Use of Elderly Donors for Liver Transplantation: Has the Limit Been Reached?

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Abstract

Background & Aim: Several solutions have been proposed for the minimization of both organ shortage and prolonged waiting time for liver transplantation (LT): expansion of the donor pool using elderly donors represents a possible solution. However, it is still not fully explained if the use of “extreme” donors could cause unacceptable post-transplant adjunctive risks. The aim of the study is to evaluate the impact of donor age on post-LT patient and graft survival. Methods: A cohort of 188 LTs were stratified in four groups according to donor age (Group 1: age < 30 years: n=34; Group 2: age 30-49 years: n=51; Group 3: age 50-69 years: n=75; Group 4: age 70-89 years: n=28). Donor, recipient and transplantation characteristics were compared in the four groups. Results: No differences were observed among the groups with regard to initial (< 1 week) graft function; vascular thrombosis was predominantly experienced in the oldest subgroup (p-value 0.03). The oldest subgroup presented a 5-year patient survival of 47.0%, with statistically worse results with respect to the 1st and 2nd group (p-value 0.005 and 0.03, respectively). Analyzing the graft survivals, Group 4 had a 5-year survival rate of 40.7%, presenting statistically worse results with respect to the 1st and 2nd group (p-value 0.003 and 0.006, respectively). Conclusions: Use of > 70 year-aged donors should be considered with caution and only in selected cases.

Key words: Age – graft failure – septuagenarian – octogenarian – primary non function – arterial thrombosis – survival.

Introduction

In the last decade, the number of patients listed for liver transplantation (LT) has increased without a significant comparable increase in the number of transplants. Several solutions have been proposed for the minimization of both the organ shortage and the prolonged waiting time: the use of elderly donors represents a possible way for donor pool expansion [1]. Elderly donors have been largely adopted in Italy, where the donor age is higher than in the United States or elsewhere in Europe [2]. However, it is still not fully explained if the use of such “extreme” donors cause unacceptable post-transplant adjunctive risks [3]. Starting from these considerations, the primary end-point of this study is to evaluate if organs procured by elderly donors impact on the long-term patient and graft survival after LT. The second outcome of this study is to compare our cohort stratified in age categories with the intent to observe the differences in terms of donor, recipient and post-transplant features.

Material and methods

From January 2001 to May 2009, 227 consecutive liver transplantations were performed in our Department. We excluded from the final analysis living donor transplants (n=9), emergencies (n=8), combined transplants (n=4), transplants for pediatric recipients (age < 18 years, n=7) and transplants with data lacking (n=11). We enrolled for the final analysis 188 cases: no lower or higher donor age limit was adopted in our study. We arbitrarily stratified the entire cohort in 4 groups according to donor age: Group 1 (age: < 30 years, n=34), Group 2 (age: 30-49 years, n=51), Group 3 (age: 50-69 years, n=75) and Group 4 (age: 70-89 years, n=28). Donor, recipient and transplantation characteristics were compared in the four groups.

According to data previously reported in the literature [4, 5] we defined “elderly” a donor > 50-year old, and senior a donor with aged over 70 years. Initially, the allocation system adopted in our centre was based on blood group and anthropometric features; from 2006, the MELD priority system was introduced. Organ selection was exclusively performed on donors...
aged ≥ 60 years; livers with a biopsy-proven microsteatosis rate > 30% or presence of fibrosis were considered not suitable for LT. No exclusion criteria were adopted for younger donors. Micro- and macrosteatosis values were post-operatively obtained on the entire cohort analyzing protocol biopsies.

Statistical analysis

Parametric distribution of the continuous variables was detected using the Kolmogorov-Smirnov test. ANOVA test and Kruskal-Wallis test were used for the comparison of continuous variables. Categorical variables were compared using the exact Fisher test or the chi-square test. A p-value ≤ 0.05 was considered statistically significant. The Kaplan-Meier test was adopted for survival analyses: the log-rank test was used for comparison among survival rates.

Subanalyses focused on intention-to treat patient and graft survival were performed. Patient survival was defined as the time interval between the waiting-list enrollment and death from any cause.

Graft survival was defined as the time interval between the waiting-list enrollment and graft loss from any cause.

Results

All the recipients experienced at least 1.5 years of follow-up, with a median value of 3.7 years (range: 1.5-10 years).

During the 10 years in the respective period of the study, 28.7% (n=54) of deaths were reported. In particular, the recipient death was caused by primary nonfunction / primary dysfunction (PNF/DGF) in 18.5% (n=10) of cases, by recurrence of viral/tumoral pathology in 16.7% (n=9), by thrombosis of hepatic artery/portal vein in 13.0% (n=7), by gastrointestinal hemorrhage in 11.1% (n=6), by myocardial infarction and infective disease, respectively, in 9.3% (n=5), by biliary complication in 7.4% (n=4), by cerebrovascular accident and de novo tumor, respectively, in 5.6% (n=3) and by chronic rejection in 3.7% (n=2).

Stratifying the total number of deaths in the four groups, the higher the donor age, the greater the percentage of deaths (14.7 vs. 23.5 vs. 32.0 vs. 50.0%), a statistical difference being observed between the groups (p-value = 0.03).

During the same period, 31.9% (n=60) of graft losses was reported. In 28.3% (n=17) of cases, a still functioning graft was lost due to a non-hepatic related recipient death. The other causes of graft loss were determined by PNF/DGF in 21.7% (n=13) of cases, by recurrence of viral/tumoral pathology in 20% (n=12), by thrombosis of hepatic artery/portal vein in 18.3% (n=11), by biliary complication in 8.3% (n=5) and by chronic rejection in 3.3% (n=2).

Analyzing the four groups, the 4th group presented the greater percentage of graft losses (17.6 vs. 23.5 vs. 37.3 vs. 50.0%) (p = 0.02).

Donor characteristics are reported in Table I.

Group 4 presented the highest rates of donor cerebrovascular cause of death (p < 0.0001), donor risk index (DRI) (p < 0.0001) and BMI (p < 0.0001).

A progressive increase of median and range values of micro- and macrosteatosis were observed in the first three groups, while their reduction was observed in the 4th group. Macrosteatosis was statistically significant among the groups (p = 0.001).

Recipient, transplant and post-operative characteristics are reported in Table II.

Regarding the recipient features, no statistical differences were observed except for a relative prevalence of the female gender in the last group (42.9%, p = 0.02). Immediate post-transplant function was not statistically different among the four groups, with similar initial poor graft function rates.

Group 4 presented the higher rates of re-transplant (17.9%), but this variable was not statistically different among the groups (p = 0.09). Observing the causes of graft loss, PNF/PDF rate was not statistically different among the groups, with a relative prevalence in the 3rd group (10.6%). Conversely, statistical significance was reported with regard to vascular thrombosis, which was predominantly experienced in the 4th group (p = 0.03).

At patient and graft survival analyses, worsening results were observed from the 1st to the last group. The first three

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=34)</th>
<th>Group 2 (n=51)</th>
<th>Group 3 (n=75)</th>
<th>Group 4 (n=28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21 (11-29)</td>
<td>43 (30-49)</td>
<td>60 (50-69)</td>
<td>74 (70-86)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>26 (76.5)</td>
<td>30 (58.8)</td>
<td>39 (52.0)</td>
<td>9 (32.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>CV cause of death (%)</td>
<td>8 (23.5)</td>
<td>32 (62.7)</td>
<td>61 (81.3)</td>
<td>26 (92.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>DRI score</td>
<td>1.3 (1.1-1.8)</td>
<td>1.5 (1.2-2.0)</td>
<td>1.9 (1.5-5.2)</td>
<td>2.2 (1.9-2.6)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total ischemia (min)</td>
<td>425 (230-615)</td>
<td>425 (250-630)</td>
<td>450 (155-665)</td>
<td>457 (200-575)</td>
<td>0.78</td>
</tr>
<tr>
<td>Cold ischemia (min)</td>
<td>390 (220-552)</td>
<td>355 (180-540)</td>
<td>395 (100-595)</td>
<td>385 (200-505)</td>
<td>0.69</td>
</tr>
<tr>
<td>Warm ischemia (min)</td>
<td>62 (25-120)</td>
<td>65 (15-120)</td>
<td>67 (25-120)</td>
<td>65 (25-120)</td>
<td>0.89</td>
</tr>
<tr>
<td>Macro-steatosis (%)</td>
<td>0 (0-25)</td>
<td>0 (0-40)</td>
<td>0 (0-70)</td>
<td>0 (0-25)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Micro-steatosis (%)</td>
<td>0 (0-30)</td>
<td>0 (0-55)</td>
<td>5 (0-70)</td>
<td>5 (0-30)</td>
<td>0.07*</td>
</tr>
<tr>
<td>BMI</td>
<td>23 (17-29)</td>
<td>25 (20-31)</td>
<td>25 (20-44)</td>
<td>26 (22-30)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>3 (1-23)</td>
<td>4 (1-18)</td>
<td>3 (1-15)</td>
<td>2 (1-20)</td>
<td>0.37*</td>
</tr>
</tbody>
</table>

* continuous variables with non-parametric distribution; Abbreviations: CV, cerebrovascular; DRI, donor risk index; BMI, body mass index; ICU, intensive care unit.
Elderly donors for liver transplantation

Groups presented acceptable 5-year patient (85.3 vs. 73.5 vs. 71.4%, respectively) and graft survivals (82.4% vs. 73.3% vs. 64.7%, respectively), while the 4th one presented markedly worse results (47.0 and 40.7%, respectively) (Figs. 1, 2).

Comparing the patient survivals with the log-rank test, Group 4 presented statistically worse results in the 1st and 2nd group (p-values 0.005 and 0.03, respectively).

Similar results were observed analyzing graft survivals: Group 4 presented statistically worse results with respect to the 1st and 2nd group (p = 0.003 and 0.006, respectively). Also, the 3rd group survivals were statistically worse than 1st group ones (p = 0.05).

Five-year intention-to-treat patient survivals were 86.7 vs. 82.0 vs. 79.3 vs. 59.7% in the four groups, respectively.

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**Table II.** Recipient, transplant and post-operative course features compared among the four groups of age.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=34)</th>
<th>Group 2 (n=51)</th>
<th>Group 3 (n=75)</th>
<th>Group 4 (n=28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 (21-65)</td>
<td>56 (26-66)</td>
<td>56 (27-67)</td>
<td>57 (35-65)</td>
<td>0.66*</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>75 (82.2)</td>
<td>48 (84.3)</td>
<td>57 (82.4)</td>
<td>33 (82.1)</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI</td>
<td>26 (19-40)</td>
<td>26 (18-38)</td>
<td>26 (19-37)</td>
<td>27 (19-43)</td>
<td>0.97</td>
</tr>
<tr>
<td>HCV (%)</td>
<td>17 (50.0)</td>
<td>24 (47.0)</td>
<td>37 (49.3)</td>
<td>16 (57.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>HBV (%)</td>
<td>5 (14.7)</td>
<td>7 (13.7)</td>
<td>16 (21.3)</td>
<td>6 (21.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>HCC (%)</td>
<td>8 (23.5)</td>
<td>19 (37.2)</td>
<td>23 (30.7)</td>
<td>9 (32.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>MELD score</td>
<td>14 (8-30)</td>
<td>15 (6-27)</td>
<td>15 (6-40)</td>
<td>15 (9-28)</td>
<td>0.77*</td>
</tr>
<tr>
<td>CTP score</td>
<td>8 (5-12)</td>
<td>9 (5-12)</td>
<td>9 (5-14)</td>
<td>9 (5-12)</td>
<td>0.96*</td>
</tr>
<tr>
<td><strong>Transplantation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piggy-back (%)</td>
<td>11 (32.3)</td>
<td>13 (25.5)</td>
<td>22 (49.3)</td>
<td>7 (25.0)</td>
<td>0.88</td>
</tr>
<tr>
<td>IPGF score ($)</td>
<td>5 (3-9)</td>
<td>5 (3-9)</td>
<td>5 (3-9)</td>
<td>4 (3-9)</td>
<td>0.11*</td>
</tr>
<tr>
<td>IPGF ($$) (%)</td>
<td>6 (17.6)</td>
<td>9 (17.6)</td>
<td>26 (34.7)</td>
<td>5 (17.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>IPGF ($$$) (%)</td>
<td>8 (23.5)</td>
<td>11 (21.6)</td>
<td>18 (24.0)</td>
<td>3 (10.7)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Post-operative course</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft loss (%)</td>
<td>6 (17.6)</td>
<td>12 (23.5)</td>
<td>28 (37.3)</td>
<td>14 (50.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Retransplant (%)</td>
<td>2 (5.9)</td>
<td>1 (2.0)</td>
<td>9 (12.0)</td>
<td>5 (17.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>PNF/PDF</td>
<td>2 (5.9)</td>
<td>2 (3.9)</td>
<td>8 (10.6)</td>
<td>1 (3.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Vascular thrombosis</td>
<td>1 (2.9)</td>
<td>1 (2.0)</td>
<td>4 (5.3)</td>
<td>5 (17.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* continuous variables with non-parametric distribution; $§$: according to the definition proposed by Gonzales et al; #: according to the definition proposed by Nanashima et al; Abbreviations: BMI, body mass index; ICU, intensive care unit; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; IPGF, initial poor graft function, PNF, primary non function; PDF, primary dysfunction.

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**Fig 1.** Patient survival in the four groups: comparison was performed using the log-rank test.
The 4th group presented statistically worse results with respect to the 1st (p = 0.001) and 2nd group (p = 0.02).

Five-year intention-to-treat graft survivals were 86.4 vs. 82.2 vs. 78.3 vs. 57.4% in the four groups, respectively. Statistical significance was observed comparing the survivals reported in the 4th vs. the 1st (p =0.003) and the 2nd group (p = 0.05).

Discussion

A great debate still exists on the safe use of elderly (> 50 years) and senior (>70 years) grafts for LT. In 1995, Detre et al [4], analyzing a cohort of 7,988 LT, reported higher graft failure and re-transplant rates after adoption of grafts procured from > 50-year old donors.

More recent large cohorts have shown similar results [5, 6], Feng et al after an analysis performed on more than 20,000 LT, observed a direct correlation between the increasing donor age and increasing relative risk of graft failure. In the same study, donor age > 70 years, when combined with other donor risk factors (i.e. cerebrovascular cause of death, height, African-American race) always resulted in the highest risk for graft failure.

Also, in some monocentre series, poor results were reported after the adoption of senior grafts: Fouzas et al reported 17 cases of LT using grafts from septuagenarian donors, observing a 5-year patient survival of 46% [7]. Petridis et al, analyzing the results of 10 LT with grafts procured from octogenarians donors, reported a 3-year patient survival of 40% and an increased incidence of complications and viral recurrence [8].

However, starting from the consideration that LT represents a scarce resource and that implementation of donor number represents the main goal for every transplant centre, arbitrary exclusion of grafts from elderly donors does not seem to be a consensus of opinion.

In fact, it is not clear if liver ageing process is correlated to a contemporaneous decline in function [9]. Theoretically, no age limit exists for the usage of cadaveric liver donors and organ selection is exclusively based on pre-LT available pathological characteristics (i.e. fibrosis and steatosis).

As a consequence, other monocentre series have reported good results after elderly graft adoption.

Anderson et al [10], performing an analysis on 741 cases, showed no statistically different survival rates between patients who received livers from donors aged more or less than 60 years.

Cescon et al showed, in their series of 17 LTs using octogenarian donors, a 3-year patient survival rate of 75%, despite an evident increased risk of viral recurrence in HCV recipients [11]. Gastaca et al, analyzing a cohort of 55 > 70-year aged donors, reported excellent patient survivals (3 years: 91%) [12].

In our experience, senior donors (> 70 years) presented the highest recipient death and graft loss rates and the lower patient and graft survivals (47.0 and 40.7%, respectively). These results were confirmed in the intent-to-treat survival analyses.

No substantial differences were reported among the groups with regard to initial graft function and post-LT complications. Biopsy-driven selection performed on ≥ 60-year aged patients probably represents the main cause for these results. A priori exclusion of grafts with increased risk for initial poor function or even for PNF/DGF may result in a reduction in the rate of these events in the 4th group and, partially, in the 3rd group.

In fact, the 3rd group was only partially composed by biopsy-selected patients (subgroup 60-69 aged), while the 4th group was entirely selected by biopsy.

Similarly, parameters such as micro- and macro-vesicular steatosis have been affected by this selection bias, resulting in the paradox that the 4th group presented lower steatosis rates with respect to the 3rd group.

Interestingly, vascular thrombosis was evidenced as the
unique complication with statistically significant increase in the 4th group. Similar data have been observed by Zoe et al [13]. In this study, a correlation was showed between the risk of graft loss from vascular complications and each decade of donor age > 50 years. According to these data, a 61% increased risk of graft loss was observed adopting >70-year old donors.

Although atherosclerotic involvement of hepatic artery is anecdotic [14], older donors might show a higher prevalence of vascular complications. It could be suggested that, besides donor age, cerebrovascular accidents as a cause of donor death represent another common risk factor for graft failure [5]. This last parameter could represent a surrogate of a chronic donor vasculopathy also involving intrahepatic vessels.

In a recent study, Fiel et al confirmed that a progressive increase in the hepatic arteriolar wall thickness and a decrease in the arteriolar cross-sectional diameter are observed in normal elderly livers [15]. Despite that these data are still not definitive, it is worth suggesting that grafts from the elderly are not fully discriminated adopting only steatosis and fibrosis rates: probably, addition of data giving information on hepatic microcirculation could improve the quality in organ selection and allocation.

The limit of our study is that it is retrospective. A second issue is the size of our cohort: however, the number of very old donors in our cohort (n=28) was one of the largest reported among the monocentre experiences.

Conclusions

The use of > 70-year aged donors leads to worse results in comparison to younger donors. However, still representing an important resource for donor pool implementation, grafts from senior donors should be considered with caution and only in selected cases. The role of hepatic microcirculation could be better investigated, with the intent to obtain more rationale in the selection and allocation of organs.

Conflicts of interest

None to declare.

Contribution

QL and FM participated in the research design; QL, FM and GBLS participated in the data collection; QL participated in the data analysis and in the writing of the paper; MR participated in the critical revision of the article; all the authors participated in the approval of the article; QL is the guarantor.

Acknowledgments

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References