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Octogenarian donors in liver transplantation grant an equivalent perioperative course to ideal young donors

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ABSTRACT

Background: Use of grafts from very old donors for liver transplantation is controversial.
Aim: To compare the perioperative course of patients receiving liver grafts from young ideal vs octogenarian donors.
Methods: Analysis of the perioperative course of patients receiving liver grafts from young, ideal (18–39 years) vs octogenarian (≥80 years) deceased donors between 2001 and 2014.
Results: 346 patients were studied: 179 (51.7%) received grafts aged 18–39 years whereas 167 (48.3%) received a graft from a donor aged ≥80 years. Intra-operative cardiovascular ($p = 0.2$), coagulopathy ($p = 0.5$) and respiratory ($p = 1.0$) complications and incidence of reperfusion syndrome ($p = 0.3$) were similar. Patients receiving a young graft required more fresh frozen plasma units ($p \leq 0.03$) but did not differ for the need of packed red cells ($p = 0.2$) and platelet ($p = 0.3$) transfusions. Median ICU stay was identical ($p = 0.4$). Patients receiving octogenarian vs young grafts did not differ in terms of death or re-transplant ($p = 1.0$) during the ICU stay. Similar cardiovascular, respiratory, renal, infectious and neurological postoperative complication rates were observed in the two groups.
Conclusions: Octogenarian donors in liver transplantation grant an equivalent perioperative course to ideal young donors.

1. Introduction

Various strategies have been developed to expand the donors pool with the specific aim of matching the ever increasing demand for liver transplantation (LT). As a result, programs of living donation, domino transplantation, donation after cardiac death and split LT have been considered with a growing interest. However, these options are limited by constrains in organ availability, technical problems or ethical issues [1–3]. Therefore, maximizing the utilization of the potential donor pool by extending the original criteria for donor acceptance remains the key strategy to increase the number of LTs [4]. Accordingly, donors with an elevated body mass index (BMI), high serum sodium levels, altered liver function tests, positive hepatitis B virus and hepatitis C virus (HCV) serology, prolonged ischemia time and intensive care unit (ICU) stay, altered hemodynamics, liver trauma, graft's steatosis, active bacterial infections and older age have been increasingly and extensively used [1,4–7]. With regard to age, although the young adult donor is universally recognized to be ideal, the utilization of liver grafts from older donors is on the rise [8–13]. In fact, in the non-transplant setting, the liver's physiologic function can remain preserved throughout life likely due to its unique regenerative capacity [8]. Accordingly, despite the lack of a consensus on which should be considered the upper age limit for liver donors, seniority is no longer considered a contraindication for liver allograft acceptance [7–13]. However, older donor age is also universally recognized as a significant risk factor that may negatively affect the outcome of a LT because of the higher risk of graft failure, complications and mortality [1,6,14–17]. As the vast majority of the studies assessing the outcomes of patients receiving a graft from elderly donors report mainly mid and long-term results, with this study we focus on the perioperative LT period. Aiming at stressing any possible difference, we speculated that, with appropriate selection and management, the perioperative period after LT of patients transplanted with octogenarian donors could be not inferior in terms

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of graft survival, complications and resources utilization to that of patients receiving a graft from a young, ideal, donor.

2. Methods

Ethical approval for this study (Study no. 807/2015) was provided by the Comitato Etico Sperimentazione Area Vasta Nord-Ovest, Pisa, Italy. This is a retrospective analysis using our prospectively-obtained database including the entire series of all the LT procedures from deceased donors performed at our centre between January 1st, 2001 and December 31st, 2014. The study focuses on deceased donor LTs performed using grafts from octogenarian (80 years or more) vs ideal young donors (18–39 years).

2.1. Recipients

All liver transplantations were performed using conventional technique with vena cava replacement and veno-venous bypass, according to our institutional guideline. A T-tube was routinely used for duct-to-duct biliary anastomosis. Intraoperative and ICU management were based on our institutional standard protocol and all cases were treated according to a fast-track LT protocol and admitted to the ICU [18]. Data included in the current analysis were: demographics, BMI, indication to LT, clinical status at transplantation as per MELD score. Other variables we analyzed were: duration of surgery, perioperative blood transfusions, ICU length of stay (LoS), postoperative duration of mechanical ventilation, intraoperative and ICU complications, postoperative liver function test sampled immediately on the day of LT and on postoperative days (POD) 1, 2, 3. Time-dependent data were censored at time of event, latest available follow-up, or as of 30 June, 2015. Patients who received a LT due to a fulminant hepatic failure, those undergoing re-transplantation or receiving a graft from an AB0 incompatible donor or a split liver (the division of a donor liver into parts in order to transplant the tissue into a child or small recipient) were excluded from analysis. Also patients receiving a graft from donation after cardiac death were excluded.

Before implementation of a consensus-based allocation model in June 2015 [19], Italy had a region-based donation and transplantation network whereby no national liver graft algorithm existed except for United Network for Organ Sharing (UNOS) status 1 patients, pediatric transplantations, and patients with MELD scores ≥30 who were granted national priority. Beyond these indications, grafts were allocated within the region(s) of origin based on center-based algorithms. In 2005 we implemented a MELD-based allocation algorithm for adult transplantation whereby, in the absence of national priorities, allocation of liver grafts <80 years was as follows: re-transplants > combined liver-kidney transplantation > MELD scores 30-25 > T3-HCC > MELD 24-23 > T2-HCC > MELD scores 22-10. Exceptions to MELD scores were graded according to international guidelines published elsewhere [20]. Donor grafts ≥80 years were deliberately not assigned to recipients with biochemical MELD score >24, except for UNOS status 1 patients.

2.2. Donors

Donor data were obtained from the clinical charts at our regional donation coordination bureau. Eligibility to liver donation was evaluated as per our institutional policy and according to the Italian National Transplant Agency guidelines [21]. The variables included in our investigation were: age, gender, BMI, cause of death, liver function tests at procurement, comorbidities (with focus on diabetes mellitus, cardiovascular disease, renal disease and dyslipidemia), use of vasopressor drugs, ICU length of stay. Based on national guidelines, reasons for discarding a reported deceased liver graft were donor HIV-positivity, history of melanoma or lymphoproliferative disease, or any intractable systemic infection [21]. History of malignancy within 5 years (10 years for breast cancer), HCV-positivity and hepatitis B surface antigen (HBsAg)-positivity required donor–recipient matching and evaluation of urgency and benefit of transplantation [21]. Liver graft biopsy was performed on demand based on surgical evaluation at procurement and histology was reviewed at the Pathology Institute of our hospital. At our center, a liver graft was discarded in the presence of macrovesicular steatosis ≥30%, necrosis ≥5%, fibrosis ≥2 as per Ishak's score, severe micro-angiopathy (with arteriolar thickening >60%) and macro-angiopathy precluding arterial anastomosis, unless otherwise indicated as per the recipient's clinical status. All grafts were routinely evaluated on the back table before LT for vessel patency and anatomical variants.

2.3. Definitions

According to the data reported in the study, (a) cold ischemia time was defined as the time passed from the donor aortic clamp-time to the moment in which the graft was put out of cold storage; (b) warm ischemia time was the time passed from the moment in which the graft was put out of cold storage to the recipient arterial de-clamping (at our center portal and arterial clamps are contemporary released); (c) donor major hemodynamic instability was defined as any episode of cardiac arrest and/or severe hypotension (pulse arterial pressure <60 mmHg) for at least 5 min; (d) recipient reperfusion syndrome was defined accordingly to Paugam-Burtz et al. [22]; (e) early graft function (EGF) was defined according to Olhoff's criteria as bilirubin ≥10 mg/dL on day 7, international normalized ratio ≥1.6 on day 7 and alanine or aspartate aminotransferases > 2000 IU/L within the first 7 days [23]. Post-LT complications were categorized accordingly to the Clavien-Dindo Classification [24].

2.4. Statistical analysis

Categorical variables were reported as number of cases and percentages; continuous variables as medians and inter-quartile ranges (IQR). Categorical variables were analyzed using the chi-square and the Fisher exact test, where appropriate. All continuous variables were tested using the Mann–Whitney U test. A multivariable regression logistic model was constructed using as covariates 12 different variables: recipient age and gender, recipient HCC or HCV positivity, donor age and gender, recipient MELD, donor cause of death, donor hemodynamic instability, donor history of arterial hypertension or diabetes mellitus, and cold ischemia time. All these variables were evaluated as risk factors for early recipient death (within 90 days), recipient hospital stay > 30 days, delayed graft function and any complication 3b-5 according to the Clavien-Dindo classification. A stepwise conditional methods was done. Odds ratios and 95% confidence intervals were reported.

Patient and graft survival were plotted using Kaplan–Meier curves. Cost analysis was performed actualizing the costs at the 2015 prices. A Propensity Score Match (PSM) was performed aiming at compensating for the non-randomized design of this retrospective study: a multivariate logistic regression model was performed using donors age (18–39 vs ≥80 years) as the independent variable and seven different possible confounders for graft's loss (donor age, recipient age, recipient gender, MELD, HCV-positive status, presence of HCC and cold ischemia time) as covariates. PSM was performed using a "nearest neighbor matching" algorithm, preferably selecting identical scores. Each pair was used once. Unpaired patients were discarded from analysis. A final 1:1 match was generated. For all the performed analyses, a p value <0.05 was considered

statistically significant. Statistical analyses and plots were performed using SPSS 23.0 (SPSS, Chicago, IL, USA).

3. Results

During the study period, a total of 1352 LTs were performed in 1297 patients. One hundred seventy-nine patients (13.3%) were transplanted with grafts aged 18–39 years (Ideal Donor Group), whereas 167 (12.3%) received a graft from a donor aged ≥80 years (Octogenarian Donor Group). For the purpose of the study, 552 donors in the considered range of age with consent to donation and no absolute contra-indication were referred to our Center, being 331 (60.0%) ≥80 years and 222 (40.0%) aged between 18–40 years. In the octogenarian group, 43 (13.0%) were discarded at chart evaluation and 110 (33.2%) at procurement. During procurement grafts were discarded due to incidental neoplasia finding in 6 cases (5.4%), macroscopic evidence of cirrhosis in 2 cases (1.8%), at bench evaluation due to severe atherosclerosis in 5 cases (4.5%). All others grafts were discarded based on surgeon evaluation routinely associated to biopsy findings. As elsewhere reported [25], a liver graft was discarded at our center in the presence of macrovescicular steatosis >30%, necrosis >5%, fibrosis ≥2 as per Ishak's score, severe micro-angiopathy (with arteriolar thickening >60%) and macro-angiopathy precluding arterial anastomosis, whilst in the presence of multiple risk factors (stage 1 fibrosis as per Ishak, 1%–5% necrosis, 10–30% macro-steatosis, 30–60% arterial wall thickening, moderate inflammaton) grafts were discarded when 3 or more of these were present or on surgeon evaluation of patient's risk–benefit ratio. Among used octogenarian donors, 118 (69.8%) were evaluated with a biopsy at the time of procurement. In 2 (1.7%) cases 30% macro-steatosis was found, in 11 (9.3%) macro-vescicular steatosis was 10–30%.

In the ideal group, 12 (5.4%) were discarded at chart evaluation and 10 (4.5%) at procurement on surgeon or biopsy evaluation.

Comparing the recipients' characteristics in the two groups, patients transplanted with grafts ≥80 years were older (median: 57 vs 46 years; $p < 0.001$) and more frequently affected by HCV-related cirrhosis with hepatocellular cancer (HCC). On the opposite, more cholestatic diseases occurred in the Ideal Donor Group. Patients in the Octogenarian Donor Group presented median lower MELD values (11 vs 13; $p \leq 0.001$), but, as expected, median higher D-MELD (902 vs 333; $p < 0.001$) (Table 1).

Table 1
Recipients characteristics by category of age. Values are median (IQR) or number (proportion).

Variables	Ideal Donor Group (18–39 years) $n = 179$	Octogenarian Donor Group (≥80 years) $n = 167$	p Value
Male gender	126 (70.4)	130 (77.8)	0.1
Age at LT, years	46 (38–53)	57 (52–61)	<0.001
Primay indication to LT[a]			0.03
HCV-related cirrhosis	62 (34.6)	70 (41.9)	
HBV-related cirrhosis	44 (24.6)	40 (24.0)	
Alcohol-related cirrhosis	12 (6.7)	23 (13.8)	
Cholestatic disease	23 (12.8)	11 (6.6)	
Other disease	38 (21.2)	23 (13.8)	
HCC	38 (21.2)	88 (52.7)	<0.001
Lab-MELD	13 (10–17)	11 (9–15)	0.001
D-MELD	333 (241–507)	902 (734–1224)	<0.001
Serum creatinine, mg/dL	0.7 (0.6–0.9)	0.8 (0.7–0.9)	<0.001
Serum bilirubin, mg/dL	2.4 (1.3–4.4)	1.4 (0.8–2.9)	<0.001
INR	1.4 (1.2–1.6)	1.3 (1.1–1.5)	<0.001
Cold ischemia time, minutes	475 (420–530)	475 (426–546)	0.3
Warm ischemia time, minutes	79 (67–87)	80 (70–97)	0.02
Post-LT hospital stay, days	15 (12–24)	14 (11–20)	0.03

IQR, interquartile ranges; LT, liver transplantation; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; D-MELD, donor-Model for End-Stage Liver Disease; INR, international normalized ratio.

[a] In presence of contemporaneous diseases, priority for LT primary indication was: HCV-related cirrhosis → HBV-related cirrhosis → alcohol-related cirrhosis → cholestatic disease → other disease.

3.1. Recipients perioperative data

Median global length of stay was shorter in the Octogenarian Donor Group (14 vs 15 days; $p \leq 0.03$). Intra-operative course showed no substantial differences between recipients transplanted with octogenarian vs ideal donors in terms of cardiovascular complications ($p = 0.2$), coagulopathy ($p = 0.5$) and incidence of reperfusion syndrome ($p = 0.3$), (Table 2). Ideal Donor Group patients required a higher median number of fresh frozen plasma units during surgery (4 vs 3; $p \leq 0.03$) but did not differ with regard of the need of packed red cells ($p = 0.2$) and platelet ($p = 0.3$) transfusions. During the ICU stay, no differences were observed between the groups in terms of death or re-transplant during the ICU stay, with only 1 re-transplant required in the Octogenarian Donor Group and 8 vs 7 deaths observed in the Ideal vs Octogenarian Donor Group. Median ICU stay (LoS) was identical in the two groups (3 days; $p = 0.4$). Fast-track extubation was slightly more commonly performed among patients receiving an octogenarian graft (144 vs 140; $p \leq 0.07$). Similar complication rates were observed in the two groups, except for a higher necessity of relaparotomy observed in the Ideal Donor Group (5 vs zero; $p \leq 0.06$). Comparing the 3b-5 complications according to the Clavien-Dindo Classification, no difference was observed between the two study groups (52 vs 50; $p = 0.9$). A slightly poorer early graft function was observed in the Ideal Donor Group, however not statistically significant (51 vs 37 cases; $p \leq 0.2$) (Table 2). Specifically looking at the costs during the ICU stay, no difference was observed in terms of costs between the groups with an identical median cost of 5499 € ($p = 0.4$).

Laboratory data during the first 3 days after LT showed that initial function of octogenarian grafts did not significantly differ from that of ideal grafts with only limited and scattered differences in selected markers (Table 3). Recipients in the Ideal Donor Group showed an initial higher peak of total bilirubin (3.9 vs 3.2 mg/dL; $p \leq 0.03$) and INR (1.8 vs 1.6; $p \leq 0.003$) and lower albumin values (2.2 vs 2.5 g/L; $p \leq 0.002$). Substantially, all of these parameters showed a fast resolution within the first 3 days in both the groups, except for the SGOT values, that showed a slower normalization in patients having received octogenarian grafts (89 vs 113 U/L in 3rd post-operative day; $p \leq 0.007$) (Table 3). Finally, the overall graft survival at 1 and 3 and 5 years was 85.9%, 72.1% and 71.1% in the octogenarian group vs 94.4%, 83.4% and 81.6% in the young ideal donor group ($p < 0.001$).

3.2. Donors data

Median donor ages were 83 (IQR: 81–85; ranges: 80–92) and 27 (IQR: 21–33; ranges: 18–39) in the Octogenarian Donor Group and in the Ideal Donor Group, respectively. Octogenarian donors were for the largest part females (66 vs 125; $p < 0.001$) and died more frequently due to cerebrovascular events and less commonly to traumas ($p < 0.001$). As expected, they had more frequently diabetes, arterial hypertension, cardiac diseases and dyslipidemia ($p < 0.001$). Ideal donors always showed higher median peak values of SGOT, SGPT, total bilirubin and sodium if compared to elderly donors ($p < 0.0001$). Hemodynamic instability events were similar between the groups, with a higher number of cardiac arrests

Table 2
Recipients: perioperative data by category of age. Values are median (IQR) or number (proportion).

Variables	Ideal Donor Group (18–39 years) $n = 179$	Octogenarian Donor Group (≥80 years) $n = 167$	p Value
Intraoperative course			
Intraoperative infusions			
PRBC, units	2 (0–4)	2 (0–4)	0.3
FFP, units	4 (2–6)	3 (0–5)	0.03
PLT, units	0 (–)	0 (–)	0.6
20% albumin 50 mL, units	0 (–)	0 (–)	<0.001
Intraoperative complications			
Cardiovascular	11 (6.1)	17 (10.2)	0.2
Coagulopathy	15 (8.4)	11 (6.6)	0.5
Reperfusion syndrome	22 (12.3)	28 (16.8)	0.3
Pulmonary edema	1 (0.6)	1 (0.6)	1.0
Any complication	38 (21.2)	43 (25.7)	0.4
Post-operative course			
Postoperative infusions			
PRBC, units	0 (0–2)	0 (0–2)	0.2
FFP, units	0 (0–2)	0 (0–1)	0.02
PLT, units	0 (–)	0 (–)	0.3
20% albumin 50 mL, units	0 (–)	0 (0–2)	0.04
ICU length of stay, days	3 (2–5)	3 (2–4)	0.4
Costs during ICU stay (€)[b]	5499 (3666–9165)	5499 (3666–7332)	0.4
MV duration, hours	0 (–)	0 (–)	0.06
Fast track extubation	140 (78.2)	144 (86.2)	0.07
Postoperative complications during ICU stay			
Cardiovascular	18 (10.1)	24 (14.4)	0.3
Respiratory	2 (1.1)	3 (1.8)	0.7
Acute kidney failure	24 (13.4)	26 (15.6)	0.6
Requiring CRRT	8 (4.5)	7 (4.2)	1.0
Infectious	8 (4.5)	7 (4.2)	1.0
Neurological	3 (1.7)	2 (1.2)	1.0
Surgical requiring relaparotomy	5 (2.8)	0 (–)	0.06
Complication 3b-5 according to Clavien-Dindo	52 (29.1)	50 (29.9)	0.9
DGF[c]	51 (28.5)	37 (22.2)	0.2
Dead or retransplant during the ICU period	8 (4.5)	8 (4.8)[a]	1.0

IQR, interquartile ranges; PRBC, packed red blood cells; FFP, fresh frozen plasma; PLR, platelets; ICU, intensive care unit; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; DGF, delayed graft function; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; LT, liver transplantation.

[a] One retransplant only in Group donors ≥80 years.

[b] All the costs actualized at 2015 costs.

[c] DGF defined as: peak of total bilirubin ≥10 mg/dL and/or peak of SGOT/SGPT ≥2000 U/L within the first post-LT 72 h.

Table 3
Laboratory data in the ICU. Values are median (IQR).

Variables	Ideal Donor Group (18–39 years) $n = 179$	Octogenarian Donor Group (≥80 years) $n = 167$	p Value
Nadir platelets count, n/μL 10^3			
LT day	56 (37–90)	59 (40–86)	0.9
1st POD	46 (33–81)	46 (31–70)	0.2
2nd POD	45 (31–77)	39 (27–65)	0.03
3rd POD	50 (32–90)	49 (29–73)	0.2
Peak total bilirubin, mg/dL			
LT day	3.9 (2.4–5.2)	3.2 (2.2–4.8)	0.03
1st POD	2.2 (1.2–4.2)	2.1 (1.4–3.6)	0.9
2nd POD	2.0 (0.9–4.3)	2.0 (1.1–3.9)	0.5
3rd POD	2.3 (1.1–4.7)	2.4 (1.3–5.2)	0.2
Peak SGOT, U/L			
LT day	781 (452–1385)	856 (609–1328)	0.2
1st POD	383 (219–736)	471 (270–732)	0.1
2nd POD	172 (106–351)	249 (139–424)	0.006
3rd POD	89 (53–129)	113 (71–199)	0.007
Peak SGPT, U/L			
LT day	502 (292–881)	472 (318–741)	0.5
1st POD	452 (222–732)	401 (260–651)	0.6
2nd POD	342 (191–647)	338 (216–607)	0.9
3rd POD	242 (123–457)	241 (168–452)	0.5
Peak lactate, mg/dL			
LT day	26.5 (17.7–38.5)	32.2 (22.7–43.3)	0.001
1st POD	18.4 (14.0–22.9)	17.2 (13.2–23.4)	0.6
2nd POD	15.3 (11.6–19.5)	15.7 (11.0–21.3)	0.5
3rd POD	13.8 (10.5–18.0)	14.4 (10.3–19.8)	0.4
Peak INR, IU			
LT day	1.8 (1.5–2.1)	1.6 (1.4–2.0)	0.003
1st POD	1.5 (1.4–1.7)	1.5 (1.3–1.8)	0.9
2nd POD	1.3 (1.2–1.5)	1.3 (1.2–1.5)	0.7
3rd POD	1.2 (1.1–1.4)	1.2 (1.1–1.4)	0.5
Peak PTT, seconds			
LT day	43.3 (37.0–50.2)	37.8 (33.6–45.5)	<0.001
1st POD	37.8 (34.4–42.0)	37.2 (32.1–43.0)	0.5
2nd POD	35.3 (30.0–39.1)	34.3 (29.3–40.4)	0.9
3rd POD	33.2 (29.7–37.4)	34.0 (29.9k37.8)	0.6
Nadir fibrinogen, mg/dL			
LT day	179 (144–219)	163 (132–208)	0.1
1st POD	306 (235–358)	279 (208–332)	0.01
2nd POD	329 (258–404)	325 (249–400)	0.5
3rd POD	342 (266–415)	324 (241–409)	0.3
Nadir albumin, g/L			
LT day	2.2 (1.9–2.6)	2.5 (2.1–2.9)	0.002
1st POD	2.2 (2.0–2.6)	2.3 (2.1–2.6)	0.04
2nd POD	2.3 (2.1k2.6)	2.3 (2.1–2.7)	0.3
3rd POD	2.3 (2.1–2.6)	2.4 (2.2–2.7)	0.01

IQR, interquartile ranges; LT, liver transplantation; POD, post-operative day; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; INR, international normalized ratio; PTT, partial thromboplastin time.

observed in the Ideal Donor Group (24 vs 5; $p < 0.001$). A higher number of young donors presented an extra-regional provenience (51 vs 17; $p < 0.001$). A greater number of biopsies was done in the Octogenarian Donor Group (118 vs 25; $p < 0.0001$) (Table 4).

3.3. Multivariable analyses

Four different end-points were examined, namely early recipient death, prolonged hospital stay, delayed graft function and severe post-operative complication. Recipient MELD strongly influenced early death and prolonged hospitalization. Similarly, HCV status was a risk factor for prolonged hospitalization and severe complication. The cerebrovascular cause of donor death was a risk factor for delayed graft function, while donor hemodynamic instability was connected with severe complication. However, interestingly enough, in none of the multivariable models, donor age was a significant risk factor (Table 5).

3.4. Propensity Score Match

Considering that it is really difficult to compare two very different groups of patients, namely recipients receiving an ideal graft from a young donor and, conversely, patients receiving a marginal graft from an octogenarian donor, a sub-analysis was performed aiming at reducing the possible confounders for graft loss. Therefore, a PSM was done using seven different confounders for graft loss (donor age, recipient age, recipient gender, MELD, HCV-positive status, presence of HCC and cold ischemia time) as tools of recipients selection among the 346 patients included in the study. All the patients without a score match were removed from the selection process: 80 recipients (40 with a graft from donor aged 18–39 and 40 with a graft from donor aged ≥80 years) were finally compared. The perioperative course of these selected patients is reported in Table 6. No substantial differences were observed between the two groups in terms of intraoperative and immediate postoperative complications, with similar rates of DGF, death

Table 4
Characteristics of the donors. Values are median (IQR) or number (proportion).

Variables	Ideal Donor Group (18–39 years) *n* = 179	Octogenarian Donor Group (≥ 80 years) *n* = 167	p Value
Male gender	125 (69.8)	66 (39.5)	<0.001
BMI, (kg/m^2)			
Cause of death			<0.001
Cerebrovascular accident	47 (26.3)	135 (80.8)	
Trauma	115 (64.2)	30 (18.0)	
Anoxia	9 (5.0)	1 (0.6)	
Other cause	8 (4.5)	1 (0.6)	
ICU stay (days)	3 (1–5)	2 (1–4)	1.0
Peak SGOT (U/L)	69 (35–118)	31 (24–45)	<0.001
Peak SGPT (U/L)	45 (24–99)	20 (15–31)	<0.001
Peak total bilirubin (mg/dL)	0.8 (0.6–1.4)	0.7 (0.5–1.0)	0.02
Peak sodium serum level (mEq/L)	155 (147–163)	147 (142–153)	<0.001
Vasopressors use	143 (79.9)	132 (79.0)	0.5
Hemodinamic instability	102 (57.0)	96 (57.5)	0.5
Cardiac arrest	24 (13.4)	5 (3.0)	<0.001
Previous history of:			
Diabetes	4 (2.2)	17 (10.2)	0.002
Arterial hypertension	10 (5.6)	109 (65.3)	<0.001
Cardiac disease	4 (2.2)	58 (34.7)	<0.001
Dyslipidemia	1 (0.6)	24 (14.4)	<0.001
Renal disease	2 (1.1)	5 (3.0)	0.2
Extra-regional procurement	51 (28.5)	17 (10.2)	<0.001
Pre-LT biopsy	25 (14.0)	118 (70.7)	<0.001
Biopsy findings[a]			
Macrovescicular steatosis 25–29%	3 (12.0)	3 (2.5)	0.07
Necrosis 1–4%	2 (8.0)	3 (2.5)	0.2
Fibrosis stage 1	2 (8.0)	14 (11.2)	0.4
Inflammation (mild, moderate)	13 (52.0)	98 (83.1)	0.002

IQR, interquartile ranges; BMI, body mass index; ICU, intensive care unit; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; LT, liver transplantation.
[a] Comparison calculated on the number of biopsied cases.

Table 5
Multivariable logistic regression analyses for the risk of early recipient death, prolonged hospital stay, delayed graft function and severe post-operative complication.

Variables	OR	95% CI	p-Value
Recipient death (within 90 days) (HL test p-value 0.45)			
Recipient MELD	1.1	1.0–1.1	0.07
Hospital stay >30 days (HL test p-value 0.47)			
Recipient HCV positivity	2.4	1.1–5.2	0.02
Recipient MELD	1.1	1.1–1.2	<0.01
DGF (HL test p-value 0.26)			
Recipient age	1.0	0.9–1.0	0.004
Recipient male gender	2.5	1.3–5.1	0.01
CVA as donor cause of death	1.8	1.0–3.1	0.04
Any complication 3b-5 Clavien-Dindo (HL test p-value 0.97)			
Recipient HCV positivity	2.0	1.2–3.2	0.008
Donor hemodinamic instability	1.8	1.1–2.9	0.03

OR, odds ratio; CI, confidence intervals; HL, Hosmer–Lemeshow; MELD, model for end-stage liver disease; HCV, hepatitis C virus; CVA, cerebro-vascular accident.

and re-LT during the ICU stay. Similar costs were also observed in the two groups.

4. Discussion

Although a few studies have assessed donor age as a factor influencing outcomes after LT, the evidence on current patterns of utilization and outcomes of elderly donors is still limited [9,26,27]. The main finding of the current analysis is that the intra- and immediate post-operative courses of patients receiving a liver graft from octogenarian vs young donors are not different. In our series, the need of transfusions, the rate of complications, the possibility to fast-track the patients and ICU LoS were similar. Accordingly, the calculated costs for the ICU stay were comparable. Laboratory data during the first 3 days after LT showed only very limited differences that resolved quickly without being associated with an increased graft loss in those who received a graft from a very old donor. Previous data showed comparable outcomes in graft and patient survivals using older donors regardless of recipient age without increased rate of complications representing an important strategy to reduce mortality on the waiting list [13,14,27]. Now, we show that octogenarian donors grant an equivalent perioperative course to ideal donors. This is an important finding in the view of encouraging clinicians not to discard grafts even from very old donors because they have concerns of a more challenging and complicated perioperative course.

Table 6
Propensity Score Match: perioperative and postoperative data by category of age.

Variables	Ideal Donor Group (18–39 years) (n = 40)	Octogenarian Donor Group (≥80 years) (n = 40)	p Value
	Median (IQR) or n (%)		
Intraoperative course			
Intraoperative infusions			
PRBC, units	2 (0–9)	2 (2–4)	0.5
FFP, units	4 (2–7)	3 (1–5)	0.1
PLT, units	0 (–)	0 (–)	0.2
20% albumin 50 mL, units	0 (0–2)	0 (–)	0.01
Intraoperative complications			
Cardiovascular	4 (10.0)	2 (5.0)	0.7
Coagulopathy	7 (17.5)	1 (2.5)	0.06
Reperfusion syndrome	6 (15.0)	5 (12.5)	1.0
Pulmonary edema	0 (–)	0 (–)	1.0
Any complication	12 (30.0)	6 (15.0)	0.2
Post-operative course			
Postoperative infusions			
PRBC, units	1 (0–3)	0 (0–2)	0.03
FFP, units	0 (0–2)	0 (0–2)	0.3
PLT, units	0 (–)	0 (–)	0.2
20% albumin 50 mL, units	0 (–)	0 (–)	0.3
ICU length of stay, days	4 (2–8)	3 (2–5)	0.1
Costs during ICU stay (€)[a]	6416 (3666–14206)	5499 (3666–8707)	0.21
MV duration, hours	0 (0–6)	0 (–)	0.03
Fast track extubation	26 (65.0)	35 (87.5)	0.03
Postoperative complications during ICU stay			
Cardiovascular	7 (17.5)	8 (20.0)	1.0
Respiratory	1 (2.5)	0 (–)	1.0
Acute kidney failure	9 (22.5)	5 (12.5)	0.4
Requiring CRRT	4 (10.0)	3 (7.5)	1.0
Infectious	5 (12.5)	3 (7.5)	0.7
Neurological	1 (2.5)	1 (2.5)	1.0
Surgical requiring relaparotomy	0 (–)	1 (2.5)	1.0
Complication 3b-5 according to Clavien-Dindo	18 (45.0)	15 (37.5)	0.7
DGF[b]	13 (32.5)	11 (27.5)	0.8
Dead or retransplant during the ICU period	6 (15.0)	6 (15.0)	1.0

Abbreviations: IQR, interquartile ranges; PRBC: packed red blood cells; FFP: fresh frozen plasma; PLR; platelets; ICUintensive care unit; MVmechanical ventilation; CRRTcontinuous renal replacement therapy; DGFdelayed graft function; SGOTserum glutamic oxaloacetic transaminase; SGPTserum glutamic pyruvic transaminase; LTliver transplantation.
[a] All the costs actualized at 2015 costs.
[b] DGF defined as: peak of total bilirubin ≥10 mg/dL and/or peak of SGOT/SGPT ≥2000 U/L within the first post-LT 72 h.

Multiple studies have shown that older donor age is associated with higher rates of primary non-function, graft loss, and mortality [8]. This is due to the decline of the physiologic reserve of all organs linked to the aging process [28–30]. Moreover, older age is associated with a higher prevalence of medical comorbidities including diabetes, hypertension, and hyperlipidemia [8,30,31]. Finally, it has been suggested that older donor grafts are more susceptible to preservation injury and cold ischemia time than younger ones [32,33] are characterized by a high degree of steatosis and by a more frequent presence of atherosclerosis leading to a significant associated potential for increased arterial thrombosis [30,34]. All these factors make a whole liver from a brain dead donor less than 40 years of age who died of trauma the ideal deceased donor liver [8]. However, although there is a remarkable heterogeneity in the age cut-offs used to define an older donor, worse outcomes and decreased patient and graft survival rates have been reported regardless of the age cut-off used [31,35,36]. In fact, older donors are undoubtedly heterogeneous and, among older individuals of the same age, general health status and physiologic reserve vary markedly [26,30]. Compared with other organs and tissues in the body, the liver seems to better tolerate the process of aging with only minimal morphologic, ultrastructural, and functional alterations [28]. Moreover, the aging process of the liver is counterbalanced by its large functional reserve, regenerative capacity and its dual blood supply. Finally, for reasons that are still not determined, abdominal visceral vessels seem to be less frequently affected by atherosclerosis [29]. All these observations represent the biological basis for expanding eligibility to older donors and give a rationale to the observed continuous rise in the utilization of livers from elderly deceased donors [9,26]. Notwithstanding the biological bases for expanding the donor pool to very old donors, some clinical and organization factors have been highlighted as key factors for favorable outcomes when a liver transplant is performed using an elderly deceased donor: (a) the use of stringent selection criteria; (b) being confident with the use of these grafts; (c) allowing a short cold ischemia time; (d) the use of liver biopsy to assess the level of steatosis and fibrosis; (e) a careful assessment of vessel quality and patency at back table; (f) a policy of selective donor-to-recipient matching [8,13]. A skilled anesthetic management and a careful ICU monitoring also have a primary role. In fact, they are a continuum of care where hemodynamics, coagulation, renal function, ventilation and, in some cases, brain function are intensively monitored and managed with the aim to allow the best graft's and patient's recovery [37,38]. An effective and experienced perioperative care will therefore support a transplant program's ability to consider higher risk donors like octogenarians and thus broaden the number of those who will benefit from the treatment.

One may argue about the "universality" of the results herein presented. Indeed, the demographic characteristics of Tuscany (the Italian region where our centre is located and where the vast majority of the donors come from) population, the epidemiology of brain death and the deceased donor organizational model in place in our region, all account for the large proportion of very old (≥80 years) donors available annually [13]. Also in the rest of Europe life expectancy has risen. In fact, it has been calculated that it increased by 2.5 years per decade for 150 years (in the past 50 years, life expectancy at birth in Europe has increased by about 10 years for both men and women) and further gains are expected to be achieved mostly from the reduction in mortality at older ages [39,40]. Therefore, if death occurs in increasingly older individuals, it is reasonable to expect deceased donor age to rise as well. At our centre, the median donor age increased significantly ($p < 0.001$) in a linear fashion ($r^2 = 0,89$, Fig. 1). According to this model, at our centre, we will reach a donor median age of 80 years in year 2019. Another limitation could be represented by confounders for graft loss. Aiming at minimizing this issue, we performed a PSM between old and ideal grafts. This sub-analysis shows that ideal and octogenarian grafts share comparable courses when allocated to very selected and homogeneous populations of recipients. A potential explanation of the good results in terms of early graft function, early complications rate and patients' survival using aged grafts might derive from the specific allocation model, the rigorous graft selection criteria and the strict medical follow-up both in the waiting list and in the perioperative period. We want to emphasize that

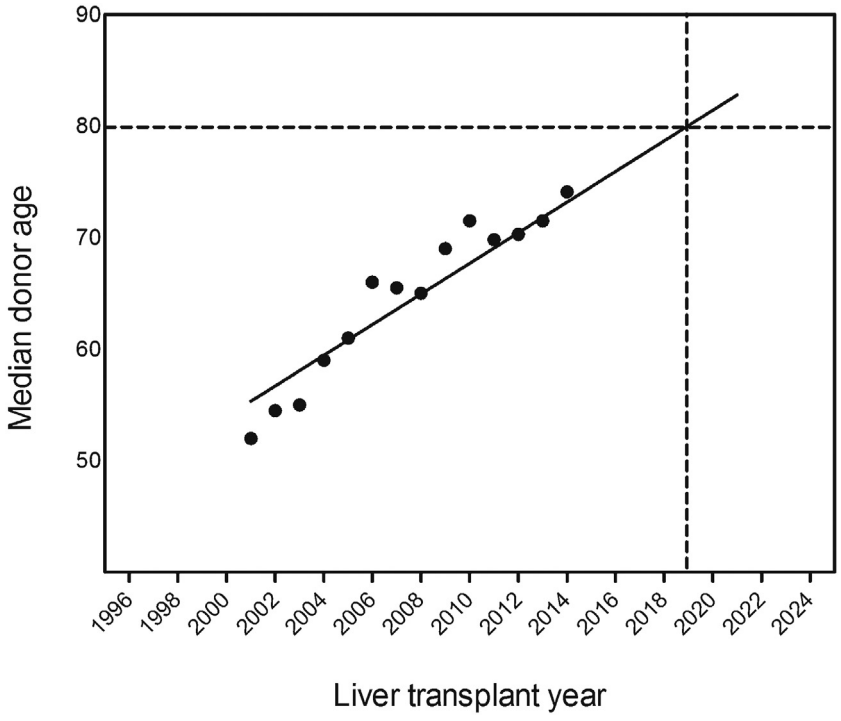

Fig. 1. Median donor age at Pisa OLT centre.

long-term results in older donors were inferior to those observed when ideal grafts were used. Such a result is mainly due to the higher rates of biliary complications and HCV recurrence that are observed in the mid- and long-term period in recipients receiving aged donors [13,41–43]. However, in the current decade, the use of perfusion machines and the control over HCV infection by new antiviral drugs may lessen concerns on accepting and allocating very old grafts [44,45]. Finally, in this study we selected the studied groups by voluntarily defining very "distant" age thresholds: very young vs very old. This, in the aim to magnify any possible donor age-related difference, in terms of outcomes, using ideal, young vs marginal, very old grafts.

In summary, although the potential risks and benefits associated with the use of livers from octogenarian donors must be closely weighed, with careful donor evaluation, selective donor-to-recipient matching and skilled perioperative care, octogenarian grafts do not affect the short-term course of patients undergoing LT. Accordingly, anesthesiologists and intensivists should not label liver allografts from donors aged ≥80 years as "unusable" or "high risk" basing on chronological considerations alone. However, it must be considered that recipient HCV positivity is a risk factor for poor mid/long term outcomes of transplants performed with very old donors and that very old donors are more prone to cause biliary complications. Finally, better and extensive reporting of short-term patients and allografts outcomes will help to identify areas of perioperative transplant care that require further improvements.

Conflict of interest

None declared.

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