

# Living Donor Liver Transplantation and Hepatitis C

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## Abstract

Preliminary results indicate that living donor liver transplantation (LDLT) recipients infected with HCV develop earlier and more severe recurrence than their cadaveric counterparts. The mechanisms underlying this observation are unknown, but could include hepatic regeneration, differences in LDLT recipient demographics, immune homology between donor and recipient, or other factors not previously considered. The optimum clinical approach is to consider LDLT in HCV-infected recipients only as a life-saving procedure and to attempt to eradicate HCV before LT to prevent recurrent infection.

## Key words

Living donor liver transplantation - viral C hepatitis - prevention

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## Rezumat

Rezultate preliminare indică faptul că recipientii de transplant hepatic (LDLT) de la donator viu infectați cu virusul hepatitic C (HCV) dezvoltă recurență mai timpurie și mai severă decât cei cu transplant hepatic de la cadavru. Mecanismele ce produc această diferență nu sunt cunoscute, dar pot include regenerarea hepatică, deosebirile dintre demografia recipientului LDLT, omologia imună dintre donor și recipient, sau alți factori încă neevaluați. Abordarea clinică optimă este aceea de a considera LDLT la recipientii infectați cu virus C drept o procedură salvatoare de viață și de a încerca eradicarea HCV înainte de transplant pentru a preveni infecția recurentă.

## I. The need for living donor liver transplantation

Liver transplantation (LT) has become the therapeutic option for patients with fulminant liver failure, end-stage chronic liver disease, and certain metabolic liver diseases for which no effective therapies are available. More than 50,000 patients have benefited from LT worldwide with an actuarial one-year, 3-year, and 5-year survival of 90%, 80%, and 70% respectively, at many leading centers for LT (1). In addition to longer survival, LT recipients are now experiencing improved quality of life, including resumption of active social and professional life, as well as reproductive capacity (2). Despite these excellent results, LT still faces several major challenges. One of the most important of these is dealing with the increasing shortage of graft organs. Currently, the number of patients listed for LT exceeds the cadaveric organ supply by nearly four-fold (1). There were 5,177 LTs performed in 2001 in the United States, but by the end of the year, there were still 18,537 candidates on the waiting list for LT. As a result, 11% of listed patients died on the waiting list that year (3). Similar figures were shown in European studies (Fig.1).

Since the LT program successfully began in Romania in April 2000, the severe shortage of cadaveric livers has emerged as the most critical issue. With only 44 LTs from deceased donors (DD) performed over 4 years (4) in a population of 21,698,181 inhabitants (2002 Census) (5), the grossly estimated rate of available cadaver grafts in Romania is 1 for 2 million inhabitants per year, which represents one of the lowest figures in Europe (Fig.2) (Table I). The leading cause for this is the low referral rate of potential DD to the transplant coordinators in our country, instead of family acceptability or religious considerations. With such a marked discrepancy between the ever-increasing number of patients demanding LT (Fig.3) and the very low number of DD, the proportion of patients who die while on the waiting list in our LT program has increased dramatically, achieving 30% at July 1, 2004 (Fig.4) (6).

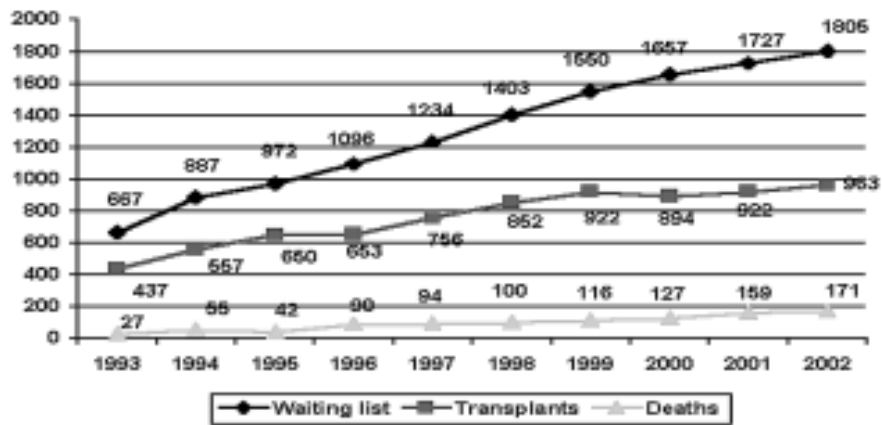
Given the growing organ shortage, a number of new innovative techniques to expand the donor pool are

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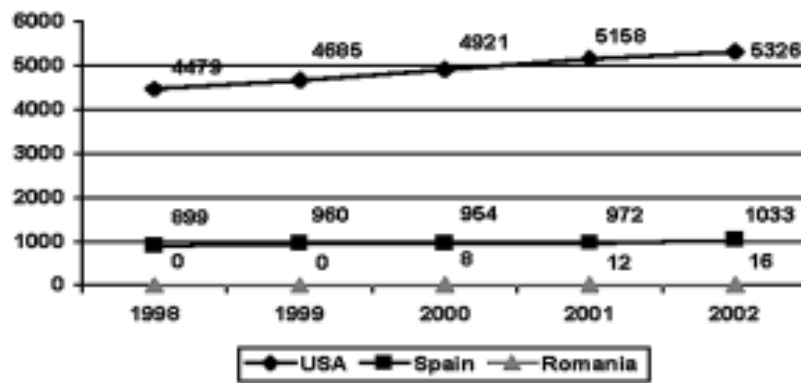
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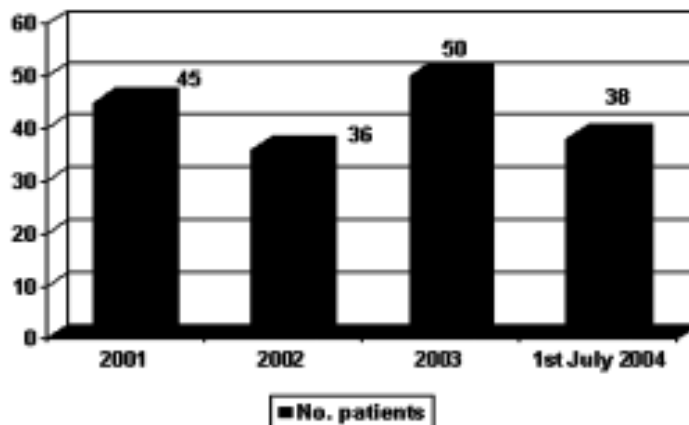
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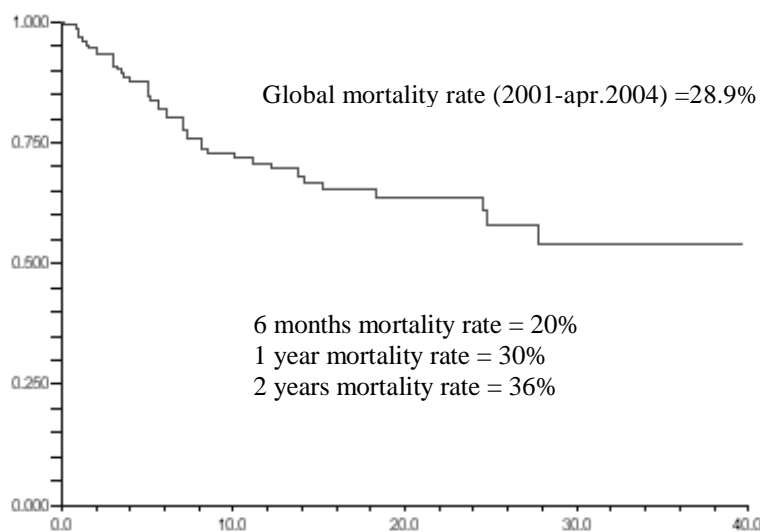
**Fig.1** Dynamics of the waiting list for liver transplantation in adults between 1993 - 2002: number of candidates, transplant recipients and deaths while on waiting list. Data available on internet: <http://www.msc.es/profesional/transplantes/estadisticas> (Accesed July 8, 2004).



**Fig.2** Number of liver transplants performed in the United States, Spain and Romania between 1998 – 2002. Data available on internet: <http://www.msc.es/profesional/transplantes/estadisticas> (Accesed July 8, 2004)



**Fig.3** Patients included on the waiting list for liver transplantation between April 1, 2001 – July 1, 2004 at the center for liver transplantation, Fundeni Clinical Institute, Romania. Data from Popescu I et al (4).



**Fig.4** Mortality rates while on the waiting list in the Romanian program for liver transplantation. Data from Popescu I et al (4).

**Table I** Number of liver transplants performed in the world and percent per million population (PMP)

Year Country	2001		2002	
	Number	PMP	Number	PMP
Australia	120	6.22	153	7.89
Austria	128	15.86	155	19.28
Belgium	201	19.51	226	21.94
Canada	340	10.94	381	12.19
Croatia	20	4.57	25	5.71
Denmark	32	5.89	39	6.84
Finland	38	7.34	47	9.04
France	803	13.38	882	14.72
Germany	757	9.21	756	9.2
Greece	18	1.8	21	1.91
Hungary	19	1.88	17	1.7
Israel	51	7.85	53	8.15
Italy	794	13.74	863	15.33
Malta	3	7.5	1	2.5
Norway	37	8.19	25	5.52
Poland	103	2.67	148	3.83
Portugal	184	18.4	191	19.1
R. Ireland	35	9.36	38	10
Romania	12	0.55	16	0.76
Slovak Rep.	5	0.95	3	0.57
Slovenia Rep.	9	4.5	11	5.5
Spain	972	23.65	1033	24.69
Sweden	102	11.45	102	11.46
Switzerland	88	12.22	83	11.53
The Netherlands	107	6.69	109	6.81
USA	5158	18.1	5326	18.52
United Kingdom	675	11.41	702	11.9

Data available on internet: <http://www.msc.es/profesional/transplantes/estadisticas> (Accesed July 8, 2004)

becoming increasingly popular (Table II). To deal with the severe donor shortage, most of these new techniques have been already performed within the Romanian Liver Transplantation Program: use of marginal donors in one patient (7), split LT in 6 patients, domino LT in one patient

**Table II** Resources aimed to expand the donor pool

Using marginal donors
Older donors (>50 years)
Donors with fatty liver infiltration
Hepatitis B virus (HBV)- and hepatitis C virus (HCV)-infected donors for HBV- and HCV-infected recipients, respectively
Split liver transplantation
Domino transplantation
Living donor liver transplantation
Swap transplantation
Xenotransplantation

(8), swap LT in two patients and living donor liver transplantation (LDLT) in 16 patients (4).

The first LDLT was performed in 1988 (9). Subsequently, the procedure has become popular in Asia, particularly in Japan, where cultural beliefs proscribe the use of cadaveric organs for transplantation. In the early 1990, LDLT was introduced in the United States and Europe (10). Typically, the left lobe or left lateral segment (segment 2-3) of an adult liver was resected, usually from a parent, and grafted into a child. This procedure was tremendously successful, with patient and graft survival approaching that achieved with DD livers (11). Adult-to-pediatric LDLT is currently a standard procedure in many pediatric LT programs worldwide. The first right hepatic lobe LDLT was reported in 1994 (12) and the first adult-to-adult right hepatic lobe LDLT in the United States was performed at University of Colorado in 1997 and reported in 1998 (13). In this procedure, the right hepatic lobe (segment 5-8), representing 60-65% of the liver, is resected from a living donor and grafted into recipient. Outcomes with transplantation of the larger right hepatic lobe in adults were superior to left hepatic lobe LDLT, which often did not provide sufficient hepatic mass for a caucasian adult recipient. Given the success of this procedure, coupled with the critical cadaveric organ

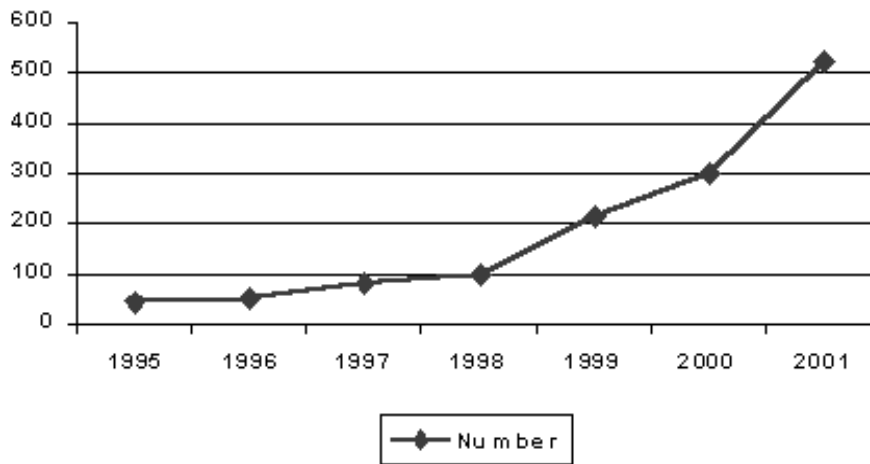


Fig.5 Increasing number of living donor liver transplant recipients between 1995 – 2001 (3).

shortage, adult-to-adult LDLT has evolved rapidly between 1997 and 2001, with more than 500 procedures performed in the United States in 2001 (Fig.5) (14).

Adult-to-adult LDLT is particularly successful in elective situations such as patients in UNOS 2B or UNOS 3 status or a Model for End-Stage Liver Disease (MELD) score lower than 25 and is less suitable for urgent situations such as patients in UNOS 1 or 2A status or a MELD score higher than 25 (15). Adult-to-adult LDLT is also indicated in transplant recipients with hepatocellular carcinoma who cannot wait long time on the waiting list due to the disease progression and occurrence of exclusion criteria. Although adult-to-adult LDLT is an attractive procedure to expand the donor pool, it is technically demanding and has several disadvantages associated with receiving a partial graft: only about 1/3 of potential living donors is suitable after undergoing evaluation; complications due to reduced graft size and bile duct strictures were reported; living donors experienced a 20-30% rate of morbidity and a 0% (16), 0.4% (14), and 0.8% (17) rate of mortality in Japan, United States, and Europe, respectively; living donor costs (comprising donor evaluation, donor surgery and postoperative donor

care) is 21% higher than those associated with the procurement of a DD graft (18) (a living donor evaluation is a complex and multistadial procedure which varies from 24 hours to 4 weeks and costs approximately 10 000 Euros); both donor and recipient may experience psychological problems (1, 15, 19). In patients receiving LDLT for hepatitis C, preliminary studies suggest that recurrent hepatitis C may be more common and occur earlier compared to DDLT.

## II. Hepatitis C virus infection and liver transplantation

End-stage liver disease associated with chronic hepatitis C virus (HCV) infection currently represents the most common indication for orthotopic LT, accounting for approximately 50% of cases performed in the United States and European transplant centers (1,20) (Fig.6). Given the high prevalence of chronic HCV infection in the general population and the limited success of the available antiviral therapy, the predicted peak of HCV-related disease burden is estimated to occur around 2010 (21). It will be associated

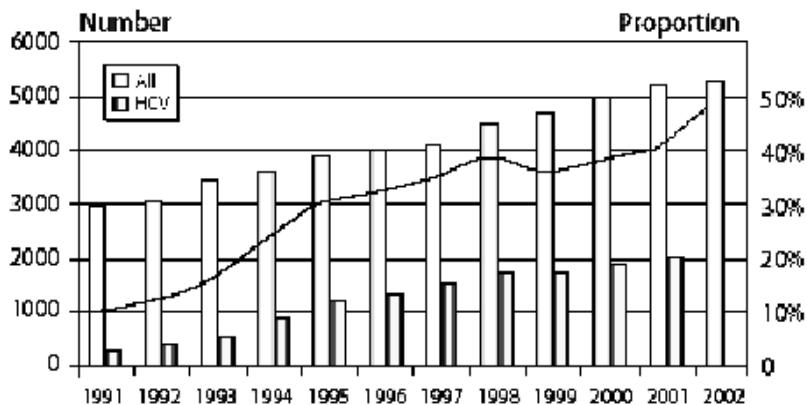


Fig.6 Number of liver transplantations per year in the United States (white bars), number due to chronic HCV (gray bars), and proportion due to HCV (line). Data from Davis GL (21).

with a two third increase in the prevalence of HCV-related cirrhosis and hepatocellular carcinoma when compared with the current levels (21). If correct, the projected increase of liver failure due to HCV infection is expected to increase the need of LT (either primary or re-transplantation) fivefold by the year 2020 (Table III) (21).

**Table III** Projected prevalence of cirrhosis and its complications over the next 20 years and its impact on the need for liver transplantation

Cirrhosis/ Complication	Year		Change (%)
	2000	2020	
HCV infection	2,940 678	2,681 556	-9.7
Cirrhosis	472,103	858.788	45
Decompensated cirrhosis	65,294	134.743	51.5
Hepatocellular carcinoma	7271	13,390	44.9
Liver-related death	13,000	36,483	64.4
Patients listed for transplant	10,893	30,000	-
Transplants performed	4893	Unknown	-
Transplants performed for HCV	1920	Unknown	-

Data from the Organ Procurement and Transplantation Network (OPTN) Database and Davis GL et al. Liver Transpl 2004; 4: 7-17

Recurrence of HCV infection after cadaveric LT is an universal phenomenon (22). Histological evidence of recurrent hepatitis in the graft has been shown to occur in 20-30%, 60%, and 80% of patients at 1, 3, and 5 years, respectively (23). The natural history of post-LT HCV infection in the recipient population is characterized by an accelerated progression to allograft cirrhosis shown to be as high as 3.7%, 16%, and 28%, respectively, over the same period (24). Recurrence of hepatitis C results in allograft failure in approximately 10% of recipients by the fifth postoperative year (25). As a result, the overall long-term outcome in HCV-infected LT recipients is not as good as in patients without HCV infection. A recent retrospective study of 11,036 patients undergoing cadaveric LT provided the first definitive evidence of significantly worse outcomes in HCV-infected recipients. This study found a 23% higher mortality rate in patients transplanted for HCV infection and a 30% rate of graft failure compared with non-HCV infected patients (26). To date, meaningful data regarding posttransplantation follow-up in HCV-infected recipients are available only for means of 3 to 5 years. As the duration of post-LT follow-up of HCV-infected recipients lengthens, the impact of HCV recurrence on long-term patient and graft survival is likely to increase (27).

### III. Living donor liver transplantation outcomes and recurrent hepatitis C

Recurrent HCV infection requires special consideration in LDLT recipients. Outcome of LDLT recipients infected

with hepatitis C (HCV) is one of the most important and controversial issue in LT (28).

Adult LDLT has evolved as a second option to increase the availability of organs and decrease the already-saturated waiting lists. To date, it has been performed in approximately 1000 cases in the United States (29). At this time, there is little data on the long-term outcomes of LDLT recipients. Data from the United Network of Organ Sharing (UNOS) reported an 85.9% 1-year survival rate in 588 adult LDLT recipients, similar to the 86.3% 1-year survival rate in cadaveric recipients (3). However, these survival figures may be not directly comparable because of the important differences between LDLT and cadaveric recipients (30). At the time of transplantation, LDLT recipients are generally in a better condition compared with their DD counterparts; they are far less sick, younger, thinner, less likely to be hospitalized in the intensive care unit, and have a lower MELD score (Table IV). These differences are tremendously important when one considers the post-transplantation outcomes suggesting that direct comparisons between LDLT and DD recipients are not realistic without adjusting for the severity of illness at the time of LT. Although LDLT offers candidates liver grafts before they become too ill for LT or die on waiting lists, it is associated with more common and distinct complications compared to those reported after DDLT such as biliary tract complications, reported in 10-30% of LDLT, or the small-for-size syndrome, a condition unique to LDLT, due to reduced graft size (31, 32). These conditions may overcome the advantages of LDLT. Although patient and graft survival may look similar for LDLT and DD recipients, the relative outcome for LDLT recipients is actually worse because they are significantly less sick at transplantation than DD recipients (33). An 88% and 123% higher relative risk of patients and graft survival, respectively, was recently reported in LDLT recipients compared with DD recipients ( $p < 0.001$ ) (34).

**Table IV** Comparison between the characteristics of living donor and deceased donor recipients at the time of LT

	LDLT	Cadaveric
UNOS status		
1	4%	13%
2A	1%	21%
2B	38%	55%
3	34%	8%
ICU hospitalization	6%	21%
BMI > 31 kg/m <sup>2</sup>	9%	18%
Age > 50	36%	50%

Data from Kam I. Liver Transpl 2002; 8: 347-349

End-stage liver disease from chronic hepatitis C is also the leading indication for LDLT (3). To date, there are no data on the long-term outcomes in HCV-infected LDLT recipients compared with cadaveric recipients. Some small preliminary studies suggest that recurrent hepatitis C occurs more commonly and earlier after LDLT compared to DDLT (35-38). Other studies, most of them using protocol biopsies,

have failed to show that LDLT recipients infected with HCV develop earlier, more frequent and more severe recurrence than their cadaveric counterparts (29, 39, 40).

#### **IV. Natural history and factors affecting HCV recurrence after cadaveric liver transplantation**

Recurrence of HCV infection after cadaveric LT, defined as HCV RNA detection by PCR, is nearly universal. A recent study on posttransplant HCV kinetics demonstrates that the presence of circulating HCV coming from bloodstream or extrahepatic sites can be detected during and immediately after the transplantation procedure and that intrahepatic viral replication can begin within few hours after surgery (41, 42). Serum HCV RNA increases rapidly after LT, peaking at 1-3 months and achieving 10-20 fold higher 1-year posttransplant levels compared with pretransplant viremia.

Several risk factors have been identified to increase the severity of recurrent hepatitis C following cadaveric LT. They fall into the following categories: 1) viral factors; 2) recipient factors; 3) donor factors; 4) post-LT clinical variables.

##### **1) Viral factors**

High pretransplant levels of viremia have been consistently shown to predict poor outcomes in HCV infected LT recipients (25, 43). Early severe cholestatic recurrence is associated with particularly high levels of HCV RNA, often in the setting of minimal inflammatory and fibrosis activity on liver biopsy, suggesting a cytopathic mechanism of allograft injury (44). Posttransplant levels of viremia are less reliably predictive for severe outcomes of recurrent hepatitis C (45).

Other viral factors that have putatively been reported to affect posttransplant disease severity include HCV genotype and the emergence of quasispecies (46-48). There are six major HCV genotypes with 11 subtypes (49). HCV genotype 1b has been reported to be associated with more severe allograft injury following cadaveric LT in several studies (46, 50-53). In one series, genotype 1b infected patients had posttransplant rates of acute and chronic hepatitis of 77% and 58%, respectively, whereas recipients infected with other genotypes had rates of 40% and 20%, respectively (50). On the contrary, a comparable number of studies have found no association between HCV genotype and severity of recurrence (23,25,54,55). Most of the reports that found a correlation between more severe allograft injury and genotype 1b have been performed in Europe, whereas most of the reports coming from the United States have not found this association. It has been postulated that a more virulent strain of genotype 1b may exist in Europe (55). Major pretransplant variants of HCV quasispecies have been implicated in efficient propagation of HCV infection after LT. A quasispecies evaluation of the hypervariable region (HVR1) of the second envelope protein (E2) found that mutations in the HVR1 area have been associated with a

low probability of viral clearance, the development of acute HCV infection, resistance to antiviral therapy and a higher risk to develop hepatocellular carcinoma, while the genetic diversity in the E1-5' genomic region has been associated with asymptomatic or mild recurrence (47, 48, 56). The impact of HCV genotype and quasispecies on posttransplant outcomes is, however, far too ambiguous to influence clinical decision-making (25).

##### **2) Recipient factors**

Recipient race and ethnicity play an important role in the outcome following cadaveric LT whether or not the recipient is infected with HCV. A recent study showed that at 2 years post-LT, whites had a 9% higher rate of survival than African American and a 14% higher rate of survival than Asians, whereas the rate of survival in Hispanics was similar to that of white Americans (57). For HCV-infected recipients, non-white race is associated with a relative risk of death of 2.1 (27).

Analysing a large cohort involving 11,036 recipients, the female gender was found to be associated with lower patient and graft survival in HCV-infected patients, 56% and 51%, respectively, compared with female recipients without HCV infection (25, 28).

A recipient age higher than 49 years was an independent risk factor for recurrent HCV following cadaveric LT (25, 55).

Immunogenetic background of donor and recipient may influence the severity and time to recurrent hepatitis C. The most important host factor associated with more severe course of posttransplant HCV infection is T-cell responsiveness. Despite immunosuppression, HCV-specific, major histocompatibility complex class II – restricted CD4+ T-cell response is detectable in patients with minimal histologic recurrence in contrast with patients showing severe recurrent hepatitis (58). These findings suggest that the ability to develop HCV-specific T-cell response is important in protecting against posttransplant HCV allograft injury (27). There is an inverse correlation between the degree of donor-receptor HLA matching and severity of HCV recurrence. Recipients who shared the HLA-DRB1, -DRB3, -B14 alleles with their donors had significantly more severe recurrent hepatitis C (59). However, other studies have failed to confirm this finding (23,25,52).

Absence of HBV co-infection in HCV recipients who underwent cadaveric LT was found to be associated with a 1.7 increase in relative risk for HCV recurrent hepatitis after cadaveric LT. Viral interactions within the allograft leading to suppression of HCV by HBV infection and subsequent prevention of HBV reinfection by administration of hepatitis B immunoglobulin (HBIG) following LT may exert a protective role (55). A favorable influence of posttransplant polyclonal HBIG administration on HCV infection was also postulated (60).

##### **3) Donor factors**

Donor factors associated with poor outcomes in HCV-infected recipients include: donor age, donor liver fat content, use of living donors, and ischemic time.

There is increasing evidence that older donors (>50 years) are associated with increased severity of HCV recurrence, fibrosis progression rate and time to cirrhosis (36, 61). A recent study showed that allograft steatosis does not differ in HCV and non-HCV infected patients and does not predict the severity of HCV recurrence (61). Prolonged warm ischemia time (63) and use of living donors for HCV-infected recipients (36, 38) is also associated with increased severity of HCV recurrence. The greater susceptibility of organs from older donors, living donors and organs with prolonged warm ischemia time to more severe recurrence of HCV infection may be based on increased susceptibility of regenerating hepatocytes to HCV infection (27).

#### 4) Posttransplant clinical variables

Several post-LT clinical variables have also been associated with more severe course of recurrent HCV infection of the graft: rejection episodes treated with bolus corticosteroids, steroid-resistant rejection and immunosuppressive protocols, histologic activity of the recurrent hepatitis C, and CMV infection.

The administration of specific immunosuppressive agents is associated with increased activity and virulence of HCV. In one study, HCV levels increased by 4- to 100-fold 2-weeks after 1g per day of methylprednisolone bolus for 3 days for acute cellular rejection (51). A strong correlation was demonstrated between acute cellular rejection episodes treated with bolus corticosteroids and increased histologic severity of HCV infection. The relative risk of death in these patients was 2.9 compared with HCV-infected recipients not treated for rejection (64). Steroid-resistant rejection episodes were accompanied by a higher and earlier recurrence of HCV reinfection (65). The use of antilymphocyte globulin (OKT3) for steroid-resistant rejection has been associated with an even higher relative risk of mortality and increased graft loss from recurrent HCV (66). The optimal immunosuppressive regimen for HCV recipients has not been defined and the overall degree of immunosuppression seems to be more important than the relative activity of individual components of the immunosuppressive regimen (27). There is, however, no difference in outcomes of HCV-infected recipients who received tacrolimus-based versus cyclosporine-based immunosuppression (52).

Three large trials have found that CMV infection is associated with increased severity of HCV recurrence (67-69). CMV infection is an independent risk factor for graft failure in HCV-infected patients. Specific prophylaxis against CMV (12 weeks postoperatively of oral valganciclovir) might reduce the impact of HCV-CMV co-infection on the outcome of recipients transplanted for HCV end-stage liver disease.

Histologic activity index seen on protocol biopsies at 4 months posttransplantation correlated significantly with the progression of fibrosis and it was highly accurate in identifying subjects who rapidly developed cirrhosis (45).

## V. Factors affecting hepatitis C recurrence after living donor liver transplantation

The mechanisms that influence the different course of recurrent HCV infection in LDLT recipients are still unclear. There are several factors which affect positively or negatively the recurrence of HCV infection after LDLT (30).

**Table V** Factors affecting recurrent hepatitis C following LDLT (30)

Positive	
	Less immunosuppression
	Lower posttransplant HCV viremia
	Younger, less sick recipients
	Pretransplant eradication of HCV
Negative	
	Immune homology between donor and recipient (increased HLA-antigen matching)
	Increased hepatic regeneration
	Increased expression of LDL receptor
	Increased intrahepatocyte HCV replication

Graft size is one of the most obvious differences between LDLT and DDLT. The donor right hepatic lobe is about half the size of the cadaveric graft. As a consequence, it undergoes intense proliferation immediately after LDLT, achieving full size within a few weeks after transplantation. In a recent study, it was shown that the right hepatic lobe in the LDLT recipient increased by 87%, 101%, 119% and 99% at 7, 14, 30, and 60 days after transplantation, respectively, as assessed by MRI. This indicates that the donated right lobe from a living donor nearly doubles its volume in a week after transplantation. Generally, the normal liver contains approximately 200 billion hepatocytes. The right lobe graft contains approximately half as many, meaning 100 billion hepatocytes. To regenerate 100 billion hepatocytes in one week, the right lobe graft must produce over 150,000 hepatocytes every second for 7 days (30). Increased hepatocyte mitotic activity of the graft may adversely affect the natural history of HCV infection in LDLT recipients. There is a 4- to 5-fold up-regulation of low density lipoprotein (LDL) receptor gene transcription in the regenerating hepatocytes (70). The LDL receptor represents the pathway used by HCV to enter the hepatocyte by way of receptor-mediated endocytosis (71). Increased expression of LDL receptor, in conjunction with higher posttransplant HCV-RNA, could result in higher accumulation of HCV in the LDLT allograft. The increased hepatocyte mitotic activity in the donated right hepatic lobe is correlated with a higher activity of the internal ribosome entry site (IRES), which mediates the translation of the HCV polyproteins (72). This may result in a higher intrahepatocyte HCV replication, which could result in a more severe allograft damage in LDLT compared with DDLT.

As noted above, HLA-antigen homology between the donor and recipient is associated with a more severe course of recurrent HCV infection in cadaveric LT, where the

deceased donor and recipient are unrelated. As in LDLT the donor is often a family member, usually a first-degree relative of the recipient, the HLA-antigen matching between the living donor and recipient is at least 50% (30). The higher degree of HLA-matching could explain, almost in part, the more severe recurrent HCV infection in LDLT recipients.

On the counterside, LDLT recipients may not require as much immunosuppression and acute cellular rejection occurs less frequently in LDLT than in deceased donor recipients. This could result in less aggressive recurrent hepatitis C. Demographic factors such as the better condition of LDLT recipients (younger, thinner, less sick, less co-morbidities) may also favor LDLT in HCV infected patients. Another factor that may positively impact the outcomes of LDLT recipients is represented by racial and ethnic differences between LDLT and DDLT recipients. The higher percentage of white Americans and Hispanics who undergo LDLT compared to African Americans and Asians should favor a better outcome of LDLT recipients (3, 57).

## VI. Therapy for recurrent hepatitis C after liver transplantation

The lack of an efficient strategy to prevent HCV reinfection of the graft and the aggressive course of recurrent hepatitis C after LT indicate the need for an effective antiviral therapy. Unfortunately, interferon-based therapy in LT recipients has been disappointing. Interferon or ribavirin monotherapy have been inadequate (limited efficacy, poor tolerability) to treat hepatitis C in the posttransplantation setting (73, 74). Monotherapy has failed to clear serum HCV RNA despite ALT normalization in a subset of patients (0-

28%). Relapse after treatment discontinuation is almost the rule and histologic improvement is uncommon. Combination therapy with interferon plus ribavirin for 48 weeks has been associated with sustained virologic response in 21% of treated patients compared with 0% in controls (75). Tolerance was an important limiting factor imposing dose reduction or discontinuation of the therapy in 43% of patients, mainly because of hematologic adverse events (75). To date, there are 10 available studies using combination therapy (interferon 1.5-3 MU x 3/week plus ribavirin 400-1200 mg/day) for recurrent hepatitis C after LT (75-84). Response rates are suboptimal ranging between 3% for patients treated for 12 weeks to 27% for patients treated for 30 weeks. Reasons that may explain these low figures are the high levels of HCV RNA in the posttransplantation setting, the high frequency of genotype 1 in LT recipients and the low tolerability profile due to cytopenia as a result of immunosuppression and persistent hypersplenism (85).

Several therapeutic approaches have been proposed. It was attempted to reduce the viral load or eliminate HCV while on WL using either standard/pegylated interferon alpha monotherapy or in combination with ribavirin (prophylactic pretransplantation therapy). However many patients do not meet the inclusion criteria and experience serious adverse events, mostly due to low platelet count (86). Treatment may be initiated in the first weeks after LT prior to the onset of biochemical or histologic evidence of recurrent hepatitis (preemptive or prophylactic posttransplantation therapy) (87). Although effective in some patients, this regimen has limited tolerability in the early posttransplantation period and its efficacy has not been directly compared to delayed treatment. Therefore, most transplantation centers currently use protocols aimed to

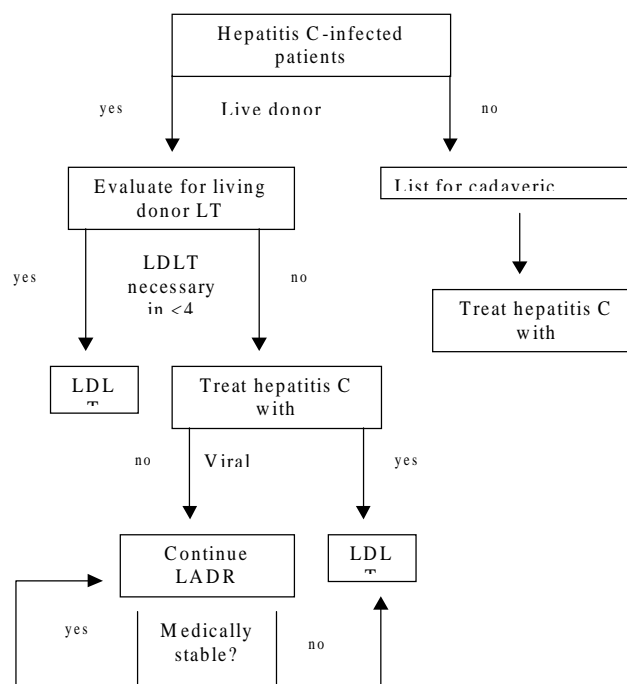


Fig.7 Evaluation of hepatitis C-infected LDLT candidates.

treat biochemical and histological HCV recurrence (therapy of posttransplantation recurrent hepatitis).

Many centers currently use pegylated interferons combined with ribavirin in patients with recurrent hepatitis C. However, published data on this therapy are scarce. In a recent pilot study, a sustained virological response of 45% accompanied by histologic improvement was reported after a 12-month course of combination therapy. Adherence to the treatment and HCV genotype non-1 were the main predictors of successful therapy (88).

Because LDLT recipients develop earlier and more severe HCV recurrence, antiviral therapy should be administered earlier and may be even less effective than in orthotopic LT recipients. On the other hand, LDLT recipients require less immunosuppression resulting in less side effects and better tolerability of antiviral therapy. Therefore, the optimal strategy to prevent posttransplantation recurrent hepatitis C in LDLT recipients is to eradicate HCV by pretransplant therapy. Using progressive doses of interferon and ribavirin (low-accelerated-dose regimen) to 3 million units interferon three times weekly and 1 to 1.2 g ribavirin per day, a recent study showed a sustained virological response of 22%. Granulocyte-colony-stimulating (GCS) factor and human recombinant erythropoietin were given to maintain a neutrophil count above 800/mm<sup>3</sup> and a hemoglobin above 10 g/dl. All pretransplant HCV-RNA negative recipients have remained negative after LT (89).

## VII. Selection of liver transplantation candidates for living donor liver transplantation

The problems facing recurrent hepatitis C in LDLT recipients have important implications in the selection of candidates for the procedure (Fig.7). For patients with compensated cirrhosis who have a suitable donor, LDLT offers the potential of an elective LT. However, the potential benefit of an elective procedure in these patients must be balanced by the risk for developing severe recurrent hepatitis C after LT. The clinical course of patients who develop severe recurrent hepatitis C is often significantly worse than the natural history of compensated HCV cirrhosis. For this reason, the widespread application of LDLT in the unselected population with HCV compensated cirrhosis is an unwise approach (30).

The proportion of HCV-positive antibodies in general population is highly variable (51). As a result, a fraction of donors evaluated for LDLT may be infected with HCV. Using an HCV-infected living donor might adversely impact the donor outcome after hepatectomy and the recipient and graft survival. The only situation when a potential HCV-infected donor could be considered for LDLT would be an HCV-antibody positive, HCV-RNA negative donor with normal liver histology (30).

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