Transplant of Elderly Patients

Is There an Upper Age Cutoff?

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KEY POINTS

- Chronologic age is not a contraindication for liver transplant (LT); physiologic age is a more accurate indicator of functional status.
- The volume of wait-listed LT patients older than 65 years increased from 8.1% to 24.1% from 2002 to 2018.
- The volume of transplanted patients more than 65 years of age has increased from 6.8% in 2002 to 21.5% in 2019.
- Elderly LT recipients (older than 60 years) with body mass index greater than 30, hypertension, and diabetes mellitus type 2 have a 50% increased risk of postoperative cardiovascular mortality at 12 months and therefore need additional scrutiny during selection.
- Patient and graft survival rates after liver transplant in elderly recipients are lower compared with young recipients, but the survival benefit gained from LT is significant.

INTRODUCTION

Recent decades have witnessed an overall increase in life expectancy, particularly in developed countries, which in combination with decreased fertility rates has led to an increased prevalence of rapidly aging populations on a global landscape.[1] According to the 2019 United Nations (UN) data, 1 in 4 persons in Europe and North America will be more than 65 years old and those older than 80 years of age are expected to triple in number by 2050.[2] The increased life expectancy in the general population is also

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associated with an increased number of elderly patients who have end-stage liver disease (ESLD) and are in need of a liver transplant (LT). Based on a report from the World Health Organization, cirrhosis is the seventh most common cause of mortality in people older than 60 years.[1] Based on the Organ Procurement and Transplantation Network (OPTN) 2018 annual data report, the volume of wait-listed LT patients older than 65 years has steadily increased over time, representing 24.1% in 2018.[3] Not only the wait-listing trend but also the volume of LT in the same age group from 2002 to 2019 increased from 8% to 23% according to OPTN database[3] (**Fig. 1**). There are other noticeable trends with regard to the cause of ESLD and the indications for LT in the aging population. On one hand, chronic hepatitis C virus (HCV) in the elderly is decreasing but, in contrast, nonalcoholic steatohepatitis (NASH), alcoholic liver disease, and hepatocellular carcinoma (HCC) are increasing indications for LT.[4] As per current American Association for the Study of Liver Diseases (AASLD) guidelines, chronologic age in itself is not an absolute contraindication for LT.[5] Biological or physiologic age is the current strategy for patient selection for LT, accounting for factors other than just the chronologic age, such as nutritional status, functional status, lifestyle, and comorbid conditions. The stringent and individualized pretransplant selection of elderly patients has led to favorable posttransplant outcomes in several studies.[4,6–11] Although the feasibility of LT in elderly population does not seem to be problematic in terms of surgical technique and outcomes, the controversial issues are with regard to the ethical principles of utility and equity. This article reviews and summarizes the transplant outcomes in elderly patients, with a specific focus on patients older than 70 years of age, unless specified otherwise.

DISCUSSION
Pretransplant Evaluation Strategies

Cardiovascular
A rigorous cardiovascular pretransplant evaluation is paramount for every patient but more so in elderly NASH candidates because of increased prevalence of cardiovascular disease (CVD).[12] However, the ability to identify suitable candidates a priori who would
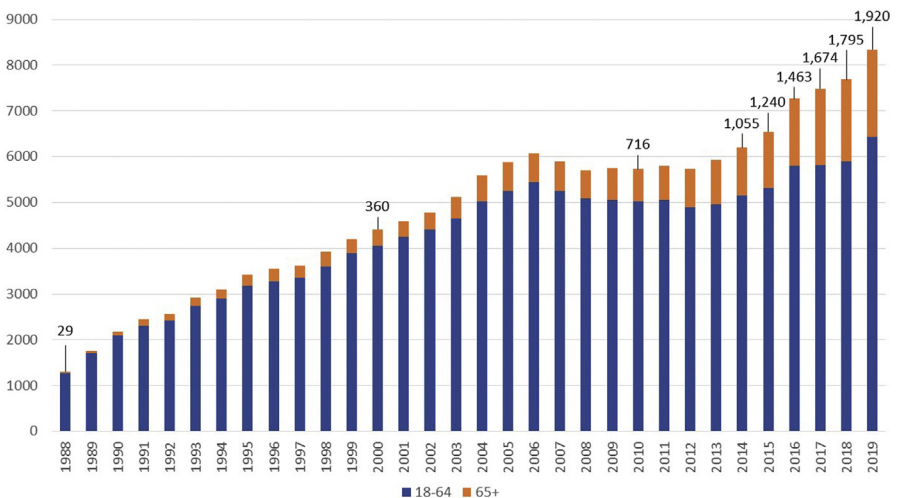

Fig. 1. Total adult LTs by recipients age from 1988 to 2019 (based on OPTN database as of June 18, 2020).

benefit from LT is difficult and is not well established. Patients with NASH have higher prevalence of coronary artery disease (CAD) and cardiovascular mortality at 1 year post-LT compared with other causes of liver diseases.[12] Age more than 60 years, a body mass index (BMI) greater than 30, hypertension, and diabetes mellitus (DM) type 2 are associated with an increased risk, as high as 50%, for early post-LT mortality.[13] Moderate to severe CAD is prevalent in up to 27% in LT candidates more than 50 years of age.[14] Cirrhotic cardiomyopathy, characterized by a blunted stress response, diastolic dysfunction, and QT prolongation is also a frequent finding during pre-LT screening (up to 50%) and its presence is associated with increased risk of overt heart failure in the early post-LT period.[15] Presence of atrial fibrillation pre-LT has been associated with increase intraoperative cardiac events, ventricular arrhythmias, cardiogenic shock, cardiac arrest, and deaths.[16] Portopulmonary hypertension (PPHTN) is prevalent in 4% to 8% of LT candidates, characterized by mean pulmonary artery pressure greater than 25 mm Hg in the setting of portal hypertension and is associated with higher perioperative mortality. However, data from large population studies do not show any significant difference in the rates of atrial fibrillation or PPHTN in the elderly.[16–18]

AASLD guidelines suggest electrocardiogram (ECG), transthoracic echocardiography (TTE), and pharmacologic stress test for all LT candidates. Cardiac computed tomography angiography, a noninvasive screening tool, has high sensitivity and specificity to detect coronary plaques and has a negative predictive value of 83% to 99% to screen for hemodynamically significant CAD.[19] Coronary artery calcium score (CACS) greater than 400 correlates well with high-risk CAD,[20] early cardiovascular events, and cardiac death after LT.[21] Older age and DM have also been associated with CACS greater than 400 in LT recipients.[21]

Coronary angiogram remains the gold standard for diagnosis and treatment of symptomatic CAD. Coronary angiography is endorsed in high-risk LT candidates with 3 or more risk factors: age older than 60 years, tobacco use, hypertension, DM, or dyslipidemia,[22] or in those with abnormal noninvasive cardiac testing. Revascularization before LT is recommended in those with coronary stenosis greater than 70% regardless of symptoms.[5] However, the role of angiogram in patients with asymptomatic ESLD is controversial because of the high incidence of postprocedure complications, bleeding, and contrast nephropathy, and the unclear survival benefit of revascularization in the absence of symptoms.[23] Uniform CVD screening protocols for the elderly transplant candidates are not well established; nonetheless, a thorough cardiovascular evaluation is imperative, especially in elderly and high risk patients.

Malignancies

Elderly patients with ESLD are at high risk of developing extrahepatic cancers (EHCs), with different incidence rates that vary with the cause of underlying liver disease. A recent population-based analysis reported increased rates of extrahepatic and liver malignancies among patients with chronic liver diseases.[24] Non-Hodgkin lymphomas, especially B-cell lymphomas and leukemias, are frequently observed in viral liver diseases (hepatitis B virus [HBV] and HCV), whereas gastrointestinal malignancies involving the colon, esophagus, and oropharynx are common in NASH and alcoholic liver disease.[24,25] Incidence of EHCs, both lymphoid and solid organ cancers, peaks in men after 65 years of age and in women after 75 years of age.[26] In LT recipients older than 70 years, malignancies are responsible for 20% of all-cause mortality after transplant.[4] Ear-nose-throat and lung malignancies are common in elderly transplant candidates with active or prior history of smoking. Most transplant centers require a tumor-free interval of 1 to 5 years for LT candidacy, except for some cancers that have curative expected survival that exceeds post-LT survival (eg, a few histologic

variants of renal cell carcinoma) that have curative expected survival that exceeds post-LT survival.[27,28] No defined screening protocols are in place for elderly LT candidates; however, it is prudent to screen for EHCs based on the risk factors.

Nutritional and functional status

Pre-LT evaluation must include evaluation of candidates' functional and nutritional status. Sarcopenia, defined as a loss of skeletal muscles, is commonly seen in elderly patients,[29] as is malnutrition. Other markers of functional and nutrition status are also notably impaired in the elderly. Elderly patients more than 65 years old have more functional impairment and lower Short Physical Performance Battery (SPPB) scores than their younger counterparts. SPPB score less than 9 in elderly LT candidates was associated with higher waiting-list mortality compared with younger, not impaired patients with SPPB score more than 9.[30] Taking the intrinsic vulnerabilities and increased health burden from the comorbid conditions into consideration, the pre-transplant evaluation of elderly transplant candidates should be more inclusive and multidisciplinary than for the general population.[5]

Intraoperative Morbidity

Intraoperative hemorrhage, volume status, ascites, and cardiomyopathy can cause serious alterations in cardiac output, especially in the elderly.[31] However, operative time does not seem to be affected by recipient age.[6,10,32] Higher requirement for fluid resuscitation and transfusions, packed red blood cells (PRBCs), platelets, and fresh frozen plasma among the elderly had been reported in older studies,[32] but recent studies have reported no differences.[6,10] Cardiovascular events are responsible for 40% of early post-LT mortality (within 30 days) and is more frequent in the elderly, especially in those with NASH, DM, hypertension, and chronic obstructive pulmonary disease (COPD). Older age, DM, and COPD have been associated with higher rate of cardiac arrest.[33] Patients older than 50 years have a higher cardiac event rate of 7.5% (compared with 5.1% in younger patients) and a mortality of 0.8% to 1.2%.[33,34] Intraoperative complications could be higher than the reported rates because the data are possibly biased by the strict selection and may not apply to all elderly transplant candidates. Nonetheless, advanced age and NASH seem to have a negative impact on the early post-LT survival because of higher rates of cardiovascular events.

Posttransplant Complications

Graft survival

In general, acute cellular rejection is less frequent in elderly solid organ transplant recipients. A combination of factors, such as reduction in the proportion of naive T cells, dysfunction of memory cells, and age-related altered metabolism of immunosuppressant, are implicated as plausible mechanisms for the low rates of rejection in elderly LT recipients.[35] Aging also reduces the tolerance of foreign antigens and self-antigens (autoimmunity).[35] According to the OPTN database, early graft survival rates were similar among younger recipients and recipients older than 65 years of age, but the survival rate diminishes in the elderly in subsequent years. Graft survival at 1, 3, and 5 years is 89.1%, 79.8%, and 71% in the younger recipients, whereas it is 86.6%, 75.2%, and 65.9% in elderly recipients (Fig. 2). Graft survival at 10 years post-LT in the elderly more than 70 years old is 41.7% compared with 60.9% in younger recipients.[6] According to the OPTN database, early graft survival rates were comparable among younger and older recipients but the survival rate diminishes in the elderly in subsequent years. Data regarding immunosuppressive regimens in the elderly are scarce and have been limited to single-center experiences. It is common practice in
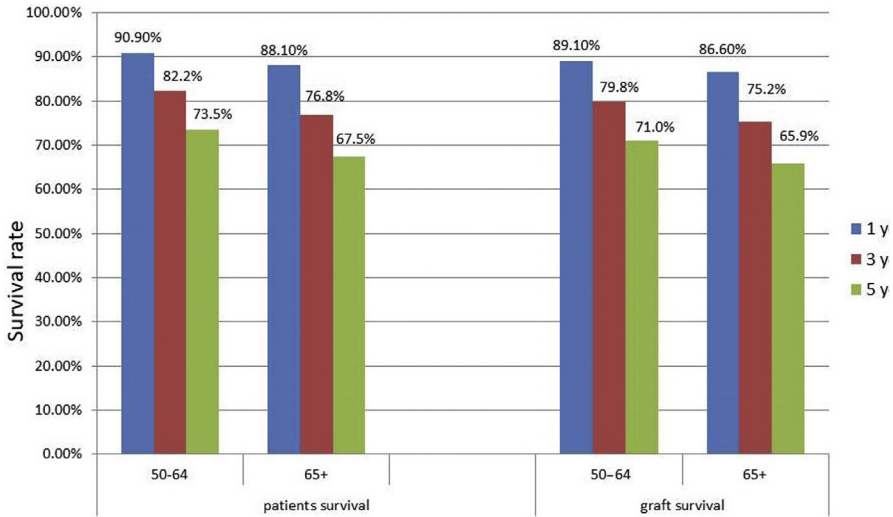
Fig. 2. Patient and graft survival rates for transplant from 2008 to 2015 in United States (based on OPTN database as of June 12, 2020).

most centers to administer lower doses of immunosuppression in most elderly transplant recipients because they are generally at high risk for DM, hypertension, CVD, and renal impairment.[36] Immunosenescence and immunosuppression may play a role in HCC recurrence in elderly recipients. Biliary complications account for 9.6% of graft failures and have similar incidences in younger and elderly LT recipients.[37]

Patient survival

Elderly patients with chronic liver disease are at higher risk of other comorbidities, such as malignant neoplasms, CVD (hypertension, ischemic heart disease, arrhythmias, cardiomyopathies, aortic dissection), respiratory illnesses, diabetes, dyslipidemia, gout, hypothyroidism, cerebrovascular disease, and renal failure.[38] The presence of these comorbidities, as well as other characteristics inherent to the elderly, in particular an impaired immune system, increases the likelihood of opportunistic infections and other complications, such as erectile dysfunction, osteoporosis, malignancy, and depression.[11] The utility and benefit of LT in this population have been evaluated since the 1990s, reporting what were initially contradictory and variable posttransplant survival rates ranging from 35% to 83% at 3 years.[39,40] Most of the early evidence showed that selected elderly (adults >60 years of age) had variable outcomes and survival compared with younger adults.[41–48] In 1991, a single-center retrospective analysis of 156 LT patients more than the age of 60 years found that the 3-year survival rate in the elderly population was comparable with the younger recipients, concluding that advanced age was not a contraindication to LT.[43] In another prospective trial including 735 LT recipients between 1990 and 1994, recipients older than 60 years had longer hospital/intensive care unit (ICU) stay and lower 1-year post-LT survival rate compared with the younger recipients: 81% versus 90% respectively.[47] The excess mortality among the older recipients was attributable to infections, cardiac events, or neurologic events.[47] Advances in immunosuppression and management of chronic comorbidities have improved outcomes in more recent years across all ages and in the elderly.

A single-center analysis from the Mayo Clinic included all LTs performed between 1998 and 2004, reporting that mortalities at 1, 3, and 5 years after transplant for elderly recipients were 10%, 14%, and 27% respectively, compared with those of younger patients, which in turn were 12%, 21%, and 24%.[32] An analysis of 46,772 LTs performed from 1994 to 2005 in the United Network for Organ Sharing (UNOS)/OPTN database found that 17% of the recipients were older than 60 years. Out of the 5 strongest factors that would predict poor patient survival, 4 of those elements were inherent to the recipients, such as the need for mechanical ventilation, history of DM, positive HCV serology, and creatinine levels of 1.6 mg/dL or higher. The fifth factor was a combined recipient and donor age of 120 years or more. Taking these variables into account, an older recipient prognostic score (ORPS) was created, with each variable accounting for 1 point. ORPS groups ranged from 1 to 5, and patients in ORPS group 1 experienced 1-year, 3-year, and 5-year survival rates of 85%, 77%, and 69%, whereas those in ORPS group 5 had 1-year, 3-year, and 5-year survival rates of 73%, 48%, and 41% respectively. In this patient population, data from this study found that the Model for End-stage Liver Disease (MELD) score was a poor posttransplant prognostic indicator.[49]

A retrospective study that analyzed LT recipients from the UNOS/OPTN registry between 2002 and 2012 reported an overall 5-year survival of 59% in elderly (>70 years old) HCC recipients and 68.6% in younger HCC recipients. In those without HCC, the 5-year survival rate was 61.2% versus 74.2% in elderly and younger patients, respectively. Similar trends were noted in those with or without HCV, 5-year survival in HCV-positive elderly versus younger patients was 60.7% and 69%, and in HCV-negative elderly versus younger patients was 62.6% and 78.5% respectively.[50]

Another retrospective analysis of 3104 recipients from a single-center database in the United States, transplanted from 1998 through December 2016, aimed to determine other factors that were related to decreased overall patient survival, identifying those in the pretransplant, peritransplant, and posttransplant settings. In terms of the recipients, they found that advanced age, HCC history, the need for hospitalization before LT, and increasing PRBC requirement were significant. Around the time of transplant, a longer total operating time, the cold ischemia time (CIT), and the warm ischemia time all correlated negatively with survival. Posttransplant events such as hospital length of stay, need for ICU management, and donor characteristics (University of California, Los Angeles, extended criteria donors [ECD] score equal or higher than ≥2 and cerebrovascular/stroke as the cause of death) were significantly associated with decreased overall patient survival.[6]

Another study used information from a national database in Korea that included all adult patients who underwent LT from 2007 to 2016, totaling 9614. Of these, a cohort of 84 LT patients more than 70 years of age was evaluated; elderly patients had increased in-hospital mortality and hospitalization costs.[51] Despite this and other data supporting worse transplant survival in the elderly, some investigators argue that, without transplant, these patients would also have a lower survival than younger patients at any MELD score, and therefore support transplant, finding that these patients do have a survival benefit derived from it.[4] **Table 1** summarizes results of studies evaluating outcomes after LTs in elderly patients since 2002 (post-MELD era). In the postoperative period, the care of elderly recipients poses a few characteristic challenges compared with younger patients, in order to avoid complications that could negatively affect posttransplant morbidity and mortality, such as decline of bone health, worsening of CVD, and development of malignancies.[39]

Table 1
Reported data for patients and graft survival in literature

Study, Year	Area	Donor Type	Sample Size (n)	Age at LT (y)	Patients Survival
Goldberg et al,[80] 2020	United States UNOS 2002–2018 SLK	NA	93	≥70	5 y: 68.8% (without CKD) 5 y: 57.8% (with CKD)
Mousa et al,[6] 2019	United States Single center	DDLT	162	≥70	5 y: 70.8% 10 y: 43.6%
Cullaro et al,[7] 2020	United States UNOS 2003–2017	LDLT-DDLT	11,775	≥65	HCC: 1 y: 90% 5 y: 79% No HCC: 1 y: 87% 5 y: 78.5%
Kollmann et al,[102] 2018	European Union (Austria) Single center	NA	76	≥65	1 y: 71% (73% MELD era) 5 y: 48% (60% MELD era)
Sharma et al,[50] 2017	United States UNOS/OPTN 2002–2012	DDLT	1514	≥70	5 y: 60%
Su et al,[4] 2016	United States UNOS 2002–2014	LDLT-DDLT	1666	≥70	5 y: 62%
Sonny et al,[9] 2015	United States Single center 2004–2010	NA	223	≥60	5 y: 75.8%
Wilson et al,[8] 2014	United States SRTR/UHC	DDLT	323	≥70	1 y: 85% 5 y: 64%
Malinis et al,[37] 2014	United States UNOS 2002–2011	LDLT-DDLT	4254 1265	60–69 ≥70	5 y: 65% 5 y: 57.5%
Schwartz et al,[103] 2012	United States UNOS 2010	DDLT 1 LDLT	480	≥70	5 y: 55%
Taner et al,[104] 2012	United States Single center	DDLT	13	≥75	5 y: 54%
Aloia et al,[49] 2010	United States UNOS 1994–2005	NA	631	≥70	5 y: 56%
Aduen et al,[32] 2009	United States Single center	DDLT	42	≥70	5 y: 63%
Lipshutz et al,[105] 2007	United States Single center	DDLT	62	≥70	1 y: 73.3% 3 y: 65.8% 5 y: 47.1% 10 y: 39.7%
Safdar et al,[11] 2004	United States Single center	DDLT	33	≥70	1 y: 78.79% 3 y: 71.43%,
Zetterman et al,[47] 1998	Multiple centers	NA	135	≥60 y od	1 y: 81%
Rudich & Busuttil,[45] 1999	United States Single center	DDLT	33	≥70	1 y: 60%

Abbreviations: CKD, chronic kidney disease; DDLT, deceased donor LT; LDLT, living donor LT; NA, not available; SLK, simultaneous liver-kidney transplant; SRTR, Scientific Registry of Transplant Recipients; UHC, University HealthSystem Consortium.
Data from Refs.[4,6–9,11,32,37,45,47,49,50,80,102–105]

Bone health in post–liver transplant setting

Bone loss accelerates in the first 6 months after LT, regardless of the pretransplant bone mineral density, and it is associated with increased risk of fractures, which in turn causes significant morbidity and reduced quality of life; 6 to 12 months after LT, bone loss reverses and there is a gain in bone density.[52] Osteoporosis is reported in up to 36% of elderly LT candidates compared with 5% in age-matched healthy peers regardless of gender.[53] There is a substantial risk of decline in bone health and an increase in pathologic fractures of up to 35% in the immediate posttransplant period.[54] Of the 360 LT recipients with cholestatic liver disease transplanted at the Mayo, 20% had a fracture in the pre-LT period. There was a sharp increase in fracturing, with a 30% cumulative incidence of fractures at 1 year post-LT, and the strongest risk factors were pretransplant fractures, severity of osteopenia, and glucocorticoid use.[55] Limiting the exposure to corticosteroids is generally possible because of the decreased requirement for immunosuppressants in the elderly. Single-center studies have found a lower incidence of rejection and higher rates of infection and cancer in the elderly.[11,32,43] The changes of the immune system in the elderly seem to confer a protective effect against rejection, because most cell-mediated and humoral immune responses decline with advancing age. Both T-cell and B-cell activation, transit through the cell cycle, and subsequent differentiation are significantly diminished in the elderly.[56]

Cardiovascular diseases

Cardiovascular health can significantly affect the perioperative period, as well as posttransplant outcomes. In the past, evidence suggested that patients with angiographically proven CAD had an overall mortality of 50% over a follow-up period of 1 to 3 years.[57] Physiologic changes in this age group, such as increased left ventricular mass, increased arterial stiffness, coronary atherosclerosis, and altered vascular regulation, can be responsible for their limited reserve. Data from a multicenter study that evaluated the outcomes of 630 patients who had undergone coronary angiography as part of their pretransplant evaluation, comparing the 151 patients who had CAD with the rest, were published in 2013. Despite the presence of several cardiovascular risk factors, revascularization and medical therapies used before LT were shown to be effective did not affect survival post-LT; patients with a history of severe CAD who underwent preoperative coronary intervention were able to safely undergo LT without being at a higher risk for short-term mortality.[58]

Malignancies

De novo malignancies represent another leading cause of mortality in the elderly after LT[59–61] and are mostly triggered by the immune dysregulation caused by immunosuppressive agents and opportunistic infections with carcinogenic viruses (Epstein-Barr virus, human papilloma virus), primary sclerosing cholangitis, smoking, and alcohol abuse.[52] In a registry that included 175,732 solid organ transplant recipients (21.6% for liver) in the United States, incidence of overall cancers was 1375 per 100,000 person years, with the most common malignancies being non-Hodgkin lymphoma and cancers of the lung, liver, and kidney.[62] An analysis of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplantation Database, including liver recipients from 3 clinical centers, showed that 22% of transplanted patients developed a de novo malignancy during the 12.6-year study period. The incidences of de novo malignancy within 1, 5, and 10 years were 3.5%, 11.9%, and 21.7%, respectively, with highest risk of solid organ malignancies (hazard ratio [HR], 1.26) and skin malignancies (HR, 1.81) in the elderly recipients.[59,63,64]

Does donor age matter in elderly liver transplant recipients?

With increasing demand for organs, transplant centers have used several donor pool expansion strategies, such as the use of living donors, cadaveric split livers, and ECDs. ECDs have underlying factors associated with poor graft function and increased risk of graft failure, such as hypernatremia, prolonged warm ischemia time, pressor requirement, donation after cardiac death, and advanced donor age.[65] Older liver grafts could have unfavorable age-related attributes, such as fibrosis, steatosis, atherosclerosis, and increased activation of proinflammatory and apoptotic genes, which can result in higher risk of injury during ischemia-reperfusion.[66] Grafts from older donors also carry a higher susceptibility to CIT,[67,68] primary nonfunction, and delayed graft function[69] and is independently associated with poor 5-year graft survival.[37] A single-center, retrospective analysis of LT from 1990 to 2007 that included 91 older donors (>60 years old) and 650 younger donors reported that neither patient survival rates nor graft survival rates had any disadvantage.[70] In 2016, Barbier and colleagues[71] compared 253 recipients of younger grafts with 157 recipients of older grafts (>75 years old) and reported no significant differences in primary nonfunction, hepatic artery thrombosis, biliary complications, graft survival, or retransplant rates among both cohorts. A very small, single-center study had also reported favorable outcomes with donors older than 80 years, using morphologic appearance of the liver at time of harvesting and presence of steatosis as factors that determined the use of these organs.[72] A larger cohort study from Italy also found comparable 1-year, 3-year, and 5-year survival rates in recipients of grafts from octogenarian and younger donors. However, the study pointed out that increased donor age may portend worse outcome if the donor had increased transaminase levels and if the graft was used in sicker recipients (HCV positive, higher MELD scores).[73] Since 2006, the donor risk index, a model based on quantified surrogates of donor quality, has been used to differentiate between lower-risk and high-risk donors, with higher scores correlating with decreased survival.[74] Evidence from the analysis of 8070 liver recipients aged 60 years or older, transplanted from 1994 to 2005, suggested that the strongest prognostic factor for LT recipients 60 years old or older was the allocation of a liver allograft from an older donor that created a recipient and donor age combination equal to or greater than 120 years, because in those cases there was a 20% reduction in postoperative survival.[49] In an age-matched LT study, older recipients were at higher risk of death posttransplant, independent of age matching, and the predictors of poor prognosis were high MELD scores, retransplant, and prolonged CIT.[75] Elderly donors did not affect patient survival, and, even though the recipient's age independently increased the risk of death, matching older donors to older recipients did not confer an additional risk. The optimal recipients of older donor grafts are first-time recipients, those with body mass index less than 35, non–status 1, low biological MELD score, and CIT of less than 8 hours. Resulting evidence therefore supports the use of older livers in older recipients, as long as other risk factors are minimized.[75] Grafts from donors older than 70 years of age are still underused in some parts of the United States, with a discard rate of approximately 26%, but the use of older donor organs could be optimized by adjusting for aforementioned recipient-specific factors. Current UNOS/OPTN allocation for livers does not follow age matching, but transplant centers assign the livers from elderly donors in the appropriately selected patient populations in whom the strategy was proved to be safe.[76,77]

LIVING DONOR LIVER TRANSPLANT IN THE ELDERLY

Scarce data mostly derived from single-center non-US transplant centers is available with regard to living donor LT (LDLT) in the elderly. Ethics discussion for LDLT in the

elderly is even more difficult and needs to balance the operative risks of the younger donor to be justified by recipient gain of life years and quality of life. Japanese and Korean studies reported no survival differences in the elderly and the younger LDLT recipients.[61,78] Moreover, a significantly lower incidence of graft failure in recipients older than 65 years was observed.[61] In US studies, Su and colleagues[4] reported 3% of LDLT in recipients older than 70 years, but the post-LT survival rate for this subgroup was not reported. LDLT in elderly recipient seems to be feasible and confers a reasonably good survival rate in high-volume LDLT centers. However, the existing data are limited and the impact of LDLT in the elderly needs to be evaluated in a more systematic fashion.

SIMULTANEOUS LIVER-KIDNEY TRANSPLANT IN ELDERLY

Current data with regard to simultaneous liver-kidney transplant (SLK) in the elderly are limited. An age cutoff of 65 or 70 years has been proposed because of previous reports of unfavorable outcomes in SLK recipients.[79] A recent study analyzing the UNOS database of SLK recipients from 2002 to 2018 reported a constant increase of older recipients with chronic kidney disease. Among the total SLK recipients, 17% were older than 65 years of age and 3% were older than 70 years. The latter age group showed a statistically significant increased mortality risk after SLK compared with all other age groups. Comparison between young nondiabetic recipients and older recipients (independent of DM status) showed survival rate differences of 10.3%, 25%, and 31% at 1, 5, and 10 years. Among all age groups, the elderly cohort (>70 years old) experienced a 5-year survival less than 60%.[80] Therefore, in the SLK setting, a chronologic age of 70 years seems to be a reasonable cutoff, at least until more systematic data become available in the future.

ETHICS

In 1984, the National Organ Transplant Act (NOTA) established the OPTN and the initial policies regarding an equitable organ allocation system.[81] In 1998, the OPTN Final Rule was adopted by Congress, with the goal of establishing the regulatory requirements for the OPTN and improving the effectiveness and equity of the transplant system, furthering the objectives established in NOTA.[82] However, this document was not meant to be an ethical guide, enumerating only the minimal legal and governmental policy requirements that must be included in a just allocation policy. A report adopted in 1992 by the OPTN Ethics Committee, then revised in 2010, describes the ethical principles that should be applied in the allocation of organs. These principles include:

- Utility, which is described as maximizing the benefits of available resources
- Justice, which ensures the fair distribution of these benefits
- Respect for persons or autonomy,[83] in a background of equity as described by NOTA when referring to desired outcomes of organ allocation[81]

The liver allocation system based on the MELD follows a justice system that prioritizes patients with the highest risk of waiting-list mortality. An ideal allocation system would consider the principle of utility and parameters such as predicted graft survival and predicted years of life added after transplant. These parameters are some of the standardized measures used to determine the strategies for organ allocation and are balanced with the potential negative consequences of transplant, such as mortality, postoperative complications, and long-term outcomes.[83] In this setting, the recipient

age unequivocally becomes a major determinant because transplant of an elderly patient would be expected to result in a time-limited benefit (fewer years added after transplant compared with nonelderly recipients). Several guiding principles have been endorsed to overcome this age paradox; some contend that all patients in liver failure have equal worth and, as such, the sickest should have an equal chance at getting an organ, regardless of their age.[84]

Others argue in favor of intergenerational equity, or the principle of fair innings, claiming that everyone is entitled to a normal lifespan, and that anyone who is deprived of that is at a disadvantage. Therefore, prolonging the lives of those who had achieved an older age with transplant and taking away the organ from the nonelderly recipient should not be the priority.[85] In 2012, Ross and colleagues[86] evaluated the role that age can play in the allocation of deceased donor kidneys, based on a model that they called Equal Opportunity Supplemented by Fair Innings. This principle allows allocation of kidneys based on 2 strategies: the first was that all waiting-list candidates had an equal chance of getting a deceased donor kidney transplant, regardless of age. Second, this was supplemented by the principle of fair innings, which prioritized patients developing end-stage renal disease at a younger age as being worse off than those who developed it later in life. Hence, the proposed allocation of higher-quality organs (using donor age as proxy for quality) to younger patients (a young-to-young allocation) provides them with a higher probability of achieving a full lifespan.[86,87] A few years later, a group of Italian investigators published the results of a study that evaluated how recipient and donor ages affected allocation and therefore affected the life expectancy of LT recipients. The study analyzed 2476 candidates and 1371 grafts and the effect of fair innings, age matching, and age mapping. Age mapping defends that all candidates have an equal chance of getting a liver, good-quality organs (typically from younger donors) being offered to the sickest. Such liver allocation based on age mapping resulted in a significant reduction (33%) in the gap between years of life lost between youngest and oldest candidates, and showed improved equity and efficiency compared with those observed in prognostic models.[84]

UNOS provides age-specific risk adjustment that is capped at a recipient age of 65 years and is potentially discouraging to the centers toward transplant in the elderly population, because their increased mortality risk is not adjusted for.[88] Based on the most recent data reports from UNOS, a total of 20,810 patients more than the age of 65 years have been transplanted from 1988 to date; more than 60% of these patients were transplanted after 2010, with cases almost doubling every year since 2016, indicating more frequent transplants in this population. In 2020, there are 3496 candidates more than 65 years of age wait-listed for an LT in the UNOS database.[89] In a study of 122,606 adults listed for transplant and 60,820 that underwent liver transplant from 2002 to 2014, the proportion of registrants aged more than 60 years increased from 19% to 41%; those more than 65 years old increased from 8.1% to 17% and those more than 70 years old increased from 1.4% to 3.1%. Increased age was significantly associated with increased waiting-list mortality and also increased posttransplant mortality. However, older age did not affect the transplant-related survival benefit.[4] Similar results had also been described by Wilson and colleagues,[8] who analyzed the Scientific Registry of Transplant Recipients (SRTR) and the University HealthSystem Consortium databases of 12,445 patients who underwent LT from 2007 to 2011. Whether or not current policies should be modified to include the age of the recipient as part of the allocation algorithm for LT, akin to the kidney allocation system, remains a topic of discussion.[88]

CORONAVIRUS DISEASE-19 AND TRANSPLANT IN ELDERLY

Severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) virus and its related disease COVID-19 (coronavirus disease 2019) continue to spread worldwide, affecting 6,713,881 persons globally with 393,709 deaths as of June 5, 2020.[90] In the early half of 2020, COVID-19 has dramatically changed the medical world and the approach to managing chronic diseases. The rapid spread of COVID-19 has affected the most vulnerable first: older patients and those with comorbidities such as DM, HTN, and CAD. The overall impact of the COVID-19 pandemic on the elderly population has been devastating people who have the highest risk of mortality.[91,92] A report from China on the elderly population affected by SARS-CoV-2 showed that age older than 60 years was associated with more severe disease than the general population.[91] Recent data from an Italian LT unit in Milan reported 3 deaths among long-term LT recipients in a short time frame of 3 weeks. Interestingly, the fatalities occurred in patients older than 65 years with multiple comorbidities (HTN, DM, hyperlipidemia, overweight), who underwent LT longer than 10 years previously and were on minimal immunosuppressive regimen.[93] A report from the Italian epicenter of the pandemic, Bergamo, concluded that immunosuppression does not constitute a risk factor in solid organ recipients.[94] Data from Spain on 18 solid organ tumor recipients reported a median age of 71 years, among which 6 were LT recipients. The study reported severe disease presentation and course in most the patients, with a case-fatality rate of 27.8%.[95] Contradictory results in terms of mortality in solid organ recipients infected with SARS-CoV-2 have been published so far in the United States. Data from the New York area showed an overall mortality of 18% in solid organ recipients positive for SARS-CoV-2. Recipient age older than 65 years was associated with a 60% rate of severe disease presentation.[96] A different cancer center reported data from 21 solid organ transplant recipients with only 5 patients older than 65 years. In this cohort, 67% of patients were hospitalized and half of them required ICU care, with only 1 deceased patient (mortality 4.8%) reported.[97] Liver transplant practices have also changed because of the COVID-19 pandemic, which mandates aggressive screening of donors and recipients for SARS-CoV-2. Wait-listed patients with acute SARS-CoV-2 infection are ineligible for LT. The high rates of false-negative results and accuracy of the assays at various phases of the COVID-19 infection have to be taken into consideration for appropriate patient selection.[98] Polymerase chain reaction on bronchoalveolar lavage testing for SARS-CoV-2 has been proposed as a better screening test, with a sensitivity of 93%, than nasopharyngeal swabs.[99,100] LT candidates who test positive for SARS-CoV-2 can be considered for transplant after 14 to 21 days of symptom resolution and after 2 negative tests for SARS-CoV-2.[98] Immunosuppression in itself would likely prolong the viral shredding rather than increase the severity of the infection.[94] Current consensus does not recommend empiric reduction of immunosuppression in LT recipients, even in the elderly.[98] More robust data are needed for a better understanding of the disease and its implications in immunosuppressed patients.

SUMMARY

Advances in medicine and population behavior led to increased life expectancy in developed countries until the COVID-19 pandemic, which has been significantly deleterious in the elderly. Effective antiviral therapies for HCV and HBV and improved management of cirrhosis complications and hepatocellular carcinoma have led to an increased prevalence of elderly patients with ESLD who need LT. Current epidemiologic trends show decreasing prevalence of chronic HCV and progressively increasing

prevalence of NASH, alcoholic liver disease, and hepatocellular carcinoma as indications for LT in the elderly population. Recent evidence suggests that elderly LT recipients are generally healthier and have comparable functional status with their younger counterparts. According to the UNOS database, the oldest transplant recipient is 88 years old and there is a steady surge in the transplant volume in those older than 70 years of age.[101] The volume of LTs performed in patients older than 65 years increased from 716 in 2010 to 1920 in 2019 (see Fig. 1). Posttransplant survival and graft outcomes in patients older than 70 years have also reportedly been similar to younger patients, which provides a favorable argument for advocating that chronologic age should not be considered as an absolute contraindication for LT. However, elderly transplant candidates are carefully selected with stringent pre-LT screening, which could explain the favorable outcomes and survival data observed in the cohort. Specific algorithms for elderly patient selection for LT are not well established; however, consensus agreement is that elderly LT candidates need a more rigorous selection process. Presence of comorbidities such as CVD, obesity, DM, and HTN have a negative impact on early post-LT survival, especially in the growing NASH population. In conclusion, there is no specific upper age cutoff for liver transplant. Elderly patient selection for transplant must be individualized and strategies from high-volume centers that transplant the elderly need to be validated in future studies to assess how far clinicians can "push the envelope" in this aging cohort.

CLINICS CARE POINTS

- Increased life expectancy and aging population has led to a trend of increasing LT volume in the elderly.
- Elderly LT candidates typically have an age-associated burden of comorbid conditions that can pose several clinical challenges during the selection/evaluation process for LT.
- Cardiovascular complications and de novo malignancies are the most common causes of post-LT mortality in elderly LT recipients.
- Although the early survival rate after LT is comparable with the younger recipients, the delayed patient and graft survival rates are lower in the elderly recipients. However, the number of years gained in elderly patients after LT is significant and, therefore, there is no strict chronologic age cutoff for LT.
- A thorough individualized evaluation is the current strategy, but development of rigorous transplant protocols geared to improving outcomes in the elderly cohort are necessary in the future.

DISCLOSURE

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