Review

JOURNAL OF HEPATOLOGY

Age and liver transplantation

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Summary

The average age of liver transplant donors and recipients has increased over the years. Independent of the cause of liver disease, older candidates have more comorbidities, higher waitlist mortality and higher post-transplant mortality than younger patients. However, transplant benefit may be similar in older and younger recipients, provided older recipients are carefully selected. The cohort of elderly patients transplanted decades ago is also increasingly raising issues concerning long-term exposure to immunosuppression and aging of the transplanted liver. Excellent results can be achieved with elderly donors and there is virtually no upper age limit for donors after brain death liver transplantation. The issue is how to optimise selection, procurement and matching to ensure good results with elderly donors. The impact of old donor age is more pronounced in younger recipients and patients with a high model for end-stage liver disease score. Age matching between the donor and the recipient should be incorporated into allocation policies with a multistep approach. However, age matching may vary depending on the objectives of different allocation policies. In addition, age matching must be revisited in the era of direct-acting antivirals. More restrictive limits have been adopted in donation after circulatory death. Perfusion machines which are currently under investigation may help expand these limits. In living donor liver transplantation, donor age limit is essentially guided by morbidity related to procurement. In this review we summarise changing trends in recipient and donor age. We discuss the implications of older age donors and recipients. We also consider different options for age matching in liver transplantation that could improve outcomes.

Keywords: Liver transplantation; Age; Deceased donor transplantation; Donation after circulatory death; Living donor liver transplantation; Waiting list mortality.

Received 19 August 2018; received in revised form 21 November 2018; accepted 11 December 2018

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Introduction

The face of liver transplantation has changed in the last decades. Significant improvements have been achieved in terms of post-transplant survival and quality of life. The number of liver transplants performed each year increased up to 2005 in the United States[1,2] and up to 2010 in Europe,[3–6] before becoming relatively stable thereafter. The steady increase in donation after circulatory death (DCD) has contributed to the expansion of the donor pool. However, less stringent criteria in the selection of donation after brain death (DBD) donors along with a growing number of DCD donors has not covered the gap between the number of organs and the number of patients who could derive a benefit from transplantation.[7–10] Due to this imbalance between donors and recipients, there is a clear incentive to push the age limits for donation in liver transplantation. Indeed, good results have been extensively reported with older DBD donors.[11–13] In the current context of organ shortage, the issue is not whether older donors should be used, rather how to use them and in which recipients.

In parallel with improvements in post-transplant results, more liberal policies have been adopted allowing transplantation as an option in recipients older than 65. The proportion of registrants older than 60 has already increased significantly in the United States and in Europe.[9,10,14] Age at registration will probably continue to increase as decompensated hepatitis C virus (HCV)-related cirrhosis represents a lower proportion of candidates, while non-alcoholic steatohepatitis (NASH) has become a leading indication for transplantation.[15,16] Indeed, patients with decompensated cirrhosis or NASH-related hepatocellular carcinoma (HCC) tend to be older than patients with other causes of liver disease.[10,17]

The aims of this review are to present and summarise data concerning trends in age at registration for liver transplantation according to different aetiologies, impact of aging in candidates for transplantation and recipients, impact of older donors, interactions between older donors and older recipients and how to optimise the management in this population. This review is based on both a systematic review of the literature and expert opinion.

Age of the recipients

Trends in epidemiology and corresponding trends in recipients age

The age of liver transplant recipients has increased steadily over the last 15 years in the United States and Europe (Fig. 1A,B). For instance, the propor-

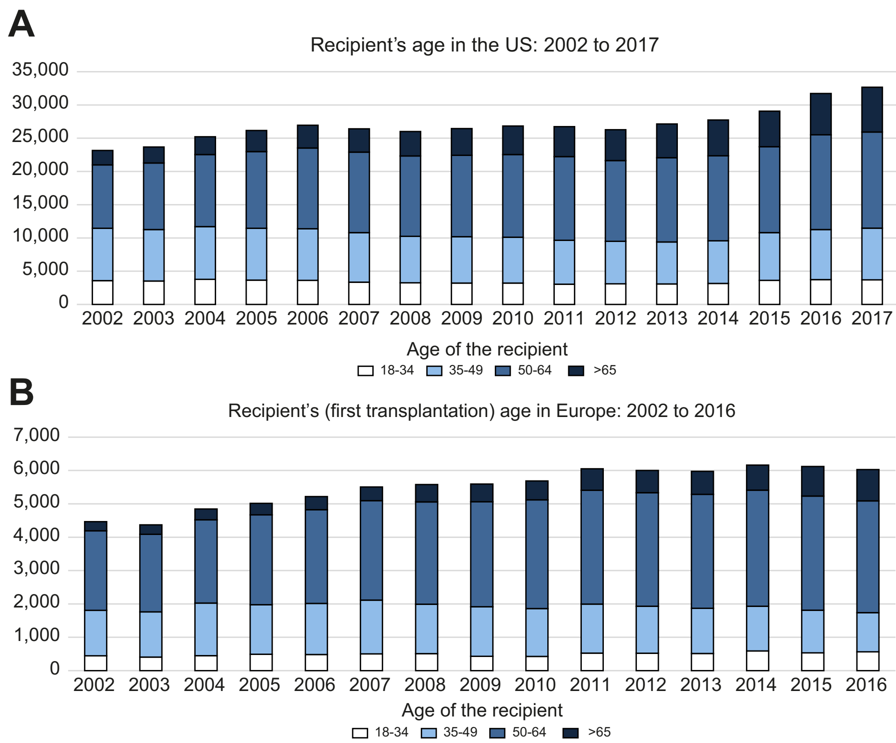

Fig. 1. Distribution of recipients by age categories in the United States and Europe. (A) Data from the United Network for Organ Sharing (https://unos.org) (B) Data from the European Liver Transplant Registry (www.eltr.org).

tion of liver transplant recipients aged 65 or more increased from 9% in 2002 to 20% in 2017 in the United States.[2] In the Eurotransplant area, there has been a 16% increase in the number of liver transplant recipients aged 65 years or more between 2012 and 2016.[6] Similar trends have been observed in the mean age of new registrants for transplantation which increased from 51.2 years in 2002 to 55.7 years in 2014 in the United States.[10] During the same period, this trend was even more prominent in HCV-infected patients (from 50.9 to 57.9 years on average).[10]

There may be several reasons for these changes. During the last decades, the results of liver transplantation have improved, leading to a relaxing in the age limits of candidates.[7,10,18] Second, indications for transplantation have changed leading to an increasing number of candidates older than 65 being registered. For years, hepatitis C has represented the leading cause of chronic liver disease in candidates for transplantation. Even though the introduction of highly effective direct-acting antivirals (DAAs) is relatively recent (2013–2014),[8,14] broad use of these agents has already had a major impact on the prevalence of HCV infection on the waiting list. In the United States, a more than 30% decrease in the proportion of patients newly registered with decompensated HCV-cirrhosis has been observed in the DAA era compared to the interferon era.[9,19,20] The proportion of patients undergoing transplantation for decompensated HCV-cirrhosis has also decreased.[9,16] In addition to preventing progression from compensated to decompensated HCV-cirrhosis, DAAs allow about 30% of treated patients to be removed from the waiting list following clinical improvement.[21] In parallel with the decrease in new registrants for HCV-cirrhosis, an increasing proportion of patients have been placed on the waiting list for NASH and/or HCC.[16,20] Since, on average, patients with NASH and HCC are older than patients with HCV-related cirrhosis, these changes in waiting list characteristics have resulted in an older average age at registration. This trend may continue in the future with the continuing decrease in the prevalence of HCV and the increasing prevalence of NASH in patients placed on the waiting list.[10,15]

Key point

On average, candidates for transplantation with NASH and/or HCC are older than candidates with decompensated HCV-cirrhosis which contributed to older age at transplantation in recent years.

Impact of age on waiting list mortality and post-transplant outcomes

In patients without HCC, older age at registration is associated with higher waitlist mortality across different categories of model for end-stage liver disease (MELD) score.[10] Advanced age is a significant risk factor behind patients being too sick to be transplanted. In a large series, competing risk analysis has shown that increasing age was associated with increased waiting list mortality (adjusted hazard ratio of 1.73 and 2.04 in patients aged 64 to 69 years and ≥70 years, respectively) and decreased likelihood of transplantation (adjusted hazard ratio of 0.89 and 0.86 in patients aged 64 to 69 years and ≥70 years, respectively)

(Table S1).[10] Even though the impact of age on waitlist mortality seems to be similar across different MELD categories, advanced age is associated with a lower MELD score at death, dropout or transplantation, suggesting that older candidates tolerate high MELD scores poorly.[10]

In patients with HCC, advanced age is also associated with an increased risk of removal from the waiting list due to death or tumour progression independent of MELD, serum alpha-fetoprotein (AFP), and maximum tumour size.[22]

Older age at transplantation inevitably impacts long-term survival. Even though similar outcomes can be achieved 1 year after liver transplantation in patients below or over 60 years of age,[23] most series have shown that 5-year post-transplant survival is significantly lower in recipients older than 60–70 years of age (Table 1). Five-year survival is generally 10 to 20% lower in patients aged ≥60–70 years than in younger recipients.[3,5,10,24] The survival gap between older and younger recipients increases over the years after transplantation.[10] Five-year survival probability declines by a similar degree in older transplant recipients compared to the general population for similar age groups.[10] Increased early mortality is typically observed in older patients with a high MELD score (>25–28).[10,25,26] However, similar outcomes have been reported in septuagenarians with and without HCC.[24] There is no evidence that a high MELD score is associated with significantly increased late mortality in older patients. Post-transplant mortality in older recipients is also affected by donor factors with a negative interaction between extended criteria donors and recipient age.[27] For instance, the sum of donor and recipient age ≥120 years was shown to be predictive of a worse post-transplant outcome independent of other confounding factors.[28] Pre-transplant coronary artery disease is a predisposing factor for post-transplant mortality in older recipients.[29] Advanced age is significantly associated with the risk of death due to cardiovascular events and malignancy.[30]

Considerations in the selection of older candidates for liver transplantation

With the average age of listing for liver transplantation increasing significantly in the last decade, 25% of patients receiving liver transplantation in the United States are over 65 years of age,[9] with a similar trend in other countries. Above the standard evaluation, the selection of older candidates should pay particular attention to cardiovascular diseases, functional status, and the assessment of malignancy risk. Both ischaemic (coronary artery disease) and non-ischaemic (cardiomyopathy, heart failure, arrhythmia, valvular heart disease) assessments become equally important during the evaluation in the older population. Age is a significant risk factor for all of these complications. Thus, at a minimum, initial transthoracic echocardiography, electrocardiography, non-invasive stress testing and consultation with a cardiologist familiar with end-stage liver disease haemodynamics are warranted. A recent evidence-based guideline emphasised a multidisciplinary approach to assess risks and prepare for peri/post-operative cardiac complications.[31] Cardiopulmonary exercise testing and other functional measures such as 6-minute walk distance also add prognostic data for candidates and correlate with the presence of frailty.[32,33]

Recent data have provided evidence that frailty predicts waitlist mortality independent of MELD score and that older candidates are more likely to be frail with less physiological reserve.[34,35] Although there are no universal standard criteria for frailty and multiple tests are available, simple to perform performance-based tests of muscle function may have more clinical applications than imaging-based measures of sarcopenia.[36] A recent frailty assessment called the Liver Frailty Index demonstrated that less than half of patients become “robust” after transplantation, supporting the need for pre- and post-transplant rehabilitation.[37]

Finally, extrahepatic malignancy directly increases with age, and most centres are reluctant to transplant patients with recent diagnoses of malignancy other than non-melanoma skin or early, treated, less aggressive localised cancers, for fear of relapse following transplantation.[38] All candidates should undergo age and risk factor appropriate cancer screening prior to listing, such as colonoscopy, mammography, prostate screening, *etc.* Ongoing tobacco consumption should be strongly discouraged.[39] Liver transplant candidates with a prior extrahepatic malignancy should have received definitive treatment with adequate tumour-free survival before liver transplant listing.[40] Most programmes would consider adequate tumour-free survival to be at least 1 to 5 years, depending again on the particular malignancy. As each patient often presents a unique clinical scenario, consultation with oncologists having specific experience in estimating the general risk of relapse, as well as additional risk with immunosuppressive therapy, is warranted particularly in the older population. Older recipients are at higher risk of developing *de novo* malignancy. However, the excess in cancer incidence compared to the general population is higher in the youngest recipients than in older recipients.[41]

Considerations in the management of older liver transplant recipients

While most complications occurring after liver transplantation are increased in the elderly population, specific issues related to immunosuppressive therapy, kidney function, cardiovascular disease, malignancy risk and metabolic bone disease are most heightened with advancing age (Fig. 2).[42] The risk of rejection is inversely related

Key point

Older age at transplantation is associated with higher post-transplant mortality, especially in patients with a high MELD score.

Key point

Older age at registration is associated with higher waitlist mortality across different categories of MELD score.

Table 1. Post-transplant survival according to different recipients age categories.

Author	Year	Region	Age cut-off values (yr)	Patients	Follow-up (yr)	Post-transplant survival
Rudich S & Busuttil R.[138]	1999	US	≥70	30	6	57%
			<70	30		73%
Collins BH, *et al.*[5]	2000	US	≥60	91	5	52%
			<60	387		75%*
Garcia CE, *et al.*[26]	2001	Europe	≥60	174	5	69%
			<60	707		76%
Cross TJ, *et al.*[23]	2007	Europe	≥65	77	1	82%
			60–64	137		86%
			18–59	202		83%
Bilbao I, *et al.*[3]	2008	Europe	≥65	72	5	52%
			<65	313		75%*
Aloia TA, *et al.*[28]	2010	US	≥70	627	5	58%
			<70	7,325		68%*
Schwartz JJ, *et al.*[24]	2012	US	≥70	480	5	55%
			<70	22,296		73%*
Sonny A, *et al.*[29]	2015	US	≥60	223	5	89%
			<60	515		90%
Su F, *et al.*[10]	2016	US	≥70	581	5	62%
			65–69	1,738		68%
			60–64	2,663		72%
			50–59	6,801		73%*

* $p < 0.05$ between groups.

to age,[3,43]] and thus immunosuppressive requirements to prevent rejection lessen with increasing age, particularly for non-immune conditions such as NASH and alcoholic cirrhosis. In addition, as the elderly are generally more affected by immunosuppressive complications, there should be a focus on reducing or minimising immunosuppressive therapy in this lower rejection-risk population. Dual or triple immunosuppressive therapy is typically not needed and may increase the risk of infectious and neoplastic complications. Finally, clearance of immunosuppressive agents generally declines with age because of modifications in body weight, drug absorption, volume of distribution, metabolism and elimination.[44] Therefore, dosages can often be reduced over time. While not standard of care, slow withdrawal of immunosuppressive therapy is possible with advancing age and time from transplantation and could be considered in patients with related complications.[45]

Key point

On average, patients with HCC are older than patients with decompensated cirrhosis. With the growing proportion of patients being transplanted for HCC, the interactions between advanced age and post-transplant outcomes may weight even more heavily in the future.

That said, a careful assessment of graft function and histology is warranted in recipients being considered for significant weaning or withdrawal of immunosuppression. Studies have shown that a small percentage of recipients can develop immune-mediated graft injury resulting in advanced fibrosis, without having biochemical indices of liver injury.[46,47] This is more prevalent in a younger (paediatric/adult) population but can still be seen in older recipients. The effect of older donors and the aging liver itself is not well known, but it is possible that these recipients may have less reserve or recovery from overt or occult immune graft injury. We recommend that recipients being considered for aggressive weaning or withdrawal of immunosuppressive therapy should have baseline liver biopsy assessment, as subacute rejection or significant inflammation would preclude these interventions – as in a younger population.[48]

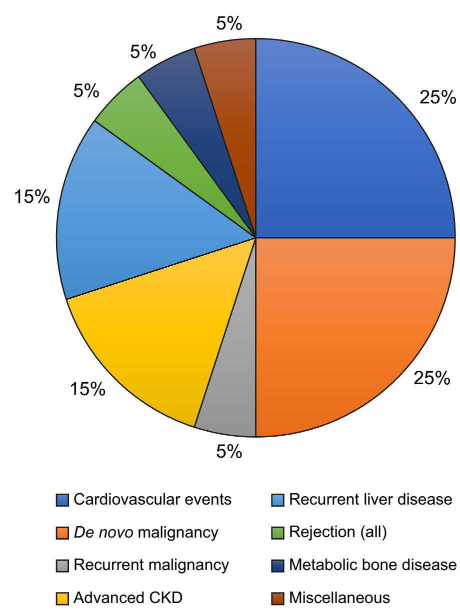

Fig. 2. Main contributors to morbidity and mortality in older liver transplant recipients. CKD, chronic kidney disease.

Aging liver transplant recipients are at significant risk of chronic kidney disease due to pre-existing kidney disease, metabolic factors, calcineurin inhibitors nephrotoxicity and other insults.[49] Age at liver transplant is one of the leading factors for progressive kidney disease and death after transplant.[50,51] Prevention and management of renal disease should follow guidelines for the general population, but there should be even more consideration for reducing calcineurin inhibitor therapy and following KDIGO chronic kidney disease guidelines with advancing age.[52]

The overall incidence of malignancy in adult liver transplant recipients is 10–15 times higher than in the general population.[53] In particular, age correlates directly with a higher rate of non-melanoma skin cancer, *de novo* solid organ malignancies,[30] and haematological malignancies such as lymphoma. Screening should follow the general population with the following considerations, particularly in older recipients: i) yearly skin examinations; ii) yearly colonoscopy for history of inflammatory bowel disease and primary sclerosing cholangitis; iii) more frequent colonoscopy than the general population (*e.g.* every 5 years);[54] iv) yearly low-dose computed tomography in current or recent smokers who are 55 to 80 years of age.[55–57]

Finally, increased bone loss due to advancing age leads to an increased incidence of bone fractures post-liver transplant.[58] All patients should be advised to perform weight-bearing exercise, take vitamin D and calcium supplements, and have bone density examination at least every 1–3 years, depending on other risk factors (steroid therapy, prior bone loss, family history). Treatment with anti-resorptive therapy should be considered in all patients with osteoporosis, recent fracture or declining bone density.

Age of the donor

Aging of the normal liver

The functional impact of aging is less pronounced on the liver than on the kidney or the heart. However, several aspects of the mechanisms involved in aging of the normal liver are important to better understand why donor age matters in liver transplantation.

As the liver ages, it tends to shrink in size with a 20 to 40% volume reduction, more marked in women than in men (Fig. 3). The hepatic arteriolar walls are thicker with a reduction in the endothelial cell fenestration and a decrease in liver blood flow. Bile acid secretion is also reduced. However, major liver functions are globally preserved in elderly individuals, although a reduction in liver cytochrome p450 activity and an increased production of pro-inflammatory cytokines have been described.[59] Metabolic modifications also occur in old livers: the gluconeogenic capacity of the liver declines with age and a physiological increase in liver lipid accumulation promotes lipotoxicity and more steatosis in the elderly.[60–62] The aging process is globally driven by an unbalanced stimulation and response of the immune system. Monocytes/macrophages, natural killer cells, regulatory T cells and peripheral B cells have decreased functions[63] and aged dendritic cells show a defect in antigen presentation and T cell activation. Finally, aged liver has been shown to have reduced regenerative capacities which must be considered when transplanting an old organ. It has been shown that a multiprotein complex involving C/EBPα, BRM (encoded by SMARCA2) and HDAC1 accumulates in the aged liver, occupying E2F-dependent promoters and modifying corresponding gene expression.[64] As human aging is associated with a decline in growth hormone, the somatotropic axis has also been involved in the

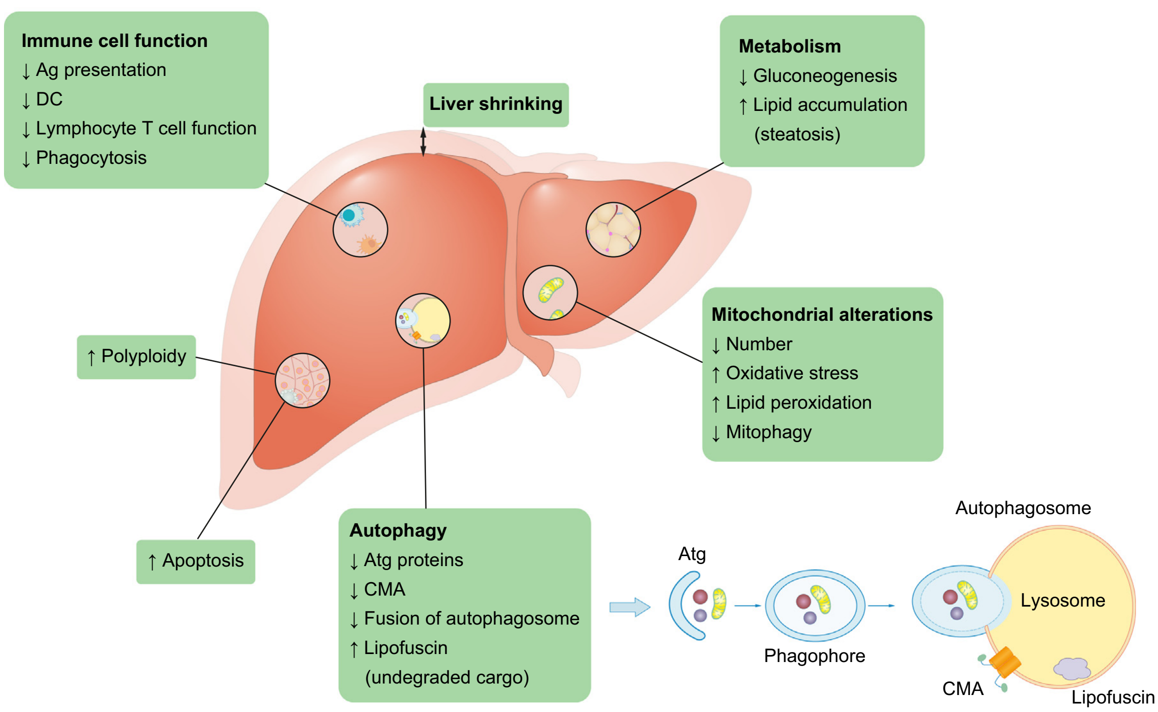

Fig. 3. Major modifications of the liver with physiological aging. *Tetraploid hepatocytes. CMA, chaperone-mediated autophagy; DC, dendritic cell.

regeneration defect of aged livers.[65] Indeed, both pathways are linked since growth hormone administration in mice lifts the age-induced regeneration break by removing this C/EBPα, Brm inhibitory complex from its promoters.[66]

Aging is also a matter of cellular senescence. Two major kinds of cellular senescence are usually described: replicative senescence (correlated with telomere shortening) and premature senescence (induced by oxidative stress or DNA damage). In normal aged livers, telomere attrition is observed in Kupffer cells and stellate cells, but not in hepatocytes.[67,68] Specific age-related liver changes have been reported at a cellular level such as reduced mitochondrial number and increased hepatocyte size, which is correlated with increased polyploidy. Polyploid cells represent 6–15% of hepatocytes in a 20-year old adult and 25–42% in the liver of an 80-year old adult.[69,70] Polyploidy is thus regarded as a marker of cellular senescence as well as a response to stress that limits the proliferation of damaged cells.[71,72]

Age-related mitochondrial dysfunction is known to cause DNA damage and lipid peroxidation, inducing a vicious cycle of increased levels of oxidative stress and higher cell sensitivity to this stress. Although oxidative damage is known to generally accumulate with age, conflicting results have been reported for the liver.[73]

While apoptosis globally increases with liver aging,[74] senescent cells are generally considered resistant to apoptosis and it has been shown that targeting apoptosis of senescent cells restores liver homeostasis modified by aging.[75] It is however expected that a balance of apoptosis should be maintained to achieve liver homeostasis.[76] Accordingly, inducing activated stellate cell senescence limits liver fibrosis[77] and targeting autophagy, which declines with age, could also be an interesting therapeutic consideration.[78]

Susceptibility to liver fibrosis also increases with age, whatever the aetiology. A higher recruitment of inflammatory cells oriented toward alternative M2-type macrophage activation is partly responsible for this higher susceptibility.[79] By increasing the production of inflammatory cytokines, decreased autophagy in phagocytic cells contributes to this predisposition.[80]

The role of senescence in carcinogenesis is more complex and still controversial. On the one hand, as long as epithelial cells are senescent, they are blocked in their proliferation, a state preventing them from being considered as tumour initiating cells. On the other hand, they can also be regarded as a reservoir of damaged cells, at risk of generating oncogenic mutations as soon as they re-enter the cell cycle. Moreover, senescent cells produce pro-inflammatory and matrix-degrading molecules. While this secretome stimulates cancer cell proliferation and epithelio-mesenchymal transition and recruits cells favouring immune tolerance, it might also attract immune cells capable of eliminating cancer cells.[81,82]

Impact of donor age on post-transplant outcome

In several series, advanced donor age was predictive of graft loss and worse post-transplant outcome.[83–89] Older donor age is also predictive of decreased survival after re-transplantation.[90] The impact of donor age on post-transplant mortality appears in donors as young as 40 years of age and increases progressively thereafter.[89] In a seminal study from the United States that derived the donor risk index (DRI),[89] the 95% confidence interval for adjusted 1-year post-transplant survival estimates dropped from 85–86% to 61–76% for donors younger than 40 years of age *vs.* donors over 70 years of age, respectively. These findings suggest that older donor age impacts early mortality after transplantation. The impact of donor age was especially important in HCV-infected patients. Advanced donor age was associated with accelerated fibrosis progression in patients with HCV recurrence along with a significant decrease in graft and patient survival.[91–94] This interaction between donor age and HCV recurrence may no longer exist following the advent of DAAs, as all HCV-infected patients can be cured either before or after transplantation. Beyond HCV-infected patients before the advent of DAAs, the mechanisms leading to increased graft loss and increased mortality when using older donors have not been clearly identified.

The DRI that combines different donor variables including age has been designed to help stratify donor-related risk of graft failure.[89] Donor age weighs heavily on the DRI. Adjusted 3-year graft survival drops from 81.2% in the lower range of DRI (≤0.1) to 60% for the highest range of DRI (>2).[89] The DRI which was originally created in the United States has been validated in Europe.[87] Since then, several scores combining donor and recipient variables have been created to better predict outcomes and to help match donors and recipients (Table S2).[83,85,86,88] While all of these scores include donor age, not all include recipient age. Again, the impact of donor age is seen in donors as young as 40 years of age.[86,88,89] A substantial amount of variability in post-transplant survival is determined by age and DCD donors.[95] However, these scores were derived before the advent of DAAs where donor age had a more important impact on HCV-infected patients. They should be revised in the era of DAAs.

Even though advanced donor age was almost always associated with worse outcomes in large populations, several series have shown acceptable results with septuagenarian or octogenarian donors.[11,96–102] Similar results have been reported with older donors as younger donors up to 5 years after transplantation, with survival rates exceeding 70% in most cases. However, it was emphasised that donors older than 70 years of age should be carefully selected and that cold ischaemia time should be reduced.[103,104] Recipients of older donors should also be selected according to the indication for transplantation. For instance, while donor age may not affect post-transplant survival in hepatitis B virus-infected patients, donor age over 60 years may result in decreased graft survival in patients without viral hepatitis.[105]

The proportion of liver transplants performed with donors older than 60 years of age has significantly increased from the early 1990 s to the early 2000 s in the United States and then tended to stabilise.[104] For transplantations using donors older than 60 years, both patients and graft survival improved over time. For instance, 5-year graft survival in the United States was 45.9% in the period 1990–1994 compared to 70.4% during the period 2010–2014.[104] Five-year patient survival increased from 56.6% to 73.2% during the same 2 periods.[104] As a consequence, the absolute difference between donors older or younger than 60 years of age in terms of graft and patient survival decreased significantly.[104] Of note, cold ischemia time for donors older than 60 years of age decreased significantly from 1990–1994 (10 hours) to 2010–2014 (6 hours).[104] Several studies suggest that the difference in post-liver transplant survival between older and younger donors mainly occurs during the first year following transplantation and stabilises thereafter.[84,97,100] However, data from the United Kingdom suggest that donor age remains predictive of mortality more than 1 year after transplantation.[106]

Overall, there is no universally accepted upper age limit for liver transplant donors, which means that donor age can be pushed over 80 years of age on the grounds of careful selection. Significant improvements have been achieved with older donors.[104] Differences in post-transplant outcomes between younger and older donors have been narrowing. Machine perfusion techniques, which are currently under development, may help further improve outcomes when transplanting older donors as well as other extended criteria donors.[107,108]

Impact of donor age in specific situations

While the association of donor age and other factors included in the DRI have been recognised to negatively impact on the results of deceased donor liver transplantation, the issue of whether advanced donor age also jeopardises the outcomes of living donor liver transplantation or transplantation using grafts from DCD donors remains a matter of debate.

The definition of advanced donor age in living donor liver transplantation logically differs from the generally accepted limits in deceased donor liver transplantation. From a donor perspective, the inherent risk associated with living donor hepatectomy implies a selection of healthy and physiologically young donors in order to reduce the risk in the donor while providing the highest volume of functional parenchyma to the recipient. It is therefore generally accepted that donor hepatectomy should preserve at least 30–35% of functional parenchyma in donors older than 50 years of age[109] and that larger liver grafts can only be harvested safely in younger donors without steatosis, provided preservation of the middle hepatic vein is achieved.[110] From a recipients' perspective, the regenerative capacity of a partial liver graft is a key factor for restoring its function after transplantation. In this setting, accumulated evidence suggests that the regenerative capacity of liver grafts from younger donors is superior to that of older donors.[111,112] In addition to better regeneration, young grafts also seem to display higher compliance and lower vascular resistance, which may lead to decreased rates of postoperative ascites.[113] Finally, the effect of aging on the arterial wall in a context of a technically challenging arterial anastomosis related to smaller vessels may intuitively lead to a higher risk of vascular and biliary complications. Although one recent series showed that a donor age of >20 years carried a higher post-transplant mortality,[114] several series suggest that donor age over 50 years or even 60 years does not affect survival after living donor liver transplantation (Table 2).[109,115–118]

The influence of donor age on the results of DCD liver transplantation is debatable, with recent series showing a significant impact of age over 60 years on graft survival,[119,120] while others failed to stratify patient and graft survival using a similar cut-off value.[121] Nevertheless, it is generally agreed that the combination of an advanced donor age and prolonged warm ischaemia time represents a risk factor for the development of ischaemic cholangiopathy and lower graft survival. Several centres traditionally discard DCD livers from donors older than 60 years of age especially in the presence of other risk factors such as increased donor body mass index or high recipient MELD score.[121] To expand the pool of available grafts using elderly DCD livers, development of strategies aimed at limiting warm ischaemia time are currently being investigated. In this situation, hypothermic[122,123] or normothermic[107] oxygenated perfusion before implantation have shown promising results in reducing reperfusion injury and intrahepatic biliary complications, both experimentally and in human DCD livers. Furthermore, these strategies may allow *ex situ* evaluation of the liver graft using various parameters to test its viability and provide additional information before proceeding to implantation.

Key point

Even though advanced donor age is associated with worse post-transplant outcomes good results have been reported with septuagenarian and octogenarian donors, with 5-year post transplant survival exceeding 70% in most series.

Table 2. Post transplant survival according to different donors and recipients age categories in adult-to-adult living donor liver transplantation.

Post-transplant survival according to donor's age in LDLT							
Author	**Year**	**Region/country**	**Patients**	**Age categories**	**Follow-up (yr)**	**Survival**	***p* value**
Kuramitsu K, *et al.*[117]	2007	Japan	434	<60 ≥60	5	72% 74%	n.s.
Shah SA, *et al.*[118]	2007	Canada	130	<44 ≥44	1	84% 86%	n.s.
Dayangac M, *et al.*[109]	2011	Turkey	150	<50 ≥50	1	83% 79%	n.s.
Goldaracena N, *et al.*[115]	2016	Canada	469	<50 ≥50	5	83% 79%	n.s.
Kim SH, *et al.*[116]	2017	Korea	540	<50 ≥50	1	95% 95%	n.s.
Post-transplant survival according to recipients' age in LDLT							
Yoshihizumi T, *et al.*[139]	2010	Japan	267	<60 ≥60	5	78% 70%	n.s.
Ikegami T, *et al.*[140]	2014	Japan	411	<65 ≥65	5	79% 89%	n.s.
Ushigome H, *et al.*[141]	2016	Japan	76	<60 ≥60	5	83% 83%	n.s.

LDLT, living donor liver transplantation.

Age matching between donors and recipients

Lessons learned from kidney transplantation

Because of an organ shortage in kidney transplantation, there has been a trend towards the use of older donors, although it has become evident that kidneys from older donors have reduced functional reserve and graft survival.[124] Because older recipients have shorter life expectancy than younger recipients and frequently die with a functional graft, transplant nephrologists have proposed allocation policies including age matching.[125,126] The aim is to allocate the highest quality grafts to recipients likely to derive the highest long-term benefit. Interestingly, factors influencing both organ quality and post-transplant survival are donor and recipient age, factors which have been incorporated in the scores guiding graft allocation in Europe and the United States.

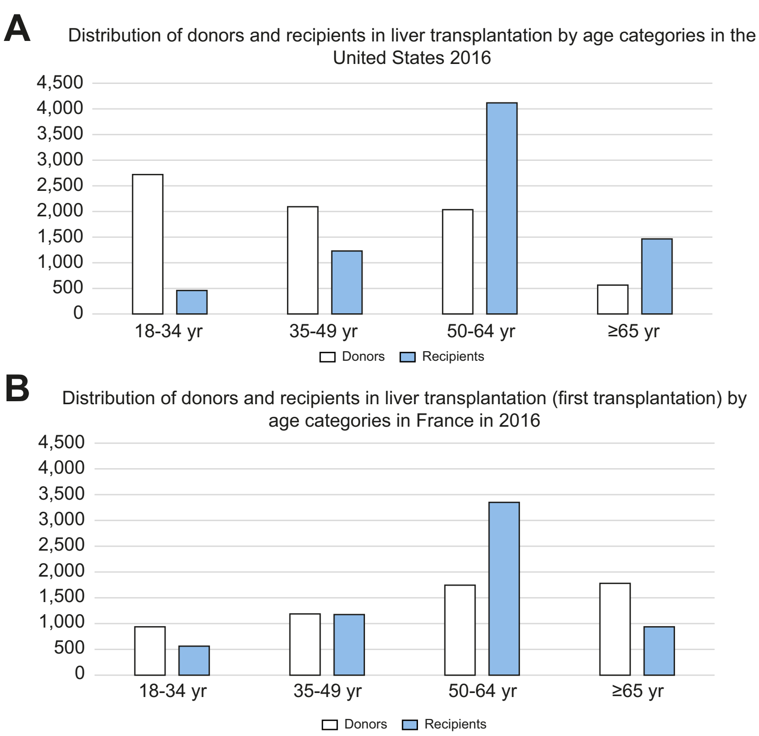

Fig. 4. Distribution of donors and recipients by age categories in the United States and Europe in 2016. (A) Data from the United Network for Organ Sharing (https://unos.org) (B) Data from the European Liver Transplant Registry (www.eltr.org).

Age matching between donors and recipients in liver transplantation: A complex issue

The scenario in liver transplantation is much more complex than in kidney transplantation since aging of the liver has less functional consequences. In addition, by contrast to patients with end-stage renal diseases who can be placed on dialysis, no effective artificial liver support exists. So far, in contrast to kidney transplantation, no allocation policy including age matching has been implemented for liver transplantation. Even though good results can be achieved by using old donors in young recipients,[127,128] it clearly appears that the impact of old donor age is more pronounced in younger recipients[129] and that redistributing young donors to young recipients might improve outcomes.[130] However, there is an imbalance between the age of the donors and the age of the recipients (Fig. 4A and 4B)

Numerous factors involving donors, recipients and interactions between donors and recipients in specific situations should be considered to optimise age matching in liver transplantation (Box 1). In addition, age matching is fundamentally driven by allocation policies and the pre-defined objectives of these policies (equity *vs.* utility) (Fig. 5). For instance, the main objective of the MELD score-based "sickest first" allocation policy is to guarantee equal access to organ allocation for any patient with end-stage liver disease and to reduce waiting list mortality, provided expected

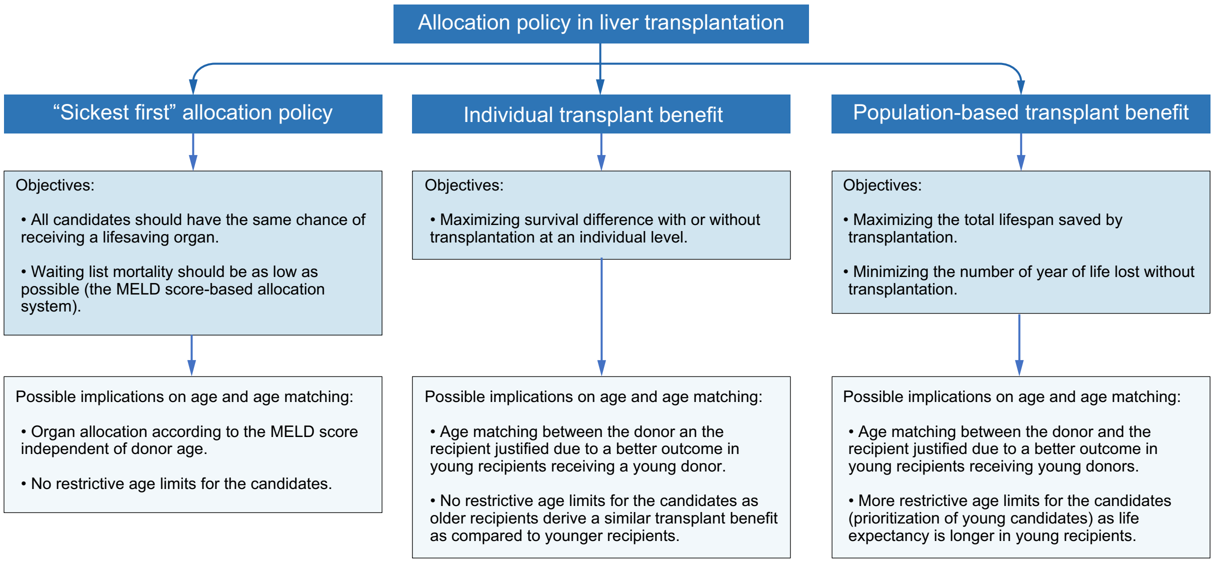

Fig. 5. Examples of possible implications age limits in candidates for transplantation and age matching between the donor and the recipient according to different allocation policies. MELD, model for end-stage liver disease.

Box 1. Factors that need to be considered for age matching in liver transplantation

Factors

- Different distribution of age categories between donors and recipients
- Waiting risk mortality and risk of dropout
- Post-transplant mortality
- Post-transplant morbidity
- Transplant benefit (difference between survival without transplantation and survival with transplantation)
- Years of life lost without transplantation at an individual level
- Years of life lost without transplantation at the level of the whole population of transplant recipients
- Costs related to pre- and post-transplant management
- Post-transplant quality of life
- Interactions between the age of the donor and the MELD score in the recipient
- Interactions between the age of the donor and the severity of disease recurrence after transplantation

5-year post-transplant life expectancy is of at least 50% (a pre-requisite that is commonly referred to but may be considered too liberal). In order to achieve these objectives, the sickest candidates should be prioritised irrespective of the age of the donor. In a context of equity, older candidates may be given similar access to transplantation as younger candidates. Of note, age matching is not considered in the MELD score-based policy which is a limitation.

Moving from an MELD score-based allocation policy to a different policy based on utility would inevitably change the rules concerning age matching. For instance, the objective of a survival benefit-based allocation policy is to maximise the difference between life expectancy after transplantation and life expectancy without transplantation.[131,132] In order to achieve this goal, age matching between the donor and the recipient would be recommended as the harmful effect of older donors on post-transplant survival is more pronounced in younger recipients.[129] However, prioritisation of younger candidates may not be mandatory as transplant benefit is similar in younger and older recipients.[10]

Finally, the objective of a population-based transplant benefit policy would be to optimise the number of years of life saved by transplantation. To achieve this goal, age matching would be justified as the outcome is better in young recipients receiving young donors.[129,130] However, by contrast to the individual transplant benefit-based policy, younger recipients should be prioritised whatever the age of the donor as life expectancy is higher in younger patients (Fig. 5). Such a policy would result in limited access to transplantation for older candidates. In a recent European study where the mean age of the donors was 55.2 ± 19 years and the mean age of the candidates was 53 ± 9 years, an allocation policy based solely on age matching starting from the youngest candidates would only supply organs for candidates up to 56.7 years of age.[130]

Scores that utilise donor and recipient variables to predict post-transplant outcomes have been designed to guide organ allocation. The SOFT score and the BAR score typically include age matching.[85,86] However, the predictive value of these scores is weak with c-statistics lower than 0.7 (Box 1). The lack of accuracy could be related to the fact that important variables such as steatosis are not considered.

The issue of interactions between age matching and the MELD score of the recipient have not been explored specifically. However, high DRI seems to be harmful in recipients with a low or intermediate MELD score while patients with a high MELD score derive a similar transplant benefit regardless of DRI.[133,134]

Overall, no ideal age matching exists and the way to incorporate age matching depends upon the allocation policy. Strong arguments suggest that the existing allocation policies should be revised to include age matching. A 2-step process with prioritisation according to the risk of dying without transplantation and then some degree of age matching would likely result in improved post-transplant outcomes without affecting waiting list mortality. For instance, statistical models applied in a European population suggest that age matching between the donor and the recipient would reduce the lifespan gap between younger and older recipients by 33% and would achieve a 14% overall reduction in years of life lost.[130]

Key point

Age matching between the donor and the recipient is driven by the objectives of different allocation policies based on either individual or population-based benefit or either equity or utility.

Conclusions

There is no universal age limit for transplantation but physiological condition including frailty and comorbidities are important to consider in older candidates. Efforts should be made to identify combinations of age, comorbidities and frailty that reduce transplant benefit in older recipients up to the point that transplantation may be futile.

In parallel, the cohort of elderly patients who were transplanted 1 to 3 decades ago is growing and these patients are mainly exposed to non-liver related complications. Aging of the liver does not seem to be associated with major impairment in liver function. However, little is known about aging of the transplanted liver. As mentioned previously, it is generally accepted that immunosuppression should be reduced as much as possible in older recipients and/or patients transplanted more than 10 years ago. Yet, various liver changes, such as immune-mediated graft injury and *de novo* cryptogenic cirrhosis, are observed in patients undergoing late liver biopsy.[135] The possible role of "occult" rejection, especially humoral rejection, should be clarified to better tailor long-term immunosuppression[136,137] and biopsies performed prior to more aggressive weaning or withdrawal of immunosuppression are warranted to avoid stimulating significant immune injury.

There is no donor age limit in DBD liver transplantation. Due to organ shortage, older donors are needed. However, careful selection and short cold ischaemia times are mandatory to achieve good results. A number of arguments support age matching in liver transplantation. Age matching is a difficult issue as age categories are not equally distributed in donors and recipients. In addition, age matching depends upon the objectives of different allocation policies (individual *vs.* collective benefit). A multistep approach to matching that considers waitlist mortality but also transplant benefit seems a reasonable approach that needs to be explored. Flexible allocation algorithms including age matching should be developed from the perspective of periodic assessment of the global results of a given policy (waitlist mortality, post-transplant outcomes, transplant benefit…) and changes in epidemiology. Finally, relatively stringent age limits have been established in DCD transplantation. These limits might be challenged with the advent of machine preservation techniques.

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Acknowledgments

The authors are indebted to Dr Vincent Karam who provided ELTR data on donors and recipient's age in Europe

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.009.

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