-y graft survival: LT, 55.9%; RT, 35.5%</td>
</tr>
<tr>
<td>Wong et al. (1997), [16]</td>
<td>1987-1994 (King’s College)</td>
<td>303</td>
<td>70</td>
<td>PNF, HAT (30%) HCV (7)</td>
<td>Recipient age, postoperative creatinine, bilirubin, and UNOS status.</td>
<td>-</td>
</tr>
<tr>
<td>Markmann et al. (1997), [19]</td>
<td>1984-1996 (UCLA)</td>
<td>2,053*</td>
<td>356*</td>
<td>PNF, HAT (52%) HCV (7)</td>
<td>Recipient age, interval to RT, total number of grafts, UNOS status.</td>
<td>-</td>
</tr>
<tr>
<td>Markmann et al. (1999), [20]</td>
<td>1992-1996 (UCLA)</td>
<td>1,067</td>
<td>150</td>
<td>PNF and others HCV (7)</td>
<td>Age &gt;18 y, MV, cold ischemia &gt;12 h, MELD &gt;15 mg/dL and bilirubin &gt;13 mg/dL.</td>
<td>R = 0.726 × cold ischemia + 5.56 × ventilator status + 0.292 × creatinine + 0.202 × creatinine + 0.026 × age.</td>
</tr>
<tr>
<td>Rosen et al. (1999), [27]</td>
<td>1990-1996 (UNOS)</td>
<td>-</td>
<td>1,356*</td>
<td>PNF (37%) HCV (23.6%)</td>
<td>Recipient age, UNOS status, cause of graft failure, creatinine and bilirubin. (Univariate: donor age and HCV infection)</td>
<td>R = 0.024 (recipient age) + 0.112 (bilirubin) + 0.236 (log, creatinine) + 0.074 (cause of graft failure) + UNOS coefficient</td>
</tr>
<tr>
<td>Ghobrial et al. (2002), [21]</td>
<td>1990-2000 (UCLA and UNOS)</td>
<td>UCLA: 510, UNOS: 25,272</td>
<td>130 (UCLA)</td>
<td>PNF (20%), warm ischemia: 112 h, HCV (100%) UNOS (n=85)</td>
<td>Donor and recipient age, creatinine, bilirubin, prothrombin time, warm ischemia (m), oximetric ischemia time (h) and second transplant.</td>
<td>R = 0.094 × donor age + 0.129 × recipient age + 0.08 x log creatinine + 0.034 × warm ischemia + 0.096 × second transplant + 0.10 × log bilirubin + 0.0057 × PT - 0.01 × cold ischemia.</td>
</tr>
<tr>
<td>Azoulay et al. (2002), [22]</td>
<td>1986-1999 (H, Paul Brousse, Pitié-Salpêtrière)</td>
<td>1,038</td>
<td>139 (Pitie-Salpetriere)</td>
<td>PNF (37%) HCV (20%)</td>
<td>Recipient age, PNF, cold ischemia &gt;12 h, bilirubin, and preoperative creatinine.</td>
<td>R = 0.04 × recipient age + 0.15 × bilirubin + 1.28 × PNF + 1.38 × super-urgent + 1.27 × urgent + 0.23 × bilirubin + 1.38 × log, factor II + 0.05 × (vitamin K, factor X, factor I, PNF, super-urgent, and urgent: 1 if yes and 0 if no).</td>
</tr>
<tr>
<td>Yoo et al. (2003), [23]</td>
<td>1987-2001 (UNOS)</td>
<td>30,087</td>
<td>4,189</td>
<td>PNF, donor and recipient age, African-American race, creatinine, UNOS status and HCV-infection*</td>
<td>PN1: donor and recipient age, African-American race, creatinine, UNOS status and HCV-infection*</td>
<td>-</td>
</tr>
<tr>
<td>Neff et al. (2004), [27]</td>
<td>1996-2004 (Univ. of Cincinnati and Miami)</td>
<td>1,141</td>
<td>127</td>
<td>HCV (44%) PNF (35%) HCV (17%)</td>
<td>Univariate: Physical condition, CTP and HCV-infection, Multivariate: Physical condition.</td>
<td>CTP, MELD score and Physical Score classification.</td>
</tr>
<tr>
<td>Pelletier et al. (2005), [8]</td>
<td>1997-2002 (SRTR)</td>
<td>1,178</td>
<td>119 (11%)</td>
<td>PNF (25%) HCV (27%)</td>
<td>Donor and recipient age, admission in ICU condition, creatinine and HCV-infection.</td>
<td>-</td>
</tr>
<tr>
<td>Linnanias et al. (2006), [26]</td>
<td>1986-1999 (Pitt)</td>
<td>303</td>
<td>139</td>
<td>PNF (25%) HCV (25%)</td>
<td>Early failure of LT (R &lt; 10), urgency of RT, recipient age (y), creatinine (μM)</td>
<td>R = 1 (age &lt; 40 y) + 0.11 (age &lt; 40 y) + 0.13 (age &lt; 40 y) + 0.14 (age &lt; 40 y) + 0.15 (age &lt; 40 y) + 0.16 (age &lt; 40 y).</td>
</tr>
</tbody>
</table>

LT, liver transplantation; RT, retransplantation; HCV, hepatitis C recurrence; HAT, hepatic artery thrombosis; PNF, primary non-function; MV, mechanical ventilation; ELTR, European Liver Transplant Registry; SRTR, Scientific Registry of Transplant Recipients database; y, years; d, days; h, hours; m, minutes; R, risk score; INR, international normalized ratio; UNOS (United Network for Organ Sharing) status; 1 (intensive care unit-bound), 2 (hospitalized), 3 (medical care), 4 (stable at home); HR, hazard ratio; 95% CI, 95% confidence interval. (*) Liver grafts.

The studies identifying HCV-infection as a risk factor of mortality on multivariate analysis are marked with a star.
### Table 3. Studies and predictive models for RT (excluding patients with graft failure by PNF).

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Period and population</th>
<th>LT (n)</th>
<th>RT (n) HCV (n)</th>
<th>Variables associated with worse outcome after RT</th>
<th>Predictive model</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facciuto et al. (2000), [35]</td>
<td>1989-1997 (Mt. Sinai)</td>
<td>964 HCV (n = 414)</td>
<td>48, HCV (n=21) Excluded RI &lt;6 m (n = 123)</td>
<td>Recipient age &gt;50 y, creatinine &gt;2 mg/dl and use of intraoperative platelets.</td>
<td>-</td>
<td>1-y survival: 60% 5-y survival: 42%</td>
</tr>
<tr>
<td>Watt et al. (2003), [32]</td>
<td>1996-2002 (UNOS)</td>
<td>22,120 HCV (43.2%)</td>
<td>2,129, HCV (42.2%) Excluded RI &lt;30d</td>
<td>Creatinine (mg/dl), bilirubin (mg/dl) and Prothrombin time (INR).</td>
<td>R = 0.957 x log (creatinine) + 0.378 x log (bilirubin) + 1.120 x log (INR).</td>
<td>MELD&gt; 25 5-y survival &lt;60%</td>
</tr>
<tr>
<td>Rosen et al. (2003), [31]</td>
<td>1986-1999 (UNOS, European)</td>
<td>-</td>
<td>979, HCV (25%) Excluded RI &lt;15d (n = 163)</td>
<td>Recipient age (y), RT &lt;60 days after LT, creatinine (mg/dl) and bilirubin (mg/dl).</td>
<td>R = 10 x [0.0236 (recipient age) + 0.125 (v/bilirubin) + 0.438 (log, creatinine)- 0.234 (RI)]. [RI= 0 for 15-60 d and 1 for &gt;60d]</td>
<td>1-y survival: R ≥ 20.5: 42% R ≤ 16: 75%</td>
</tr>
<tr>
<td>Roayaie et al. (2003), [24]</td>
<td>1989-2001 (Mt. Sinai)</td>
<td>1,738 HCV (n = 646)</td>
<td>51, HCV (n = 42) Excluded RI &lt;90d (n = 82)</td>
<td>Prothrombin time (seconds), donor age (y) and HCV-infection.*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yao et al. (2004), [26]</td>
<td>1988-2002 (Univ. of California)</td>
<td>1,162</td>
<td>40, HCV (20%) Excluded RI &lt;90d (n = 36)</td>
<td>Univariate: Hepatic encephalopathy, creatinine, CTP ≥10 MELD &gt;25, ICU status, and HCV-infection. Multivariate: Hepatic encephalopathy.</td>
<td>CTP and MELD scores.</td>
<td>CTP ≥ 10, MELD &gt; 25 1-y survival:50%, 53% 5-y survival:40%, 47%</td>
</tr>
<tr>
<td>Feng et al. (2006), [37]</td>
<td>1998-2002 (SRTR)</td>
<td>20,023 HCV (1.8%)</td>
<td>-</td>
<td>Donor: age &gt;40 (y), donation after cardiac death (DCD), split/partial grafts, African-American race, less height and cerebrovascular accident (CVA). Recipient: cause of graft failure.</td>
<td>RTDRI = DRI + [(0.119 if biliary) + (0.094 if recurrent disease) + (0.063 if rejection) + (0.187 if vascular thrombosis) + (0.017 if all other)].</td>
<td>RTDRI &gt; 2.5 survival &lt;53%</td>
</tr>
<tr>
<td>Northup et al. (2007), [34]</td>
<td>2002-2006 (UNOS)</td>
<td>1,327 HCV (1.8%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ghabril et al. (2008), [28]</td>
<td>1994-2005 (UNOS)</td>
<td>46,982</td>
<td>2,283, HCV (n = 1034) RI &lt;90d, 90-365d, &gt;365d</td>
<td>Recipient age, MELD &gt; 25, RI&lt; 1 year, donor age &gt;60, a warm ischemia time ≥ 75 minutes.</td>
<td>MELD score.</td>
<td>1-y survival: &lt;70% 3-y survival: &lt;59%</td>
</tr>
</tbody>
</table>

**Note:** LT, liver transplantation; RT, retransplantation; HCV, hepatitis C recurrence; PNF, primary non-function; RI, retransplant interval; UNOS, United Network for Organ Sharing; SRTR, Scientific Registry of Transplant Recipients database; CTP, Child–Turcotte-Pugh; MELD, model for end-stage liver disease; ICU, intensive care unit; RTDRI, Retransplant Donor Risk Index; y, years; m, months; d, days; INR, international normalized ratio. DRI (Donor Risk Index), exp [(0.154 if 40 < age ≤ 50) + (0.274 if 50 < age ≤ 60) + (0.424 if 60 < age ≤ 70) + (0.501 if 70 < age) + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African-American) + (0.126 if race = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.086/(170 – height)/10) + (0.105 if regional share) + (0.244 if national share) + (0.010 x cold time)].

The studies identifying HCV-infection as a risk factor of mortality on multivariate analysis are marked with a star.
Frontiers in Liver Transplantation

The International Liver Transplantation Society Expert Panel [29] established that bilirubin $\geq 10$ mg/dl, creatinine $\geq 2.0$ mg/dl (or creatinine clearance $<40$ ml/min), recipient age $>55$, donor age $>40$ and early HCV recurrence (cirrhosis $<1$ year after LT) were variables associated with a worse outcome after RT. The worse outcome after RT in cases of early severe hepatitis C recurrence has been shown in some studies [28] but may reflect the poor liver function in individuals with cholestatic forms of hepatitis C at the time of RT [10].

Predictive models of survival following retransplantation

Due to the lack of a clear consensus, different models based on logistic regression analysis of donor and recipient variables have been developed to help in the decision-making process of patients listed for RT. Most predictive models are derived from retransplanted individuals including urgent (PNF or HAT) and elective indications for RT [17,20–22,27,30] (Table 2). The first predictive models identified the need for mechanical ventilation [17,20], UNOS status [27] and the urgency of RT [22,30] as prognostic factors of mortality. Markmann et al. [20] identified five variables (recipient age $>18$ years, requirement for preoperative mechanical ventilation, cold ischemia time $>12$ h, creatinine and bilirubin levels) as independent prognostic values to estimate patient survival after RT. These authors identified a subgroup of patients with a score $>2.3$ with an expected 1-year survival $<40\%$ in whom RT was not justified. Recently, Linhares et al. [30] constructed a model that included recipient age, creatinine, urgency of RT, and early failure of the initial LT. The 1-, 3-, and 5-year survival rates reached 85%, 82%, and 77% for scores $<24$ and 69%, 66%, and 61% for scores $>24$—32 whereas survival rates for scores $>32$ were significantly lower (21%, 19%, and 16%).

Hepatitis C recurrence is usually an indication for elective RT. Therefore, scores used for urgent RT [17,20–22,27,30] are probably not useful in candidates with hepatitis C (Table 2). Scores more commonly used in this setting include: (1) the Rosen score [31], (2) the MELD score [26,28,32], (3) the Child–Turcotte–Pugh score [25,26,33], and (4) the Donor Risk Index (DRI) [34] (Table 3). The variables with the highest impact on survival after RT are serum bilirubin [17,18,20–22,27,31,32] and creatinine [6,17,18,20–23,26,27,30–32,35] (both included in the MELD and Rosen scores). Rosen et al. [31] validated a model based on recipient age, bilirubin, creatinine and retransplant interval time (RT) in patients who underwent RT from the UNOS registry ($n = 773$) in five European and one Australian center ($n = 206$). The patients with an R score $<16$ had the best 1- and 3-year survival (75% and 70%) while in patients with an R score $>20.5$, survival was only 42% and 38%, respectively (Table 3). The first study evaluating the MELD score in RT candidates was published in 2003 [32] including a total of 22,120 primary LT (43.2% with HCV-infection) and 2129 RT (42.2% with HCV-infection) from 1996 to 2002. Patients with malignancy or those who underwent RT within 30 days after LT were excluded. Survival after RT did not differ for HCV-infected patients in comparison with other causes of elective RT (metabolic, genetic, alcohol, cryptogenetic, primary biliary cirrhosis, primary sclerosing cholangitis), and only autoimmune hepatitis and hepatitis B showed a higher survival. In contrast, a MELD $>25$ was a clear risk factor of short-term survival after RT, suggesting that liver and kidney function (MELD score) could be more important than etiology in elective RT. Bussutil and Ghobrial [21] elaborated a model to calculate survival in patients with LT or RT based on recipient and donor age, creatinine, bilirubin, prothrombin time, and warm and cold ischemia times. Three years later, the same authors [36] substituted the preoperative serum creatinine, bilirubin, and prothrombin values for the MELD score and included the time between first and second transplantation. These authors reported a 1-year survival benefit $>65\%$ in 30- to 40-year-old recipients with any MELD score and in 50-year-old candidates with a MELD $\leq 24$. They recommended avoiding RT in older recipients or those with a MELD $>28$. Another interesting model is the Donor Risk Index (DRI) developed by Feng et al. [37]. These authors identified seven donor variables that independently predicted a higher risk of graft failure after RT: donor age $>40$ years (particularly $>60$ years), donation after cardiac death, split/partial grafts, African-American race, low height, and cerebrovascular accident. Northup et al. [34] recently evaluated the DRI in 1327 patients who underwent RT. The authors showed that the addition of the cause of graft failure to the DRI significantly increased its predictive value.

Improving survival in HCV-infected patients after RT

Severe hepatitis C recurrence is one of the leading indications for RT. RT for this indication ranges from 3.6% to 44% [15] and has shown an increase during recent years. In Spain, 14,223 patients underwent LT between 1984 and 2008 and 4925 (34.6%) had HCV-infection. This figure is probably higher since most patients with hepatocellular carcinoma (HCC) are infected with the HCV. Among all the transplanted patients, 1410 (9%) underwent RT and in 438 (31%) the indication was severe hepatitis C recurrence [14].

One of the most difficult issues in RT is to determine the optimal timing to perform elective RT. This may be explained by the high number of variables that should be taken into account (as mentioned above), such as liver function, donor characteristics, and post-operative complications [38]. Recent studies using some of the above described prognostic scores as screening tools have shown similar survival rates in HCV-infected compared to non-HCV-infected patients [33,39] (Table 4). McCashland et al. [39] did not find any differences in survival between HCV- and non-HCV-infected patients undergoing RT when the selection was performed using the Rosen [31] and Markmann [20] scores. The 1- and 3-year survival in HCV-infected patients and non-HCV-infected patients who underwent RT was similar. The 1- and 3-year survival after RT was 69% and 49% for HCV-infected patients and 73% and 55% for non-HCV-infected individuals. Thus, an appropriate selection of candidates for RT results in acceptable outcomes. Recently, Marti et al. [33] evaluated 108 patients who underwent non-urgent RT adopting the Rosen score. Only HCV-infected patients who developed cirrhosis $>3$ years after primary LT underwent RT. Applying these selection criteria, the authors did not find significant differences in survival after RT at 1, 5, and 10 years between patients with hepatitis C recurrence (70%, 57%, and 57%, respectively) and all other causes (72%, 50%, and 45%, respectively).

Although the Rosen [31] and Markmann [20] prognostic models have been validated, the pros and cons of one model versus the other have not been investigated and more studies evaluating the utility of MELD score to select RT candidates are needed.
before recommending one model or another. Moreover, the indication of RT for HCV recurrence at an early stage could improve survival.

**Considerations in retransplantation of HCV-infected patients**

Several considerations may influence (directly or not) the decision to indicate RT in HCV recurrence: donor shortage, the efforts and resources utilized in LT, and in some cases, the emotional relationship established with the patient after the first LT. However, in order to maintain a principle of equity, it seems reasonable to indicate RT in HCV-infected patients if a minimal probability of survival of 50–60% at 1 year is reached. As mentioned above, bilirubin [17,18,20–22,27,31,32] and creatinine [6,17,18,20–23,26,27,30–32,35] levels are essential for discriminating RT candidates. Other variables such as center experience [40] or the age of the recipient [41] are more controversial. The use of prognostic models in HCV-infected patients can identify recipients with an acceptable prognosis after RT and their use should be recommended in the evaluation of RT candidates [33,39]. As shown above, several models have demonstrated a subgroup of patients with a high risk of death after RT: candidates with a Markmann score ≥2.3 [20], Rosen score ≥20.5 [31], Child-Pugh score ≥10 [26], MELD ≥25 [32] or a Linhares model ≥36 [30]. The use of a new organ in these candidates seems unreasonable.

The increasing number of patients on the waiting list has prompted the use of extended criteria donors (ECD) [38]. The precise definition of ECD remains elusive but this definition includes grafts with characteristics that can produce initial poor function or graft failure after transplantation [42]. Some authors have shown similar survival rates using ECD in patients with HCV-infection compared to other grafts. Northup et al. [34] showed that the use of ECD in patients with HCV-infection did not incur a worse survival. Actually, it has been suggested that the risk/benefit ratio is clearly better when using ECD in high-risk recipients (high MELD score) [45]. However, the use of ECD for RT is controversial for different reasons: (1) long-term data of LT and RT with ECD are lacking, (2) recipients of ECD grafts frequently have sub-optimal characteristics, and (3) the use of these grafts could be detrimental due to the additive effect of sub-optimal donors and recipients resulting in a higher mortality. For these reasons, some authors do not consider the use of ECD in high-risk recipients, such as the use of grafts with moderate steatosis in recipients, such as the use of grafts with moderate steatosis in recipients with a high MELD score [42]. Some authors have shown similar survival rates using ECD in patients with HCV-infection compared to other grafts.

**Prevention of need for retransplantation**

The first step to prevent liver RT in HCV-infected patients is to identify those patients at risk of developing severe hepatitis C recurrence. It is well known that early histological damage in protocol liver biopsies correlates with severe hepatitis C recurrence and poor long-term outcome after LT [46,47]. The International Liver Transplantation Society Expert Panel [29] established the administration of antiviral treatment if moderate to severe (grade 3 to 4) inflammation or significant fibrosis (stage 2) was
Frontiers in Liver Transplantation

present in protocol liver biopsies. Interestingly, the hepatic venous pressure gradient (HVPG) has demonstrated to be more accurate than liver biopsy at identifying patients at risk of clinical decompensation [48,49]. Recently, transient elastography (a non-invasive method to determine liver stiffness) has been shown to accurately identify liver fibrosis in LT patients [50,51]. It is therefore essential to identify patients who are at risk of progressive hepatitis C recurrence early after LT, since antiviral treatment can stabilize liver fibrosis progression and portal pressure [52] (see below). Thus, antiviral treatment of patients with severe hepatitis C recurrence or early after RT could have an important impact on graft and patient survival.

Antiviral treatment of HCV-infection in the transplant setting is currently based on pegylated interferon and ribavirin. However, most of the studies published on antiviral efficacy in LT patients are retrospective, uncontrolled and have a small sample size. Two recent systematic reviews [53,54] have shown a sustained virological response (SVR) rate of around 30–40%. The first review [53] of 19 studies from 2002 to 2007 (16 using pegylated interferon with ribavirin) with 611 patients reported a SVR of 30%. The second review between 1999 and 2008 [54] analyzed only six controlled studies with 242 patients and reported a median SVR rate of 31%. Although the rate of viral clearance in the transplant setting is significantly lower than in the immunocompetent patients, antiviral treatment decreases the progression of liver fibrosis [55,56] and reduces portal pressure [52] particularly in individuals who achieve SVR. In a recent prospective randomized control study using pegylated interferon plus ribavirin in HCV-infected patients who underwent LT, antiviral therapy was the only variable independently associated with histological response and was clearly associated with hemodynamic improvement [52]. The authors described stabilization and improvement in liver fibrosis and portal pressure even in patients with biochemical response who did not achieve viral clearance. Importantly, some authors have recommended the use of maintenance therapy to modulate the severity of disease progression and prevent graft failure [57]. The long-term outcome of patients who achieve SVR has recently shown to improve the natural history of HCV recurrence, with a significantly lower progression to cirrhosis and clinical decompensation and higher rates of survival compared to non-responders [58,59].

Another strategy to prevent HCV recurrence is the treatment of HCV-infected patients before LT. Antiviral treatment before LT has been shown to avoid graft infection in a significant proportion of patients [60,61]. However, treatment is usually restricted to Child-Pugh class A patients (in whom the indication of LT is HCC) or in selected Child-Pugh class B patients [62]. Regrettfully, this scenario is very unusual in patients who need RT, since most are in advanced liver failure and are not good candidates for antiviral treatment due to the high risk of bacterial infection (particularly spontaneous bacterial peritonitis) [62].

Other important issues could affect the natural history of HCV recurrence. Early treatment of biliary complications [63] and intensive treatment and control of diabetes mellitus [64] may have a beneficial influence on HCV progression after LT. Donor age [44] is a well known factor affecting long-term outcome in HCV recipients and efforts are made to match donors and recipients without disturbing the equity principle of recipients with other etiologies. At present, there is no evidence in favor of the use of a particular immunosuppressive regimen [65] to modify HCV progression after LT, and some reports on the use of a specific regime during antiviral treatment are controversial. However, active management of those factors which can accelerate fibrosis progression (avoidance of high dose corticosteroids, prevention and early treatment of diabetes) might reduce the incidence of severe forms of hepatitis C recurrence.

In summary, the best approach to prevent RT in HCV-infected patients is to administer antiviral treatment to patients at high risk of severe hepatitis C recurrence (i.e. those with significant fibrosis or portal hypertension soon after transplantation). Since antiviral therapy only eradicates HCV-infection in around one-third of treated individuals, RT is the only choice for individuals progressing to graft cirrhosis. Regrettfully, survival after RT is significantly lower compared to survival after primary liver transplantation. In the current era of donor shortage, RT should be indicated only in patients with a reasonable survival probability. In this setting, the use of well-validated predictive scores is helpful and should be implemented in liver transplant programs.

Key points

- HCV-infection recurs universally after liver transplantation (LT) and fibrosis progression is accelerated in the graft. Retransplantation (RT) is the only therapeutic option to achieve long-term survival in patients with decompensated cirrhosis after LT.
- Patient and graft survival rates after RT are inferior to those after primary LT.
- It is generally accepted that severe hepatitis C recurrence (cholestatis, cirrhosis, and portal hypertension) has a poor survival after RT. However, it is not clear whether rapid fibrosis progression in the first graft will be followed by the same rate of fibrosis progression in the second graft.
- The use of prognostic scores as screening tools has shown an improvement in survival in HCV-infected patients after RT, reaching similar survival rates as those obtained in non-HCV-infected patients. Moreover, these scores can identify candidates with a high risk of mortality in whom the use of a new organ would be unreasonable.
- Prevention of severe hepatitis C recurrence could be the first step to avoid RT. Thus, antiviral treatment on the waiting list (if possible) and early identification and treatment of patients with severe hepatitis C recurrence may be a good strategy to avoid RT.
- In addition, active management of factors which can accelerate fibrosis progression (donor age, post-transplant diabetes, high dose of corticosteroids) might reduce the incidence of severe forms of hepatitis C recurrence.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgment

X.F. received support by “Instituto de Salud Carlos III” (PI080239).
Reference


