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ORIGINAL ARTICLE

Advanced donor age increases the risk of severe recurrent hepatitis C after liver transplantation

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Summary

The association between donor age and the severity of recurrent hepatitis C and, whether there is any donor age above which severity of recurrence increases significantly, were analyzed. A total of 131 liver grafts of hepatitis C virus (HCV)-infected recipients were selected for the study. Distribution of donor age was compared between grafts with and without severe recurrence. The risk of developing severe recurrence as well as the hepatitis-free, severe hepatitis-free and HCV-related graft survival was compared between different donor age groups. Mean donor age was higher for grafts with severe recurrence ($P = 0.007$). The risk of developing severe recurrence within 2 years post-transplant increased with donors aged ≥50 years (RR = 1.34) and donors aged ≥70 years (RR = 1.61). Five-year severe hepatitis-free survival rates decreased progressively when donor age was over 50 years ($P < 0.001$). The study shows 50 and 70 years as the donor age cut-off points above which the evolution of HCV-infected recipients worsens.

Introduction

Hepatitis C virus (HCV) cirrhosis is the main indication for liver transplantation in many transplantation units around the world [1,2]. In an attempt to improve the poor evolution of recurrent hepatitis C in a fairly high percentage of HCV-infected recipients, many studies have been performed to identify the factors associated with severity of recurrence. Few factors have been identified and far from improving, recent studies suggest a decrease in patient survival among these patients in recent years [3]. However, in an attempt to enlarge the donor pool, the criteria for liver donor selection have been broadened and the donor age has been increased in recent years. Few authors have studied the association between donor age and the severity of recurrent hepatitis C after liver transplantation, suggesting an increase in the latter with advanced donor age [3–9]. However, a donor age limit has not been clarified. As confirmation of such an association could change donor selection criteria for HCV-infected recipients, we designed this study with the following goals: (i) to analyze the association between donor age and the severity of recurrent hepatitis C after liver transplantation, (ii) to establish whether there is any donor age limit above which the severity of recurrence increases significantly.

Materials and methods

Patients

The study population was made up of 131 liver grafts of HCV-infected recipients, selected from among 875 liver transplants performed in our department between April 23, 1986 and October 1, 2002, following the next selection criteria: (i) inclusion criteria: recipient age >15 years old, grafts which had histological diagnosis (biopsy or necropsy) of hepatitis with grade 3–4 fibrosis in Scheuer's score or fibrosing cholestatic hepatitis (severe hepatitis) and grafts without severe hepatitis with at least 2 years of follow up; (ii) exclusion criteria: positive HBsAg at transplantation

day or during the follow-up and simultaneous liver–kidney transplantation. Patients with other secondary diagnoses were not excluded because there is no big evidence in the literature that they affect the evolution of hepatitis C recurrence, and in order not to decrease the size of the study group. End of follow-up was on July 31, 2002 or when death, graft loss or retransplantation occurred. Mean recipient age was 51.3 ± 9.7 years (17–70). Male/female ratio was 85/46. The mean clinical follow-up was 1848.5 ± 1000.7 days and the mean histological follow-up was 929.8 ± 906.5 days.

Definitions

The HCV infection was established by the detection of viral RNA in serum samples by nested polymerase chain reaction, which was positive for all patients at transplantation date and 90 days post-transplantation. Recurrent hepatitis was diagnosed only under histological confirmation, when a biopsy showed hepatocyte necrosis and portal or lobular infiltration by mononuclear cells. Scheuer's score [10] was used for histological assessment of recurrence severity. A diagnosis of fibrosing cholestatic hepatitis was made when histology showed periportal fibrosis, interstitial infiltrate by neutrophils, cholestasis and ductus proliferation, with or without typical features of HCV hepatitis [11]. We defined severe recurrent hepatitis when the biopsy showed grade 3 or 4 fibrosis in Scheuer's score or fibrosing cholestatic hepatitis. We also considered severe hepatitis when the biopsy showed signs of progression to fibrosing cholestatic hepatitis (hepatitis with severe cholestasis but still without fibrosis) in the absence of biliary tract obstruction and the presence of progressive liver failure (two cases). Early severe recurrent hepatitis was defined as severe recurrent hepatitis diagnosed within 2 years (730 days) from liver transplantation. Late severe recurrent hepatitis was defined as severe recurrent hepatitis diagnosed between 2 (>730 days) and 5 years after liver transplantation. Although it is not an approved definition worldwide, other authors have defined early recurrence when it develops within the first year post-transplant. We extended this definition to 2 years because of two reasons: (i) in order to avoid to include an early severe recurrence into the late recurrence group because we do not perform biopsies routinely at 1 year follow-up (see histological assessment); (ii) and to increase the number of patients in this group making it better for statistical analysis. For HCV-related graft survival estimation we considered only HCV-related deaths or graft loss, considering patients with other causes of death or graft loss as 'lost in follow-up' at that event date.

Methods

In order to establish an association between donor age and severity of recurrence, the study population was divided into three groups: group A, grafts with early severe recurrent hepatitis ($n = 28$); group B, grafts with late severe recurrent hepatitis ($n = 13$); control group, grafts without severe recurrent hepatitis diagnosis at completion of follow-up (2 years at least because of selection criteria) ($n = 85$). Mean donor age was compared among these three groups. Five grafts that developed severe recurrent hepatitis later than 5 years postliver transplantation were not considered for this analysis. Moreover, in an attempt to detect a donor age range associated with a poorer outcome among these patients, grafts were distributed into seven groups depending on donor age (≤29, 30–39, 40–49, 50–59, 60–69 and ≥70 years). We estimated the severe recurrent hepatitis-free survival in each group and, based on these results, we redistributed the study population into four new groups (≤29, 30–49, 50–69 and ≥70 years) combining those groups with similar severe recurrent hepatitis-free survival (30–39 plus 40–49 and 50–59 plus 60–69). Distribution of donor age was compared between early severe recurrent hepatitis, late severe recurrent hepatitis and control groups. Hepatitis-free, severe recurrent hepatitis-free and HCV-related graft survival were estimated and compared between the different donor age range groups. Linear correlation between donor age and severe recurrent hepatitis-free survival was also analyzed.

Histological assessment

Biopsies were performed when an altered liver function test was observed (liver transaminases 1.5 above the normal value). All biopsies were reviewed by two pathologists. Although we are aware of the possibility of a severe recurrence without enzymatic abnormalities, it is very unlikely that a graft with early severe recurrent hepatitis would be included in the control group, taking into account the minimum follow-up (2 years) and the prolonged mean follow-up (over 5 years) of the control group. Moreover, the control group was numerous enough to overcome the effect of such an error on the study results.

Immunosuppression

Induction immunosuppression consisted of triple therapy with CyA, azathioprine and steroids, double therapy with FK and steroids or quadruple therapy with CyA, azathioprine, steroids and basiliximab (five patients

included in a multicenter clinical trial). CyA was switched to FK in 36 patients and FK to CyA in five because of side effects, AR or chronic rejection. The doses used for each drug have been described elsewhere [12].

Antiviral therapy

No patient included in this study received antiviral drugs to treat hepatitis C recurrence.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation and compared by the Student's *t*-test. Categorical variables were expressed as frequencies and percentage, and compared by chi-squared test (Fisher's exact test when indicated). Graft survival distributions were estimated by the Kaplan–Meier method and compared by the log-rank test. A probability of <0.05 was considered significant. Statistical analyses were performed with SPSS 9.0 (SPSS Inc., Chicago, IL, USA).

Results

The main features of early severe recurrent hepatitis, late severe recurrent hepatitis and control groups are shown in Table 1. No statistically significant differences in these features were detected among the groups except for a lower mean clinical follow-up in the early severe recurrent hepatitis group versus controls ($P = 0.007$). Mean donor age was significantly higher among grafts with early severe recurrent hepatitis [48.9 ± 21.3 years (15–87)] than in controls [37.4 ± 18.2 years (11–86)] ($P = 0.007$). This was also higher in late severe recurrent hepatitis group [50.7 ± 19.4 years (21–89)] than in controls ($P = 0.017$). Severe recurrent hepatitis-free survival were similar for donors aged 30–39 and 40–49, as well as for donors aged 50–59 and 60–69 (data not shown). Comparison of donor age distribution (<30, 30–49, 50–69 and ≥70) among the three groups showed significant differences between severe recurrent hepatitis groups (early severe recurrent hepatitis: 25%, 14%, 43%, 18%; late severe recurrent hepatitis: 15%, 23%, 46%, 15%) and controls (41%, 33%, 22%, 3.5%) ($P = 0.003$ versus early severe recurrent hepatitis and $P = 0.047$

Table 1. Main features of early severe recurrent hepatitis, late severe recurrent hepatitis and control groups.

Variables	ESRH ($n = 28$)	LSRH ($n = 13$)	Controls ($n = 85$)
Mean recipient age (years)	51.6 ± 9.6	50.92 ± 9.7	51.4 ± 9.8
Sex (male/female) (%)	19/9 (68/32)	8/5 (62/39)	53/32 (62/38)
Mean clinical follow-up (days)*	1363.9 ± 1189.1	1769.4 ± 595.1	1965.2 ± 938
Mean histological follow-up (days)	911.6 ± 976.8	1219.2 ± 431.4	804.1 ± 862.1
Indication for LT (%)			
HCV	16 (57.1)	9 (69.2)	50 (58.8)
HCV + alcohol	7 (25)	3 (23.1)	19 (22.3)
HCV + HCC	2 (7.2)	1 (7.7)	4 (4.7)
HCV + chronic rejection	1 (3.6)	0	3 (3.5)
HCV + porphyria	1 (3.6)	0	0
HCV + hemochromatosis	1 (3.6)	0	1 (1.2)
HCV + gall bladder ca. in donor	0	0	1 (1.2)
HCV + fulminant liver failure	0	0	2 (2.4)
HCV + PGD	0	0	1 (1.2)
HCV + PBC	0	0	3 (3.5)
HCV + SBC	0	0	1 (1.2)
Genotype (%)			
1a	1 (3.6)	1 (7.7)	6 (7.1)
1b	21 (75)	7 (53.8)	58 (68.2)
1a1b	1 (3.6)	0	1 (1.2)
1	2 (7.1)	2 (15.4)	5 (5.9)
3	0	0	2 (2.4)
Unknown	3 (10.7)	3 (23.1)	13 (15.3)
Acute rejection (%)	19 (67.9)	8 (61.5)	46 (54.1)
Immunosuppression			
CyA (%)	19 (67.9)	10 (76.9)	55 (69.7)
FK506 (%)	7 (25)	3 (23.1)	27 (32)

*$P < 0.05$.

ESRH, early severe recurrent hepatitis; LSRH, late severe recurrent hepatitis; LT, liver transplant; HCC, hepatocellular carcinoma; Ca.: carcinoma; PGD, primary liver graft dysfunction; PBC, primary biliary cirrhosis; SBC, secondary biliary cirrhosis; CyA, cyclosporine.

Table 2. Relative risk of developing early severe recurrent hepatitis depending on donor age.

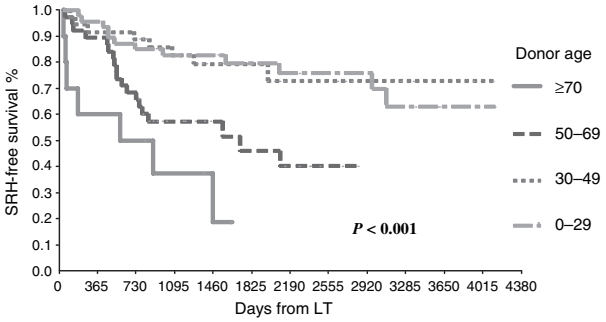
Donor age	*n*	ESRH (%)	No-ESRH (%)	*P*-value	Relative risk (confidence interval 95%)
<30	47	15	85	0.175	No association with ESRH
≥30	84	25	75		
<50	83	13	87	0.002	RR = 1.34 (1.07–1.68)
≥50	48	35	65		
<70	121	19	81	0.036	RR = 1.61 (0.86–3.02)
≥70	10	50	50		

ERSH, early severe recurrent hepatitis.

versus late severe recurrent hepatitis). In both early and late severe recurrent hepatitis groups donor age was ≥50 years in more than 60% of grafts while only 25% in the control group came within this donor age range.

Advanced donor age represented a risk factor for developing early severe recurrent hepatitis (Table 2). Donors aged over 30 did not increase the risk of developing early severe recurrent hepatitis compared with donors aged below 30 years. However, the risk of developing early severe recurrent hepatitis increased with donor age ≥50 (RR = 1.34). The risk of developing early severe recurrent hepatitis for the donor age ≥60 group was similar to that of donor age ≥50 (data not shown), however the risk increased again with donor age ≥70 (RR = 1.61).

Hepatitis-free, severe recurrent hepatitis-free and HCV-related graft survival was significantly lower among donors age range of 50–69 and even lower among grafts from donors aged ≥70 (Figs 1–3). It should be noted that there were no differences between the donor group aged under 30 and the group between 30 and 49. At 5 years

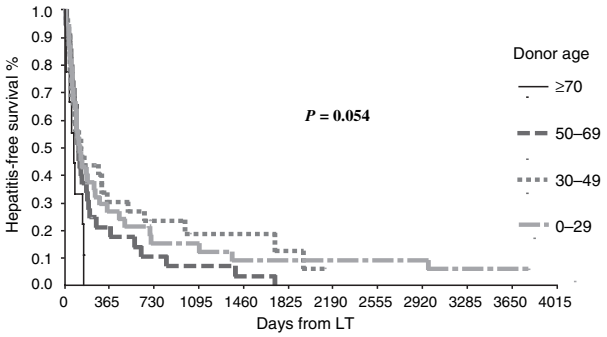


Donor age	*n*	1 year % (&)	3 years % (&)	5 years % (&)	8 years % (&)	SRH-free survival mean estimate, days (CI 95%)	*P*
≤29	47	96 (45)	83 (35)	80 (23)	76 (13)	3208 (2766;3650)	<0.001
30–49	36	92 (33)	83 (27)	79 (15)	73 (4)	3262 (2741;3782)	
50–69	38	89 (35)	57 (15)	46 (8)	40 (0)	1661 (1293;2029)	
≥70	10	60 (6)	37 (3)	19 (1)*	–	784 (376;1192)	

SRH: severe recurrent hepatitis; & grafts with no SRH diagnosis continuing surveillance; CI: confidence interval; *4 years follow-up.

Figure 2 Severe recurrent hepatitis-free survival by donor age.

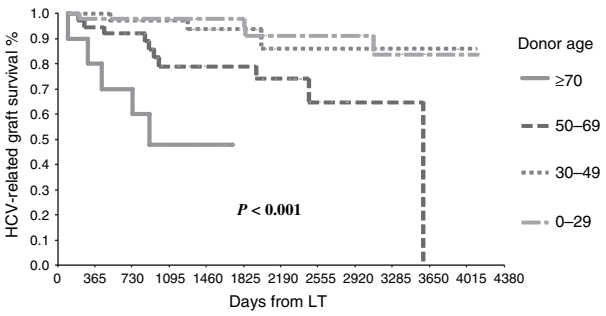
follow-up only 20% of grafts with donor age under 50 years developed severe recurrent hepatitis, while 81% of grafts with donor aged ≥70 have already developed severe recurrent hepatitis at 4 years follow-up. Mean estimated time to developing severe recurrent hepatitis was 8.8 years for grafts from donors aged under 50, while this was 4.5 and 2.1 years for grafts from donors aged 50–69 and ≥70 years respectively. Moreover, a linear correlation between donor age and severe recurrent hepatitis-free survival was also established ($P < .001$) with a Pearson coefficient of −0.379 (Fig. 4). It should be observed that there are two main cut-off points in severe recurrent hepatitis-free survival at donor ages 50 and 70, but there are no



Donor age	*n**	1 year % (&)	3 years % (&)	5 years % (&)	8 years % (&)	Hepatitis-free survival mean estimate. days (CI 95%)	*P*
≤29	39	27 (10)	15 (5)	9 (3)	9 (3)	550 (222;878)	0.054
30–49	32	30 (9)	19 (3)	13 (2)	6 (0)	531 (275;787)	
50–69	35	21 (6)	7 (2)	0 (0)	–	279 (136;421)	
≥70	9	0 (0)	–	–	–	84 (46;123)	

*Only grafts with histological follow-up over 100 days were included & grafts with no hepatitis diagnosis continuing surveillance; CI: confidence interval.

Figure 1 Hepatitis-free survival by donor age.



Donor age	*n*	1 year % (&)	3 years % (&)	5 years % (&)	8 years % (&)	HCV-related graft survival mean estimate, days (CI 95%)	*P*
≤29	47	98 (46)	98 (39)	98 (30)	91 (15)	3819 (3532;4105)	<0.001
30–49	36	100 (36)	97 (31)	94 (16)	86 (5)	3746 (3350;4148)	
50–69	38	95 (36)	79 (22)	79 (16)	65 (2)	2779 (2337;3261)	
≥70	10	80 (8)	48 (3)	48 (2)*	–	1087 (684;1489)	

HCV: hepatitis C virus; & grafts continuing surveillance; CI: confidence interval; *4 years follow-up.

Figure 3 HCV-related graft survival by donor age.

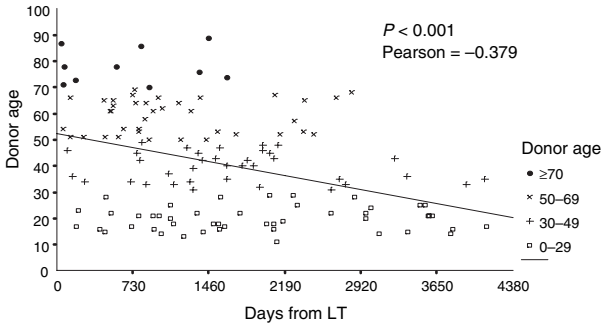


Figure 4 Donor age-severe recurrent hepatitis-free survival correlation.

significant differences in this survival rate between grafts included in the same defined range of donor age.

Discussion

The association between donor age and the severity of recurrent hepatitis C after liver transplantation have been suggested previously by other authors [3–7]. However, the cut-off point or points of donor age after which the risk of severe recurrence is increased have not been clearly established. In addition, these studies did not include donors as old as those in our study. Wali *et al.* [5] found an increased fibrosis progression rate in grafts from donors over 49 years, however the oldest donor was 67 years. The same study also found differences between donors aged 40–49 and <40 years. Other authors [3] detected a higher probability of developing graft cirrhosis among those who received the organ from donors over 59 years, and also differences in this probability between grafts from donors aged 31–59 and <31 years. There was a wide donor age range for each group in this study and the group over 59 years even included grafts from donors over 80 years. This fact makes it difficult to detect a cut-off point for changes in the probability of developing graft cirrhosis. Neumann *et al.* [6] found that donor age greater than 33 years was associated with the fibrosis development within the first year after liver transplantation. However, in this study the mean donor age was low (34 years) and no donor was over 70 years (range 8–68). Machicao *et al.* [7] found a higher incidence of high-grade fibrosis within the first year post-transplant among grafts from donors over 50 years of age, which agree with our results. The results of the present study show that the risk of developing early severe recurrent hepatitis is increased when the donor age is over 50 years, and markedly increased when over 70 years, without differences between grafts within the donor age range of 50–69 years. The time to developing grade 3–4 fibrosis or cholestatic hepatitis is significantly shortened by advanced donor age. Therefore, the study confirms the association between donor age and the severity of recurrent hepatitis C, and shows 50 and 70 years as the donor age cut-off points above which the evolution of HCV-infected recipients worsens. In contrast with the studies by Wali *et al.* and Neumann *et al.* we did not find significant differences between grafts from donors aged <30 and >30 years.

The results of the studies which analyzed the effect of donor age in the outcome of liver transplantation in non HCV-infected recipients are contradictory. Although few studies showed advanced donor age (with different age limits) as a factor associated with a poorer graft and patient survival rate [13–16], most of the authors did not consider advanced donor age *per se* as a contraindication for liver transplantation [17–23], however other factors such as steatosis, vascular conditions and others must be taken into account in this decision. Rifai *et al.* [24] have found in a recent study that donor age influences liver graft histology independently of hepatitis C infection. This study clarifies the deleterious effect of donor age on graft survival among non-HCV infected recipients, however it does not take into account the other donor factors we mentioned above. Nevertheless, studies in HCV-infected recipients considered cirrhosis or progression of fibrosis as the end point [3,5–7], so advanced donor age does clearly affects the evolution of hepatitis C, regardless of its effect on graft histology and survival due to steatosis, ischemic injury or other reasons. This is to say, apart from the influence of donor age on graft and patient survival, regardless of the indication for liver transplantation, advanced donor age affects graft survival in HCV-infected liver recipients by accelerating the evolution of recurrent hepatitis C to high grade fibrosis or cirrhosis and liver failure.

The cause of the deleterious effect of advanced donor age in the evolution of recurrent hepatitis C after liver transplantation is unclear. Age-related changes in liver immune response to HCV have been proposed [5,8], but further studies must clarify the issue. In any event, whatever may be the cause, we consider there is enough evidence to reject donors aged over 70 years for HCV-infected recipients, and to try to avoid donors over 50 for these recipients. We realize, however, that this could be difficult, because of the current problem of organ shortage and the high number of HCV-infected patients in the waiting lists.

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