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ORIGINAL ARTICLE

# Improving the Outcome of Liver Transplantation with Very Old Donors with Updated Selection and Management Criteria

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Advanced donor age is a risk factor for poor outcome in liver transplantation (LT). We reviewed 553 consecutive transplants according to donor age categories [group 1 (n = 173): <50 years; group 2 (n = 96): 50-59 years; group 3 (n = 132): 60-69 years; group 4 (n = 111): 70-79 years; group 5 (n = 41): ≥80 years]. Clinical parameters were comparable between groups. Group 5 had the highest proportion of pretransplant liver biopsy (85%), with only 1 graft showing macrovesicular steatosis > 30%, and the lowest ischemia time. Five-year graft survival was significantly higher in group 1 (75%) versus groups 3 (60%) and 4 (62%; $P = 0.01$ and $P = 0.001$, respectively) and in group 5 (81%) versus groups 3 and 4 ($P = 0.04$ and $P = 0.01$, respectively). Donor age of 60-79 years, recipient hepatitis C virus–positive status, Model for End-Stage Liver Disease score ≥ 25, and emergency LT were predictors of poor survival. In hepatitis C virus–positive patients, 5-year graft survival was 72% in group 1, 85% in group 2, 52% in group 3, 65% in group 4, and 71% in group 5 (group 1 versus group 3, $P = 0.04$; group 2 versus group 3, $P = 0.03$). In conclusion, older donor grafts managed with routine graft biopsy and short ischemia time may work effectively, regardless of the severity of the recipient's liver disease. ***Liver Transpl 14:672-679, 2008.*** © **2008 AASLD.**

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The growing discrepancy between the number of patients listed for liver transplantation (LT) and the inadequate organ supply is a common problem in the medical community. Expansion of the donor pool is currently achieved with living donor transplantation, split LT, and the so-called extended criteria donors (ECDs). The first 2 options are limited by the low contribution of organ availability, by technical difficulties, and by ethical issues.[1,2] The third option is based on the wider acceptance of parameters commonly defining ECDs, such as older donor age, elevated body mass index (BMI), high serum sodium level, altered liver function tests, positive hepatitis B virus and hepatitis C virus (HCV) serology, non–heart-beating donors, prolonged ischemia time and intensive care unit (ICU) stay, altered hemodynamics, significant liver trauma, active bacterial infections, and history of malignancy. On the other hand, it also implies a higher risk of primary nonfunction (PNF), delayed graft nonfunction (DGNF), and lower patient and graft survival.[3-6]

The use of older donors has long been recognized as one of the most important prognostic factors for patient and graft survival.[7] The contribution to LT outcome of different decades of donor age, including those > 80 years old, has not been extensively investigated, especially when we consider the recent adoption of the Model for End-Stage Liver Disease (MELD) score and

**Abbreviations**: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DGNF, delayed graft nonfunction; D/R, donor/recipient; ECD, extended criteria donor; FHF, fulminant hepatic failure; HBcAb, hepatitis B anticore; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; M/F, male/female; MOF, multiorgan failure; PNF, primary nonfunction; PRBC, packed red blood cell; UNOS, United Network for Organ Sharing.

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**TABLE 1. Utilization Rates, Causes for Refusal, and Biopsies Performed at Procurement in 893 Proposed Liver Grafts According to Donor Age Categories**

| | Group 1: <50 Years (n = 252) | Group 2: 50–59 Years (n = 163) | Group 3: 60–69 Years (n = 214) | Group 4: 70–79 Years (n = 199) | Group 5: ≥80 Years (n = 65) |
|---|---|---|---|---|---|
| LT performed | 173 (69)‡ | 96 (59) | 132 (62) | 111 (56) | 41 (63) |
| LT not performed | 79 (31) | 67 (41) | 82 (38) | 88 (44) | 24 (37) |
| Cause of discarding | | | | | |
| Graft alterations* | 34 (13) | 43 (26) | 50 (23) | 48 (22) | 17 (26) |
| Donor virology/infections | 8 (3) | 9 (6) | 10 (5) | 12 (6) | 2 (3) |
| Donor malignancies | 5 (2) | 4 (2) | 12 (5) | 16 (8) | 3 (5) |
| Donor hemodynamics | 7 (3) | 7 (4) | 3 (1) | 5 (2) | 2 (3) |
| D/R size discrepancy | 21 (8) | 3 (2) | 6 (3) | 6 (3) | — |
| Donor behavior | 4 (2) | 1 (1) | 1 (0.5) | 1 (0.5) | — |
| Graft biopsy† | 51 (20) | 75 (46) | 127 (59) | 136 (68) | 62 (95) |

NOTE: Numbers in parentheses represent percentages.
**Abbreviations:** D/R, donor/recipient; LT, liver transplantation.
*Including microscopic and/or macroscopic abnormalities.
†$P < 0.05$ for all comparisons.
‡$P < 0.05$ versus groups 2 and 4.

the dismal results in HCV-infected patients compared to HCV-negative patients.[8,9]

We analyzed the outcome of LT in a single institution according to different categories of donor age, with particular reference to octogenarian donors.

## PATIENTS AND METHODS

From November 1998 to August 2006, 553 primary, isolated, whole LTs with AB0-identical or AB0-compatible grafts were performed at the Liver and Multiorgan Transplant Unit, University of Bologna. Outcomes were analyzed by the division of the study population according to 5 categories of donor age: donor age lower than 50 years (group 1), donor age between 50 and 59 years (group 2), donor age between 60 and 69 years (group 3), donor age between 70 and 79 years (group 4), and donor age equal to or above 80 years (range: 80-95, group 5). The starting date of the study period was determined by the fact that the first LT using a donor over 80 years old was performed in November 1998. Results were retrospectively analyzed with a prospectively updated database. The degree of liver failure and the priority of patients listed for LT were categorized according to the Child-Pugh score up to March 2003. Subsequently, the MELD score[9] was adopted as the first criteria for organ allocation. An additional score was given to patients with metabolic diseases, recurrent cholangitis, or hepatocellular carcinoma.[10] The real MELD score without any additional score at the time of LT is reported for the purposes of the present study, and it was retrospectively applied to patients transplanted up to March 2003.

In the immediate postoperative period, unsatisfactory functional recovery of the graft in the absence of technical problems, including PNF,[11] was managed with infusion of prostaglandins.[12]

Acute cellular rejection episodes were classified according to the Banff schema.[13] Initial treatment of acute cellular rejection consisted of intravenous bolus(es) of methylprednisolone (1 g), followed by rapid steroid tapering to reach the prednisone dose administered before rejection. Monoclonal CD3 antibodies (OKT3) were used in the event of steroid-resistant rejection.

In the case of increased aminotransferases (>1.5-2–fold normal values) without vascular, biliary, drug, or infectious causes, liver biopsy was performed to confirm the diagnosis of HCV recurrence, which included various degrees of portal or lobular inflammation with mononuclear cells, piecemeal/lobular necrosis, hepatocellular steatosis, and/or fibrosis.[14] No protocol biopsies were performed, but the diagnosis of HCV recurrence was always biopsy-proven.

No preemptive antiviral protocols were used. Antiviral treatment for HCV recurrence was potentially offered to all patients with clinical and histological evidence of HCV recurrence. Treatment was continued until a complete virological and biochemical response was obtained and for at least 6 months. It was avoided or discontinued in the event of uncontrollable side effects or clinical contraindications.

Antiviral treatment consisted of a combination of interferon alfa-2b and ribavirin. After 2002, pegylated interferon alfa-2b was used in the majority of cases. All patients who died or lost their graft because of post-transplant hepatitis C had histological confirmation of recurrent disease.

The evaluation and comparison between donor age groups of graft survival rates was the primary endpoint of the study. The analysis of graft loss due to HCV recurrence in HCV-positive/hepatitis B surface antigen (HBsAg)–negative patients was the secondary endpoint.

**TABLE 2. Donor Profile and Operative Parameters According to Donor Age Categories**

| | Group 1: <50 Years (n = 173) | Group 2: 50–59 Years (n = 96) | Group 3: 60–69 Years (n = 132) | Group 4: 70–79 Years (n = 111) | Group 5: ≥80 Years (n = 41) |
|---|---|---|---|---|---|
| Sex (M/F) | 113/60* | 50/46 | 72/60 | 57/54 | 19/22 |
| Cause of death | | | | | |
| Cerebrovascular | 48 (28)† | 64 (67) | 99 (75) | 86 (77) | 30 (73) |
| Trauma | 101 (58) | 17 (18) | 21 (16) | 10 (9) | 9 (22) |
| Other | 24 (14) | 15 (15) | 12 (9) | 15 (14) | 2 (5) |
| HBcAb-positive | 16 (9)‡ | 22 (23) | 20 (15) | 19 (17) | 7 (17) |
| HCV-positive | 3 (2) | 1 (1) | 6 (4) | 8 (7) | — |
| ICU stay (days) | 3.8 ± 3.6 | 4.4 ± 4.6 | 4.3 ± 4.2 | 3.5 ± 3.0 | 3.0 ± 2.2§ |
| ICU > 5 days | 41 (24) | 23 (24) | 36 (27) | 18 (16) | 5 (12) |
| BMI ≥ 35 | 2 (1) | 2 (2) | 1 (1) | 1 (1) | — |
| Diabetes | 1 (0.6)‖ | 6 (6) | 15 (11) | 10 (9) | —¶ |
| Cardiac arrest | 24 (14)# | 7 (7) | 6 (4) | 2 (2) | — |
| Use of norepinephrine | 58 (33) | 29 (30) | 35 (26) | 27 (24) | 16 (39) |
| Graft biopsy** | 24 (14) | 28 (29) | 69 (52) | 85 (77) | 35 (85) |
| Macrosteatosis | 15 (9) | 22 (23) | 49 (37) | 58 (52) | 24 (58) |
| Macrosteatosis > 30% | 3 (2) | 6 (6) | 5 (4) | 9 (8) | 1 (2) |
| AST (U/L) | 83.3 ± 105.1 | 86 ± 254.8 | 51.6 ± 70.8 | 43.4 ± 44.5 | 33.7 ± 24.3 |
| ALT (U/L) | 64.6 ± 91†† | 49.1 ± 84.8 | 43.8 ± 57.4 | 33.7 ± 43.8 | 23.7 ± 17.4 |
| AST or ALT > 500 U/L | 4 (2) | 3 (3) | 1 (0.8) | — | — |
| Bilirubin > 2 mg/dL | 14 (8) | 7 (7) | 9 (7) | 11 (10) | 1 (2) |
| Serum Na > 170 mEq/L | 3 (2) | 2 (2) | 2 (1) | 1 (1) | — |
| Ischemia time (minutes) | 428 ± 114 | 434 ± 106 | 457 ± 125‡‡ | 442 ± 102 | 408 ± 105 |
| Ischemia time > 12 hours | 2 (1) | 2 (2) | 6 (4) | — | — |
| Donor risk factors > 1‖‖ | 65 (38)§§ | 50 (52) | 70 (53) | 64 (58) | 21 (51) |
| PRBC transfusions (mL) | 3115 ± 2766 | 3966 ± 5792 | 3497 ± 3708 | 3047 ± 3078 | 3277 ± 4501 |

NOTE: Numbers in parentheses represent percentages.
**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HBcAb, hepatitis B anticore; HCV, hepatitis C virus; ICU, intensive care unit; M/F, male/female; PRBC, packed red blood cell.
*Group 1 versus groups 2, 4, and 5, $P < 0.05$.
†Group 1 versus other groups, $P < 0.0001$.
‡Group 1 versus groups 2 and 4, $P < 0.05$.
§Group 5 versus groups 2 and 3, $P < 0.05$.
‖Group 1 versus groups 2, 3, and 4, $P < 0.05$.
¶Group 5 versus group 3, $P = 0.02$.
#Group 1 versus groups 3, 4, and 5, $P < 0.05$
**$P < 0.05$ for all comparisons, except group 4 versus group 5.
††Group 1 versus groups 4 and 5, $P < 0.001$.
‡‡Group 3 versus groups 1 and 5, $P < 0.05$.
§§Group 1 versus groups 2, 3, and 4, $P < 0.05$.
‖‖Donor risk factors are considered according to the criteria reported by Tector et al. (see reference 5).

## Statistical Analysis

Results were expressed as mean ± standard deviation. Differences between continuous variables were evaluated with the 1-way analysis of variance test with least significant difference for multiple comparisons. Differences between categorical variables were calculated with the $\chi^2$ test or Fisher's exact test. Graft survival was calculated from the date of LT to the date of the last visit, patient death, or graft loss. Patient survival was calculated from LT to the last visit or patient death.

Actuarial survivals were computed with the Kaplan-Meier method, and the differences between groups were compared by the log-rank test. The Cox proportional hazard model was used with variables that significantly impacted on graft survival at the univariate analysis. A $P$ value $< 0.05$ was considered statistically significant in all the analyses. Statistical analysis was carried out with the SPSS software packaging, version 13.0 (SPSS, Inc., Chicago, IL).

## RESULTS

### Evaluation of Proposed Donors During the Study Period

With the exclusion of donors refused because of organizational problems and those accepted for retransplantation, split or reduced LT, or LT combined with other organs, a total of 893 deceased liver donors were proposed to our center during the study period (Table 1).

The transplantation rate was significantly higher in

**TABLE 3. Recipient Profiles According to Donor Age Categories**

| | Group 1: <50 Years (n = 173) | Group 2: 50–59 Years (n = 96) | Group 3: 60–69 Years (n = 132) | Group 4: 70–79 Years (n = 111) | Group 5: ≥80 Years (n = 41) |
|---|---|---|---|---|---|
| Age | 50.3 ± 10.3 | 52.1 ± 10.1 | 51.6 ± 8.9 | 53.7 ± 8.3 | 52.5 ± 10.0 |
| Sex (M/F) | 123/50 | 70/26 | 103/29 | 78/33 | 28/13 |
| Indication for LT | | | | | |
| Postnecrotic cirrhosis | 76 (44) | 42 (43) | 56 (42) | 45 (40) | 11 (27) |
| HCC on cirrhosis | 47 (27) | 28 (29) | 47 (36) | 43 (39) | 19 (46) |
| Alcoholic cirrhosis | 15 (9) | 11 (11) | 12 (9) | 5 (4) | 2 (5) |
| Cholestatic disease | 12 (7) | 6 (6) | 3 (2) | 9 (8) | 2 (5) |
| FHF | 6 (3) | 3 (3) | 4 (3) | — | 3 (7) |
| Other | 17 (10) | 6 (6) | 10 (8) | 9 (8) | 4 (10) |
| HCV-positive/HBsAg-negative patients | 75 (43) | 45 (47) | 59 (45) | 55 (49) | 17 (41) |
| MELD score | 17.3 ± 7.4 | 18.2 ± 8.2 | 17.1 ± 7.8 | 19.7 ± 7.5 | 19.5 ± 8.5 |
| MELD score ≥ 25 | 29 (17) | 21 (22) | 24 (18) | 28 (25) | 14 (34)* |
| UNOS status | | | | | |
| 1 | 10 (6) | 5 (5) | 5 (4) | 3 (3) | 4 (10) |
| 2A | 22 (13) | 10 (10) | 14 (10) | 12 (11) | 5 (12) |
| 2B | 106 (61) | 69 (72) | 88 (67) | 79 (71) | 29 (71) |
| 3 | 35 (20) | 12 (12) | 25 (19) | 17 (15) | 3 (7) |
| Child-Pugh score | 9.9 ± 1.9 | 9.9 ± 2.1 | 9.8 ± 2.0 | 10.2 ± 2.0 | 9.9 ± 2.2 |

NOTE: Numbers in parentheses represent percentages.
**Abbreviations:** FHF, fulminant hepatic failure; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; M/F, male/female; UNOS, United Network for Organ Sharing.
*Group 5 versus groups 1 and 3, $P < 0.05$.

group 1 donors (69%) compared to group 2 and 4 donors. The utilization rate of group 5 donors was 63%. The cause of discarding was mostly related to macroscopic or microscopic graft alterations, with a lower prevalence among group 1 donors compared to other groups.

The rate of liver biopsy performed at procurement to confirm graft suitability for transplant was higher among older donors, with the highest percentage in group 5 (95%).

## Donor Profiles and Operative Parameters

There were 173 (31%) patients in group 1, 96 (17%) patients in group 2, 132 (24%) patients in group 3, 111 (20%) patients in group 4, and 41 (7%) patients in group 5.

Donor characteristics and operative parameters are reported in Table 2. Group 1 donors were predominantly male, with trauma as the cause of death, a lower prevalence of serum hepatitis B anticore–positive subjects and of diabetes, a higher prevalence of cardiac arrests, and higher levels of alanine aminotransferases. Group 5 donors had a shorter ICU stay before procurement, compared to group 2 and 3 donors, and a lower prevalence of diabetes, compared to group 3. Ischemia time was longer in group 3 versus group 1 and 5 donors. In particular, 39 of 41 (95%) group 5 grafts had ischemia < 10 hours.

The mean ischemia time was 391 ± 88 minutes (median: 378; range: 175-586) for 138 donors, 60 years old or older, used since January 2003.

The number of biopsies performed to confirm graft acceptance was significantly higher among older donors with a stepwise increase, with group 4 and group 5 donors having comparable rates (77% and 85%, respectively).

ICU stay > 5 days, BMI ≥ 35, use of norepinephrine, prevalence of steatosis, and percentages of donors with markedly elevated levels of aminotransferases, total bilirubin, and serum sodium were comparable between groups. Positive serum hepatitis B anticore, positive serum HCV, ICU stay > 5 days, BMI ≥ 35, cardiac arrest before or during procurement, use of norepinephrine, aspartate or alanine aminotransferases > 500 U/L, bilirubin > 2 mg/dL, serum sodium > 170 mEq/L, ischemia time > 12 hours,[5] graft steatosis, cardiac arrests, and diabetes were considered donor-related risk factors of graft failure. The rate of donors with more than 1 risk factor (excluding age) was significantly lower in group 1 versus groups 2, 3, and 4.

The LT procedure was routinely performed with the piggyback technique; the conventional technique, with or without the use of the venovenous bypass, was used in 39 (7%) cases only, without any significant difference between the 5 study groups (data not shown). The total amount of blood transfusions was similar between groups.

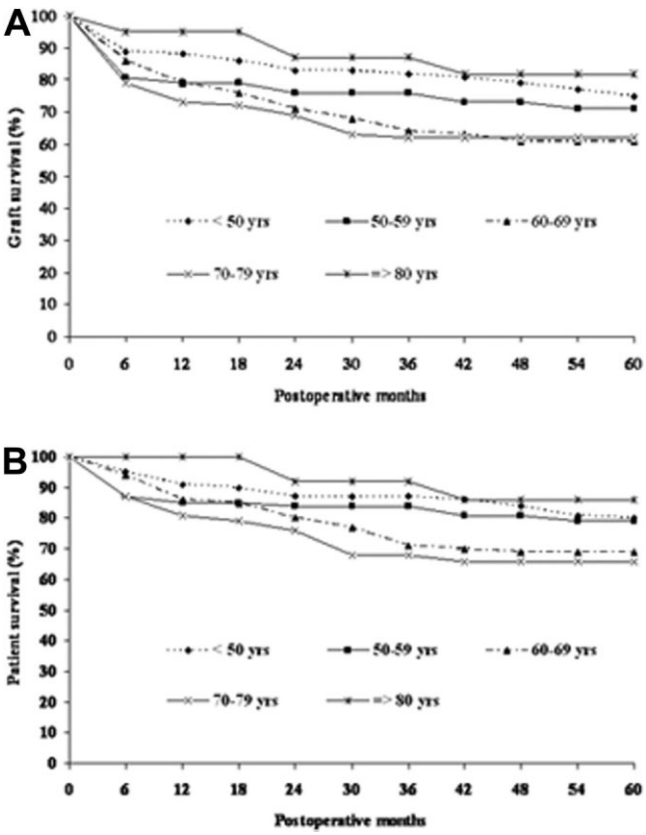


**Figure 1. (A) Graft survival according to the different categories of donor age. Donor age ≤ 50 years versus donor age of 60-69 years, *P* = 0.01. Donor age ≤ 50 years versus donor age of 70-79 years, *P* = 0.001. Donor age ≥ 80 years versus donor age of 60-69 years, *P* = 0.04. Donor age ≥ 80 years versus donor age of 70-79 years, *P* = 0.01. (B) Patient survival according to the different categories of donor age. Donor age ≤ 50 years versus donor age of 60-69 years, *P* = 0.03. Donor age ≤ 50 years versus donor age of 70-79 years, *P* = 0.001. Donor age ≥ 80 years versus donor age of 60-69 years, *P* = 0.05. Donor age ≥ 80 years versus donor age of 70-79 years, *P* = 0.01.**

## Patient Profiles

Patient characteristics are reported in Table 3. The study groups were comparable with respect to age, sex, indications for LT, prevalence of HCV-positive subjects, MELD score, United Network for Organ Sharing (UNOS) status, and Child-Pugh score. However, group 5 had a higher prevalence of patients with MELD score ≥ 25 compared to groups 1 and 3. The number of patients with hepatocellular carcinoma was higher and the number of HCV-positive subjects was lower (in both cases without statistical relevance) in group 5 compared to the remaining study groups.

The induction immunosuppression was based on calcineurin inhibitors (cyclosporine or tacrolimus), mostly in combination with steroids and, in a minority of cases, with monoclonal antibodies, with sporadic use of azathioprine or mycophenolate mofetil. The immunosuppression regimens were not distributed differently between the 5 categories of donor age (data not shown).

## Survival Analysis

The mean follow-up time of the entire study population was 39.3 ± 29.2 months (range: 0-95).

At the end of the observation period, 121 (21.9%) patients had died: 28 (16.2%) within group 1, 21 (21.9%) in group 2, 36 (27.3%) in group 3, 32 (28.8%) in group 4, and 4 (9.8%) in group 5.

Graft survival rates are reported in Fig. 1A. Three- and five-year graft survival rates were 82% and 75% in group 1, 76% and 71% in group 2, 63% and 60% in group 3, 62% and 62% in group 4, and 81% and 81% in group 5. Group 1 patients had a significantly higher survival compared to groups 3 and 4 ($P = 0.01$ and $P = 0.001$, respectively). Graft survival was also significantly better in group 5 compared to groups 3 and 4 ($P = 0.04$ and $P = 0.01$, respectively).

Patient survival rates are depicted in Fig. 1B. Three- and five-year patient survival rates were 87% and 80% in group 1, 84% and 79% in group 2, 71% and 68% in group 3, 68% and 66% in group 4, and 86% and 86% in group 5, respectively. Patient survival was significantly higher in group 1 versus groups 3 and 4 ($P = 0.03$ and $P = 0.001$, respectively). Survival was also better in group 5 versus groups 3 and 4 ($P = 0.05$ and $P = 0.01$, respectively).

Prevalence and causes of graft loss in the different study groups are shown in Table 4. Groups 3 and 4 had a higher proportion of graft losses due to hepatitis recurrence compared to the other groups. Group 5 had no cases of PNF or DGNF leading to graft loss, and 5% of graft losses were due to HCV recurrence.

## Predictors of Graft Survival

The following donor-related factors were used for univariate analysis of association with lower graft survival: age ≥ 60 years, age of 60-79 years, age > 79 years, cause of death (cerebrovascular versus other), positive serum hepatitis B anticore, positive serum HCV, length of ICU stay > 5 days, BMI ≥ 35, cardiac arrest before or during procurement, use of norepinephrine, graft macrovesicular steatosis > 30%, aspartate aminotransferases or alanine aminotransferases > 500 U/L, total bilirubin > 2 mg/dL, and serum sodium > 170 mEq/L. The following operative or recipient-related variables were used: age > 55 years, indication for LT, positive serum HCV, MELD score ≥ 25, urgent transplant (UNOS score = 1), and total ischemia time > 12 hours.[3-6]

Donor age ≥ 60 years ($P = 0.01$), donor age of 60-79 years ($P = 0.001$), recipient positive HCV status ($P = 0.0002$), MELD score ≥ 25 ($P = 0.004$), and UNOS score of 1 ($P < 0.0001$) were found to be correlated with lower graft survival.

In multivariate analysis, donor age of 60-79 years [odds ratio = 1.84, 95% confidence interval = 1.33-2.53, $P < 0.0001$], recipient positive HCV status [odds ratio = 2.08, 95% confidence interval = 1.49-2.90, $P < 0.0001$], MELD score ≥ 25 [odds ratio = 1.55, 95% confidence interval = 1.06-2.29, $P = 0.02$], and UNOS

**TABLE 4. Causes of Graft Loss According to Donor Age Categories**

| | Group 1: <50 Years (n = 173) | Group 2: 50–59 Years (n = 96) | Group 3: 60–69 Years (n = 132) | Group 4: 70–79 Years (n = 111) | Group 5: ≥80 Years (n = 41) |
|---|---|---|---|---|---|
| Follow-up (months) | 44.5 ± 30.3 | 42.1 ± 30.0 | 40.3 ± 28.7 | 28.7 ± 25.9† | 37.7 ± 26.1 |
| Surviving grafts | 136 (79) | 68 (71) | 86 (65) | 71 (64) | 35 (85) |
| Cause of graft loss | | | | | |
| Technical* | 6 (3) | 3 (3) | 7 (5) | 8 (7) | 2 (5) |
| PNF/DGNF | 9 (5) | 8 (8) | 8 (6) | 8 (7) | — |
| MOF/sepsis | 6 (3) | 4 (4) | 10 (8) | 4 (4) | — |
| Hepatitis recurrence | 6 (3) | 6 (6) | 12 (9) | 14 (13) | 2 (5) |
| Malignancies | 3 (2) | 2 (2) | 4 (3) | 4 (4) | 1 (2) |
| Rejection | 2 (1) | 1 (1) | 1 (1) | 1 (1) | — |
| Other | 5 (3) | 4 (4) | 4 (3) | 1 (1) | 1 (2) |

NOTE: Numbers in parentheses represent percentages.
**Abbreviations:** DGNF, delayed graft nonfunction; MOF, multiorgan failure; PNF, primary nonfunction.
*Includes intraoperative deaths due to technical problems and postoperative vascular or biliary complications.
†Group 4 versus all other groups, $P < 0.005$.

score of 1 [odds ratio = 3.57, 95% confidence interval = 1.91-6.68, $P < 0.0001$] were independent predictors of lower graft survival.

### Survival Analysis in HCV-Positive/HBsAg-Negative Patients

There were 5 (7%) graft losses due to HCV recurrence in group 1, 6 (15%) in group 2, 11 (21%) in group 3, 11 (25%) in group 4, and 2 (12%) in group 5.

Three- and five-year graft survival rates were 78% and 72% in group 1, 89% and 85% in group 2, 55% and 52% in group 3, 65% and 65% in group 4, and 82% and 71% in group 5, respectively (group 1 versus group 3, $P = 0.04$; group 2 versus group 3, $P = 0.03$; Fig. 2A).

Three- and five-year patient survival rates were 84% and 78% in group 1, 92% and 88% in group 2, 57% and 53% in group 3, 70% and 64% in group 4, and 82% and 71% in group 5, respectively (group 1 versus groups 3 and 4, $P = 0.008$ and $P = 0.01$, respectively; group 2 versus groups 3 and 4, $P = 0.02$; Fig. 2B).

## DISCUSSION

Advanced donor age is one of the main factors affecting the outcomes of LT.[3,7] This study focused on the variability of results of LT depending on different decades of donor age. The analysis of a single-center experience warranted standardized surgical techniques and medical care during the observation period.

This series includes the highest number of donors older than 80 years ever reported. A previous multicenter study outlined the feasibility of LT with octogenarian donors in favorable settings (absence of donor-related, recipient-related, and logistic-related risk factors); even so, patient survival was lower than that of recipients of younger grafts.[15]

We observed a progressive decrease of survival rates with advancing donor age, with a nadir in the decade of 70-79 years. Grafts from donors ≥ 80 years old showed survival rates significantly higher than those from 60- to 79-year-old donors and quite comparable to those of much younger grafts.

There were no significant differences in the average degree of liver dysfunction among recipients of different classes of donor age. The higher number of older grafts transplanted into patients with liver cancer is probably due to our pre-MELD policy of matching ECDs with recipients with less advanced liver disease, such as those with hepatocellular carcinoma.[16] This did not finally result in a real selection based on preoperative conditions, especially with respect to the MELD score, although it was retrospectively calculated. Conversely, recipients from over 80-year-old donors had the highest proportion of MELD score ≥ 25 and UNOS status 1 or 2A. Of note, MELD score ≥ 25 and UNOS status 1 were 2 of 4 independent negative predictors of graft survival.

The analysis of proposed grafts showed that donors < 50 years old had a significantly higher rate of usage, whereas other groups had a discarding rate of around 40%.

The implementation of graft biopsy reflected the changing of the donor evaluation protocol with time and with the availability of a real-time pathological assessment. In recent years, we have been indicating biopsy in all >60-year-old donors, and we currently obtain histological reports from a regional centralized laboratory during organ recovery in regional hospitals or from extraregional sites during retrieval at distant hospitals. The greatest benefit of this policy is for grafts from octogenarian donors, whose use has expanded more recently[15] than that of grafts from donors aged 60 to 79 years, which have been employed for a longer period but in a less selective way. Indeed, only 15% of livers from donors ≥ 80 years old were harvested without histological evaluation, with only one showing macrovesicular steatosis > 30%, which is our upper limit for acceptance of donors > 60 years. Conversely, the fact

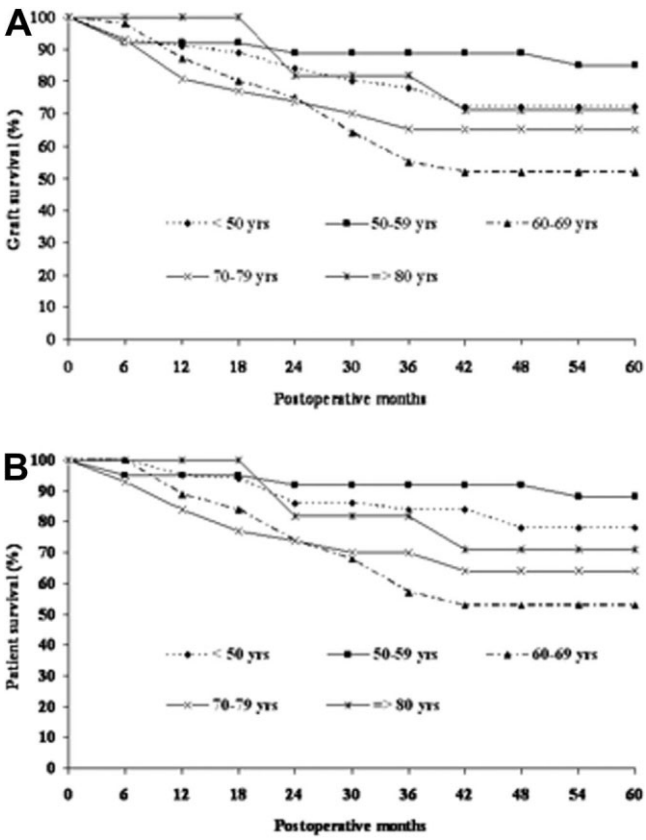


**Figure 2. (A) Graft survival of hepatitis C virus–positive/hepatitis B surface antigen–negative patients according to the different categories of donor age. Donor age ≤ 50 years versus donor age of 60-69 years, *P* = 0.04. Donor age of 50-59 years versus donor age of 60-69 years, *P* = 0.03. (B) Patient survival of hepatitis C virus–positive/hepatitis B surface antigen–negative patients according to the different categories of donor age. Donor age ≤ 50 years versus donor age of 60-69 years, *P* = 0.008. Donor age ≤ 50 years versus donor age of 70-79 years, *P* = 0.01. Donor age of 50-59 years versus donor age of 60-69 years and donor age of 70-79 years, *P* = 0.02.**

that as many as 37% of grafts from donors 60-79 years old did not undergo biopsy might have led to an underestimation of abnormalities, with a possible negative impact on the outcome.

Because in the large majority of cases the donor aorta could be cross-clamped simultaneously with transportation of the recipient to the operation room and just after knowledge of the liver graft histology, this procurement organization also permitted a minimization of the ischemia time, which is nowadays expected to be shorter than 9 hours. These management criteria can at least in part explain the absence of PNF and DGNF as causes of graft loss and the satisfactory outcomes of recipients from donors > 80 years old.

The presence of more than 1 donor-related risk factor (excluding age) was similar among different categories of donor age, with the exclusion of those < 50 years old. Although the length of ICU stay, the level of liver enzymes, and the prevalence of diabetes were more favorable in donors ≥ 80 years old, these and other variables contributing to the definition of ECD are more susceptible to interpretation and should not be considered, either separately or together, as a strict contraindication for transplant, unless dramatically represented (that is, severe hemodynamic changes or marked elevation of aminotransferases) and with a corresponding altered pathology (that is, necrosis).

One of the major causes of loss of older grafts was HCV recurrence, and HCV-related cirrhosis was an independent predictor of lower graft survival. Donor age strongly affects survival of HCV-infected patients, starting from 40 years and with the highest impact after 60 years.[8]

Our evaluation of patients with isolated HCV infection suffered from the lack of protocol biopsies, from the unavailability of pre-LT HCV-RNA in the early period, and from the low number of patients receiving grafts from octogenarian donors, which probably precluded a reliable comparison with other donor age categories. Nevertheless, we observed survival rates significantly higher in recipients from donors < 60 years old compared to those transplanted with grafts from donors 60-79 years old but not compared to those transplanted with grafts from donors ≥ 80 years old.

Together with advanced donor age, several factors, such as recipient HCV viral load, genotype, post-LT cytomegalovirus infections, and use of OKT3 and corticosteroid pulse doses, have been correlated with severe HCV recurrence and/or poor outcome in HCV+ patients.[17] Two recent studies pointed out the negative impact of prolonged donor hospitalization and of histological evidence of early preservation injury on HCV recurrence and survival of HCV+ recipients, respectively.[18,19] The effect of ischemia/reperfusion injury can be the sum of a number of factors, such as donor age, protracted ICU stay, graft steatosis, and long ischemia time, even if the mechanisms for a more aggressive HCV reinfection are unknown.[19]

In our series, group 5 recipients had an advantage over other old donor age categories from the quality of their grafts, which in turn may account for the acceptable outcomes of HCV+ recipients of octogenarian donors. Although a comparison between groups of the course of HCV recurrence and of adherence to antiviral treatments was not possible because of the previously reported limitations, a good functional recovery might allow an early and safe treatment initiation, the importance of which has been demonstrated in previous studies.[20-23]

The worse outcome of LT for HCV cirrhosis compared to other indications raised the question of whether the MELD system is the most appropriate in this setting.[18] This score is widely employed, but variables that can be effectively controlled in matching donors and recipients remain limited. With waiting lists with 40%-50% HCV-positive subjects, there are few possibilities of assigning a graft to an ideal recipient, and although ECDs should theoretically be matched with mildly to moderately sick, HCV-negative patients,[24] this choice is often impossible. Transplant programs are still faced with an inadequate and aging donor pool, and most of our efforts

must be focused on organization and control of logistic aspects during organ procurement.

Even if no definitive conclusions can be drawn, we have shown that very old organs may work effectively regardless of the severity of the recipient's liver disease, provided that donors are evaluated with routine biopsy and have a short ischemia time. A good graft functional recovery may contribute to acceptable outcomes also in HCV-infected patients.

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