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TOPIC HIGHLIGHT

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Using old liver grafts for liver transplantation: Where are the limits?

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Abstract

The scarcity of ideal liver grafts for orthotopic liver transplantation (OLT) has led transplant teams to investigate other sources of grafts in order to augment the donor liver pool. One way to get more liver grafts is to use marginal donors, a not well-defined group which includes mainly donors > 60 years, donors with hypernatremia or macrosteatosis > 30%, donors with hepatitis C virus or hepatitis B virus positive serologies, cold ischemia time > 12 h, non-heart-beating donors, and grafts from split-livers or living-related donations. Perhaps the most practical and frequent measure to increase the liver pool, and thus to reduce waiting list mortality, is to use older livers. In the past years the results of OLT with old livers have improved, mainly due to better selection and maintenance of donors, improvements in surgical techniques in donors and recipients, and intra- and post-OLT management. At the present time, sexagenarian livers are generally accepted, but there still exists some controversy regarding the use of septuagenarian and octogenarian liver grafts. The aim of this paper is to briefly review the aging process of the liver and reported experiences using old livers for OLT. Fundamentally, the series of septuagenarian and octogenarian livers will be addressed to see if there is a limit to using these aged grafts.

Key words: Old liver donors; Liver transplantation; Aging liver; Liver graft; Liver disease; Aging; Donor management; Septuagenarian donors; Octogenarian donors

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INTRODUCTION

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with end-stage chronic liver diseases, acute liver failure, and certain metabolic liver diseases. The excellent results of OLT have led to an increasing number of patients on the waiting list, while the number of liver donors remains stable. Thus, the main limitation factor for OLT is having access to a liver graft. Moreover, the best results are obtained using ideal liver grafts that are defined as those obtained from donors younger than 40 years, trauma as the cause of death, brain death, hemodynamic stability at the time of procurement, and absence of steatosis, chronic liver disease, and transmission disease[1]. However, the ideal graft is becoming less and less frequent, mainly due to a progressive and dramatic reduction in traffic accidents. According to the Spanish

Liver Donor Registry, during the year 2000 the rate of donors between 15 and 45 years old was 40.6% versus 20.9% during the year 2012[2]. This liver organ shortage has led liver transplant teams to expand the donor pool using so-called marginal donors, a not well-defined group which mainly includes donors > 60 years, donors with hypernatremia, steatosis greater than 30%, or positive serologies for hepatitis C virus (HCV) or hepatitis B virus (HBV), livers with a cold ischemia time > 12 h, non-heart beating donors, and grafts from split-liver and living-related donations[3-11]. The most frequent and practical measure to augment the liver donor pool, and thus to reduce waiting list mortality, is to increase donor age[4,12-16]. However, the use of older livers for transplantation is subject to debate because several authors reported a negative impact of increased donor age on survival after OLT[17-20]. On the other hand, other transplant groups have found similar patient and graft survival rates using liver grafts older than 60 and even older than 70 and 80 years[13,15,21-26]. In an attempt to clarify the influence of the aged liver donor on the results of OLT we will review this issue in the literature especially regarding donors older than 70 years, and establish as accurately as possible if there is an age limit for utilizing a liver graft.

AGING PROCESS OF THE LIVER

Aging is characterized by normal progressive declines in functions that, cumulatively, diminish the capacity of cells and organs to respond to intrinsic and extrinsic stimuli. Functional changes that develop with aging should eventually lead to significant alterations in clinical practice. The synthetic, excretory and metabolic changes of liver function are potentially affected by aging and these effects may have clinical relevance[27]. Although this aging process does not cause death, it appears to contribute to the onset of diseases, including liver pathologies[28]. The major age-related changes in the liver are a reduction in mass and blood flow. However, the main differences and consequently the major advantages with respect to other organs are the maintenance of a good functional reserve, regenerative capacity, and large blood supply, all of which support the use of older donor livers for OLT[29,30]. Experimental findings in rodents, related with the aging process are generally very difficult to extrapolate to humans.

Morphologic changes

The old liver tends to be smaller and dark-colored, and generally suffers brown atrophy (brownish aspect), an appearance attributable to the increased accumulation of lipofuscin (highly oxidised insoluble proteins) and fibrous thickening of Glisson capsule[30-32]. There are few macroscopic and microscopic changes in the liver with aging, and the most widely recognized alteration is a decrease in weight[27]. In healthy people, the liver accounts for about 2.5% of the total body weight until about 50 years old. After that, the liver becomes gradually smaller, so that by the age of 90 it represents about 1.6% of total body weight[33]. The decrease in hepatic weight parallels a reduction in body weight[27]. There are other gradual changes such as in shape, moulding the liver with other organs or structures (ribs), and acquiring ridges and bosses on its surface[33].

Morphometric and ultrastructural changes

A 60% thickening of the endotelial lining and an 80% decline in the number of endothelial cell fenestration with increasing age was reported in a study that examined surgical and postmortem samples of human livers[34].

There are several morphological changes of hepatocytes associated with aging, such as an increase in mean volume and greater variance in the size of liver cells, a decrease in the number of hepatocytes, and increase in the size of liver cell nuclei and the volume of nuclear DNA in proportion to nuclear size. There is also an increased aneuploidy and a decreased number of mitochondria, but an increase in mitochondrial volume[35]. These morphological changes suggest that the liver cells in advanced old age are in a hyperfunctioning state possibly trying to compensate for the decline in absolute cell number[33]. In liver biopsy samples, of both healthy subjects and subjects with chronic liver disease, a progressive decline in telomere length with increasing age has been observed[36]. Recently changes in the hepatic sinusoid with old age have been identified that probably contribute to the substantial age-related changes in liver function[37].

Blow flow and volume changes

In the elderly population, there is an approximately 30% loss of liver volume and hepatic blood flow between the ages of 30 and 100[31,38].

This process starts at 25 years, at a rate of 0.3%-1.5% per year[39], and it would be expected that the liver blood flow of a 65-year-old is expected to be 40%-45% less than that of the same person at 25 years old[40]. A decrease in liver volume and liver blood flow with aging may be a major component of age-related alterations in the liver, leading to a fall in the clearance of many drugs whose pharmacokinetics have been found to be altered with age[31]. Atherosclerotic occlusive disease of visceral arterial branches of the abdominal aorta (celiac trunk and branches, mesenteric and renal arteries) occurs in 2.6% of all cases, and tends to be localized in the proximal or mid-proximal portions of the arterial bed; these lesions can be surgically amenable, but not in the occasional case where atherosclerosis is located in the distal portion of the bed[41] where the hepatic artery may be affected[42,43].

Synthetic and functional changes

The rate of total protein synthesis was 37% less in the 69-91 than in the 20-23 year old population, and the hepatic synthesis of clotting factors is also presumably impaired in the older patients[33].

It seems that the routine biochemical liver function tests (serum bilirubin, alkaline phosphatase and transaminase levels) do not alter with increased age, and are in

reality more a reflection of liver damage than a marker of poor function[29,33].

A fall in functional hepatic mass may be the most important change in the liver during normal aging, but that liver cells are little changed with age alone[29]. It has been suggested that aging has a limited effect on liver functions but more on its response to extrahepatic factors[44], disease states or increased metabolic demands to which elderly people may have an impaired ability to respond[29,33]. Some hypotheses state that, while enzymes responsible for normal metabolism or detoxification are adequate in the aged liver, the system is unable to respond to the increased stress of an external hepatotoxic agent[33]. Moreover, aging appears to compromise liver regeneration by influencing several pathways, the result of which is a reduction in the rate of regeneration, but not in the capacity to restore the organ to its original volume[45]. The aging process does not increase the susceptibility to hypoxia-reoxygenation injury in the rat liver, and although one should be cautious when extrapolating data on aging from rats to man, this finding lends additional support to the increasing use of older livers for OLT in humans[46].

ASSESSMENT AND MANAGEMENT OF THE LIVER DONORS

The definition of an ideal allograft is different from that of an ideal donor. Thus, the ideal allograft may be influenced by some variables that are introduced after procurement such as prolonged cold ischemia time (CIT), or partial or split-liver grafts[47]. Donors are generally considered marginal or extended criteria donors if there is a risk of initial poor function (IPF) or primary nonfunction (PNF). There is a lack of agreement on the definitions of primary dysfunction, IPF and PNF. It has been suggested that primary dysfunction can be used to describe all grafts that function poorly in the post-OLT period (*e.g.*, PNF and IPF). PNF refers to liver grafts that fail to support life in the early post-OLT period (first week) and die or required a retransplant for the patient to survive. On the other hand, IPF is defined as an aspartate aminotransferase (AST) level of more than 2000 IU/L, prothrombin time more than 16 s and ammonia level of more than 50 μmol/L on post-OLT days 2 to 7 in a context of graft supporting life[48].

Although marginal liver grafts may not be optimal, they are a viable alternative to dying while candidates are on a waiting list for OLT[7]. At present, there is not a clear and established definition of a marginal liver donor. Among the most important donor characteristics that may influence the development of PNF or IPF in the recipient are increasing age, prolonged ischemia, hypotension and inotropic support, gender mismatch, non-heart-beating donors, and steatosis[7,49,50]. A literature review revealed at least 13 donor variables that may be associated with poor graft survival and increased recipient mortality. These variables were donor age, race, gender, weight, ABO status, cause of brain death, hospital stay, pulmonary insufficiency, vasopressor use, cardiac arrest, alterations of blood chemistry, prolonged CIT, graft steatosis, hypernatremia, donation after cardiac death, and positive serologies for HBV or HCV[1,3,7]. However, there is a great variability in the number and type of variables included in the term extended criteria. Thus, seven donor characteristics were identified using Cox regression models that independently increase the risk of graft failure: donor age over 40 years (particularly over 60 years), donation after cardiac death, and split/partial grafts were strongly associated with graft failure, while black race, less height, cerebrovascular accident and other causes of brain death were less but still significantly associated with graft failure[1]. Other research regarding extended criteria found donor age > 55 years, donor hospital stay > 5 d, cold ischemia time > 10 h, and warm ischemia time > 40 min as predictive risk factors of poor outcome after OLT[51]. With the aim to analyze the influence of several marginal criteria in donors, a marginal liver score was elaborated with the following variables: donor > 60 years, ICU stay > 4 d, CIT > 13 h, hypotensive episodes < 60 mmHg for > 1 h, bilirubin > 2.0 mg/dL, alanine aminotransferase (ALT) > 170 U/L, and AST > 140 U/L (each variable assigned a value 1), use of dopamine doses > 10 μg/kg, and serum sodium > 155 mEq/L (each variable assigned a value of 2). Recipients who received marginal livers with a score of 3 or more showed significantly lower graft survival and delayed graft function[52].

Evaluation and support of older liver donors

Between 70%-88% of donors older than 70 years die because of cerebrovascular disease[13,23,53-55]. When brain death is declared and liver donation is being considered, the primary goal is maintenance of the organ´s viability. Thus, the measures for the protection of the liver graft must be as follows: resuscitation in the event of cardiac arrest, maintenance of an effective circulation to prevent ischemic injury, therapy of hypovolemia to maintain a systolic blood pressure (SBP) or central venous pressure above 10 cm H_2O, blood transfusion if hematocrit is less than 25%, oxygenation to maintain P_aO_2 between 70-100 and O_2 saturation at 95%, prevention of infection and maintenance of normothermia and diuresis greater than 1 mL/kg per hour. A SBP between 80-100 mmHg maintained during more than one hour has been considered a criterion of a marginal liver donor by some authors[13,56]. When SBP is less than 100 mmHg, dopamine infusion is indicated to increase mesenteric and renal blood flow. Initially the dose is 2-5 mcg/kg per minute, bearing in mind that renal function impairs and that acute tubular necrosis can develop when the dose of dopamine is > 10 mcg/kg per minute. Several groups define a dose of dopamine > 15 mcg/kg per minute as a marginality criterion[13,49,56]. The use of a dopamine dose > 15 mcg/kg per minute associated with SBP < 90 mmHg increases significantly the grade of graft preservation injury[49]. Cardiac arrest during a period of 15 min does not significantly affect PNF

or graft function[57], although one German team does not use graft livers from septuagenarian donors with cardiac arrest[58].

Prolonged ICU stay of donors can modify post-transplant liver function due to hemodynamic, hormonal and nutritional alterations and other alterations produced by vasopressor drugs[59]. According to some authors the rates of PNF and graft dysfunction increase with a mean ICU stay of > 3 d[60], while others find for the same ICU period only find transaminase values higher than 2000 IU/L but without affecting graft survival[49]. More recently, a study considered an ICU stay of > 4 d as a marginal criterion due to the associated higher rate of preservation injury[56]. According to several series using liver grafts over 70 years, mean ICU stay is < 3.5 d[13,23,26,53,55,58,61]. The deleterious effect of hypernatremia (peak serum sodium > 155 mEq/L) on graft function is thought to be a result of cell swelling and exacerbation of reperfusion-mediated injury[7]. The presence of hypernatremia has been associated with marked graft dysfunction[62,63], and even with significantly lower 1-month graft survival[64]. However, donor serum sodium showed normal mean values in five series of donors older than 70 years[23,53,55,58,61,65]. The elevation of liver enzymes [glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and gamma glutamyl transpeptidase (GGT)] in donors may reflect a process of cytolysis, cholestasis, hypoperfusion due to hypovolemia, or cardiac arrest, and liver enzymes values can rise to 400 IU/L during short periods of ischemia or asystolia[66]. The presence of values of GOT > 150 IU/L and GPT > 170 IU/L[56], and of GGT > 100 IU/L in donors older than 70 years have been considered as marginal criteria[13]. Several reports using donors older than 70 years showed mean values of GOT, GPT and GGT within normal limits[26,30,53,55,58]. In the absence of hepatobiliary disease, the presence of hyperbilirubinemia in the donor can be due to hemolysis, and it is not demonstrated that bilirubin > 2 mg/dL is associated with lower graft survival or graft dysfunction in comparison with lower bilirubin values[49]. Mean bilirubin values in several studies using liver donors older than 70 years range between 0.7 and 0.95 mg/mL[13,23,53,55,58]. In comparative series that analyze donors older than 70 years, liver function tests are more favorable in older donors, a finding that reflects the meticulous selection of older donors[23,30,53,55] in order to counterbalance the risks associated with the aging process[55].

In the process of evaluation of donors older than 70 years an ultrasonography is recommended to exclude benign or malignant hepatobiliary diseases, liver steatosis, and other abdominal tumors. During the procurement procedure it is necessary to explore the abdominal cavity to confirm the absence of tumors or abscess. A liver biopsy is highly recommended in octogenarian[30,53] and in septuagenarian liver donors to exclude liver disease (steatosis, cholestasis, hepatitis, or fibrosis).

Steatosis of liver graft

A liver is considered steatotic when the lipid content exceeds 5% of the body weight, and the reported incidence is between 9%-26% among the liver donor population[67,68]. Steatosis is more frequent among old donors, and has been attributed to alcohol intake, obesity, malnutrition, and diabetes[69,70].

Steatosis is classified as mild (10%-30%), moderate (30%-60%), or severe (> 60%)[69], but it is believed that steatosis will disappear after OLT.

Steatotic liver grafts are more prone to developing preservation injury, and a short ischemic injury is recommended to prevent preservation injury[70,71].

We observed a higher rate of overall steatosis in donors older than 60 years at the expense of macrosteatosis[55], although the liver grafts with any degree of isolated microsteatosis can be safely used, except for the risk of initial dysfunction, because it does not adversely affect patient or graft survival[5,72,73]. The experience of the surgeon is essential for the evaluation of the presence of steatosis during liver procurement and it must be confirmed by microscopic examination. It has been confirmed that the combination of increased BMI, elevation of ALT, presence of type II diabetes, history of heavy alcohol consumption, and ultrasonography signs of steatosis can identify steatosis > 30%[74]. OLT with livers with macrosteatosis < 30% has similar results as OLT with non fatty livers, assuming there are no other concomitant donor or recipient risk factors[3,7]. The implant of a liver graft with moderate-severe macrosteatosis precipitates severe ischemia-reperfusion injury and puts a patient at increased risk of initial poor graft function[48,67,73,75-77], PNF[69,70,75] and lower graft and patient survival[73]. It has been reported that liver grafts with macrosteatosis > 30% can be safely used in low-risk patients, but should be avoided in patients with high model for end-stage liver disease (MELD) scores[78]. Other investigators report a comparable 3-year patient survival in a control recipient group and a study group showing severe macrosteatosis (> 60%), and the authors conclude that severely steatotic livers should be considered for OLT at least in low-risk patients, but that short ischemia times must be observed and perioperative management must be optimized when using steatotic liver grafts[76]. In a recent report using liver grafts with severe macrosteatosis from donation after cardiac death (DCD), it was concluded that these grafts should only be considered for OLT in selected patients with preserved liver function (*e.g.*, sclerosing cholangitis) and favorable MELD scores, without the presence of additional risk factors such as livers from DCD[77].

In series of donors older than 70 years, the incidence of steatosis was between 16% and 50% of cases, and hepatocytes was involved in less than 30% of all reported cases[13,23,53-55,65]. All series of octogenarian donors avoid the use of liver grafts with macrosteatosis > 30%[14,24,30,53,58,79,80].

Ischemia times

Prolonged CIT of liver causes a microvascular injury, called ischemia-reperfusion (IR) injury, which can lead to PNF or IPF and increased rejection and morbidity.

IR injury of liver grafts develops in four stages: pre-preservation injury in the donor, cold preservation, rewarming, and reperfusion injury. The incidence and grade of IR injury may be affected by several factors related to donor medical history, such as use of donors older than 60 years, prolonged ICU stay, alcohol intake, drug abuse, liver steatosis, hemodynamic instability after brain death, hypotension, high doses of inotropic drugs, prolonged CIT, and surgical trauma during the procurement process[7,56]. In other series comparing donors younger and older than 65 years, no significant impact was observed of donor age or CIT (< 8 h and ≥ 8 h) on the incidence of IR injury, short-term liver function, and 1-year patient and graft survival[81]. However, it is known that recipients of old livers have a greater sensitivity to IR injury, as reflected by a notable cholestatic pattern after OLT[23,53,82]. Furthermore, CIT of older donors must be kept as short as possible to obtain good liver function after OLT[13,53,55,83]. Thus, in eight series that included septuagenarian donors, the mean CIT was between 5 and 8 h[23,26,53-55,58,61,65], and only one series showed a mean CIT of 9 h[13]. Older grafts with a CIT > 8 h are at much greater risk for failure; with a CIT > 12 h the risk approximately doubles[84].

Prolongation of warm ischemia time (WIT) increases cold ischemia injury and consequently impairs post-transplant liver function[85]. Deleterious effects on patient and graft survival have been reported when WIT was longer than 40 min[51], and on graft survival alone when WIT was greater than 45 min[86], but usually most series of donors older than 70 years report a mean WIT between 45 and 65 min[13,53,55,58,61].

Allocation of older donors to recipients

The MELD score has been used as a measure of mortality risk in patients with end-stage liver disease and it is deemed suitable for use as a severity index for guiding organ allocation priorities[87]. Mortality on the waiting list increases in direct proportion to the MELD score at the time of listing[88]. The implant of marginal livers into suboptimal recipients constitutes a bad combination. At present, there is a tendency to allocate livers from old donors to stable patients[7,58,71]. Moreover, an octogenarian donor liver can be implanted into a sexagenarian recipient, but many groups would be reluctant to accept such a liver for a child[89].

Having in mind that the sickest patients must be transplanted first, livers from high-risk donors should be used for low-risk recipients only, whereas high-risk recipients should only be transplanted with low-risk organs[90]. More specifically, younger donor livers should be preferentially transplanted into HCV-positive recipients and livers from older donors into older HCV-negative recipients. This preference is based on the observations that the worse patient and graft survivals correlated with highest HCV recurrence, when liver grafts from donors older than 40-50 years[91-97], or older than 70 years are transplanted into HCV-positive recipients[7,14,55,79,80]; exceptions are the series of Doyle *et al*[98] and our series[55], where no significant differences in terms of 1-, 3-, and 5-year patient and graft survival were observed between HCV-positive recipients of liver grafts younger than 60 years and HCV-positive recipients of liver grafts older than 60 years. However, in our study there was a tendency towards decreased patient survival at 5 years, taking into account that our rate of HCV-positive cirrhosis was significantly higher in recipients of donors older than 60 years[55]. In some series HCC and ethylic cirrhosis were the most frequent indications for using donors older than 70 years[13,27,58,99,100].

Similar MELD scores have been found in several series of recipients transplanted with livers from donors older than 70 years[26,55,58].

POST-TRANSPLANT EVOLUTION OF OLD LIVERS AND COMPLICATIONS

A correlation between the incidence of PNF/IPF and older donors has been pointed out[48,60]. The incidence of PNF was reported to be between 2.7% and 8% in 6 series of recipients of donors older than 70 years[13,54,61,65,100], whereas in 4 other series there was not any case of PNF[23,26,55,58].

The non-rejection-related cholestasis pattern after OLT was significantly more frequent in recipients of donors older than 70 years in comparison with recipients of younger donors[23]. Synthesis parameters (serum albumin, partial thromboplastin time) were normalized at one week after OLT, while liver function tests (ALT, AST), and bilirubin showed normal values at three months post-OLT[99]. In our experience, the serum values of GOT, GPT, GGT, and bilirubin, at one month post-OLT, were similar in recipients of donors younger and older than 70 years. Moreover, prothrombin rate and serum albumin levels were significantly lower on the 30th day after OLT in recipients of donors older than 70 years[55], and these findings were attributed to a decrease in protein synthesis[101] and coagulation factors that run parallel to the liver aging process[102].

Intensive care unit stay (between 4 and 7 d) and hospital stay (between 20 and 25 d) were similar for recipients of donors younger or older than 70 years[23,53,55]. Likewise, the rates of acute and chronic rejection did not differ between recipients of donors older and younger than 70 years[23,53,58,100]. In several series there were no differences in the rate of biliary and hepatic artery complications[23,53,58], but recently it was emphasized that ischemic-type injury rates increase significantly with donor age over 70 years[100]. A recent series from united network for organ sharing database reported that the risk of graft loss from hepatic artery thrombosis (HAT) increased progressively with each decade of donor age > 50 years, such that a 61% increased risk of HAT-related graft loss was associated with use of donors older than 70 years[103]. More recently, an experience with donors older than 70 years showed a low incidence of HAT (4.7%), and im-

Table 1 Series of orthotopic liver transplantation with liver grafts > 60 or > 65 years old

Ref.	Cases > 60 or > 65 yr (*n*)	Donor mean age (yr)	Cold ischemic time (h)	Recipient mean age (yr)	Primary non-function	Patient survival (yr)	Graft survival (yr)
Marino *et al*[12]	54 > 60	65.2	12.8	53.8		2-yr: 62%	2-yr: 43%
Washburn *et al*[106]	29 > 60	63.7	10.6		6.7%	1-yr: 58.6%	1-yr: 44.8%
Grande *et al*[107]	40 > 60	68	6.5		5%	1-yr: 82%	1-yr: 77%
						5-yr: 75%	5-yr: 66%
Rodríguez *et al*[22]	100 > 60	69	4.1	54	1%	1-yr: 82%	1-yr: 77.8%
						5-yr: 74.5%	5-yr: 71.4%
Neipp *et al*[111]	67 > 60	65	10.3	49	12%	1-yr: 79%	1-yr: 68%
						5-yr: 62%	5-yr: 53%
Moore *et al*[20]	35 > 60					5-yr: 48%	5-yr: 35%
Anderson *et al*[15]	91 > 60			54	3.3%	1-yr: 86.8%	1-yr: 82.4%
						5-yr: 67.6%	5-yr: 62.5%
Rauchfuss *et al*[110]	54 > 65		8.4			1-yr: 70%	1-yr: 70%
Martins *et al*[81]	50 > 65	73.9	7.3	57.6	4%	1-yr: 78%	
Jiménez-Romero *et al*[55]	125 > 60	69.1	6.1	51.2	0.8%	1-yr: 80.7%	1-yr: 78.2%
						5-yr: 68.5%	5-yr: 65.1%

proved results were attributed to more appropriate technical management, whereas the presence of anatomical variations and use of jumping grafts were independent predictors of HAT[104].

The incidence of infections was similar[58] or even lower in recipients of liver donors older than 70 years[55]. Most reports have found similar rates of retransplantation comparing recipients from 70-year-old donors and younger donors[13,23,55,58,100].

Most common causes of mortality in recipients of donors older than 70 years are medical complications, *de novo* tumors, and cirrhosis due to HCV recurrence[53,55].

PATIENT AND GRAFT SURVIVALS USING OLD LIVERS

Liver grafts younger than 70 years

The use of aged liver grafts has progressively increased during the past decade due to improving results related to better management and procurement techniques of liver donors, and better hepatectomy and implant techniques in the recipients. In the nineteen nineties livers from donors older than 50 years were considered to be aged livers. However, several comparative series with younger donors demonstrated no significant differences regard to the rates of primary graft failure, retransplant, and patient and graft survivals, leading to the conclusion that liver grafts older than 50 years can be safely used for transplant[71,82,105].

The first two comparative series using liver grafts older than 60 years showed significantly lower 1-year graft survival[106], and 2-year graft survival in recipients of older livers, which was attributed to the more frequent ischemic injury in this group[12]. In two posterior reports comparing recipients of livers older and younger than 60 years, the rates of patient and graft survival, primary graft failure, and graft dysfunction were similar, but the mean CIT ranged between 5 and 6.3 h[22,107], significantly less than the previous series with a CIT of 12.8 and 10.6 h, respectively[12,106]. It has been established that prolonged CIT impairs liver graft function, and when CIT is longer than 14 h the graft preservation injury doubles[56]. In an analysis of liver transplants from the Scientific Registry of Transplant Recipients, donor age over 60 years was the strongest risk factor for graft failure[1]. Other small series obtained significantly worse results using donors older than sixty years[20], but more recently larger series of 91 OLT[15] and 125 OLT[55] confirmed no significant differences when comparing the use of donors older and younger than 60 years.

In a comparative series of five groups divided according to donor age categories (donors < 50 years; donors between 50-59 years; donors between 60-69 years; donors between 70-79 years; and donors ≥ 80 years), the predictors of poor graft survival were donor age between 60-79 years, HCV-positive recipients, MELD score ≥ 25, and emergency OLT[26].

In two comparative studies using liver donors older and younger than 65 years, graft survival was lower in the group of recipients of older donors, and the rate of graft dysfunction was higher when the grafts presented steatosis[108,109]. However, two more recent studies did not find any significant differences in patient and graft survival using liver grafts younger or older than 65 years[81,110].

These and other experiences using donors older than 60 years are shown in Table 1[12,15,20,22,55,81,106,107,110,111].

Liver grafts older than 70 years

Most authors have established that the use of liver grafts from septuagenarian donors *per se* is not a contraindication for their utilization in OLT[13,23,26,54,55,58,99,100,112]. However, some authors reported significantly worse patient and graft survival when they used liver grafts older than 70 years[19,61,65] (Table 2).

The way to get good results when using liver grafts older than 70 years is to make a good donor selection, avoiding, as far as possible, the use of grafts with marginal donor criteria that are known to be associated with IPF and PNF of the graft. It is also important to avoid recipient risk factors (advanced age, obesity, renal dis-

Table 2 Series of orthotopic liver transplantation with liver grafts older than 70 years

Ref.	Cases (*n*)	Donor mean age (yr)	Cold ischemic time (h)	Recipient mean age (yr)	Primary non-function	Patient survival (yr)	Graft survival (yr)
Emre *et al*[13]	36	73.5	9	55	5.5%	1-yr: 91%	1-yr: 85%
Kim *et al*[54]	25	74	7.6	49	8%	1-yr: 95.4%	1-yr: 82.7%
						3-yr: 89.8%	3-yr: 71.7%
Gastaca *et al*[23]	55	-	5	-	0%	1-yr: 93.8%	1-yr: 92.6%
						3-yr: 90.6%	3-yr: 89.4%
Borchert *et al*[99]	41	73.4	8.9	50.9	2.4%	1-yr: 91%	1-yr: 86%
						3-yr: 83%	3-yr: 81%
						5-yr: 77%	5-yr: 75%
Segev *et al*[25] (UNOS)	1043	74.8				3-yr: 81.2%	3-yr: 74.9%
Cescon *et al*[26]	111	-			7%	5-yr: 66%	5-yr: 62%
Fouzas *et al*[65]	17	73	7.2	57	11.8%	1-yr: 69.7%	
						3-yr: 57.5%	
						5-yr: 46.2%	
Lai *et al*[61]	28	74	6.4	57	3.6%	5-yr: 47%	5-yr: 40.7%
Sampedro *et al*[112]	24	78.3	3.7	53.9	0%	1-yr: 78%	
						5-yr: 63%	
Darius *et al*[58]	58	77	8	61	0%	1-yr: 90%	1-yr: 88%
						5-yr: 84%	5-yr: 79%
Jiménez-Romero *et al*[55]	50	75.7	6.1	51	0%	1-yr: 76%	1-yr: 73.9%
						5-yr: 62.9%	3-yr: 64.6%
							5-yr: 58.3%

UNOS: United network for organ sharing.

ease, HCV cirrhotic recipients, retransplant) related with increased graft loss and mortality[14,23,54,55,58,71,99,100]. When using liver grafts older than 70 years in preferred recipients (first time recipients over the age of 45 years, BMI < 35 kg/m^2, non-status 1 registration, CIT < 8 h, and either hepatocarcinoma or an indication for transplantation other than HCV cirrhosis), the results are similar to outcomes with younger liver grafts[25].

When using donors older than 70 years, 1-year patient survival varies between 66% and 95.4%, 3-year patient survival between 57.5% and 90.6%, and 5-year patient survival between 46.2% and 84%[13,23,25,26,55,58,61,65,99,112]. In addition, 1-year graft survival varies between 73.9% and 92.6%, 3-year graft survival between 64.6% and 89.4%, and 5-year graft survival between 40.7% and 79%[13,23,25,26,58,61,99]. It must be taken into consideration that some series excluded septuagenarian donors for transplant recipients with HCV cirrhosis, so that the results are better[58,99].

Liver grafts older than 80 years

Since the first reported case of successful use of an 86-year-old liver graft[113], several series of octogenarian liver grafts have been published[24,26,30,79,80] (Table 3). Moreover, other isolated cases of nonagenarian liver grafts were recently reported[114-116].

Cerebrovascular diseases are the causes of death of between 73% and 81.7% of octogenarian donors[26,53,80].

The general acceptance criteria of octogenarian liver grafts were: normal gross appearance and consistency, no alteration of liver function tests, hemodynamic stability with use of low doses (< 10 mcg/kg per minute) of vasopressors before procurement, ICU stay < 3 d, no relevant histological alterations in the pre-transplant biopsy, such as fibrosis, hepatitis, cholestasis, macrosteatosis > 30%), and short cold ischemia time (< 10 h)[30,53,79]. Liver biopsy during octogenarian donor procurement is generally recommended before accepting the use of the liver graft[14,26,30,79,80].

The reported rate of octogenarian grafts discarded is significantly higher than that of younger donors, and the principal reasons for graft refusal were moderate-massive steatosis, HCV cirrhosis and malignancies[53]. In series that compared octogenarian and younger donor characteristics, no significant differences were seen regarding ICU stay > 5 d, BMI ⩾ 35 kg/m^2, use of norepinephrine, prevalence of steatosis, total bilirubin, alteration of liver function tests, serum sodium, hypotensive episodes or vasopressor use[26,53]. In our series[30], with ICU stays between 12 and 24 h, there was no cardiac arrest in any of our four donors, and the blood pressure was maintained above 90 mmHg with the use of up to 15 mcg/kg per minute of dopamine in three donors. With a CIT of less than 9 h all of our recipients attained a good early post transplant liver function. Thus, the current tendency for use of octogenarian donors is to minimize ICU stay (< 3 d), CIT (< 9 h), and steatosis[24,26,30,80] to prevent the development of ischemia-reperfusion injury that contributes to recurrence in HCV-positive recipients[117].

The worse outcome associated with the use of older donors for HCV-positive recipients has undergone a dramatic shift in the past years, so that nowadays octogenarian donor livers are mainly transplanted into patients with hepatocarcinoma and ethylic cirrhosis, avoiding OLT in viral C cirrhosis[26,79]. Thus, in this group the MELD score is higher than in recipients of younger donor livers where the rate of recipients who underwent OLT due to hepatocarcinoma is lower[26].

One-year patient survival ranges between 75%

Table 3 Series of orthotopic liver transplantation with liver grafts older than 80 years

Ref.	Cases (*n*)	Donor mean age (yr)	Cold ischemic time (h)	Recipient mean age (yr)	Primary non-function	Patient survival (yr)	Graft survival (yr)
Jiménez-Romero *et al*[55]	4	85.7	5.5	50.2	0%	1-yr: 75%	1-yr: 75%
Nardo *et al*[53]	30	82.3	7.5	52.5	0%	1-yr: 80%	1-yr: 77%
Zapletal *et al*[24]	5		9.5	52	0%	1-yr: 100%	1-yr: 100%
Cescon *et al*[26]	41			52.5	0%	3-yr: 86%	3-yr: 81%
						5-yr: 86%	5-yr: 81%
Petridis *et al*[79]	10	83.5	5	57.4	10%	1-yr: 80%	
						3-yr: 40%	
Singhal *et al*[80] (UNOS)	197			58.5		1-yr: 81%	1-yr: 75.5%
						3-yr: 69.1%	3-yr: 61.2%

UNOS: United network for organ sharing.

and 100%, 3-year patient survival between 40% and 86%[24,26,30,53,79,80], and 5-year patient survival is 86%[26]. One-year graft survival varies between 75% and 100%, 3-year graft survival between 61.2% and 81%[24,26,30,53,79,80], and 5-year survival of 81%[26].

CONCLUSION

At the present time, there are enough studies regarding the use of sexagenarian and septuagenarian donors that demonstrate similar results in comparison with the use of younger donors. With respect to the use of octogenarian donors for OLT, experiences are less and shorter, but at least in Spain the utilization of such grafts is progressively increasing because of the necessity to expand the donor pool with the aim to decrease waiting list mortality. In order to get good results using old liver grafts with no age limit, careful donor selection must be performed (normal liver function, good hemodynamic and pre harvesting conditions, ICU stay < 72 h, CIT < 8 h, WIT < 1 h, macrosteatosis < 30%, absence of atherosclerosis in the hepatic artery, and absence of histological alterations in the biopsy), while avoiding recipient risk factors such as advanced liver disease (high MELD scores) or the presence of HCV cirrhosis frequently associated with higher HCV recurrence and additionally greater morbi-mortality. A liver biopsy should is advisable before accepting a liver graft older than 70 years, and also in doubtful cases of donors younger than 70 years.

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