World J Surg (2013) 37:2211–2221
DOI 10.1007/s00268-013-2085-7

World Journal of Surgery

Long-Term Results Using Old Liver Grafts for Transplantation: Sexagenerian Versus Liver Donors Older than 70 Years

Carlos Jiménez-Romero · Marta Clemares-Lama · Alejandro Manrique-Municio · Alvaro García-Sesma · Jorge Calvo-Pulido · Enrique Moreno-González

Published online: 24 May 2013
© Société Internationale de Chirurgie 2013

Abstract

Background The most practical measure to augment the available number of liver grafts and thus reduce waiting list mortality is to increase the donor age limit. We hypothesized that with careful selection of old liver donors without age limit it should be possible to obtain good patient and graft survival.

Methods The present study comprises 351 adults who underwent liver transplantation. They were divided into three groups according to the age of the liver donors: group 1: 226 recipients of donors <60 years; group 2: 75 recipients of donors between 60 and 70 years; and group 3: 50 recipients of donors >70 years. A comparative study among the groups was performed.

Results Patient survival rates at 1, 3, and 5 years were, respectively, 81.0, 76.1, and 71.1 % in group 1; 83.8, 74, and 72.2 % in group 2; and 76, 70.0, and 62.9 % in group 3 ($P = \text{NS}$). Graft survival at 1, 3, and 5 years was, respectively, 74.8, 69.0, and 64.1 % in group 1; 82.7, 71.4, and 69.6 % in group 2; and 71.4, 64.8, and 58.3 % in group 3 ($P = \text{NS}$). We analyzed the use of older grafts in recipients with HCV cirrhosis and did not find significant differences in patient and graft survival at 1, 3, and 5 years. In multivariate analysis increased donor body mass index and decreased recipient albumin were associated with lower patient and graft survival.

Conclusions Because patient and graft survival rates are not affected by donor age, well-selected older donor livers can be safely used if they show good function and pre-harvesting conditions.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CIT	Cold ischemia time
FFP	Fresh frozen plasma
GGT	Gamma-glutamyl transpeptidase
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
HBV	Hepatitis B virus
HCC	Hepatocarcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
ICU	Intensive care unit
IPF	Initial poor function
OLT	Ortothopic liver transplantation
PNF	Primary nonfunction
PRBC	packed red blood cells
WIT	Warm ischemia time

Introduction

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with end-stage chronic liver diseases, acute liver failure, and certain metabolic liver diseases. The excellent results of OLT have led to an increasing number of patients on the waiting list, while the number of liver donors has remained stable. The growing disparity between the number of recipients on the waiting list and the availability of liver donors is associated with an increased rate

C. Jiménez-Romero (✉) · M. Clemares-Lama · A. Manrique-Municio · A. García-Sesma · J. Calvo-Pulido · E. Moreno-González
Department of General and Digestive Surgery, and Abdominal Organ Transplantation, Hospital Doce de Octubre, Complutense University, 4ª Planta. Ctra Andalucía Km 5,4, 28041 Madrid, Spain
e-mail: carlos.jimenez@inforboe.es

of mortality of candidates on the waiting list. In Spain, 1,108 OLT (24 OLT per million inhabitants) were performed in 2008, and the rate of waiting list mortality of OLT candidates was 7.4 %. In 1998, the rate of donors older than 60 years was 28.8 %, whereas in 2008 that rate reached 43.1 %: the mean age of adult liver donors also increased during that decade, from 45 years in 1998 to 55 years in 2008. At the same time, cerebrovascular accident as the main cause of donor death has increased significantly, from 54.7 % in 1998 to 67.7 % in 2008 [1]. Thus liver organ shortage has led liver transplant teams to expand the donor pool using so-called marginal donors, a not well-defined group in which are included donors >60 years of age, donors with hypernatremia, steatosis, or positive serologies for hepatitis C virus (HCV) or hepatitis B virus (HBV), livers with a cold ischemia time (CIT) >12 h, non-heart-beating donors, and split-technique and living-related donors [2–10]. The most frequent and practical measure to augment the liver donor pool, and thus to reduce waiting list mortality, is to increase donor age [3, 11–15]. However, the use of older livers for transplantation is subject to debate because several authors [16–19] have reported a negative impact of increased donor age on survival after OLT. Other authors [12, 14, 20–24], however, have demonstrated similar patient and graft survival rates with liver grafts older than 60 and even 70 years.

We hypothesized that with careful selection of older donors we would achieve comparable results in OLT independent of donor age. Thus the aim of the present study was to compare retrospectively three groups of recipients who received livers from donors of different ages: less than 60 years old, between 60 and 70 years old, and more than 70 years old.

Patients and Methods

Study Population

Between April 1986 and December 2003, we performed 962 liver transplants on 866 patients in our institution. For the present study we excluded 140 pediatric transplants (patients less than 16 years old), 20 hepatorenal transplants, 22 split liver transplants, 23 recipients of living donor livers, 96 retransplants, 250 livers preserved with Collins solution, and 60 transplants without complete data sets to included donor, recipient, and perioperative variables. Thus, the sample comprises 351 adult recipients who underwent OLT for chronic diseases and acute liver failure. That sample was divided into three groups according to donor age: control group 1: 226 recipients (64.4 %) from donors younger than 60 years old; group 2: 75 recipients (21.4 %) from donors between 60 and 70 years old; and group 3: 50 recipients (14.2 %) from donors older than 70 years old.

Donor and Recipient Characteristics

We evaluated the following donor variables: age, sex, body mass index (BMI), cause of death, intensive care unit (ICU) stay, vasopressor use, cardiac arrest, values of liver function tests [GOT (glutamic oxaloacetic transaminase), GPT (glutamic pyruvic transaminase), GGT (gamma-glutamyl transpeptidase), total bilirubin, prothrombin rate], serum sodium level, rate and grade of steatosis, graft preservation injury, and cold and warm graft ischemia times.

The following pretransplant recipient variables were also recorded: age, sex, OLT indication, Child-Pugh score, MELD (model for end-stage liver disease) score, hematological and liver function parameters (total bilirubin, GOT, GPT, GGT, alkaline phosphatase, prothrombin rate), and serum levels of albumin, creatinine, and glucose. In the process of organ procurement, liver biopsy was performed on all liver grafts from donors older than 65 years and on livers from younger donors when liver abnormalities (steatosis, color, hard consistency, edema, fibrosis, hepatitis) were suspected by macroscopic evaluation.

Intraoperative and Post-OLT Characteristics

All liver grafts were preserved with Belzer solution, and recipient hepatectomy was performed with the vena cava-sparing technique (piggy-back). In these transplant phases we evaluated the following variables: packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelet transfusions; ICU and hospital stay; and base immunosuppression regimens (cyclosporine or tacrolimus). Serum albumin and liver graft function parameters (total bilirubin, GOT, GPT, GGT, alkaline phosphatase, and prothrombin rate) were evaluated during the first month after OLT (serum levels at 1, 3, 7, and 30 days after OLT).

Postoperative Complications, Mortality, and Patient and Graft Survival

We recorded each group's post-transplant complications, such as primary graft nonfunction (PNF), initial poor function (IPF), acute and chronic rejection, biliary complications, infections, and retransplant rate and causes. Causes of mortality and 1-, 3-, and 5-year patient and graft survival of the three groups were analyzed during the follow-up. A comparative analysis of patient and graft survival was performed between patients who underwent OLT for HCV cirrhosis versus other liver diseases. Patient and graft survival were also analyzed in patients with viral C cirrhosis who received livers from donors younger or older

than 60 years (group A and group B, respectively). PNF was defined as GOT > 1,500 IU/L and prothrombin rate <60 %, and if the recipient died or required urgent retransplantation within the first 14 days, having excluded extrahepatic causes. IPF was defined as GOT > 1,500 IU/L and prothrombin rate >60 % during the first post-transplant week, followed by spontaneous recovery of graft function.

Immunosuppression

One immunosuppressive regimen comprised cyclosporine, prednisone, and azathioprine or mycophenolate mofetil, and the other consisted of tacrolimus and prednisone. Azathioprine was discontinued 3 months after OLT. From 1996 onward, azathioprine was replaced by mycophenolate mofetil. Steroids were usually discontinued between 3 and 12 months after OLT in the cyclosporine regimen, and at 3 months after OLT in the tacrolimus regimen. More detailed immunosuppressive information has been described previously [25].

Statistical Analysis

Quantitative variables were expressed as mean values and standard deviations (SD), and qualitative variables as percentages. Differences in properties between qualitative variables were assessed by the χ^2 test. The comparison of quantitative variables was made by analysis of variance (ANOVA), using Scheffe's test when required. Graft and patient survivals were estimated by the Kaplan–Meier method. Comparison of survival curves was performed with the log rank test. A P value less than 0.05 was considered statistically significant. The variables with statistical significance in the univariate analysis were subsequently investigated in a multivariate analysis using a stepwise forward Cox regression procedure to asses the effect of multiple factors on patient and graft survival. The analyses of these data were performed with the SAS System for Windows.

Results

Donor Characteristics

Mean donor ages and the sex distribution of the groups are shown in Table 1. Body mass index was significantly less ($P = 0.0001$) in the younger donor group 1 than in groups 2 and 3. In contrast to groups 2 and 3, group 1 showed a significantly higher incidence of donor head trauma and a lower incidence of intracranial bleeding ($P = 0.0001$). ICU stay was significantly shorter ($P = 0.004$) in older donors (group 3), but the frequency of vasopressor use and previous cardiac arrest were similar among the groups. Total bilirubin and GGT values were also similar among the groups, but younger donors (group 1) showed significantly higher values of GOT and GPT ($P = 0.002$) and a lower prothrombin rate ($P = 0.007$) than donors in the other two groups. The rate of overall graft steatosis (macro and micro) was significantly higher in groups 2 and 3 than in group 1 ($P = 0.005$), but this difference was almost exclusively due to the more frequent presence of mild microsteatosis in these older donor groups.

Preservation injury was significantly more frequent in group 1 than in the other two groups ($P = 0.005$), mainly because of the higher incidence of mild grade injury. However, mean CIT was significantly shorter in recipients from younger donors (303 ± 178 min in group 1; 371 ± 193 min in group 2; and 366 ± 154 min in group 3; $P = 0.006$). By contrast, warm ischemia time (WIT) was significantly longer in recipients of younger donors ($P = 0.001$) (Table 1).

Recipient Characteristics

Mean recipient age and sex distribution were not statistically significantly different among the three groups The most frequent indications for OLT were alcoholic cirrhosis in 167 patients (47.6 %), HCV cirrhosis in 138 patients, HBV cirrhosis in 32 patients, and hepatocarcinoma (HCC) associated with cirrhosis in 21 cases. Older liver donors were statistically more frequently used in patients with HCV cirrhosis (34.5 % in group 1; 50.7 % in group 2; and 44.0 % in group 3; $P = 0.035$). Older liver donors were also used for 21 patients with hepatocarcinoma: 10 patients (4.4 %) in group 1; 6 patients (8 %) in group 2; and 5 patients (10 %) in group 3, but without significant differences among the groups. Child-Pugh distribution and MELD scores were similar among the three groups. No differences were observed among the three groups in relation to preoperative mean values of hematological parameters (hemoglobin, leukocytes, and platelets). Comparing the pre-OLT liver function tests among the groups, we found significantly higher values of GOT ($P = 0.016$) and GGT ($P = 0.031$) in group 2 than in the other two groups. The mean values of other liver function tests (total bilirubin, GPT, alkaline phosphatase, prothrombin rate, and serum albumin), serum creatinine, and serum glucose did not show any significant differences among the groups (Table 2).

Intraoperative and Post-OLT Characteristics

Group 3 patients received a significantly lower intraoperative transfusion of PRBC, but the amounts of FFP and platelets were similar among the three groups. The length of ICU stay was also similar among the three groups, but hospital stay was significantly shorter in group 3 ($P = 0.0042$). Cyclosporine-based immunosuppression was more

Table 1 Donor characteristics

Characteristics	Donors <60 years Group 1 ($n = 226$)	Donors 60–70 years Group 2 ($n = 75$)	Donors >70 years Group 3 ($n = 50$)	P value
Mean donor age (years)	31.5 ± 13.6	64.7 ± 2.5	75.7 ± 5.5	0.0001
Sex (male/female)	62.7/37.3 %	61.3/38.7 %	44/66 %	0.0085
Body mass index (BMI)	24.7 ± 3.6	27.3 ± 4.0	26.7 ± 3.7	0.0001
Cause of donor death				0.0001
Head trauma	127 (56.2 %)	7 (9.3 %)	12 (24.0 %)	
Intracranial bleeding	37 (16.4 %)	51 (68.0 %)	36 (72.0 %)	
Other causes	62 (27.4 %)	17 (22.7 %)	2 (4.0 %)	
Intensive care unit stay (h)	69.9 ± 84.7	72.6 ± 67.2	32.0 ± 25.5	0.004
Vasopressor use	164 (72.6 %)	51 (68.0 %)	37 (74.0 %)	NS
Cardiac arrest	29 (12.8 %)	7 (9.3 %)	2 (4.0 %)	NS
Total bilirubin (mg/dL)	1.1 ± 1.1	1.0 ± 1.0	0.9 ± 0.7	NS
GOT (IU/L)	80 ± 111	44 ± 43	40 ± 53	0.002
GPT (IU/L)	62 ± 95	33 ± 40	26 ± 32	0.002
GGT (IU/L)	49 ± 70	57 ± 58	29 ± 22	NS
Prothrombin rate (%)	70 ± 20	78 ± 20	73 ± 20	0.007
Sodium (mEq/L)	148 ± 15	148 ± 10	145 ± 10	NS
Rate of steatosis	58 (25.6 %)	37 (49.3 %)	20 (40.0 %)	0.005
Macrosteatosis	19 (8.4 %)	6 (8.0 %)	2 (4.0 %)	
Microsteatosis	29 (12.8 %)	24 (32.0 %)	14 (28.0 %)	
Macrosteatosis and microsteatosis	10 (4.4 %)	7 (9.3 %)	4 (8.0 %)	
Grade of microsteatosis				0.005
Absent	168 (74.3 %)	39 (52.0 %)	30 (60.0 %)	
Mild (<30 %)	30 (13.3 %)	23 (30.7 %)	11(22.0 %)	
Moderate (30–60 %)	21 (9.3 %)	9 (12.0 %)	5 (10.0 %)	
Severe (>60 %)	7 (3.1 %)	4 (5.3 %)	4 (8.0 %)	
Preservation injury				
Absent or minimal	50 (22.1 %)	29 (38.7 %)	23 (46.0 %)	0.005
Mild	107 (47.3 %)	23 (30.7 %)	15 (30.0 %)	
Moderate	56 (24.8 %)	19 (25.3 %)	12 (24.0 %)	
Severe	13 (5.8 %)	4 (5.3 %)	0 (0 %)	
Cold ischemia time (min)	303 ± 178	371 ± 193	366 ± 154	0.006
Warm ischemia time (min)	68 ± 25	60 ± 12	58 ± 11	0.001

GOT glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase, *GGT* gamma-glutamyl transpeptidase

frequently used in group 1 ($P = 0.001$), and the tacrolimus regimen was more frequently used in groups 2 and 3 ($P = 0.0001$) (Table 3).

Liver Function after OLT

Mean bilirubin values (determinations at 1, 3, 7, and 30 days after OLT) did not reveal any significant differences among the three groups. Mean values of GOT were significantly higher before OLT in group 2 and maintained that significance during the first day (482 IU in group 1, 737 IU in group 2, and 491 IU in group 3; $P = 0.046$) and the third day (183 IU in group 1; 291 IU in group 2, and 196 IU in group 3; $P = 0.024$), but the values were similar among the groups on the 7th day and the 30th day after OLT. Mean values of GPT did not change significantly from basal values before OLT to 30 days after OLT. Pre-OLT mean values of GGT were significantly lower in group 3 ($P = 0.031$), but the values of the three groups were similar from the first day to the 30th day after OLT. Alkaline phosphatase reached statistically significant lower mean values in group 1 on day 1 ($P = 0.015$), day 3 ($P = 0.001$), and day 7 ($P = 0.001$), but at one month after OLT mean values were similar among the three groups. Mean values of prothrombin rate were significantly lower in group 3 on day 1 ($P = 0.001$), day 3 ($P = 0.024$), and day 30 ($P = 0.027$) after OLT. Mean values of serum albumin were significantly higher in group 1 on day 1

Table 2 Recipient characteristics

Characteristics	Group 1 ($n = 226$)	Group 2 ($n = 75$)	Group 3 ($n = 50$)	P value
Mean recipient age (years)	48.5 ± 10.3	51.4 ± 11.1	51.1 ± 10.6	NS
Gender (male/female)	66.8/33.2 %	69.3/30.7 %	80.0/20.0 %	NS
Most frequent OLT indications				
Alcoholic cirrhosis	112 (49.6 %)	33 (44.0 %)	22 (44.0 %)	NS
Viral C cirrhosis	78 (34.5 %)	38 (50.7 %)	22 (44.0 %)	0.035
Viral B cirrhosis	15 (6.6 %)	9 (12.0 %)	8 (16.0 %)	NS
Hepatocarcinoma	10 (4.4 %)	6 (8 %)	5 (10 %)	NS
Child-Pugh distribution				NS
Grade A	12 (5.3 %)	5 (6.7 %)	2 (4.0 %)	
Grade B	85 (37.6 %)	29 (38.7 %)	23 (46.0 %)	
Grade C	128 (56.6 %)	40 (53.3 %)	25 (50.0 %)	
MELD score	16.7 ± 5.5	15.4 ± 5.3	16.1 ± 6.4	NS
Pre-OLT laboratory parameters				
Hemoglobin (g/100 mL)	11.9 ± 2.0	11.9 ± 1.8	11.8 ± 1.8	NS
Leukocytes	5,390 ± 3,582	4,950 ± 3,098	5,400 ± 4,370	NS
Platelets	89,751 ± 58,684	76,815 ± 46,135	79,865 ± 47,027	NS
Total bilirubin (mg/dL)	4.5 ± 6.4	5.7 ± 8.6	5.1 ± 10.3	NS
GOT (IU/L)	91 ± 74	283 ± 106	101 ± 56	0.016
GPT (IU/L)	72 ± 65	222 ± 213	80 ± 72	NS
GGT (IU/L)	112 ± 169	117 ± 252	61 ± 44	0.031
Alkaline phosphatise (IU/L)	305 ± 321	357 ± 425	311 ± 171	NS
Prothrombin rate (%)	58 ± 20	57 ± 17	59 ± 15	NS
Serum albumin (g/L)	3.3 ± 0.6	3.3 ± 0.5	3.3 ± 0.6	NS
Serum creatinine (mg/dL)	1.01 ± 0.51	0.96 ± 0.27	1.02 ± 0.37	NS
Serum glucose (mg/dL)	108 ± 44	121 ± 69	104 ± 29	NS

OLT orthotopic liver transplant, *MELD* model for end-stage liver disease

Table 3 Intraoperative and post-OLT characteristics

Characteristics	Group 1 ($n = 226$)	Group 2 ($n = 75$)	Group 3 ($n = 50$)	P value
Transfusion				
PRBC (mL)	4,800 ± 6,400	3,600 ± 4,400	2,800 ± 2,800	0.023
FFP (mL)	4,600 ± 3,600	4,400 ± 2,800	4,400 ± 4,400	NS
Platelets (mL)	280 ± 320	320 ± 240	240 ± 200	NS
ICU stay (days)	5.1 ± 5.6	5.1 ± 5.1	4.1 ± 4.5	NS
Hospital stay (days)	27.9 ± 20.5	24.9 ± 23.4	20.0 ± 11.1	0.042
Immunosuppression				
Cyclosporine	226 (85.4 %)	43 (57.3 %)	22 (44 %)	0.001
Tacrolimus	33 (14.6 %)	32 (42.7 %)	28 (56 %)	0.0001

($P = 0.020$), day 3 ($P = 0.0001$), day 7 ($P = 0.0001$), and day 30 after OLT ($P = 0.04$) (Fig. 1).

Post-OLT Complications and Mortality

We did not find any significant differences in the rate of PNF among the three groups of recipients, but the rate of IPF was significantly lower in recipients of younger donor livers ($P = 0.002$). In contrast, the rates of acute rejection ($P = 0.006$) and chronic rejection ($P = 0.002$) were significantly higher in recipients of livers from younger donors. The rate of biliary complications was similar among the three groups, and the rate of post-OLT infection was significantly lower in the recipients of livers from group 3 ($P = 0.0001$). The incidence of severe viral C

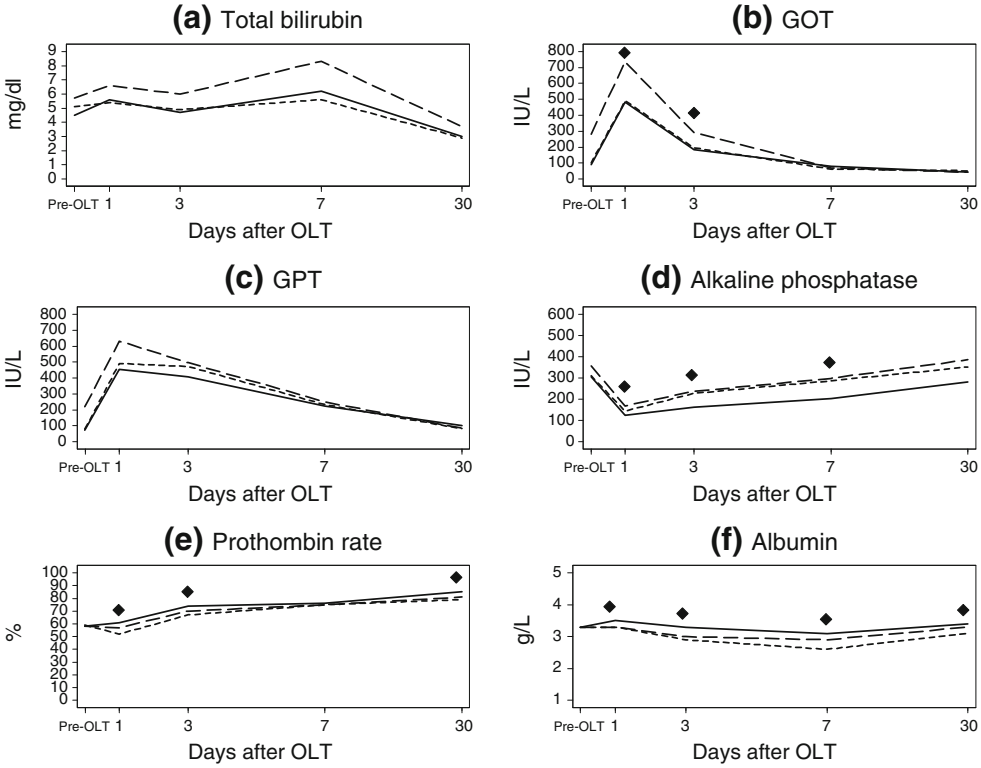

Fig. 1 Comparison of serum values of liver function parameters among the three groups. **a** Serum total bilirubin was nonsignificant. **b** Glutamic oxaloacetic transaminase was significantly higher in group 2 at day 1 ($P = 0.046$) and day 3 ($P = 0.024$). **c** Glutamic pyruvic transaminase was nonsignificant. **d** Alkaline phosphatase was significantly lower in group 1 at day 1 ($P = 0.015$), day 3 ($P = 0.001$), and day 7 ($P = 0.0001$). **e** Prothrombin rate was significantly lower in group 3 at day 1 ($P = 0.001$), day 3 ($P = 0.024$), and day 30 ($P = 0.027$). **f** Albumin was significantly higher in group 1 at day 1 ($P = 0.020$), day 3 ($P = 0.0001$), and day 7 ($P = 0.0001$) and day 30 ($P = 0.040$). $P < 0.05$ was considered statistically significant

Table 4 Post-OLT complications and retransplant rate

Complications	Group 1 ($n = 226$)	Group 2 ($n = 75$)	Group 3 ($n = 50$)	P value
Primary graft nonfunction (PNF)	11 (4.9 %)	1 (1.3 %)	0	NS
Initial poor function (IPF)	2 (0.9 %)	7 (9.3 %)	2 (4 %)	0.002
Acute rejection	151 (66.8 %)	31 (41.3 %)	18 (36 %)	0.006
Chronic rejection	35 (15.5 %)	2 (2.7 %)	2 (4 %)	0.002
Biliary complications	50 (22.1 %)	14 (18.7 %)	7 (14 %)	NS
Infection	105 (46.5 %)	31 (41.3 %)	12 (24 %)	0.0001
Retransplant cases (%)	27 (11.9 %)	4 (5.3 %)	3 (6 %)	NS
Primary non-function (PNF)	3 (1.3 %)	0	0	
Initial poor function (IPF)	0	2 (2.7 %)	0	
Chronic rejection	15 (6.6 %)	0	0	
Biliary complications	4 (1.8 %)	0	0	
Hepatic artery thrombosis	4 (1.8 %)	1 (1.3 %)	1 (2 %)	
Viral recurrence	1 (0.4 %)	1 (1.3 %)	1 (2 %)	
Donor gallbladder tumor	0	0	1 (2 %)	

recurrence, diagnosed by liver biopsy, was similar among the three groups (25, 33, and 32 %, respectively; P = NS). The rate of retransplantation was higher but not statistically significant in group 1 recipients. The most frequent cause of retransplantation was chronic rejection, an exclusive complication of group 1 (Table 4). Differences in the mortality rate during follow-up did not reach statistical significance among the groups. The causes of overall mortality are shown in Table 5.

Patient and Graft Survival: Risk Factors

The mean follow-up period was significantly different among the groups: 2,591 ± 1,642 days in group 1; 1,540 ± 1,105 days in group 2, and 1,279 ± 956 days in group 3 ($P = 0.0001$).

There were no statistically significant differences in patient survival among the three groups: 81 % in group 1, 83.8 % in group 2, and 76 % in group 3 at 1 year; 76.1 %

Table 5 Follow-up: causes and rate of recipient mortality

Causes	Group 1 ($n = 226$)	Group 2 ($n = 75$)	Group 3 ($n = 50$)	P value
Medical complications	19 (8.5 %)	10 (13.3 %)	9 (18.0 %)	NS
De novo tumors	14 (6.2 %)	3 (4.0 %)	1 (2.0 %)	
Viral recurrence	6 (2.7 %)	6 (8.0 %)	3 (6.0 %)	
Infection	12 (5.3 %)	1 (1.3 %)	2 (4.0 %)	
Chronic rejection	9 (4.0 %)	1 (1.3 %)	0	
Intraoperative death	3 (1.3 %)	0	0	
Other	21 (9.3 %)	3 (4.0 %)	3 (6.0 %)	
Overall mortality	84 (37 %)	24 (32 %)	18 (36 %)	NS

in group 1, 74 % in group 2, and 70 % in group 3 at 3 years; and 71.1 % in group 1, 72.2 % in group 2, and 62.9 % in group 3 at 5 years after OLT (Fig. 2a). With regard to graft survival, we did not find any significant differences among the groups: 74.8 % in group 1, 82.7 % in group 2; and 71.4 % in group 3 at 1 year; 69.0 % in group 1, 71.4 % in group 2, and 64.8 % in group 3 at 3 years; and 64.1 % in group 1, 69.6 % in group 2, and 58.3 % in group 3 at 5 years (Fig. 2b).

To see the influence of the association of hepatitis virus C with older donors on patient and graft survival, we separated the patients with HCV cirrhosis who received livers from donors younger than 60 years (group A; $n = 78$) and patients with HCV cirrhosis who received livers from donors older than 60 years (group B; $n = 60$). We compared the two groups and did not find significant differences in patient survival ($P = 0.074$) at 1, 3, and 5 years: 84.6, 76.8, and 70.2 %, respectively, in group A, versus 78.3, 61.9, and 57.1 %, respectively, in group B (Fig. 3a). In relation to graft survival, we also did not observe significant differences

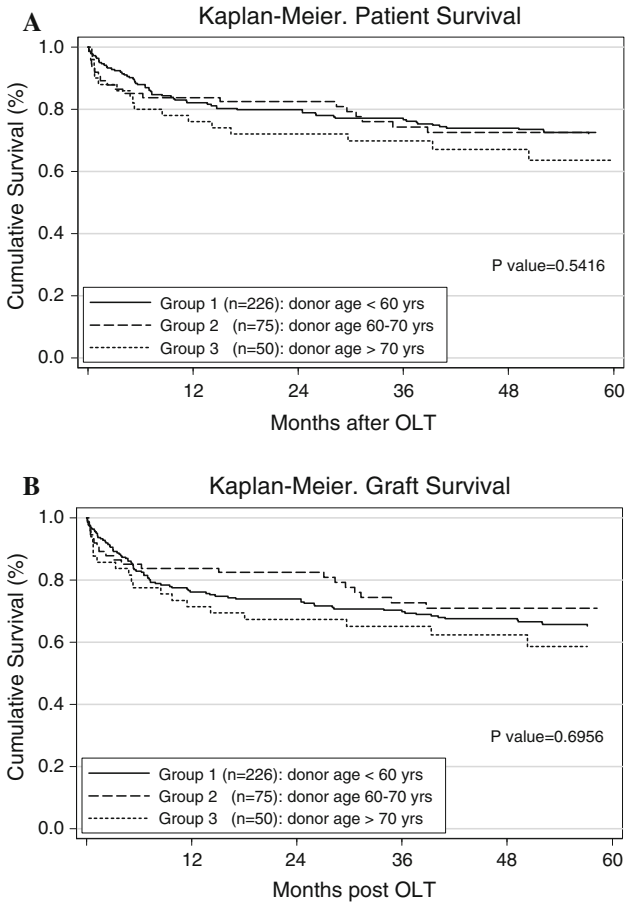

Fig. 2 a Actuarial patient survival curves after orthotopic liver transplant (OLT) in three groups according to donor age. Log rank test for a difference in survival curves showed $P = 0.5416$. **b** Actuarial graft survival curves after OLT in three groups according to donor age. Log rank test for a difference in survival curves showed a $P = 0.6956$

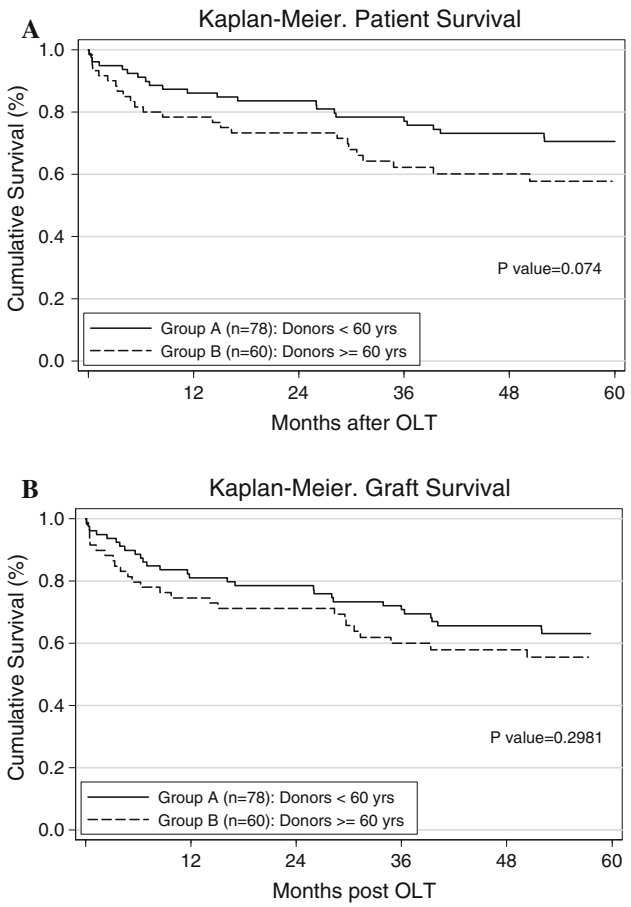

Fig. 3 a. Actuarial patient survival curves after OLT for HCV cirrhosis ($n = 138$). *Group A* HCV patients who received liver grafts <60 years. *Group B* HCV patients who received liver grafts >60 years. Log rank test for a difference in survival curves showed P = 0.074. **b** Actuarial graft survival curves after OLT for HCV cirrhosis ($n = 138$). *Group A* HCV patients who received liver grafts <60 years. *Group B* HCV patients who received liver grafts > 60 years. Log rank test for a difference in survival curves showed $P = 0.2981$

($P = 0.29$) at 1, 3, and 5 years: 78.2, 69.1, and 62.6 %, respectively, in group A versus 74.6, 59.7, and 54.9 %, respectively, in group B (Fig. 3b).

Multivariate analysis with a Cox proportional hazard model demonstrated that overall recipient survival was adversely affected by increased values of donor BMI [hazard ratio (HR) = 1.14; 95 % CI, 1.07–1.2; $P = 0.001$] and decreased levels of recipient serum albumin at one month after OLT (HR: 0.42; 95 % CI, 0.24–0.70; $P = 0.001$). The overall graft survival was also adversely influenced by an increased value of donor BMI (HR: 1.11; 95 % CI, 1.05–1.19; $P = 0.0006$) and a decreased value of serum albumin at 1 month after OLT (HR: 0.43; CI, 0.27–0.7; $P = 0.0008$) (Table 6).

Discussion

An ideal donor is defined as a donor younger than 40 years, trauma as the cause of death, hemodynamic stability, brain death, and absence of steatosis, chronic liver disease, and transmission disease. In addition, seven donor characteristics associated with an increased risk of graft failure have been identified, including donor age over 60 years as the strongest risk factor for liver failure [26].

In the univariate analysis, BMI of the donor was found to be significantly higher in older donors, a finding that has also been associated with a higher frequency of microsteatosis and macrosteatosis, as has been observed in other studies [27]. Moreover, in the multivariate analysis the increased value of donor BMI had a negative impact on patient and graft survival.

In this comparative study among three groups classified according to donor age, we found head trauma to be the most frequent cause of death in the younger donor group, and intracranial bleeding as the cause of death in the two older groups. The factors ICU stay, GOT and GPT serum values, and prothrombin rate were significantly more favorable in donors over 70 years, a finding that reflects the careful selection and maintaining of these older donors. It has been reported that an ICU stay longer than 72 h is associated with IPF and PNF [28], and in our series mean times for groups 1 and 2 were slightly below this limit, and only 32 h for donors over 70 years.

The prevalence of liver steatosis in donors is usually between 9 and 26 % [29–31], and it is more frequent in older donors, mainly because of their history of alcohol intake, obesity, malnutrition, and diabetes [32, 33]. We observed a higher rate of overall steatosis in older donor groups 2 and 3, but mainly at the expense of microsteatosis. It has been reported that liver grafts with any degree of isolated microsteatosis can be safely used [4, 34, 35]. Steatotic liver grafts are more prone to developing preservation injury, and a short ischemic time is recommended as a preventive measure in these cases [31, 32]. Several risk factors have been correlated with moderate to severe graft preservation injury, namely prolonged ICU stay, graft steatosis, prolonged cold ischemia, high doses of inotropic drugs, and use of older livers [36]. In our series the overall rate of preservation injury was significantly higher in the younger donor group, but mainly because of a higher rate of mild preservation injury. CIT is directly correlated with the development of liver preservation injury, and this incidence is higher in donors older than 60 years [37]. Therefore, the CIT of older donors must be kept as short as possible to obtain good liver function after OLT [3, 12, 38–40]. However, in six more recent series [22, 40–44] that included septuagenarian donors, the CIT was between 5 and 7.2 h. In our series the mean CIT of groups 2 and 3 was 6.1 h, significantly higher than for group 1 (5 h). Prolongation of WIT increases cold ischemia injury and consequently impairs liver function [45]. Our mean WIT in the younger group was 68 min, significantly higher than in the older groups (60 and 58 min, respectively). Deleterious effects on patient and graft survival when WIT was greater than 40 min [46] or on graft survival alone when WIT was greater than 45 min have been reported [47]. In our experience, a significantly higher proportion of recipients with HCV cirrhosis were transplanted with livers from older donors (34.5 % of group 1, 50.7 % of group 2, and 44 % of group 3), which is known to be associated with lower patient and graft survival [48–54], mainly because of

Table 6 Factors related to overall patient and graft survival: multivariate analysis

	Patient survival			Graft survival		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Donor variable						
BMI	1.14	1.07–1.2	0.0001	1.1	1.05–1.19	0.0006
Recipient variable						
Albumin (30 days post-OLT)	0.42	0.24–0.70	0.001	0.43	0.27–0.71	0.0008

Variables with $P < 0.05$ in the univariate analysis were included in the multivariate model

HR hazard ratio, *CI* confidence interval

the development of rapid progression of graft fibrosis [55, 56].

Our prevalence of hepatocarcinoma and positive HBV serology was also higher, albeit not significantly, in recipients of older livers. At the same time, Child-Pugh distribution and pre-OLT laboratory parameters were similar among the three groups, except for the worse values of GOT and GPT in group 2.

As in other studies [12, 22], our recipient ICU stay after OLT was not significantly different among the three groups. Like the numbers reported by other authors [22], overall red blood cell (PRBC) transfusion and hospital stay of this series were significantly less in the recipients of livers from donors older than 70 years. This finding reveals the careful selection of donors and candidates for OLT [40].

The recipients of older livers have a greater sensitivity to ischemic injury, as reflected by a notable cholestatic pattern after OLT [22, 40, 57] that is usually normalized within the first postoperative month [13]. By contrast, in our series all determinations of bilirubin within the first month after OLT were similar among the groups, and at the end of the first month the recipients of the three groups also showed similar values of transaminases and alkaline phosphatase. Moreover, prothrombin rate and serum albumin levels were significantly lower on the 30th day after OLT in group 3, and these findings are attributed to a decrease in protein synthesis [58] and coagulation factors that run parallel to the liver aging process [59]. In the multivariate analysis, the decreased value of serum albumin at 1 month was significantly associated with poor patient and graft survivals.

Several authors [28, 60] have pointed out a correlation between the incidence of PNF/IPF and older donors. We only found a significantly higher rate of IPF but not PNF in recipients of livers from donors older than 70 years, and other authors [40] did not find any episode of PNF/IPF in 30 recipients of octogenarian donor livers.

The rates of acute and chronic rejection were significantly higher in recipients of livers younger than 60 years, a finding that we attribute to the more frequent use of cyclosporine in this group. It is known that CyA-treated patients have higher rates of acute and chronic rejection and retransplantation [61]. Other series have reported similar rates of rejection in recipients from donors older and younger than 70 years [22, 40, 41]. As previously reported [22, 40], we did not find any significant differences among the groups for the rate of biliary or hepatic artery complications. Moreover, a recent series from UNOS reported a 61 % increased risk of hepatic artery thrombosis-related graft loss using donors older than 70 years [62]. Curiously, the rate of infection was significantly lower in our recipients of livers from donors older than 70 years. Several reports have found similar rates of retransplantation comparing recipients from 70-year-old donors and younger donors [12, 22, 41]. We found a higher rate of retransplantation—although it is not statistically significant—in recipients of younger donor livers at the expense of the incidence of chronic rejection.

In our experience the most common causes of recipient mortality were medical complications, such as development of de novo tumors, recurrent viral disease, infection, and chronic rejection, but we did not find significant differences among the groups.

Many studies show lower patient and graft survival when using liver donors older than 60 years [9, 16–19, 53, 63, 64]. On the contrary, other authors did not find any significant differences in recipients of donors older than 60 and 70 years old compared with recipients of younger donors [12, 14, 22, 41, 43, 65]. When using donors older than 70 years, it has been shown that 1-year patient survival varies between 69 and 95.4 %, 3-year patient survival between 57.5 and 90.6 %, and 5-year patient survival between 46.2 and 59.3 % [12, 14, 22, 40, 41, 43, 44]. The same authors also reported 1-year graft survival between 73 and 92.6 %, and 3-year graft survival between 69.1 and 89.4 %. There is only one report using donors older than 70 years of age that observed 5-year graft survival between 51 and 53 % [42]. Our 1- and 3-year patient and graft survivals were between the referred limits, but 5-year patient and graft survivals were somewhat better (62.9 and 58.2 %, respectively).

In the present series we found significantly poorer patient survival, but not graft survival, in the group of 138 patients who underwent OLT for HCV cirrhosis in comparison with 213 patients transplanted for other etiologies. Moreover, many authors have demonstrated significantly worse patient and graft survivals when liver grafts from donors older than 40–50 years are transplanted in HCV recipients [48–54]. However, as described in one recent report [65], we did not find significant differences in terms of 1-, 3-, and 5-year patient survival ($P = 0.074$) and graft ($P = 0.29$) survival, between HCV recipients of liver grafts younger than 60 years and HCV recipients of liver grafts older than 60 years. In contrast, because of the tendency for patient survival to decrease at 5 years, with a longer follow-up it should be possible to demonstrate a significantly poorer patient survival in HCV recipients of liver grafts from donors older than 60 years.

Conclusions

In order to augment the liver donor pool, older liver grafts with no age limit can be safely used if careful selection is performed (good liver function and preharvesting conditions, ICU stay < 72 h, CIT < 7 h, WIT < 1 h, and

macrosteatosis <30–40 %, usually associated with a high BMI). Attention must be paid to other associated recipient risk factors, such as advanced liver disease or the presence of HCV cirrhosis. In spite of an increased susceptibility of older donor livers to HCV recurrence, good long-term patient and graft survivals can be obtained when older livers are used in patients with HCV cirrhosis.

Acknowledgments The authors thank Javier de la Cruz and David Lora for contributions to the statistical analysis. We also thank Dr. M. Abradelo, Dr. F. Cambra, and Dr. F. Colina for collaboration in this article.

References

1. ONT (2008) Memoria de Actividades de la ONT 2008 (1ª Parte). Trasplante hepático. Revista Española de Trasplantes 18:32–50
2. Strasberg SM, Howard TK, Molmenti EP et al (1994) Selecting the donor liver: risk factors for poor function after orthotopic liver transplantation. Hepatology 20:829–838
3. Adam R, Sánchez C, Astarcioglu I et al (1995) Deleterious effect of extended cold ischemia time on the posttransplant outcome of aged livers. Transplant Proc 27:1181–1183
4. Ureña MA, Ruiz-Delgado FC, González EM et al (1998) Assessing risk of the use of livers with macro and microsteatosis in a liver transplant program. Transplant Proc 30:3288–3291
5. López-Navidad A, Caballero F (2003) Extended criteria for organ acceptance. Strategies for achieving organ safety and for increasing organ pool. Clin Transplant 17:308–324
6. Busuttil RW, Tanaka K (2003) The utility of marginal donors in liver transplantation. Liver Transpl 9:651–663
7. Yersiz H, Renz JF, Farmer DG et al (2003) One-hundred in situ split-liver transplantations: a single center experience. Ann Surg 238:496–505
8. Renz JF, Kin C, Kinkhabwala M et al (2005) Utilization of extended donor criteria liver allografts maximizes donor use and patient access to liver transplantation. Ann Surg 242:556–565
9. Tector AJ, Mangus RS, Chestovich P et al (2006) Use of extended criteria livers decreases wait time for liver transplantation without adversely impacting posttransplant survival. Ann Surg 244:439–450
10. Bernat JL, D'Alessandro AM, Port FK et al (2006) Report of a National Conference on Donation after cardiac death. Am J Transplant 6:281–291
11. Marino IR, Doyle HR, Doria C et al (1995) Outcome of liver transplantation using donors 60 to 79 years of age. Transplant Proc 27:1184–1185
12. Emre S, Schwartz ME, Altaca G et al (1996) Safe use of hepatic allograft from donors older than 70 years. Transplantation 62: 62–65
13. Cescon M, Grazi GL, Ercolani G et al (2003) Long-term survival of recipients of liver grafts from donors older than 80 years: is it achievable? Liver Transpl 9:1174–1180
14. Anderson CD, Vachharajani N, Doyle M et al (2008) Advanced donor age alone does not affect patient or graft survival after liver transplantation. J Am Coll Surg 207:847–852
15. Ravaioli M, Grazi GL, Cescon M et al (2009) Liver transplantations with donors aged 60 years and above: the low liver damage strategy. Transplant Int 22:423–433
16. Marino IR, Doyle HR, Aldrighetti L et al (1995) Effect of donor age and sex on the outcome of liver transplantation. Hepatology 22:1754–1762
17. Hoofnagle JH, Lombardero M, Zetterman RK et al (1996) Donor age and outcome of liver transplantation. Hepatology 24:89–96
18. Busquets J, Xiol X, Figueras J et al (2001) The impact of donor age on liver transplantation: influence of donor age on early liver function and on subsequent patient and graft survival. Transplantation 71:1765–1771
19. Moore DE, Feurer ID, Speroff T et al (2005) Impact of donor, technical, and recipient risk factors on survival and quality of life after liver transplantation. Arch Surg 140:273–277
20. Grande L, Matus D, Rimola A et al (1998) Expanded liver donor age over 60 years for liver transplantation. Clin Transplant 12: 297–301
21. Rodríguez F, Jiménez C, Romano D et al (2002) Orthotopic liver transplantation with 100 hepatic allografts from donors over 60 years old. Transplant Proc 34:233–234
22. Gastaca M, Valdivieso A, Pijoan J et al (2005) Donors older than 70 years in liver transplantation. Transplant Proc 37:3851–3854
23. Zapletal C, Faust D, Wullstein C et al (2005) Does the liver ever age? Results of liver transplantation with donors above 80 years of age. Transplant Proc 37:1182–1185
24. Segev DR, Maley WR, Simpkins CE et al (2007) Minimizing risk associated with elderly liver donors by matching to preferred recipients. Hepatology 46:1907–1918
25. Jiménez C, Manrique A, Marqués E et al (2007) Incidence and risk factors for the development of lung tumors after liver transplantation. Transplant Int 20:57–63
26. Feng S, Goodrich NP, Bragg-Gresham JL et al (2006) Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 6:783–790
27. Rinella ME, Alonso E, Rao S et al (2001) Body mass index as a predictor of hepatic steatosis in living liver donors. Liver Transpl 7:409–414
28. Greig PD, Forster J, Superina RA et al (1990) Donor-specific factors predict graft function following liver transplantation. Transplant Proc 22:2072–2073
29. Markin RS, Wisecarver JL, Radio SJ et al (1993) Frozen section evaluation of donor livers before transplantation. Transplantation 56:1403–1409
30. Karayalcin K, Mirza DF, Harrison RF et al (1994) The role of dynamic and morphological studies in the assessment of potential liver donors. Transplantation 57:1323–1327
31. García-Ureña MA, Colina F, Moreno E et al (1998) Hepatic steatosis in liver transplant donors: common feature of donor population? World J Surg 22:837–844. doi:10.1007/s002689900479
32. Adam R, Astarcioglu I, Azoulay D et al (1991) Age greater than 50 years is not a contraindication for liver donation. Transplant Proc 23:2602–2603
33. D'Alessandro AM, Kalayoglu M, Sollinger HW et al (1991) The predictive value of donor liver biopsies on the development of primary nonfunction after orthotopic liver transplantation. Transplantation 51:157–163
34. Fishbein TM, Fiel MI, Emre S et al (1997) Use of livers with microvesicular fat safely expands the donor pool. Transplantation 64:248–251
35. Verran D, Kusyk T, Painter D et al (2003) Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. Liver Transpl 9:500–505
36. Briceño J, Pera-Rojas C, Lluch M et al (2001) Intraoperative assessment of liver transplantation with marginal liver grafts. Transplant Proc 33:903–905
37. Briceño J, Marchal T, Padillo J et al (2002) Influence of marginal donors on liver preservation injury. Transplantation 74:522–526
38. Wall WJ (1999) Predicting outcome after liver transplantation. Liver Transpl Surg 5:458–459
39. Jiménez C, Moreno E, Colina F et al (1999) Use of octogenarian livers safely expands the donor pool. Transplantation 68:572–576

40. Nardo B, Masetti M, Urbani L et al (2004) Liver transplantation from donors aged 80 years and over: pushing the limit. Am J Transplant 4:1139–1147
41. Cescon M, Mazziotti A, Grazi GL et al (2001) Evaluation of the use of graft livers procured from old donors (70 to 87 years) for hepatic transplantation. Transplant Proc 33:934–935
42. Cuende N, Grande L, Sanjuan F et al (2002) Liver transplant with organs from elderly donors: Spanish experience with more than 300 liver donors over 70 years of age. Transplantation 73:1360
43. Kim DY, Cauduro SP, Bohorquez HE et al (2005) Routine use of livers from deceased donors older than 70: is it justified? Transplant Int 18:73–77
44. Fouzas I, Sgourakis G, Nowak KM et al (2008) Liver transplantation with grafts from septuagenarians. Transplant Proc 40:3198–3200
45. Piratvisuth T, Tredger JM, Hayllar KA et al (1995) Contribution of true cold and rewarming ischemia times to factors determining outcome after orthotopic liver transplantation. Liver Transpl Surg 1:296–301
46. Cameron AM, Ghobrial RM, Yersiz H et al (2006) Optimal utilization of donor grafts with extended criteria. A single-center experience in over 1000 liver transplants. Ann Surg 243:748–755
47. Ghobrial RM, Gornbein J, Steadman R et al (2002) Pretransplant model to predict posttransplant survival in liver transplant patients. Ann Surg 236:315–322
48. Berenguer M, Prieto M, San Juan F et al (2002) Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. Hepatology 36:202–210
49. Wali M, Harrison RF, Gow PJ et al (2002) Advancing donor liver age and rapid fibrosis progression following transplantation for hepatitis C. Gut 51:248–252
50. Russo MW, Galanko JA, Zacks SL et al (2004) Impact of donor age and year of transplant on graft survival in liver transplant recipients with chronic hepatitis C. Am J Transplant 4:1133–1138
51. Lake JR, Shorr JS, Steffen BJ et al (2005) Differential effects of donor age in liver transplant recipients infected with hepatitis B, hepatitis C and without viral hepatitis. Am J Transplant 5: 549–557
52. Condron SL, Heneghan MA, Patel K et al (2005) Effect of donor age on survival of liver transplant recipients with hepatitis C virus infection. Transplantation 80:145–148
53. Mutimer DL, Gunson B, Chen J (2006) Impact of donor age and year of transplantation on graft and patient survival following liver transplantation for hepatitis C virus. Transplantation 81: 7–14
54. Iacob S, Cicinnati VR, Hilgard P et al (2007) Predictors of graft and patient survival in hepatitis C virus (HCV) recipients: model to predict HCV cirrhosis after liver transplantation. Transplantation 84:56–63
55. Machicao VI, Bonatti H, Krishna M et al (2004) Donor age affects fibrosis progression and graft survival after liver transplantation for hepatitis C. Transplantation 77:84–92
56. Rayhill SC, Wu YM, Katz DA et al (2007) Older donor livers show early severe histological activity, fibrosis, and graft failure after liver transplantation for hepatitis C. Transplantation 84: 331–339
57. Yersiz H, Shaked A, Olthoff K et al (1995) Correlation between donor age and the pattern of liver graft recovery after transplantation. Transplantation 60:790–794
58. Winger DJ, Sponsilli EE (1977) Concentrations of serum protein fractions in white women: effects of age, weight, smoking, tonsillectomy and other factors. Clin Chem 23:1310–1317
59. Shepherd AM, Hewick DS, Moreland TA et al (1977) Age as a determinant of sensitivity to warfarin. Br J Pharmacol 4:315–320
60. Ploeg RJ, D'Alessandro AM, Knechtle SJ et al (1993) Risk factors for primary dysfunction after liver transplantation: a multivariate analysis. Transplantation 55:807–813
61. Mueller AP, Platz KP, Krause P et al (1999) Is the use of marginal liver grafts justified? Transplant Proc 31:401–402
62. Stewart ZA, Locke JE, Segev DL et al (2009) Increased risk of graft loss from hepatic artery thrombosis after liver transplantation with older donors. Liver Transpl 15:1688–1695
63. Deschenes M, Forbes C, Tchervenkov J et al (1999) Use of older donor livers is associated with more extensive ischemic damage on intraoperative biopsies during liver transplantation. Liver Transpl Surg 5:357–361
64. Busuttil RW, Farmer DG, Yersiz H et al (2005) Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single center experience. Ann Surg 241:905–916
65. Doyle M, Anderson C, Vachharajani N et al (2008) Liver transplantation for hepatitis C virus. Effect of using older donor grafts on short- and medium-term survival. Arch Surg 143:679–685