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ABOUT COVER

Editor-in-Chief of *World Journal of Transplantation*, Dr. Vassilios Papalois is Professor of Transplantation Surgery and Consultant Transplant and General Surgeon at the Hammersmith Hospital, Imperial College, London, United Kingdom. His clinical work focuses on high-risk and extended criteria kidney and pancreas transplantation. He has been active in surgical research for more than 30 years and has published more than 200 papers in peer reviewed journals (receiving more than 200 citations per year internationally), 20 book chapters, and 7 books. His research focuses on pre-transplant assessment and reconditioning of marginal kidney and pancreas grafts, use of stem cells for treatment of chronically scarred allografts, clinical ethics, and health policy. He has been awarded a Silver National Award for Clinical Excellence by the United Kingdom Department of the Health, and a Senior Clinical Investigator Award by the European Society of Organ Transplantation. (L-Editor: Filipodia)

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MINIREVIEWS

Liver transplantation and aging

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Abstract

An increase in the average life expectancy, paralleled by a demographic shift in the population with end-stage liver disease lies behind the rising demand for liver transplantation (LT) among the elderly. Some of the most common indications for LT including hepatocellular carcinoma, alcohol-related liver disease, chronic hepatitis C and non-alcoholic fatty liver disease tend to affect older patients. Transplant professionals are faced with an increasing demand for LT among elderly patients in an age of organ shortage and it is important that risk and benefits are carefully weighed in order to achieve the optimum use of precious liver grafts.

Key Words: Liver transplantation; Elderly; Hepatocellular carcinoma; Alcohol-related liver disease; Non-alcoholic fatty liver disease; Hepatitis C virus

Core Tip: An increase in the average life expectancy paralleled by a demographic shift in the population with end-stage liver disease raises the demand for liver transplantation (LT) among the elderly. The most common indications for LT such as hepatocellular carcinoma, alcohol-related liver disease, hepatitis C virus and non-alcoholic fatty liver disease tend to affect older patients more and more. However, risks need to be weighed against the benefits since the effects of associated age-related co-morbidities in older individuals may affect transplant outcomes.

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INTRODUCTION

Liver transplantation (LT) is one of the great stories of success of modern surgery and medicine. However, due to the complexity of the procedure and associated complications, LT used to be a therapy saved for patients from younger age groups. Over the years, as the experience has increased and the results have improved, we have seen a shift from the upper age limit around 50 years of age to the present situation where most transplant centers do not have a strict age limit when wait-listing the patients for LT[1].

During the last century a dramatic increase in the average life expectancy has occurred, from 45 to over 80 years[2]. This was paralleled by a demographic shift in the population with end-stage liver disease. Epidemiologic factors lie behind the rising demand for LT among the elderly. Some of the most common indications for LT including hepatocellular carcinoma (HCC), alcoholic cirrhosis and non-alcoholic fatty liver disease (NAFLD) tend to affect older patients[3]. Until recently, hepatitis C virus (HCV) was the leading indication for LT. With the advent of direct acting antiviral (DAA) therapies most of the infected patients can now expect the cure from the virus, however the patients who acquired HCV infection at younger age will continue to present with sequela of hepatitis C infection such as HCC and cirrhosis in years to come[4-7].

Despite the increase in experience and generally excellent results of LT, it is relatively self-evident and universally accepted that the results in the elderly will be inferior to the results in younger patients. This is primarily due to the fact that older individuals will naturally survive for less time, and that the survival is affected in any population as age of the patient increases. There are also the effects of associated age-related co-morbidities in older individuals that may significantly affect transplant outcomes[8,9]. LT definitely has its place in the elderly population with end-stage liver disease. However, with the scarcity of organs for transplantation in mind, careful selection of patients is crucial in order to achieve outcomes that provide the best possible transplant-related benefit to this growing and sensitive part of the population.

CHANGING DEMOGRAPHICS IN THE PRESENT AND IN THE FUTURE

In the recent years we have seen a sharp increase in life expectancy due to a multitude of factors that include advancement of healthcare and improved social and economic conditions. Currently, epidemiological studies show that 11% of the world's population is older than 60. According to the World Health Organization, this percentage is about to double by 2050, amounting to 1500 million people[10]. These developments are a particular problem in the developed countries. Between 2000 and 2030, the percentage of population who are 65 years of age and older is projected to increase from 12.4% to 19.6% in the United States and from 12.6% to 20.3% in Europe[11]. Apart from general increase in morbidity, mortality, disability and healthcare costs, the aging of the population has significant consequences for the care of the patients with liver diseases since the incidence of liver diseases increases with age as well[12].

RISKS AND BENEFITS OF LT IN THE ELDERLY

According to the 2013 Guidelines for the evaluation of pre-transplant candidates issued by the American Association for the Study of Liver Diseases, "in the absence of significant co-morbidities, older recipient age (> 70 years) is not a contraindication to LT"[13]. Accordingly, most transplant centers do not have a strict age limit for LT wait list registrants, and there is a tendency to put more emphasis on the "physiological" than "chronological" age[14]. A number of studies reports very good results of LT in elderly recipients. They include both single center analyses and analyses of registry data, and they all show that the outcomes for the elderly in terms of survival are similar or not much worse than in matched younger patient groups[8,15-19]. Indeed, a recent meta-analysis on LT in the elderly, shows that patient and graft survival rates are not different between younger and elderly LT recipients[1].

When considering medical and ethical aspects of LT in the elderly, it is useful to start from the well-known concepts of urgency, utility and transplant-related benefit in allocation of liver grafts. Most of the current LT prioritization schemes in Europe and the United States are based solely on urgency, considering the risk of death without a

transplant as measured by patients' MELD scores[20]. In an era of organ shortage, transplant-related survival benefit, a measure of impact of transplantation both on the pre-transplant mortality and on the post-transplant survival, needs to be taken into account as well. Increasing age was found to be associated with both increased pre-transplant mortality and an increased risk of post-transplant mortality[21-23]. However, when transplant-related survival benefit is considered, there is no significant difference across different age groups. Elderly patients have decreased survival on the waiting lists compared to the MELD-matched younger registrants. Therefore, in spite of lower post-transplant survival, elderly patients may have transplant-related benefit similar to younger patients if they also have lower survival without transplantation[18]. Achievement of normalization of the expected life span is another way to measure the outcomes of LT in the elderly. Despite the increased risk for post-transplant morbidity and mortality, the elderly recipients of LT regain their anticipated life expectancy as defined by age-equivalent members of the general population. On the other hand, elderly candidates who are denied LT mostly have a short life course and die within a year[15].

Even though age should not be a discriminating criterion for LT candidates, centers still need to be cautious in selection of elderly recipients who would have the most benefit from transplantation. Identification of candidates with a good functional status and without major comorbidities is crucial for good post-transplant outcomes[15,24,25]. Also, increased surgical complexity (reflected in prolonged warm ischemia time and increased transfusion requirements) was found to negatively affect graft and patient outcomes in elderly LT recipients[15].

HCV AND LT IN THE ELDERLY

The increasing life expectancy and the chronic nature of HCV shape the growing trend of advanced age in patients with HCV infection. The prevalence of advanced fibrosis is greater in the elderly than in the younger population, and the proportion of elderly patients with advanced liver disease is expected to rise in the next decade[6,26]. Indeed, since 2002 there has been an increase in number of elderly registrants on the LT lists, aged 65 years or more, with the trend even more prominent in patients with HCV-related liver disease[18].

In the era without efficacious antiviral treatment, recurrent hepatitis C after LT resulted in rapid liver damage especially in elderly grafts, affecting graft and patient survival[27]. Since 2014, the use of DAA therapy has revolutionized the treatment of HCV infection and decreased the burden of chronic infection[28]. However, HCV is still among the leading causes for LT both in males and females[29].

DAA agents are highly efficacious, with sustained virologic response (SVR) rates more than 95% in all HCV genotypes and special populations, including transplant recipients, with excellent safety profiles[28,30]. Achieving SVR leads to short and long-term clinical benefits; reduces the risk of developing liver cirrhosis[31], improves decompensated liver disease[32,33], reduces the need for LT along with liver specific and all-cause mortality[34]. Successful antiviral therapy decreases, but does not eliminate the risk of HCC[7].

Historically, elderly patients have been considered difficult-to-treat, due to higher risk of complications, discontinuation and mortality rates. The concomitant co-morbidities, in particular cardiovascular, renal and metabolic along with hematologic conditions limited the use of interferon treatments[6]. This scenario has changed since interferon-free antiviral therapy regimens with DAAs have been introduced, enabling high efficacy with improved safety profiles also in elderly populations.

The initial results with ledipasvir (LDV)/sofsbuvir (SOF) demonstrated high sustained virologic response (SVR, 97% *vs* 98%) and similar discontinuation rates between patients aged < 65 years and those aged ≥ 65 years, respectively[35]. Similar results have also been demonstrated for SOF/velpatasvir (VEL) in patients aged ≥ 65 years who achieved SVR12 by 100%, compared to 97.8% SVR rate in patients aged < 65 years[36].

Further on, in the real-world setting different DAA-based regimens (SOF + ribavirin, simeprevir/SOF ± ribavirin, LDV/SOF ± ribavirin; daclatasvir/SOF ± ribavirin; paritaprevir/ritonavir-ombitasvir ± dasabuvir ± ribavirin, and ombitasvir/paritaprevir/ritonavir ± ribavirin) showed high efficacy in HCV patients aged ≥ 65 years with advanced fibrosis/cirrhosis with SVR12 of 94.7% and low discontinuation rate (1.4%)[37]. Similarly, high efficacy (SVR 98%) of different combination of DAAs regimens in a real-world setting has been reported for elderly

patients (≥ 65 years) with cirrhosis. However, the elderly are at increased risk for drug-to-drug interaction (DDI) and associated adverse events due to more frequent use of concomitant medications (in particular cardiovascular drugs and diuretics) reflecting the increasing age-related morbidity[38]. However, careful management during antiviral therapy in multi-morbid elderly patients, may effectively prevent DDI-associated adverse events and improve the outcomes. Therefore, as effective and safe therapies are becoming widely more available, the number of treated HCV elderly patients is expected to increase. Also, as the consequence of treatment of higher proportion of elderly patients with more advanced liver disease, greater numbers of HCV-related HCCs might be expected in the future[5].

In the context of donors, grafts from seropositive HCV donors have increased by 20% in recent years, with almost one third of them being non HCV viremic[39,40]. Traditionally, HCV positive grafts were reserved for recipients already infected with HCV, which showed no impact on the severity of HCV-related graft disease, graft or patient survival if younger donors (aged < 50 years) were used[41]. The use of DAAs has dramatically shift our attitude towards HCV positive grafts. As more patients are being treated, the percentage of people who are HCV antibodies positive but HCV RNA negative is likely to increase. Furthermore, the use of DAAs has increased the use of HCV-positive organs in recipients who are infected with HCV, but also in those who are HCV negative[42,43]. Utilization of organs from these donors provides an opportunity to expand the limited organ availability, also for elderly patients who are at higher risk of death or dropout on the liver waiting lists[18].

ALCOHOL-RELATED LIVER DISEASE AND LT IN THE ELDERLY

Alcohol accounts for 3.8% of global mortality and alcohol-related liver disease (ALD) is one of the most disastrous consequences of prolonged alcohol use. ALD encompasses a spectrum of liver pathology including steatosis, steatohepatitis, liver fibrosis and cirrhosis and/or HCC[44,45]. Across all of the adult age groups, ALD is one of the commonest indications for LT both in Europe and in the United States[46,47]. Cirrhosis in ALD patients is often diagnosed at an older age and the referral for LT may be delayed since these patients are primarily managed by primary care physicians as opposed to patients with viral hepatitis or NAFLD who are usually in the care of a hepatologist[48].

Excessive alcohol use is a well-known health risk among elderly people[49]. Despite the statistics showing decreasing alcohol use with age, the number of older adults drinking excessively is expected to rise in the future. This is primarily due to the age cohort born in the 1950s (baby boomers) with heavy drinking habits reaching old age[50,51].

There is a number of factors affecting morbidity and mortality both before and after LT in elderly patients with ALD. Physiological changes associated with aging often lead to more pronounced effects of alcohol in elderly patients compared to their younger counterparts. Old and very old adults are particularly vulnerable to the alcohol-related effects due to metabolic and other changes in their bodies and high rate of concomitant chronic diseases[52-54]. Elderly patients with a history of alcohol use are more likely to suffer from cognitive impairment or dementia resulting from a prolonged alcohol use[55-57]. In the context of LT, the associated metabolic and neurological changes can have profound effects both on the wait-list mortality and on the results of LT in elderly patients undergoing LT for ALD. As the risk of graft rejection is inversely related to age[58], the demands for immune control to prevent rejection lessen with increasing age, especially for non-immune conditions such as ALD. As such, elderly ALD patients after LT represent a lower rejection-risk population in which the reduction or minimization of immunosuppressive regimens is feasible along with the reduction of immunosuppression-related complications[59]. ALD patients have survival rates similar to LT recipients without ALD, however some of the causes of death among ALD patients tend to be especially prevalent among elderly patients[46]. Elderly ALD patients generally suffer from more co-morbidities, including alcohol-induced cardiomyopathy, skeletal myopathy, Wernicke's encephalopathy, chronic pancreatitis and malnutrition. Tobacco use is also more prevalent among ALD patients and associated with cardiovascular deaths and *de novo* cancers among LT recipients. The effect of tobacco tend to accumulate with years of smoking and it is therefore clear that elderly smokers tend to present with the largest health risks affecting the outcomes of LT[60].

HCC AND LT IN THE ELDERLY

HCC is a major health problem being the fifth most common cancer and second most frequent cause of cancer-related deaths worldwide. Most cases of HCC are attributable to chronic liver diseases associated with hepatitis B virus infection, HCV infection or alcohol use[61]. Aging is a well known risk factor for the development of HCC and an age-specific increase in the incidence of HCC among patients 75-years old or older has been shown both in the West and in the East. For instance, in Japan, the average age of HCC patients is increasing as well as the proportion of elderly HCC patients[62,63]. In the United States, the latest estimates suggest that HCC incidence peaks above 70 years of age[64].

Chromosomal changes in the liver associated with aging include shortening of the telomeres and aberrant DNA methylation. These changes are related to carcinogenesis, suggesting that aging alone is a risk factor for the development of HCC[62-64]. HCC in the elderly has been shown to be associated with less advanced liver fibrosis than HCC in younger patients. Also, there are prognostic factors of HCC that tend to be more favorable in the elderly – tumors in the elderly population tend to be encapsulated more frequently, they have better differentiation and there is less vascular invasion than in younger patients[65]. Therefore, some authors speculate that HCC in the elderly is less aggressive and that it may be more amenable to being cured compared with younger patients[65].

Treatments for HCC include surgical resection, LT, transcatheter arterial chemoembolization, percutaneous microwave coagulation, radioembolization, percutaneous ethanol injection and molecular therapies. Treatment decisions in patients with HCC are generally based on tumor-related factors, liver function, performance status and co-morbidities. However, current guidelines do not take the age of the patient into account[66,67].

LT is a well-established curative therapy for patients with HCC. Due to the rising incidence of the disease and excellent results of LT in carefully selected patients, the proportion of recipients with HCC has been increasing over the last years and currently makes up to 18% of all patients undergoing LT in Europe[4]. Patients with HCC are older than patients without HCC and this trend therefore contributes significantly to the overall aging of the population of LT recipients[4].

As for the outcomes of LT in elderly patients, the literature abounds with conflicting evidence. Contrary to the results in elderly patients undergoing liver resections for HCC where survival rates have been shown to be equivalent to those of younger cohorts[68,69], age greater than 60 years correlated negatively with short-term and long-term outcomes in patients with HCC undergoing living donor LT[70-72]. On the other hand, a large retrospective study of OPTN data showed that, while survival of all LT patients older than 70 years yields outcomes inferior to younger cohorts, in the setting of HCC, patients fare no worse than patients with other indications for transplantation[8].

NAFLD AND LT IN THE ELDERLY

The global prevalence of the metabolic syndrome is rapidly rising, given the changes in eating habits and inclination towards sedentary lifestyle. Metabolic syndrome characterized by the morbidity cluster of obesity, type 2 diabetes (T2D), hypertension and dyslipidemia, has become a growing epidemic. As a consequence, its liver manifestation - NAFLD is becoming the most common cause of chronic liver disease[73].

Non-alcoholic fatty liver comprises a spectrum of clinical and pathological entities which may lead to cirrhosis and HCC[74]. In the initial process fat is increasingly stored as triglycerides in hepatocytes. When fat storing capacity of hepatocytes is exceeded, steatosis is accompanied with ballooning cell degeneration and an inflammatory cell infiltrate, resulting in steatohepatitis. Consequent pro-inflammatory signaling and insulin resistance lead to further liver injury, where long-standing liver damage and repair responses result in cirrhosis and the development of HCC[75]. Notably, the whole process is consistently associated with an increased risk of cardiovascular disease. Indeed, NAFLD patients often have one or more components of metabolic syndrome - they are often obese with hyperlipidemia, T2DM and/or hypertension[76].

In the context of aging, changes are reflected in liver morphology, physiology, and oxidative capacity. Aging is associated with an increase in lipid accumulation in non-adipose tissues; heart, skeletal muscle and liver, increasing incidence of disorders such as atherosclerosis, insulin resistance and T2D, hyperlipidemia, hypertension, all of

which increase the chances of developing NAFLD and metabolic syndrome[77,12]. Thus, the prevalence of NAFLD increases with age, mainly affecting individuals in their fourth to sixth decades of life[78]. Even though the NAFLD prevalence increases with age, in the very elderly there is a trend of decline as shown in the Rotterdam study. The prevalence of NAFLD in participants aged < 70 years was 35.8%, aged 70-74 years was 36.6%, aged 75-79 years was 39.6%, aged 80-84 years was 32.1%, and in participants aged older than 85 years was only 21.1%[79].

NAFLD in the elderly is broadly related to the same metabolic risk factors as in the non-elderly, however female gender is no longer protective with the increasing age[80]. It is important to stress out that elderly patients (> 65 years old) have higher prevalence of steatohepatitis and advanced fibrosis, as well as other features of severe liver disease than patients of younger age[80,81]. A recent analysis of the third National Health and Nutrition Examination Survey (NHANES III) showed the high prevalence (40.3%-39.2%) of NAFLD in the elderly with no differences among the age subgroups (60-74 *vs* > 75 years old). NAFLD was associated with increased risk of mortality for 60-74-year-old individuals, but the risk was not increased in those older than 75 years[82].

As HCV burden is decreasing by highly effective antiviral treatments, NAFLD is becoming one of the leading indications for LT based on decompensated cirrhosis with or without HCC[83]. In the context of NAFLD-related HCC, epidemiological evidence show that HCC is rare before the age of 40, and it increases progressively with older age, peaking in incidence around ages 70-75 after which it steadily drops[61,84].

The proportion of patients who are older than 65 years and candidates for LT is increasing in Europe and the United States[18,59]. In general, NAFLD recipients are older than recipients who are listed for autoimmune etiologies or chronic viral hepatitis[76]. Moreover, NAFLD-related cirrhosis has become the most common non-HCC indication for LT in patients aged 65 or older[85].

Additionally, in the context of donors, donor age is considered as one of the variables with the strongest influence on donor risk estimates, associated with worse early outcomes and burdened with complications such as primary graft non-function, hepatic artery thrombosis and biliary complications[86-88]. Severe graft steatosis has been associated with worse outcomes, therefore as a general rule, only grafts with mild (< 30%) and moderate (30-60%) steatosis are accepted[89]. A combination of risk factors, rather than a single one, affects the outcomes of steatotic grafts[90]. As the increasing trend of older donors is likely to continue[4,47], in addition to NAFLD epidemic, more elderly steatotic grafts can be expected in the future.

In conclusion, as the world's elderly population and the prevalence of metabolic syndrome continues to grow at an unprecedented rate, NAFLD, as an indication for LT is projected to increase.

CADEVERIC LIVER GRAFTS FROM ELDERLY DONORS

Significant gap exists between the need for organ transplants and the number of available cadaveric grafts[91]. One of the strategies to deal with this issue is the use of extended criteria grafts[92]. These are the grafts with donor factors that are associated with poor graft function and increased risk for graft loss. Advanced donor age is one of the independent risk factors for graft loss after LT[93,94]. Actually, Feng *et al*[95] showed that donor age > 65 years was the strongest predictor of graft failure. However, a number of case series and registry analyses have shown that the use of elderly and even very old (> 80 years) livers yields good outcomes quite similar to outcomes when using much younger grafts[94,96-99]. It seems that minimization of other risk factors for poor graft function is crucial for achievement of favorable results with elderly grafts. Old liver grafts are highly susceptible to ischemia-reperfusion injury and, therefore, cold ischemia time should be kept to minimum while steatotic elderly grafts should be used very selectively[100-103]. Several studies provide evidence that the use of older livers is associated with an increased incidence of biliary and vascular complications[88,99,104]. Strategies to minimize the incidence of procurement- and transplant-related biliary injuries, including machine perfusion are currently subject of intensive research[92]. Careful donor-to-recipient matching is crucial in obtaining good results using elderly liver grafts. It is generally accepted that elderly grafts should be allocated to the less severe, clinically stable recipients who can tolerate possible delay in graft function[100,105]. In contrast to allocation of kidneys where old grafts are often allocated to old recipients ("old for old"), old liver grafts were shown to have unfavorable outcomes in old recipients so very old and very young recipients are best avoided[92].

In conclusion, elderly grafts are a valuable tool to expand the donor pool and should be used, although cautiously, after careful donor evaluation, selective donor-to-recipient matching and optimization of all aspects of the procurement, transplantation and post-transplantation course[94].

CONCLUSION

LT remains the best available treatment for end-stage liver disease. Once reserved for patients from younger age groups, today LT is increasingly performed in elderly patients. We are witnessing aging of the societies across the world and there is a demographic shift in patients with liver disease as well. Most common indications for LT including HCC, ALD and NAFLD tend to affect older patients. HCV until recently the leading indication for LT, is now amenable to cure using DAAs. However, the patients who acquired HCV infection at a younger age will continue to present with sequela such as cirrhosis and HCC in the years to come.

Results of LT are generally excellent, however, it is self-evident that the results in the elderly will be inferior to the results in younger patients. On the one hand, this reflects the fact that older individuals will naturally survive for less time. Secondly, the effects of associated age-related co-morbidities in older individuals may significantly affect transplant outcomes. However, with careful patient selection and minimization of risk factors, a significant transplant-related benefit can be achieved justifying the use of precious liver grafts in the elderly population.

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