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ORIGINAL ARTICLE

Liver transplantations with donors aged 60 years and above: the low liver damage strategy

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Summary

According to transplant registries, grafts from elderly donors have lower survival rates. During 1999–2005, we evaluated the outcomes of 89 patients who received a liver from a donor aged ≥ 60 years and managed with the low liver-damage strategy (LLDS), based on the preoperative donor liver biopsy and the shortest possible ischemia time (group D ≥ 60-LLDS). Group D ≥ 60-LLDS was compared with 198 matched recipients, whose grafts were not managed with this strategy (89 donors < 60 years, group D < 60-no-LLDS and 89 donors aged ≥60 years, group D ≥ 60-no-LLDS). In the donors proposed from the age group of ≥60 years, the number of donors rejected decreased during the study period and the LLDS was found to be responsible for this in a significant manner (47% vs. 60%, respectively $P < 0.01$). Among the recipients transplanted, the clinical features (age, gender, viral infection, child and model for end-stage liver disease score) were comparable among groups, but group D ≥ 60-LLDS had a lower mean ischemia time: 415 ± 106 min vs. 465 ± 111 (D < 60-no-LLDS), $P < 0.05$ and vs. 476 ± 94 (D ≥ 60-no-LLDS), $P < 0.05$. After a median follow-up of 3 years, the 1- and 3-year graft survival rates of group D ≥ 60-LLDS (84% and 76%) were comparable with group D < 60-no-LLDS (89% and 76%) and were significantly higher than group D ≥ 60-no-LLDS (71% and 54%), $P < 0.005$. In conclusion, the LLDS optimized the use of livers from elderly donors.

Introduction

Elderly donors are considered extended criteria donors (ECD) because recipient outcome after liver transplantation (LT) is inferior compared to recipients receiving grafts from younger donors [1–4].

Because of the disparity between the number of recipients on the waiting list and the number of donors available [5–8], liver transplant programs are forced to utilize elderly donors to reduce the mortality on the waiting list, even if these grafts offer a lower survival rate. The ethical issue under debate is the balance between the risk of death during the waiting time and the risk of death after LT; for the sickest of the recipients, however, who have priority on the list in most centers [7,9,10], the transplant benefit is always present, albeit with a very poor outcome after LT [11,12].

Surgical and medical innovations are under investigation to optimize the outcome of grafts out of elderly donors, in particular in liver transplant programs, where

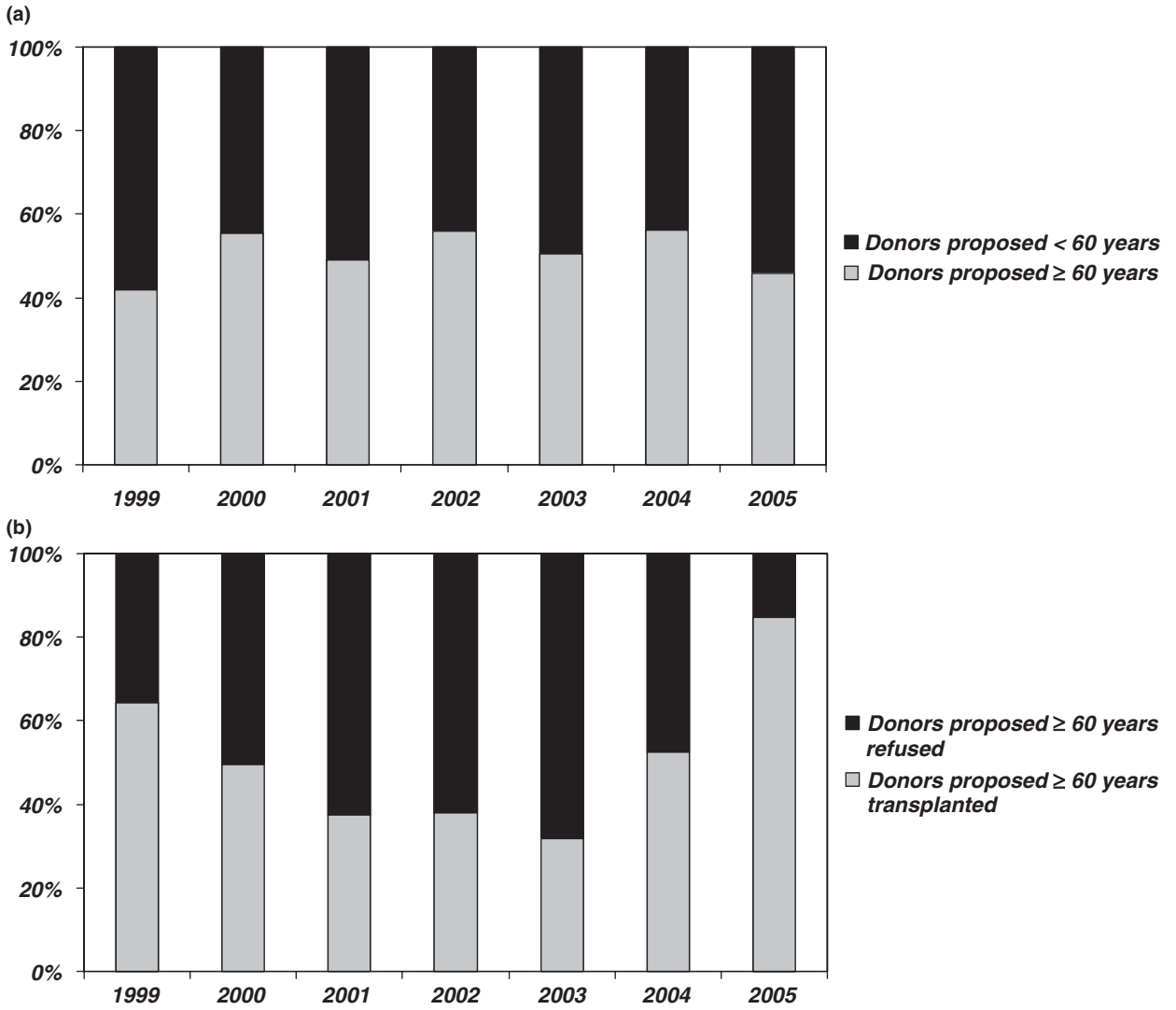

Figure 1 (a) Rate of donors proposed for liver transplantation according to donor aged: <60 years (black colons), ≥60 years (green colons). (b) Rate of donors accepted or refused for liver transplantation among donors aged ≥60 years: refused donors (black colons), transplanted donors (green colons).

the rate of usage of these donors is very high (Fig. 1). Since 2003, following some years of practice with donors aged 60 years or more, our center started to routinely perform a protocol called low liver-damage strategy (LLDS). The principal features of the protocol were to perform a liver biopsy before acceptance of the donor and to reduce the ischemia time as much as possible. We believe that our strategy improved the survival of these donor grafts to the extent of making their outcome comparable to the outcome of younger donor grafts.

This study evaluates the outcome of the grafts from donors aged 60 years and above, managed with the LLDS protocol compared with two cohorts of patients (ideal liver from a donor aged under 60 years or a marginal liver from a donor aged 60 and above) transplanted out of the protocol.

The groups were matched according to age, gender, virus infection and model for end-stage liver disease (MELD) score.

Materials and methods

Study design

From a prospectively collected database, we retrospectively reviewed the outcomes of 89 patients who received a liver from a donor aged ≥60 years managed with the LLDS protocol (group D ≥ 60-LLDS). These outcomes were compared with the outcomes of 198 matched recipients,

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whose donor livers were not managed with the LLDS protocol. Their donors were aged <60 years in 89 cases (group D < 60-no-LLDS, positive-reference expected to have an optimal outcome) and ≥60 years in 89 cases (group D ≥ 60-no-LLDS, negative-reference expected to have a worse outcome).

The sample size analysis showed that considering this population study with a ratio of 1:2, and with an expected different graft survival of 20% at 3 years between donors younger and older than 60 years, we achieved 87% power at the 5% (α) level of significance.

Selection of patients

The patients listed for LT because of chronic liver disease, who received a primary, isolated, whole LT with ABO-identical or -compatible grafts between 1999 and 2005, were evaluated and subsequently enrolled in the study if they met the match criteria.

All patients received deceased donor livers preserved with the Celsior solution, and our allocation system during the waiting time had already been published [7,8]: until March 2003, it was based on the Child–Pugh score [13] and subsequently on the MELD score [14,15].

The enrolled recipients were matched according to gender, age (±5 years), etiology of the cirrhosis (hepatitis C, hepatitis B, other) and MELD score (<15, 15–20, 21–25, >25).

Low liver damage strategy: histologic evaluation and surgical technique

Since 2003, all donors aged 60 years and above have been routinely evaluated by liver biopsy and the operation on the recipient started after receipt of the pathology result. This protocol was decided because of our previous experience with elderly donors and thanks to the round-the-clock availability of pathologists who are experts in liver disease. The donor aorta was not clamped until the definitive decision was made to accept the liver, which depended on the histologic evaluation. In our region, the organ recovery hospitals are <2 h by car from our center and all the liver biopsies are evaluated by the pathology division of our hospital.

The operation on the donor was started, performing the liver biopsy by needle (at least 2 cm) and by small sub-glissonian 'wedge' resection; we usually take one sample from the right or left lobe and the other sample from the opposite lobe.

While waiting for the pathology evaluation, the recovery of organs surgeon dissected the liver and the hepatic vessels, reducing the time for the hepatectomy in the donor during the warm ischemia period to <30 min.

Following this protocol, the ischemia time was <7 h in most cases.

Wedge and needle donor biopsies were placed on a wet surgical pad soaked with sterile 0.9% NaCl solution and sent to the centralized regional pathology center. Donor-derived biopsies were immediately embedded in OCT TissueTek media (Sakura Europe, Zoeterwoude, the Netherlands) for frozen section preparation. Five-micrometer frozen sections were cut in a refrigerated microtome (CM 1900 Leica, Wetzlar, Germany) at −20 °C and placed on charged glass slides. At least two sections of each biopsy were placed on the same slide with a gap of 50 μm between them. All frozen sections were quickly stained with hematoxylin (30 s) and eosin (15 s) and then mounted in Micromount (Diapath, Martinengo, Italy).

The histopathologic report included the following information: (i) size of the biopsy and number of portal tracts whether ≤7; (ii) separate and total semiquantitative estimation of microvescicular and macrovescicular steatosis expressed as the percentage of involved hepatocytes; (iii) degree of portal inflammation and peri-portal necrosis; (iv) presence of lobular spotty necrosis; (v) presence of PMN lobular infiltrate; (vi) presence of bridging lobular necrosis; (vii) extent of fibrosis expressed as mild portal tract fibrosis, fibrous portal expansion, portal/portal or portal/ central septa, liver cirrhosis; (viii) degree of histologic cholestasis; (ix) presence of pigments, ballooning or Mallory bodies in the hepatocytes; and (x) evaluation of intimal narrowing of the portal arterioles expressed as < or > than half of the original arteriole diameter [16,17].

The complete histopathologic examination took approximately 15–20 min from the time of sample reception at our Pathology division. Therefore, the time that elapsed between performing the donor biopsy during the recovery procedure and carrying out the histopathologic evaluation was always <2–½ h (al most 2 h by car and 30 min for the preparation and examination of the biopsy).

In the case of HCV positive or HBcAb positive donors, the same histologic information was provided as well as a brief conclusion of mild, moderate or severe chronic active hepatitis.

The absolute histologic contraindications to the acceptance of the liver were the presence of cirrhosis and severe chronic hepatitis. Among the HCV positive or HBcAb positive donors, the degree of chronic hepatitis was the principal parameter evaluated and only cases with chronic hepatitis with fibrosis stage <3 and absence of severe portal inflammation were considered suitable for transplantation. Instead, among the other donors the degree of macrosteatosis [18,19] was the principal parameter evaluated and macrosteatosis higher than 30% was considered a relevant (but not absolute) contraindication to LT. In many cases, patients with macrosteatosis higher than 30%

were considered not suitable for transplantation if it was associated with a moderate-severe portal fibrosis on the histology or multiple risk factors of the donors or hard liver at the touch of the surgeon during the organ recovery procedure.

The definitive decision to accept the liver was taken by the senior surgeons of our program (A.D.P. and G.L.G.), who consider the preoperative donor features, the histologic assessment by an expert pathologist and the macroscopic aspect of the liver as depicted by a junior surgeon during the recovery.

The LT procedure was routinely performed with the piggy-back technique and the induction immunosuppression was based on calcineurin inhibitors, mostly in combination with steroids, as previously described in our studies [7,8,20–22].

Follow-up

The demographic characteristics and clinical data of donors and recipients were recorded at the time of transplantation. All recipients were followed by our center and no patients were lost to follow-up in the postoperative course. All living cases of transplant recipients had at least 1 year of follow-up and the median follow-up was 3 years.

Statistical analysis

Results were expressed as mean ± standard deviation. Differences between continuous variables were evaluated with the one-way ANOVA test with least significant difference for multiple comparisons. Differences between categorical variables were calculated with the chi-squared test or Fisher's exact test. The graft survival was the primary end-point and was calculated from the date of LT to the date of the last follow-up examination, patient death or graft loss. Patient survival was calculated from LT to the last follow-up examination 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.

Statistical analysis was carried out with the SPSS Base 10.0 software packing (Application Guide, SPSS Inc., Chicago, IL, USA) and a P-value <0.05 was considered statistically significant.

Results

Recipient and donor features

The 89 recipients transplanted with a liver from a donor aged 60 years or above managed with the LLDS protocol had comparable clinical features to the control groups (Table 1).

The etiology of the cirrhosis was not different among the groups, but group D ≥ 60-LLDS had a higher rate of patients with hepatocellular carcinoma (HCC) (44.7% vs. 27.7% and 27.7%, $P < 0.05$).

On the other hand, in accordance with the study design, the liver function of the three groups was comparable; the median value of the MELD and Child–Pugh scores was the same for all three groups, 17 and 10 respectively.

The donor characteristics obviously showed a different age distribution among the three groups and this result was also present between groups D ≥ 60-LLDS and D ≥ 60-no-LLDS, which had donors aged 60 years and above.

Because of the advanced age of donors, these two groups had different causes of donor death when compared with group D < 60-no-LLDS (fewer cases with trauma, lower level of transaminases and lower number of cardiac arrests) and they also had a higher body-mass index (BMI).

Concerning the recipient operative data, group D ≥ 60-LLDS showed a lower ischemia time and a lower time to perform the hepatectomy when compared with groups without LLDS, while the other parameters were comparable.

The rate of cases with an ischemia time <7 h was 41.5% and it was significantly different among the study population: 56.1% in group D ≥ 60-LLDS, 36.8% in group D < 60-no-LLDS and 31.6% in group D ≥ 60-no-LLDS (A versus B and C, $P < 0.05$).

Outcomes

After a median follow-up of 3 years, the 1- and 3-year survival rates of grafts from donors aged 60 years and above, managed with LLDS (84% and 76%, D ≥ 60-LLDS) were the same as those with younger donors (89% and 76%, D < 60-no-LLDS) and significantly higher than with donors aged 60 years and above but not managed with the LLDS (71% and 54%, D ≥ 60-no-LLDS), $P < 0.005$.

Patient survival showed the same tendency (Fig. 2a and b).

In group D ≥ 60-no-LLDS, more grafts were lost than in other groups during the first 90 postoperative days for technical causes and after the first year following LT because of hepatitis recurrence (Table 2).

There were no differences between groups D ≥ 60-LLDS and D < 60-no-LLDS.

Analysis of the variables related to graft survival

Apart from the study group population and the donor age previously reported, the only donor and recipient

Table 1. Characteristic of the recipients and donors at the time of liver transplantation.

	Group A Donors aged ≥ 60 years LLDS (*n* = 89)	Group B Donors < 60 years No LLDS (*n* = 89)	Group C Donors aged ≥ 60 years No LLDS (*n* = 89)	*P*-value all groups	*P*-value comparison among groups
Recipients					
Age (years)	54.1 ± 9.0	52.4 ± 9.3	54.0 ± 8.4	NS	NS
Male gender	66 (74.2)	64 (71.9)	66 (74.2)	NS	NS
Virus hepatitis					
HCV-positive	45 (61.8)	51 (57.3)	51 (57.3)	NS	NS
HBsAg-positive	18 (20.2)	22 (24.7)	22 (24.7)		
Virus negative	16 (18)	16 (18)	16 (18)		
MELD score	18.0 ± 6.4	17.9 ± 5.8	18.4 ± 6.4	NS	NS
MELD < 15	30 (33.7)	31 (34.8)	30 (33.7)		
MELD 15–20	27 (30.3)	26 (29.2)	27 (30.3)	NS	NS
MELD 21–25	23 (25.8)	23 (25.8)	23 (25.8)		
MELD > 25	9 (10.1)	9 (10.1)	9 (10.1)		
Child–Pugh	10 ± 2.1	9.8 ± 2.1	9.6 ± 1.7	NS	NS
BMI (kg/m^2)	25.0 ± 4.2	25.0 ± 3.6	25.0 ± 3.8	NS	NS
Donors					
Age (years)	73.2 ± 6.6	39.7 ± 15.5	69.3 ± 6.1	<0.001	A–C vs. B <0.001
A versus C <0.001					
Male gender	49 (55.1)	53 (59.6)	47 (52.8)	NS	NS
Cause of death					
Cerebrovascular	69 (77.5)	35 (39.3)	62 (69.7)	<0.001	A–C vs. B <0.001
Trauma	10 (11.2)	43 (48.3)	17 (19.4)		
Other	10 (12.2)	11 (12.4)	10 (11.2)		
ICU stay (days)	4.3 ± 3.5	4.0 ± 4.0	3.1 ± 2.1	<0.05	A–B vs. C <0.05
BMI (kg/m^2)	26 ± 3.2	24.2 ± 3.0	25.2 ± 2.8	<0.001	A–C vs. B <0.05
Cardiac arrest	2 (2.2)	12 (13.5)	2 (2.2)	<0.01	A–C vs. B <0.01
Use of norepinephrine	27 (30.3)	27 (30.3)	20 (22.5)	NS	NS
AST (U/l)	47 ± 60	87 ± 142	40 ± 29	<0.001	A–C vs. B <0.001
ALT (U/l)	31 ± 34	61 ± 62	29 ± 28	<0.001	A–C vs. B <0.001
Total bilirubin (mg/dl)	0.7 ± 0.4	1.3 ± 2	0.8 ± 0.6	NS	NS
Serum Na+ (mEq/l)	144.5 ± 8.4	144.2 ± 10.0	145.5 ± 9.5	NS	NS
HBcAb-positive	17 (19.1)	10 (11.2)	11 (12.4)	NS	NS
HCV-positive	6 (6.7)	2 (2.2)	2 (2.2)	NS	NS
Recipient operation					
Ischemia time (min)	415 ± 106	465 ± 111	476 ± 94	<0.005	A vs. B–C <0.05
Blood transfusions (ml)	3194 ± 2814	3059 ± 2558	3294 ± 4033	NS	NS
Hepatectomy time (min)	111 ± 527	197 ± 89	176 ± 54	<0.005	A vs. B–C <0.005
Operation time after hepatectomy (min)	275 ± 94	287 ± 88	307 ± 142	NS	NS

Numbers in parentheses represent percentages.

HBcAb, hepatitis B anticore; ICU, intensive care unit; BMI, body mass index; AST, aspartate aminotranspherases; ALT, alanine aminotranspherases.

variables related to graft survival were HCV infection and MELD score. The HCV positive recipients had significantly lower 1- and 3-year graft survival than HCV negative recipients (80% and 65% vs. 85% and 78%, $P < 0.05$), as did patients with MELD score >20 as compared with those with MELD ≤20 (78% and 62% vs. 84% and 75%, $P < 0.05$).

By the Cox regression model, MELD score >20 and HCV-positivity were independently related to graft survival ($P < 0.05$, HR = 1.521, CI = 1.005–2.303 and $P < 0.005$, HR = 1.839, CI = 1.172–2.886).

Considering the donors aged 60 years and above in the Cox regression model, the variables independently related to the lower graft survival were HCV-positivity ($P < 0.005$, HR = 2.389, CI = 1.375–4.152) and the absence of the LLDS ($P < 0.005$, HR = 2.136, CI = 1.278–3.569).

Among the operating variables, operating time, cold ischemia time and blood transfusions were not related to graft survival.

Considering patients in group D ≥ 60-LLDS, 58 cases of allograft recipients (65%) presented a macrosteatosis of

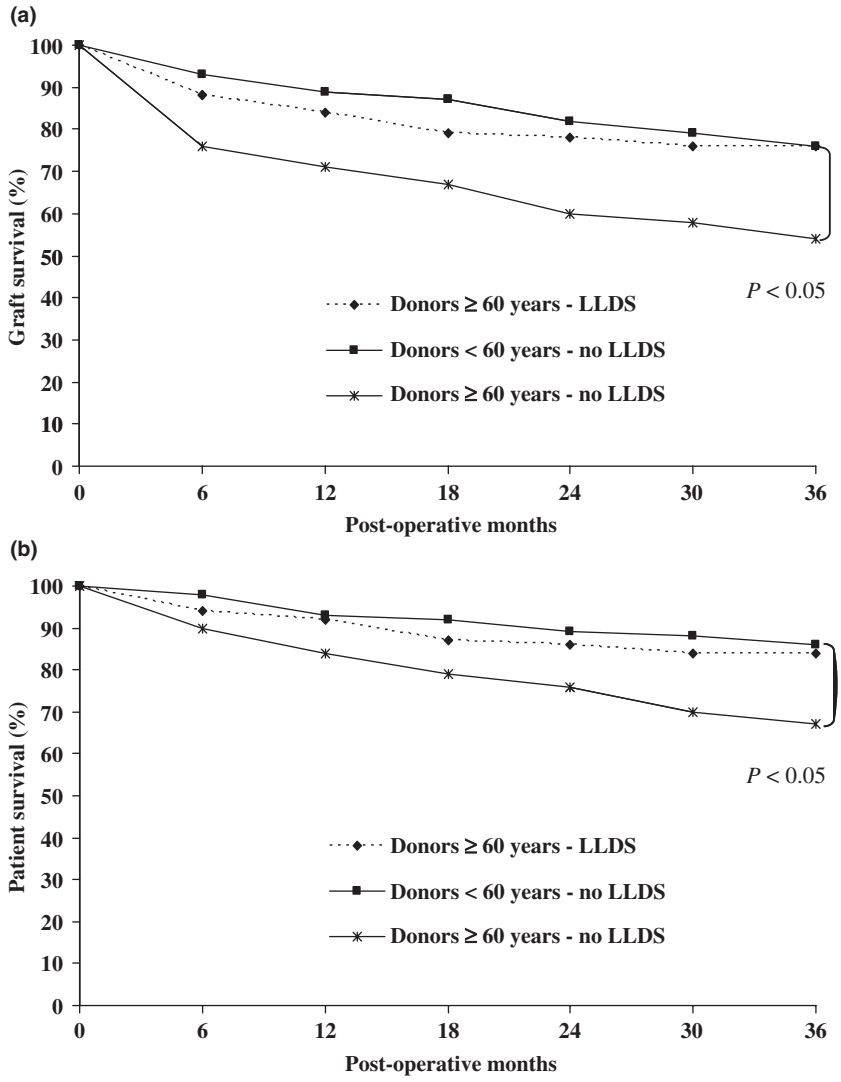

Figure 2 (a) Graft survival according to the study groups. (b) Patient survival according to the study groups.

10–30% and three (3.4%) cases had a macrosteatosis higher than 30%.

Among these last three grafts, one was lost for non-function on day 23, while the other two were functioning 2 and 6 years after LT.

The 58 grafts with macrovescicular steatosis of 10–30% had a comparable outcome to the other 28 livers with absent or lower steatosis: 84.5% and 76.7% vs. 85.7% and 76.4% at 1 and 3 years respectively (P = NS).

Features of the donors aged ≥60 years submitted to the LLDS and transplanted or rejected

During the study period, the proposed donors aged ≥60 years were progressively managed with the LLDS as reported in Fig. 3a, so in the last 2 years of the study period (2003–2005) close to 80% of elderly donors were treated with this strategy.

Among the 150 donors aged ≥60, proposed and managed with the LLDS, 71 (47%) were not considered suitable for transplantation and this rate decreased during the study period (Fig. 3b) and it was significantly lower than the rate of discharge of the donors aged ≥60 not treated with the LLDS (47% vs. 60%, respectively $P < 0.01$).

The principal causes for the rejection of the 71 donors aged ≥60 and managed with LLDS were: 29 (41%) macrovescicular steatosis >30%, 27 (38%) moderate steatosis but associated with chronic hepatitis HCV or HBV related, 10 (14%) cancers of the deceased donors revealed during the recovery procedure and five cases (7%) with moderate steatosis and an expected ischemia time higher than 12 h.

The donors aged ≥60 managed with LLDS but rejected differed from those transplanted mainly for the more severe macrovescicular stetaosis, with a consequently

Table 2. Causes of graft loss according to study group categories.

	Group A Donors aged ≥ 60 years LLDS (*n* = 89)	Group B Donors < 60 years No LLDS (*n* = 89)	Group C Donors aged ≥ 60 years No LLDS (*n* = 89)	*P*-value all groups	*P*-value comparison among groups
Grafts lost (GsL)	22 (24.7)	24 (27)	45 (50.6)	<0.001	A–B vs. C <0.001
GsL < 90 days	10 (11.2)	5 (5.6)	15 (16.9)	<0.05	A vs. B/A vs. C NS B vs. C <0.05
GsL 90–360 days	4 (4.5)	4 (4.5)	10 (11.2)	NS	NS
GsL > 360 days	8 (9)	15 (16.9)	20 (22.5)	<0.05	A vs. B/B vs. C NS A vs. C <0.05
Causes of GsL					
Technical*	4 (4.5)	2 (2.2)	9 (10.1)	<0.05	A vs. B/A vs. C NS B vs. C <0.05
PNF/DGNF	7 (7.9)	5 (5.6)	7 (7.9)	NS	NS
MOF/sepsis	1 (1.1)	4 (4.5)	7 (7.9)	NS	A vs. B/B vs. C NS A vs. C <0.05
Hepatitis recurrence	5 (5.6)	6 (6.7)	14 (15.7)	<0.05	A–B vs. C <0.05
Malignancies	4 (4.5)	4 (4.5)	3 (3.4)	NS	NS
Rejection	0	2 (2.2)	2 (2.2)	NS	NS
Other	1 (1.1)	1 (1.1)	3 (3.4)	NS	NS

Numbers in parentheses represent percentages.
PNF, primary nonfunction; DGNF, delayed graft nonfunction; MOF, multi-organ failure.
*Intra-operative deaths and postoperative vascular or biliary complications.

higher BMI of the donor, and the chronic hepatitis because of HCV or HBV infection (Table 3).

Discussion

This study indicates that the low liver damage strategy proposed by our center allows a comparable outcome between older and younger donors; thank to our strategy, donors aged ≥60 years may be considered as not ECD in the present series.

In 2003, we changed our policy with donors aged ≥60 years and we started a protocol (low liver damage strategy) based on performing a liver biopsy before accepting the graft and on keeping the ischemia time as short as possible. Over the years, we have become more confident with this strategy and most of the donors aged ≥60 years that were proposed to us were managed with the LLDS (Fig. 3a).

Because of the waiting time for the pathology result, the donor operations became longer (at least a couple of hours) and the recipients only went to the operating room after the decision to accept the donor, before the clamping of the donor aorta. Furthermore, the surgeon involved in the transplantation performed the hepatectomy as quickly as possible. As a result of this strategy, we managed to reduce the ischemia time to the lowest level possible and most of cases had <7 h of ischemia time.

We believed that this policy made the outcome of the older donor grafts comparable to the younger ones and to substantiate this hypothesis we used a study design like Remuzzi *et al.* [23] did for kidney transplantation.

We compared the graft outcome of 89 donors aged ≥60 years and managed as described to a positive-reference of 89 donors under 60 and to a negative-reference of 89 donors over 60 but not managed as before.

The study population was matched according to the demographic characteristics, MELD score and HCV-positivity, which are well-known variables related to a poorer survival after LT [4,24–26].

The only difference among the study groups was the prevalence of cases with HCC, but the degree of liver function was comparable among groups as detected by the same mean and median MELD and Child–Pugh scores (Table 1). We therefore believe that the recipient clinical conditions were comparable among the study groups and that the patients in the LLDS group were not healthier than in the other groups.

The reason for the different HCC rate was because of the higher number of HCC patients listed and transplanted in the last period of the study, when the LLDS was applied more extensively (Fig. 3a). The period with an increased number of HCC patients listed and transplanted was also reported in another recent study by our center [8].

As expected, the grafts from donors aged ≥60 years treated with this low liver damage protocol had the same outcome as those from younger donors and better graft survival than the elderly donors not included in the protocol (Fig. 2a and b).

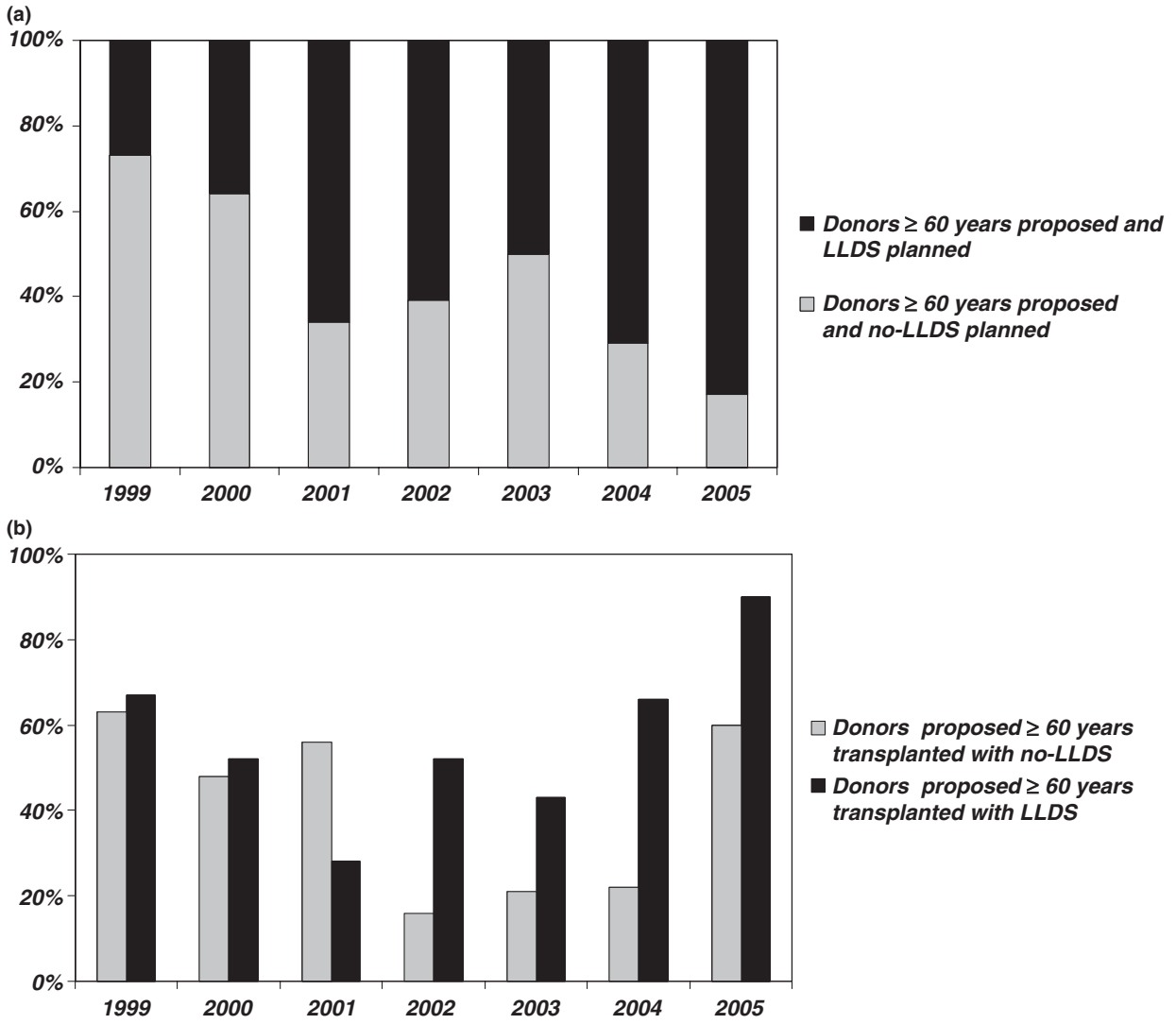

Figure 3 (a) Rate of donors proposed age ≥60 years managed with the LLDS (black colons) or without it (green colons). (b) Rate of donors proposed age ≥60 years and transplanted managed with the LLDS (black colons) or without it (green colons).

In the previously published database [1,2], donor age was constantly related to a poorer outcome after LT, but these analyses often considered periods that are not very recent and they never analyzed the centers' experience with elderly donors.

Furthermore, one issue still open is why grafts from elderly donors should have a lower outcome postoperatively and in the long-term.

Our group showed that arterial complications were more frequent with elderly donor grafts, because of the presence of atherosclerosis of the arterial vessels and calcified plaque on the hepatic artery [27]. Arterial thrombosis was the principal reason for the statistical difference of technical complications among younger and elderly donors without the LLDS (Table 2). The better knowledge of this problem acquired in recent years, and dealt with for example by avoiding arterial conduits or performing anastomoses smaller in caliber but far from the atherosclerotic plaque [27], reduced probably the technical complication rate in the LLDS group.

At the same time, some authors have reported a higher risk of primary nonfunction or dysfunction when utilizing these donors who often have some degree of steatosis [28,29].

Concerning the long-term outcome, many studies showed that hepatitis C recurrence was more severe and more rapid in elderly donor grafts [30–32].

To the best of our knowledge, our study is the first to show no differences in terms of operative complications, primary nonfunction or dysfunction and hepatitis C

Table 3. Characteristics of the donors aged ≥ 60 years submitted to the LLDS divided according to the decision to perform liver transplantation or not.

	Donors aged ≥ 60 years planned LLDS transplanted (*n* = 89)	Donors aged ≥ 60 years planned LLDS refused for transplantation (*n* = 71)	*P*-value
Donors			
Age (years)	73.2 ± 6.6	72.4 ± 6.7	NS
Male gender	49 (55.1)	38 (53.5)	NS
Cause of death			
Cerebrovascular	69 (77.5)	54 (76)	NS
Trauma	10 (11.2)	11 (15.5)	
Other	10 (12.2)	6 (8.5)	
ICU stay (days)	4.3 ± 3.5	3.5 ± 2.2	NS
BMI (kg/m^2)	26 ± 3.2	28 ± 4.0	<0.01
Cardiac arrest	2 (2.2)	3 (4.2)	NS
Use of norepinephrine	27 (30.3)	19 (26.8)	NS
AST (U/l)	47 ± 60	46 ± 31	NS
ALT (U/l)	31 ± 34	37 ± 36	NS
Total bilirubin (mg/dl)	0.7 ± 0.4	0.8 ± 0.4	NS
Serum Na+ (mEq/l)	144.5 ± 8.4	143.7 ± 7.5	NS
HBcAb-positive	17 (19.1)	22 (31)	<0.05
HCV-positive	6 (6.7)	10 (14.1)	<0.05
Macrovescicular steatosis in liver biopsy			
<10%	28 (31.4)	–	
10–30%	58 (65.2)	42 (59.1)	<0.001
>30%	3 (3.4)	29 (40.9)	

Numbers in parentheses represent percentages.
HBcAb, hepatitis B anticore; ICU, intensive care unit; BMI, body mass index; AST, aspartate aminotranspherases; ALT, alanine aminotranspherases.

recurrence between grafts from donors aged ≥60 years managed according to our policy and those from younger donors, while these differences were instead seen with grafts from donors aged ≥60 years and not included in the LLDS (Table 2).

We believe these results were because of the preoperative assessment of the donor liver histology and to the low ischemia time we were able to obtain with our protocol.

The presence of steatosis is strongly related to postoperative liver function [28,29] and its routine evaluation helped us to reject the cases where the macrovescicular steatosis was severe, even in cases where the macroscopic aspect of the liver seemed close to normal. Furthermore, the evaluation by an expert pathologist together with the clinical and macroscopic features of the donor helped the junior surgeon involved in the organ recovery procedure to better understand the overall quality of the organ. The biopsy evaluation was essential in the HCV positive or HBcAb positive donors, because a fibrosis stage of more than 3 or the presence of severe portal inflammation suggested rejection of the organ regardless of the other risk factors or features.

At the end, the donor histology evaluation was discussed by the junior surgeons involved in the organ recovery and the senior surgeons of our program (A.D.P. and G.L.G.). The decision to accept the liver was therefore mainly based on an experienced transplant surgeon's assessment, who considered the macroscopic evaluation of a transplant resident and the histologic judgment of an expert pathologist. Furthermore, the decision time was before the clamping of the donor aorta, making it possible to drastically reduce the ischemia time, which was in most cases <7 h.

The damage secondary to reperfusion injury was thus reduced and postoperative liver dysfunction was consequently observed in <5% of the cases. During the last 10 years, our center has always attached considerable importance to maintaining a low ischemia time, even in young donors. In our series, the mean ischemia time was between 7 and 8 h and this is probably why we failed to find a relationship between graft survival and ischemia time.

There are two possible criticisms regarding our strategy: the donor procedure is demanding and because of the liver biopsy we rejected several grafts, which could have been transplanted with an acceptable outcome, even if lower than the ideal graft.

According to the donor procedure, an alternative policy could be to perform a percutaneous biopsy and to have the histologic parameters evaluated by a local pathologist. On the other hand, we experienced several cases in which the histologic conclusions of the local pathologist who

evaluated the percutaneous biopsy and those of the experienced pathologist of our center who evaluated the donor biopsy according to our protocol were significantly different. In addition, the costs of this strategy need to be balanced against the costs of a possible higher rate of graft nonfunction or dysfunction leading to longer hospital stays, higher postoperative complications and deaths.

Concerning the rejection rate related to the LLDS, Fig. 3b clearly shows how this strategy helped us to accept more marginal livers instead of refusing them; the rate of transplantation among the donors aged ≥60 years was significantly higher when these donors were managed with the LLDS than without this strategy. Knowledge of the histologic features of the liver and the possibility to significantly reduce the ischemia time probably made us more audacious for the transplantation of marginal grafts. At the same time, performing the selection by considering the histologic report of the donor permitted us to obtain excellent results and the degree of steatosis did not show any influence on the outcome of the grafts.

In the end, our strategy enabled better selection of the donors by histologic evaluation and it permitted us to do this while maintaining the lowest possible ischemia time. We agree that the protocol is demanding and that some rejected livers could be transplanted by other centers (in our country this never occurred and we reduced our rejection rate by applying the protocol), but these considerations did not contradict our results according to which younger donors had the same outcome as elderly donors managed with the low liver damage strategy. We will be pleased to learn from future studies how to obtain the same results, but with a less demanding strategy.

In conclusion, our results showed that grafts from donors aged ≥60 years, managed by the low liver damage strategy proposed by our center, based on an expert pathologist's judgment and low ischemia time, can have an ideal graft outcome after LT, like the outcome with grafts from young donors. Because of these results, we believe that donor age should not be considered an extended donor criterion if the donors are managed with this strategy.

Authorship

MR, MC and AD: designed study. MR and MF: performed study. GE, GR, AL, CM and MV: contributed analysis. MDG, GV, MZ, DA, CZ, PDG and VB: collected data. GLG, AC and IP: analyzed data. MR, GLG and MC: wrote the paper.

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