Impact of Donor Age on Liver Transplants

M.ª Trinidad Serrano Aulló[1,2], Estela Solanas Villacampa[2] and Agustin Garcia-Gil[1,2]

[1]Liver Transplantation Unit, University Hospital Lozano Blesa, Zaragoza, Spain; [2]Health Research Institute of Aragon (IIS), Zaragoza, Spain

Abstract

The percentage of livers from old donors has been increasing in the last years. Several morphological and functional changes have been described in the ageing liver such as a decrease in the regenerative capacity. The impact of donor age in liver transplantation has been analyzed in several studies with contradictory conclusions. In this paper, the importance of this factor in liver transplant outcome, the role of donor age as risk factor, and the influence of ageing in liver regeneration are reviewed. **(Trends in Transplant. 2012;6:34-40)**

Corresponding author: M.ª Trinidad Serrano Aulló, utra.hcu@salud.aragon.es

Key words

Liver transplantation. Old donor. Liver regeneration. Risk factor.

Introduction

Over the past several years, the age limit for liver transplant donors has increased at many transplant centers due to the shortage of donors. The European Liver Transplant Registry shows a substantial change in donor age distribution over recent years, with an increasing percentage of livers coming from donors older than 60 years. In 1991, just 2% of livers came from donors over 60 years old; this increased to 10% in 1996 and to 20% in 2001[1]. In Spain over the last years, more than 50% of donors were 55 years or older (Fig. 1)[2]. Several morphological and functional changes have been described in the ageing liver, including a decrease in size attributable to decreased hepatic blood flow and, one of the most important age-related changes, a decrease in regenerative capacity[3]. The impact of donor age on liver transplantation has been analyzed in several studies with contradictory conclusions. Some studies reported similar graft survival with older and younger donors[4,5], but others reported higher incidences of poor initial function[6] and arterial complications[7] following transplantation from older donors. Furthermore, a relationship has been described between allografts obtained from older donors and accelerated posttransplantation fibrosis progression in hepatitis C virus (HCV)-positive recipients[8,9].

Correspondence to:
M.ª Trinidad Serrano Aulló
Unidad de Trasplante Hepático
Hospital Universitario Lozano Blesa
50009 Zaragoza, España
E-mail: utra.hcu@salud.aragon.es

Outcome of liver transplantation using old donors

Liver transplantation with deceased donors

Studies based on institutional registries have analyzed the effects of donor age on

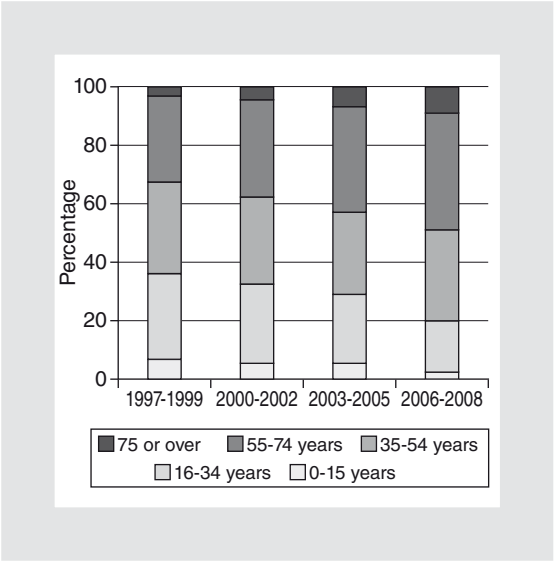

Figure 1. *Donor age in liver transplants in the last years* (adapted from ONT. Memoria de Resultados del Registro Español de Trasplante Hepático 1984-2008).

patient and graft survival in the largest patient series. In the European Liver Transplant Registry, the one-year survival of patients who received transplants between 1998 and 2001 was similar for all donor age groups[1]. Analysis of the Spanish Registry for Liver Transplantation for the period 1994-2000 showed evidence that liver transplantation from deceased donors over 60 years old had slightly lower actuarial graft survival at one year posttransplantation, compared with those performed with donors younger than 60 years. The difference in the actuarial graft survivals between the two groups was higher at five years posttransplantation. A recent analysis of donor risk factors in liver transplants performed in the USA between January 1, 1998 and December 31, 2002 found that donor age of over 60 years was the strongest risk factor for graft failure[10]. In this analysis of 20,023 transplants from the Scientific Registry of Transplant Recipients, donor age over 40 years, and particularly over 60 years, donation after cardiac death, and split/partial grafts were strongly associated with graft failure[10]. In a retrospective study performed using data obtained from the United Network for Organ Sharing (UNOS), Reese, et al.[11] found that performing liver transplants with donors who were ≥ 45 years old increased the risk of graft failure at 90 days after transplantation. Moreover, these authors found that a combination of older donor age and elevated cold ischemia time were associated with inferior allograft survival three months after liver transplantation.

Other studies show different results. Anderson, et al.[12] analyzed 741 liver transplants performed between 1990 and 2007 and demonstrated that overall graft and patient survival were not significantly different in the group using donors younger than 60 years, compared to the group using donors who were 60 or older. However, when cases with donors ≥ 60 years were compared with each other based on time frames, there was a statistically significant improvement in patient and graft survival after 2001. All transplants performed before 2001 had significantly longer cold ischemic times compared with those performed alter 2001. From this study, they concluded that donor age alone does not represent a graft or survival disadvantage, but that there was a possible interaction between donor age and other factors such as ischemia time.

All of these data were determined by retrospective studies and therefore could be subject to the bias of an indirect measurement of the risk. Prospective analyses have appeared in the last few years. We performed a prospective analysis to determine if age greater than 60 should be viewed as a risk factor for graft failure or a higher incidence of complications[13]. Only primary, non-split/partial transplants from heart-beating donors and ABO-compatible matches were included to avoid factors related to worse graft survival. We found that liver transplant outcome was clearly poorer in patients who received a graft from a donor over the age of 60 years. Initial graft function was similar in both the older and younger groups, and there were no cases of primary non-function in the older donor group. However, graft survival at 12 months decreased

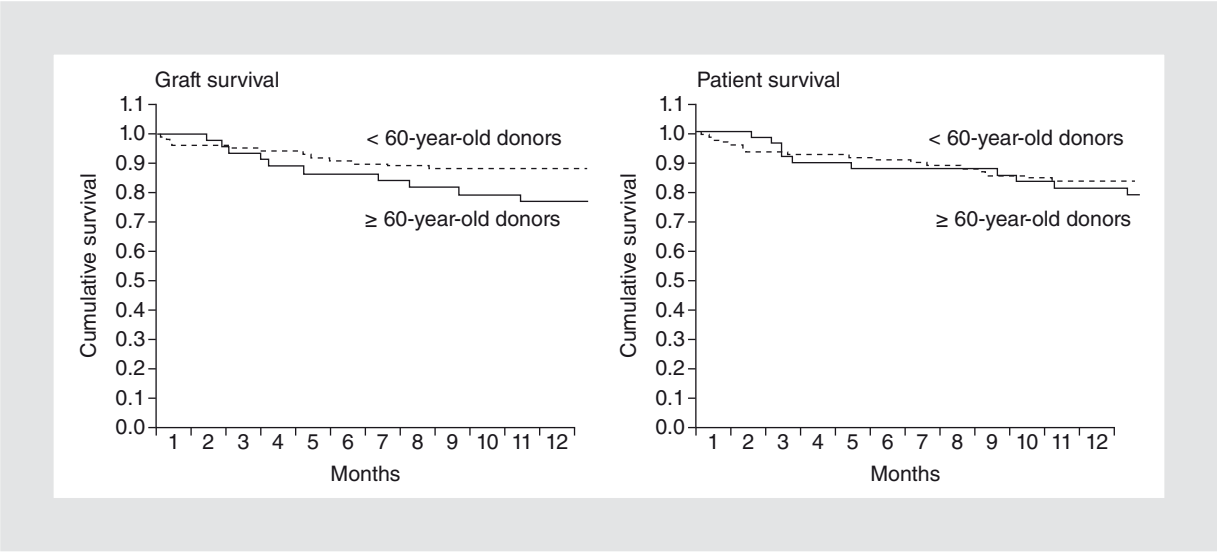

Figure 2. *Kaplan-Meyer graft and patient survival curves of liver transplants performed with livers from donors aged 60 years or older compared with those from donors younger than 60 years old[13].*

by about 15% in this group, although patient survival was not affected (Fig. 2). We also estimated graft and patient survival at two and three years after liver transplantation. The major decrease in graft survival occurred in the first year after transplantation, but this difference was maintained or even increased in the second year. Moreover, we detected that non-anastomotic biliary strictures (NABS) were four-times more frequent in the older donor group. In the multivariate analysis, receiving a graft from a donor 60 years or older and arterial complications were both independent factors that were associated with an increased frequency of NABS formation. Nearly 50% of our patients with NABS did not have an arterial complication detected by radiological tests or pathological examination.

Ischemia-reperfusion injury could play an important role in NABS development. It has also been demonstrated that one-year graft survival is lower in patients with ischemic-type biliary strictures than in patients without this complication[14]. Similar events have been described in cases with non-beating-heart/liver donors; the incidences of both ischemia-reperfusion injury and NABS are higher than with beating-heart donors[15]. Experimental data demonstrate that the biliary tract is very sensitive to ischemia-reperfusion injury. *In vitro* studies analyzing human graft samples after orthotopic liver transplantation have convincingly demonstrated biochemical and histological changes in the bile canaliculi that are associated with ischemic injury, and have indicated that this structure in the liver is the most sensitive to such injury[16]. Bile duct cells have lower levels of glutathione than hepatocytes and thus may be more susceptible to re-oxygenation injury[17]. Although, in our study, ischemia time was similar in both donor age groups, it is possible that the livers from older donors were more sensitive to ischemic reperfusion injury, like they are to HCV injury.

The relationship between donor age and fibrosis progression after liver transplantation in patients with HCV infection has been clearly demonstrated. Berenguer, et al.[8] found a significant negative impact of HCV infection on both graft and patient survivals, which appears to be a more common problem in recent years. In this study, one simple variable, donor age, predicted a worse outcome at early time points posttransplantation. Machiacao, et al.[9] analyzed protocol liver biopsies performed at 1, 16, and 52 weeks after liver

transplantation in HCV patients and demonstrated a higher fibrosis score in old donor recipients (> 50 years) than young donor recipients. Our study[13] also found higher severity of HCV reinfection, evaluated by protocol biopsies, in the group with older donors. Nearly half of patients in the older donor group had severe fibrosis (E3 or E4 Scheuer fibrosis score) only a year after transplantation. These data indicate that the preferential use of organs from younger donors in HCV recipients might be a useful strategy to improve the outcome in these patients.

Living donor liver transplantation

In living donor liver transplantations (LDLT), the impact of donor age on outcomes has been less studied, but recent reports suggest that donor age might have a major impact on recipient outcome in adult LDLT. Ikegami, et al.[18] demonstrated that liver transplantation performed with living donors ≤ 30 years old resulted in better function and regeneration tests within the first month than those performed with donors > 50 years of age. However, the outcome was not affected by the age of the liver graft. In a further study[19], the same authors demonstrated a greater incidence of small-for-size syndrome in recipients from living donors ≥ 50 years, compared to those transplanted with livers from donors ≤ 50 years old. In addition, Iwamoto, et al.[20] reported significantly higher bilirubin levels and worse survival following transplantation using donors ≥ 50 years. Very recently, Ono, et al.[21] analyzed hepatic regeneration in living donors and observed that the regeneration rate a week after hepatectomy was significantly higher in donors who were ≤ 30 years old than in those ≥ 50 years old. Nevertheless, these differences disappeared within a month after liver transplantation. These authors did not find a significant correlation between Thy-1+ cell number and liver age, but noted that Thy-1+ cells consistently tended to decline with age, suggesting that hepatic progenitor cells in the human liver change with age and this might be one cause of impaired liver regeneration in older donors.

A recent study[22] demonstrated a significant correlation between the rate of major complications and the type of surgery with donors who were ≥ 50 years old. In LDLT, extending the limits of surgery is associated with more complications in elderly donors. These authors recommend avoiding right hepatectomy with middle hepatic vein harvesting or resulting in an estimated remnant liver volume less than 35% with donors who are ≥ 50 years old.

Donor age as a risk factor

Recently, two developments have greatly impacted decision-making in liver transplantation. The first is the adoption of the model for end-stage liver disease (MELD) score to prioritize the sickest patients for transplantation. The second is the increased use of higher-risk donor livers to expand the donor pool and decrease the time to transplantation.

MELD is an objective score, based on the laboratory parameters (total serum bilirubin, International Normalized Ratio, and serum creatinine); it changed the basis of priority criteria from length of waiting time to disease severity. The implementation of the MELD score as the basis for donor liver allocation has improved the distribution of organs. Deceased-donor livers are preferentially transplanted into sicker patients, and this has reduced waiting list mortality without reducing posttransplantation survival[23].

In the past several years, donor quality has been decreasing. Some studies have tried to detect the most important factors and to develop several mathematical formulations designed to predict graft risk. Probably the

most important study was performed by Feng, et al. This group used the UNOS database[10] to identify nine donor factors predicting graft failure after transplantation (donor age, donor height, donation after cardiac death, split liver donor, black race, vascular accident as cause of death, regional sharing, and cold ischemia time). Using these risk factors, a donor risk index (DRI) was developed to predict the isolated and cumulative effects of these variables on graft survival. Recipients of a graft with a DRI < 1.2 had a graft survival higher than 80% per year, versus 71.4% in those transplanted with organs with a DRI > 2. In this study, donor age > 60 years was the strongest risk factor for graft failure (RR: 1.53 with a donor > 60; 1.65 if > 70). However, this index is not easily applicable in every country. In smaller countries, national organ transports do not result in a long delay in ischemia time and several factors are not very common in some European countries, such as African American donor race, split transplantation, or use of non-beating donors.

Since posttransplant patient survival depends on both preoperative medical condition and donor quality, physicians are often faced with the difficult decision of whether to accept high-risk donor liver offers for high-risk patients.

Halldorson, et al.[24], using the UNOS STAR national transplant database, tried to identify poor donor/recipient matches that could help to direct allocation of organs into recipients in which the survival is greatest, maximizing the benefit of donor livers. They created the D-MELD score, which was calculated as the product of MELD score and donor age and was demonstrated to be highly predictive of post-liver transplant survival. The D-Meld cut-off of 1,600 identified donor/recipient combinations with significant poorer survival. This score could predict excessive-risk donor/recipient matches and improve resource utilization.

Recently, Briceño, et al.[25] analyzed the accumulated impact of extended criteria donor variables on graft survival in a MELD-based allocation system. They concluded that primary dysfunction after liver transplantation depends on the severity of ischemia-reperfusion injury according to the number of extended criteria variables and the MELD recipient status. The combination of three or more variables and MELD ≥ 29 is the worst scenario for graft outcome.

It is important to note that this application could result in a shifting of "worse donors" away from high-MELD recipients who have a demonstrable survival benefit from transplantation, and toward low-MELD recipients, thus decreasing survival benefit in this group. Amin, et al.[26] used a Markovian model to define the risk and benefit considerations for accepting or declining a liver offer according to the organ's potential for failure and the candidate's disease severity, as specified by MELD. They determined that the one-year survival in patients with a MELD score > 20 was higher using an expanded-criteria graft versus waiting for the ideal graft.

In LDLT, it has also been demonstrated that the donor age is a risk factor. Yoshizumi, et al.[27] established a model for predicting graft function and short-term prognosis alter LDLT, correlating clinical variables to the ratio (hepatic uptake of Tc-GSA/clearance index of Tc-GSA). Graft size, donor age, and preoperative status of patients prior to surgery were predictive of early graft function for adult LDLT.

Liver regeneration and ageing

Ageing in the human liver is associated with morphological changes such as a decrease in size attributable to decreased hepatic blood flow. Hepatocytes are normally quiescent cells but, in response to partial

hepatectomy, hepatocytes undergo one or two rounds of replication to restore the original size of the liver. This cellular transition from quiescence to proliferation requires activation of S-phase- and mitotic-specific genes that are usually repressed in quiescent cells[28].

It has been proposed that age-related reduction in hepatocyte telomere length results in diminished cell mitosis and apoptosis, and thus a decline in cell proliferation. But structural changes do not always reflect functional alterations. Experiments in a telomere restriction fragment-deficient mouse model demonstrated that liver regeneration after partial hepatectomy is not compromised by the loss of telomere integrity[29]. Post-hepatectomy regeneration was accomplished, increasing cell growth and yielding polyploid cells, indicating a switch from a proliferative to a cell growth pathway.

Another important aspect is the effect of ageing on the hepatocellular response to growth factors. Hepatocyte proliferative response to epidermal growth factor (EGF) was clearly increased in young rats compared to in old animals, suggesting that ageing impaired the hepatocyte responsiveness to growth factors[28,30]. The problem does not seem to be in the number of growth factor receptors or in their binding affinity, but instead lies in the receptor phosphorylation, a critical step in EGF activation. Recent studies indicate that the molecular basis for the reduced proliferative response of aged livers might be related to alterations in signal-transduction pathways at the level of translation or post-translational modifications[31]. These reports also demonstrate a pivotal role for epigenetic silencing in inhibiting liver proliferation in old mice. It is well known that alterations of chromatin structure in senescence cells dramatically decrease their capability to proliferate through epigenetic silencing of cell-cycle genes. In old livers, the decline in regenerative capacities is associated with epigenetic silencing of E2F-dependent promoters. This epigenetic silencing is the result of age-dependent alterations of several signal-transduction pathways[30].

Reports have also described marked age-related changes in the structure of hepatic sinusoidal endothelium, including a loss of fenestrate and a thickening of the endothelial cells (pseudocapillarization). Recently, Furrer, et al.[32] demonstrated that pseudocapillarization contributes to an age-related decline in regeneration after hepatectomy in mice. Their data demonstrate that treatment with a serotonin receptor agonist in old mice improved liver regeneration, correlating with increases in the number of endothelial cell fenestrae and systemic vascular endothelial growth factor (VEGF) availability. Higher VEGF secretion levels have also been detected in cultures of isolated human hepatocytes from young donors compared to those isolated from older donors[33].

Finally it has been found that the progenitor cell population (Thy-1+) consistently tends to decline with age in LDLT. This suggests that the declining hepatic progenitor cell population might be one reason for impaired liver regeneration in older donors[21].

In summary, even though the function of the liver appears to be relatively well preserved with ageing, this process is characterized by a decline of cellular functions as cells progressively lose their capacity to successfully respond to injury. Liver regeneration is compromised in old animals and in elderly humans and it appears to be the rate of liver regeneration, rather than the regenerative capacity, that is diminished in the elderly. Ageing changes the pathways of growth arrest, and this change leads to a loss in proliferative response and regeneration. Age-related changes in liver response may be the key factor that determines the increased susceptibility of the older liver to irreversible lesions

produced by different insults, such as ischemia-reperfusion or HCV infection, and results in the higher probability of inadequate response in livers from older donors. Understanding the molecular basis for the reduced proliferative response in old livers is important and could indicate how can we can improve liver regeneration and graft survival.

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