Liver Transplantation and the Older Adults Candidate: Perioperative Considerations

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KEYWORDS

• Liver transplantation • Older adults candidate • Frailty • Preoperative evaluation
• Cardiac assessment • General anesthesia • Hemodynamic instability

KEY POINTS

- Preoperative frailty assessment is becoming imperative across all surgical specialties to ease risk stratification and shared decision-making and improve outcomes.
- Frailty is now recognized in 15% to 50% of end-stage liver disease (ESLD) patients. A user-friendly assessment tool (Liver Frailty Index [LFI]) is now available. As a growing number of older patients suffering from ESLD will be recipients of liver transplant (LT) surgery, LT series will be composed of up to 25% of older frail recipients.
- Perioperative medicine in LT surgery is an ever-expanding multidisciplinary activity. It should be managed by anaesthesiologists as "pivotal perioperative physicians" working in a multidisciplinary team. Their main aim should be to "merge" the work of hepatologists, surgeons, the "dedicated" cardiologist, physiotherapists, and nutritionists to ease the entire perioperative period in short to become the "perioperative transplant physician."
- No formal guidelines are available so far for the pre-LT assessment of the older adults candidate. The "anesthesiologist–perioperative physician" should address central nervous, cardiovascular, respiratory, renal systems conditions, and comorbidities associated with ESLD, more often represented in the older adults candidate. Functional assessment tests should be integrated in the LT evaluation.
- LT anesthesia in the older adults must be based on solid knowledge of the physiologic changes associated to ageing. Hemodynamic instability could be more common in the older surgical patients making a proactive anesthesia management key to reducing complications. Changes in pharmacokinetic and pharmacodynamic characteristics should drive pharmacologic strategies and drugs choices.

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INTRODUCTION

The number of older subjects in the population is growing worldwide. Besides wisdom, however, ageing bears a heavy burden of comorbidities and a greater risk of health problems.[1] Recent US vital statistics show that close to 10% of surgical patients are 65 years or older, surgery being a key to solve some of their health problems (ASA Headquarter, 2022, accessed in September 2022). According to the *World Population Ageing* 2013, the United Nations defined older people as those aged 60 years or more. Recently, the World Health Organization (WHO) defined older people in developed countries those aged 65 years or more or—alternatively—older persons who have passed their median life expectancy at birth.[1] In the pragmatic Europeak Community (EU) document, *Ageing Europe*,[2] old people are those aged 65 years or more, *very old people* those aged 85 years or more. Whatever the definition, by 2030 close to one-fifth of the population in developed countries will be aged 65 years or older,[1–3] and according to US statistics, every year about 21% of the older adults will undergo some form of anesthesia and surgery.[1,3] Such an increase of older patients needing any form of surgery—transplant and cardiac surgeries included—mandates improvements both in perioperative care delivery and outcomes.

AGE, AGEING, AND FRAILTY

Ageing is often associated with *frailty*, a "multisystem syndrome" closely correlated with decreases in physical, mental, and functional reserves. It is a "cumulative biological decline of multiple organ systems," leading to greater vulnerability to stressors and adverse health outcomes.[4] According to Thillainadesan and colleagues,[4] the ageing process should be considered a continuum, closely correlated with the severity and spread of biological changes in organs and tissues of older persons: the greater the changes in organs and tissues, the more likely is the individual to be frail. In 2020, George and colleagues[5] explored the association between frailty and postoperative mortality in over 2.7 million surgical patients across nine surgical specialties at various risk, stratified by operative stress scores. The investigators reported an association between frailty and postoperative morbidity and mortality in low-, moderate-, and high-risk surgical procedures. Frail and very frail patients had an incidence of 5.6% to 13.6% and 0.9% to 4.1%, respectively, of postoperative morbidity and mortality. In this very large series, George and colleagues[5] documented 10% mortality for frail patients at 180 days even in low-stress procedures and in low-intensity specialties. The results showed by George and colleagues underline once again the role of frailty, beyond the surgical stress itself, in the final surgical outcomes.[5–9] Unfortunately, preoperative frailty assessment is not routinely performed even before major abdominal surgery, as is in liver transplant (LT) surgery. According to Anderson and Wick in the accompanying editorial, frailty assessment "seems to be considered only as an afterthought."[10] Therefore, preoperative frailty assessment is imperative across all surgical specialties, regardless of case-mix, to ease risk stratification and support decision-making.[5,10] It is even more important in patients undergoing LT. Age, accumulated comorbidities, and increased vulnerability due to the reduced physiologic reserve are the mainstays of the frailty profile[6] and are included in the surgically validated Risk Analysis Index.[8,9]

AGE, FRAILTY, AND SARCOPENIA IN END-STAGE LIVER DISEASE: THE CHALLENGE OF THE LIVER TRANSPLANT INDICATION

Age and Liver Transplantation

Bajaj and colleagues[11] stress that together with the ageing of the population, diseases predominantly found in younger patients are now increasingly reported in the older

adults. Chronic liver disease (CLD) in various forms—cirrhosis, alcohol-related liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), metabolic syndrome, and autoimmune cholestatic disease—and with different severity are nowadays reported in close to 2 billion people worldwide. Liver cirrhosis was the seventh most common cause of mortality in people older than 60 years in 2015 (*WHO Ageing and Health, 2016*, reported by Bajaj and colleagues).[11] These growing numbers of older patients suffering from end-stage liver disease (ESLD) in the United States and EU are obviously likely to become potential candidates or recipients of LT surgery,[12–15] this trend being evident both in the EU countries (**Fig. 1** from WWW.ELTR.org, accessed in September 2022) and United States[13,14] (**Figs. 2** and **3**).

Frailty and Liver Transplantation

LT, pioneered in the early 1970s as a "last ditch" treatment, is now a standardized, consolidated surgical procedure, considered the only curative option for patients with ESLD both in acute and chronic conditions.[15] LT is a high-risk surgical procedure, with substantial medical and surgical cutting edges.[12–17] Besides the donor organ shortage, stringent selective criteria are mandatory, and recipient age has always been considered one of the criteria for LT. Independently of age, and despite the prevalence in older patients, frailty is now recognized in all forms of CLD including ESLD. It has been reported in 15% to 50% of the patients with ESLD[16] and in up to 25% of the LT candidates.[17–20] In ESLD, liver failure, combined with neuromuscular, endocrine, immune, and skeletal muscle dysfunctions promote frailty. The underlying mechanisms leading to frailty in liver disease are far from being well understood and area of active research.[16–18] In LT recipients, frailty *per se* has a significant impact on comorbidities, cognitive function and, in general, on overall complications and length of hospitalization.

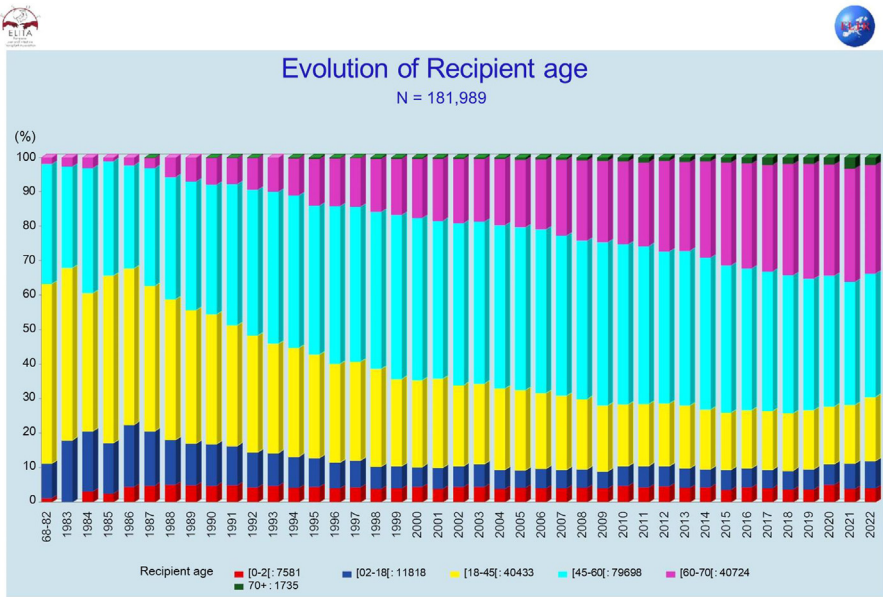

Fig. 1. Evolution of LT recipient age. (*With permission from* European Liver Transplant Registry (ELTR) registry - WWW. ELTR.org, accessed in September 2022, a service provided by the European Liver and Intestine Transplant Association (ELITA))

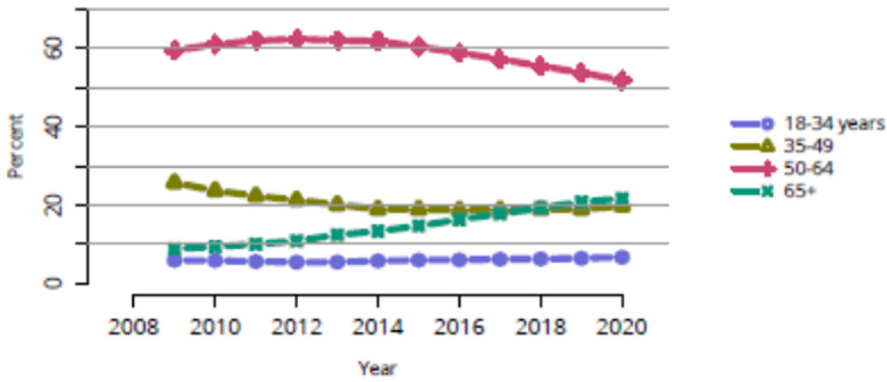

Fig. 2. Distribution of adults waiting for liver transplant by age.OPTN/SRTR 2020 Annual Data Report is not copyrighted. Readers are free to duplicate and use all or path of the information contained in this publication. Data are not copyrighted and may be used without permission if appropriate citation information is provided.

Several prognostic tools have been studied and validated in the setting of frailty, such as Fried Frailty Index, short physical performance battery, 6-minute walk test (6MWT), and the Activities of Daily Living Scale.[18] To detect frailty in an ESLD patient in the easiest, most direct, and objective way, Lai and colleagues[19] proposed the Liver Frailty Index (LFI), a user-friendly objective tool consisting of three performance-based measures (grip strength, chair stands, and balance testing), specifically adapted to "measure" physical function in cirrhotic LT candidates. It has been validated in many studies and provides better risk prediction for waitlist mortality than the model for end-stage liver disease-sodium (MELD-Na).[19,20] Although robust physical conditions are usually associated with LFI less than 3.2, debilitation starts from what is defined the "pre-frail" state (LFI 3.2–4.5), ending with frank frailty (>4.5).[18] Lai and colleagues, using the net reclassification index in candidates classified using LFI and MELD-Na, were able to reclassify 19% of the LT candidates (16% of deaths/transplant waitlist de-listings and 3% of nondeaths/de-listings). The American Society of Transplantation strongly encourages the use of LFI in baseline and longitudinal assessment of LT candidates.[18] Using LFI, Haugen and colleagues[20] demonstrated frailty in one-third of older LT candidates, frailty being more common in older LT candidates than in younger ones

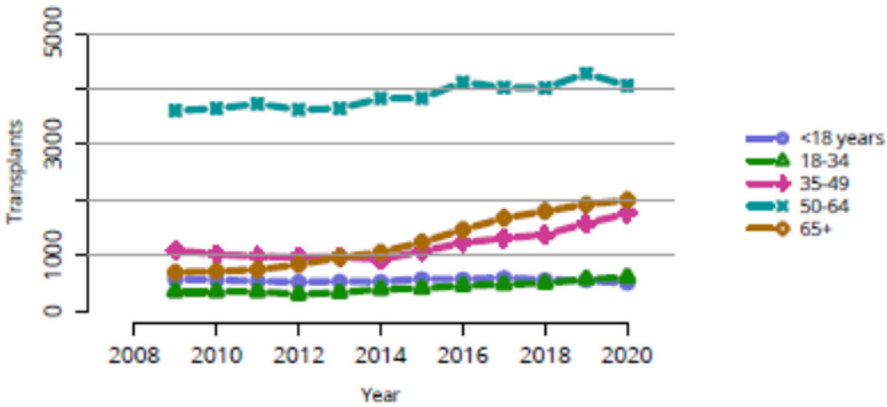

Fig. 3. Total liver transplant by age.

(33.3% vs 21.6%). However, though a higher risk of waitlist mortality was independently associated with older age and frailty, frailty per se, regardless of the candidates' age, was associated with a twofold risk of waitlist mortality independent of the MELD-Na score.[20] This observation is further supported by the results in the 2020 Scientific Registry of Transplant Recipients report, where waitlist mortality analyzed by the age of candidates showed a sharp decrease in candidates over 65 since 2016 (**Figs. 4** and **5**). Frailty unfortunately was not included in the 2020 report but should be considered in the next reports due to the relevant impact it has on outcomes.[14,20]

Sarcopenia and Liver Transplantation

Sarcopenia, often reported together with frailty and indeed part of it, was initially considered as an age-related loss of muscle mass and function but is in fact a distinct entity and is now observed in all forms of CLD.[14,15,17,18,21] Although frailty is a clinical diagnosis including physical, mental, and psychosocial components, sarcopenia is a complex pathophysiologic change of muscles, with important functional consequence.[16–18,21] The skeletal muscle index (SMI) (height-normalized total abdominal muscle area at L3 level in abdominal computerized tomography [CT] scans) is the most widely used method to estimate total muscle mass.[17,18,21] Gender-specific cutoffs are still debated, as are the interpretations of the complex relationship between sarcopenia and outcomes in LT candidates.[21] Machine learning algorithms applied to the SMI and new MRI-based techniques are emerging as tools that are being used for more appropriate sarcopenia assessments. This said, it is well demonstrated that in case of low psoas thickness (<6.8 mm/m), the survival rate is lower and the hazard ratio for mortality is higher.[18] Frailty correlates with central sarcopenia; an appropriate nutritional assessment should be mandatory when managing the frail/sarcopenic LT candidate. In fact, up to 50% of the LT candidates have moderate, if not severe, malnutrition, unequivocally calling for both a dedicated pre-LT nutritional assessment and a tailored nutritional program.[21] Interestingly, according to Xu and colleagues, frailty is more common in patients with ALD, NAFLD, and "other etiologies" and was associated with waitlist mortality independent of cirrhosis etiology.[17,18,22] These findings should strongly support the need for frailty assessment across all CLD etiologies.[17,18,21] A preoperative assessment of older adults LT should undergo a mandatory formal and timely pre-LT assessment of frailty and sarcopenia, as well as obesity, often recorded in older adults frail/sarcopenic patients.[18] If the

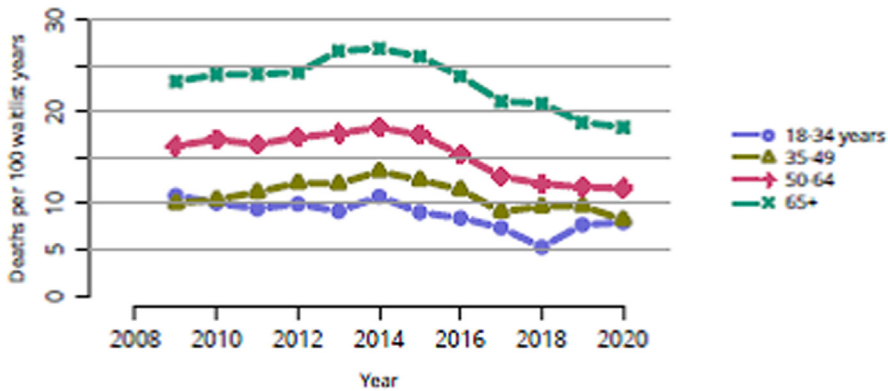

Fig. 4. Pretransplant mortality rate among adults wait-listed for liver transplant by age. (OPTN/SRTR 2020 Annual Data Report. HHS/HRSA.)

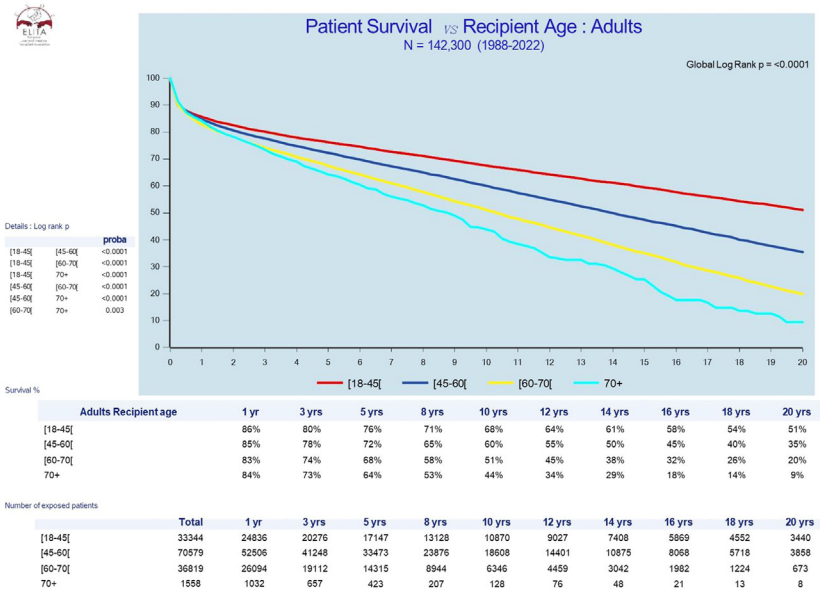

Fig. 5. Patients survival versus recipients' age in adult population. (*With permission from* European Liver Transplant Registry (ELTR) registry - WWW. ELTR.org, accessed in September 2022, a service provided by the European Liver and Intestine Transplant Association (ELITA))

postoperative LT course threatens to be suboptimal (possibly leading to an undesirable outcome) for frail candidates,[7,8,17,18] the selection of suitable candidates for a tailored comprehensive prehabilitation should be considered.

LIVER TRANSPLANTATION IN THE OLDER CANDIDATE: WHAT ANESTHESIOLOGISTS SHOULD KNOW

As already noted, the numbers of older candidates for LT are steadily rising, having nearly doubled in the last 15 years; close to a quarter of candidates are now above 65 years of age, this having been confirmed in 2020, when a quarter of the total of LT patients were more than 65 years.[14,15,17,23] LT in older candidates dates back to late 1980 to early 1990, pioneered by Starzl[24] and Belzer[25] in small groups of patients. They reported very good results in recipients more than 60 years, with survival rates and incidence of perioperative complications similar to those in younger recipients; in fact, intraoperative complications, early rejection episodes, postoperative surgical complications, and opportunistic infections were comparable. Increased confidence in widening LT indications to the older adults was initially attributed to the important improvements in immunosuppressive therapy for the late 1980. Substantial progresses in modern immunosuppressive therapy, surgical, and medical care are now mainstays of current management of LT patients. According to the current American Association for the Study of Liver Disease (AASLD) 2013[26] and European Association for the Study of the Liver (EASL) 2018[27] guidelines, chronologic age is not by itself an absolute contraindication for LT: recipients aged 65 years but also 70 years (and beyond, up to 80!). Such patients now present in appreciable numbers in medium- and high-volume centers, with the same favorable short-to-medium term outcomes.[28]

These results, however, need to be appropriately discussed to optimize outcomes while maintaining equity and ethics in the LT indication. Tailored and more selective

selection criteria ("stringent" according to Cottone and colleagues) must nowadays include biological age, assessed by frailty (LFI as an example) and should also explore functional reserve, sarcopenia, nutritional status, and comorbidities.[15,19,20] Older candidates are exposed, at least epidemiologically, to higher rates of cardiovascular (CV), respiratory, renal and neuropsychiatric comorbidities and related perioperative complications.[13,15,23,29] Two studies are relevant in this setting.[12,28] In the first one,[28] CV, respiratory, and neurologic complications had an age-related incremental increase, but unfortunately were not appropriately predicted by any of the available models. Perioperative mortality, major surgical, and medical postoperative complications, including infections, showed no difference between older adults and younger recipient groups, an effect possibly reflecting a high rate of exclusions during a "conservative" multidisciplinary pre-LT screening/selection.[28] Together with "the patient," for a comprehensive risk assessment, the "underlying liver pathology" plays a key role in LT in the older adults, hepatocellular carcinoma (HCC) and NASH being nowadays among the most common indications for LT.[12,15,23] In the second recent meta-analysis on LT in patients aged over 65 years,[12] early survival was substantially affected by the underlying liver pathology. The study, while confirming age more than 65 years as an independent prognostic factor for graft loss and mortality, clearly documented an indisputable difference in transplant survival according to the LT indication. Although mortality in HCC candidates did not differ between older adults and younger patients, survival was lower in older patients with ALD. Age might in fact have a lower impact in HCC recipients, often physically fit or "robust," whereas ALD is not infrequently associated (26%) with frailty, sarcopenia, and malnutrition and age-related comorbidities.[29] As an appropriate indication to LT is the game changer for older candidates, anesthesiologists, as important members of the pre-LT assessment team, should be aware of these problems when clearing for LT. Of course, appropriate donor–recipient matching is mandatory for the entire process to achieve the best results and avoid futile procedures.[13,30]

LIVER TRANSPLANTATION AND THE OLDER ADULTS CANDIDATE: ANESTHESIOLOGIST POINT OF VIEW

No formal guidelines are available so far for pre-LT assessment of the older adults candidate.[13,15,23] As appropriately addressed by Akhtar,[13] age and CLD-related changes can affect the physiologic profile in different ways. The "anesthesiologist–perioperative physician" comprehensively assessing the older adults LT candidate must take an account of central nervous system (CNS), CV, and respiratory and renal system conditions.[13,27,28] Comorbidities not necessarily associated with ESLD, such as obesity, coronary artery disease (CAD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), or chronic renal failure are more often reported in the older adults and may affect the perioperative period and—more important—may even worsen after LT. Their impact on medium- and long-term outcomes, in the light of recent study results, calls for further large, more granular multicenter studies.[30,31] The most recent AASLD update to guide evaluation in adult LT candidates,[32] states that "*in the absence of significant comorbidities, older recipient age (>70 years) is not a contraindication to LT*" (grade 2-B). Relevant for the anesthesiologists is several points (6, 7, 9 to 14, 19, 23) that recommend, definition of the cardiac, pulmonary, and renal profiles, together with complete nutritional and infectious disease assessment (the last two subjects are graded 1-A).

NEUROLOGIC AND NEUROPSYCHIATRIC ASSESSMENT

Neurologic screening should be performed in every LT candidate.[13] Neurologic complications (mainly central, but also peripheral) are among the main causes of

unfavorable outcomes in older adults recipients.[33–35] A thorough clinical and neurologic assessment is warranted to rule in/rule out and/or differentiate neurologic disorders. It should include risk factors and age-related comorbidities and a neuropsychiatric assessment. Among others, cerebral small vessel disease, a common neurologic condition in older patients, could become a target of pre-LT screening to establish whether it might influence postoperative outcomes.[34] Cognitive dysfunction, often considered age-related and associated with disruption of brain connectivity,[36,37] should be differentiated from diseases secondary to medical comorbidities (eg, DM or vascular pathologies).[33] These can include (1) cerebrovascular diseases, stroke/transient ischemic attack and the sleep apnea syndrome, frequently reported in NASH/NAFLD patients, and substantial risk factor for stroke, stroke recurrence, and poor functional recovery[38,39]; (2) hepatic encephalopathy (HE), a complex, CLD-CNS dysfunction, manifesting as a wide spectrum of neurologic and psychiatric deficits. HE can be precipitated by acute or chronic "hits" which can lead to increase in an influx of neurotoxins (ammonia among others) not matched by adequate clearance of toxins, mediators, and cytokines[33,40,41]; (3) neurodegenerative diseases involving progressive loss of selectively vulnerable populations of neurons, different from the selective "static" neuronal loss associated with metabolic or toxic disorders[42]; and (4) infectious diseases.[33]

THE CARDIOVASCULAR PROFILE OF THE OLDER CANDIDATE AND ITS ASSESSMENT: STILL WAITING FOR A CONSENSUS

Ageing and age-related diseases, as documented in the most recent reports from both the United States[43] and EU,[44] are unequivocally associated with a high prevalence of "extended" and cumulative CV risk factors/diseases (age, CAD, hypertension, smoking, DM, metabolic syndrome, obesity, NASH) and polytherapy.[45] According to Alexander and colleagues,[46] three or more CV risk factors provide high sensitivity and specificity for detecting severe asymptomatic CAD in LT candidates, thus supporting older guidelines.[26,27,47] This risk profile is increasingly reported among older adults LT candidates, with a higher prevalence of (1) asymptomatic CAD (reported in up to 25% of older LT recipients)[48,49]; (2) heart failure (HF); (3) arrhythmias (among others, atrial fibrillation, documented in 1%–6% of the candidates, frequently reported among the postoperative cardiac complications and able to negatively impact the early postoperative course) and prolonged corrected QT (QTc) interval, both justifying the basal electrocardiogram (EKG); (4) valvular heart disease (well tolerated if mild to moderate, but becoming a contraindication in case of severe forms and need to be discussed in multidisciplinary meetings pre-LT for possible correction)[50]; (5) cirrhotic cardiomyopathy, recently redefined and readdressed with a new definition and a new clinical and echocardiographic assessment.[51,52] CV morbidity and mortality (30-day risk of major adverse cardiac events [MACEs], mainly CV death, myocardial infarction, and stroke) can be high and are mainly determined by two factors, the patient-related risk(s), frailty included, and the high-risk surgical procedure (MACEs > 5% for LT surgery).[48,53] A detailed preoperative assessment and careful selection of the candidate are pivotal to (1) reduce the perioperative risk(s), by identifying "active" cardiac conditions which can impact intraoperative and postoperative outcomes[49,53] and (2) decide in a multidisciplinary discussion if these active condition(s) should undergo correction before LT to improve the LT outcome.[53] As an example, in AASLD 2022 update states that "cardiac revascularization should be considered in LT candidates with significant coronary artery stenosis prior to transplant"(Grade 2-C).[32]

First formally addressed in 2012,[47] a formal CV risk assessment for LT surgery was proposed by American Heart Association/American College of Cardiology guidelines in 2013[26] and EASL in 2016,[27] then comprehensively reproposed by Barman and colleagues[50] and very recently included and graded by AASLD in the short 2022 update.[32] Two main targets of the CV assessment of an LT candidate are (even more strongly recommended for an older patient) to (1) establish whether a patient can be expected to survive the operation and the immediate postoperative period and (2) understand if LT should be considered inappropriate or even futile in an older candidate with severe cardiopulmonary disease/extreme frailty because of the chronic donor organs shortage.[31,49,54–57] The wide heterogeneity in cardiac risk screening strategies very recently documented in a US survey[54] (the same is in European Union),[55] together with the variable CV disease prevalence in LT candidates worldwide, shows once again, the importance of developing and validating a modern, evidence-based, CV risk prediction model.[47,54–57]

A few more points deserve attention (1) the importance of a "dedicated" cardiologist to be involved in the multidisciplinary pre-LT evaluation team[54,57] and (2) the importance of up-to-date and finalized pre-LT echocardiographic study in the prognostication and risk stratification of transplant candidates.[50,52–60] For special considerations on "older" guidelines (concerns about stress tests in general and stress echocardiography in ESLD setting in particular)[50,51,54–57] and for up-to-date insights, we suggest the recent comprehensive reviews.[50,51,54–60]

According to Levy and colleagues,[56] particular attention should focus on echocardiography with tissue Doppler imaging and strain imaging. Anatomic and functional consequences of CAD in LT candidates should become part of the risk stratification tool,[49,53] focusing the attention on an anatomical-based approach to CAD risk stratification. As an example, coronary computed tomography angiography (CCTA), championed by the Asiatic centers but much less used in United States and Europe, should be strongly considered in view of its excellent negative predictive value (97.5%) for post-LT MI.[61] Should CCTA be abnormal or contraindicated, invasive coronary artery angiography—the gold standard—should be performed.[31,50,53,57] Fine-tuning the noninvasive anatomical imaging could be a further step forward.[62.]

Portopulmonary hypertension (PoPH), even if rare (2%–5%), should be ruled out in older LT candidates by routine echocardiography; right heart cardiac catheterization is indicated in a patient with estimated right ventricular systolic pressure $\geq$45 mm Hg or pulmonary artery systolic pressure $\geq$45 mm Hg.[31,63] PoPH is classified according to mean Pulmonary artery pressure (mPAP) at right heart catheterization as mild (25–35 mm Hg), moderate (35–45 mm Hg), or severe (>45 mm Hg). According to the most recent guidelines,[64,65] patients with moderate PoPH (mPAPs > 35 but less than 50 mm Hg) should be temporarily delisted, referred to a PoPH specialist, treated with dedicated cardiac or pulmonary consultation for vasodilator therapy,[32,64,65] and reassessed for LT if they respond to medical therapy (mPAP $\leq$35 mm Hg).[32,64,65] Moderate PoPH with preserved right ventricular function not responsive to medical treatment is a relative contraindication to LT,[66] while persistent severe PoPH with right HF, not responsive to medical therapies, is an absolute contraindication, as the risk of right ventricular failure and post-LT mortality is extremely high.[63–66]

Even though pre-LT cardiac assessment is worldwide considered a priority,[50,55,56,67,68] it is still defined "a challenge."[67] Many questions, particularly *Who* should be screened for CAD, *Which* screening modality should be used, and *When* should the asymptomatic LT candidate repeat cardiac evaluation, do await consistent, evidence-based recommendations.[49,50,54,66]

THE FUNCTIONAL ASSESSMENT IN THE OLDER CANDIDATE: THE WAY TO ENHANCED RECOVERY AFTER SURGERY

A recent document dealing with enhanced recovery after surgery (ERAS), after LT,[69,70] states that functional assessment has a major role in this setting.[69–71] The DASI Score (Duke Activity Status Index) is a more objective version of the "old" metabolic equivalent of tasks score and is based on a well-defined questionnaire[72,73]; the cardiopulmonary exercise testing (CPET)[74] and the 6MWT[75] have a consolidated role in preoperative risk stratification and in predicting adverse cardiac and respiratory events after major noncardiac surgeries, including LT.[73–75] CPET and 6MWT have recently been defined as "reliable tests" to provide information on the cardiopulmonary endurance and the burden of physical deconditioning.[74,75] CPET, perhaps the most accurate marker of cardiopulmonary fitness, has two main limitations: the specialized equipment/personnel required and conducting it in critically ill patients. The 6MWT is a simpler and more user-friendly tool and can provide a viable alternative option; however, data to support the 6MWT for risk stratification in the LT setting, in general and in ERAS protocols in particular, are lacking so far.[69] Tracking the physiologic progress in functional capacity during tailored prehabilitation training programs should enable physicians to understand whether or not the frail candidates will tolerate the physiologic stress imposed by the LT, optimizing the entire LT program and improving outcomes.[69]

THE PERIOPERATIVE PERIOD OF LIVER TRANSPLANTATION: FACING A MARATHON!

The safety of modern anesthesia management relies, among others factors, on attention to the changes induced by surgery on the patient's physiologic profile and appropriate intraoperative monitoring strategy.[76] Anesthesia in the older adults candidates should be based on solid knowledge of the physiologic changes associated to ageing and response to various phases of surgery.[13,37,77]

Intraoperative hypotension, a feared and increasingly reported complication during anesthesia, is more common in the older adults surgical patients and a major problem during LT.[76,78–81]: Changes in pharmacokinet / pharmacodynamic (PK/PD) characteristics should drive pharmacologic strategies and drugs choices.[13,37,77] The extensive, tailored, thorough preoperative assessment, "able to clear a patient for a surgical procedure close to running a marathon"[82] is more than justified by what every LT anesthesiologist experiences during the various phases of the LT.[78–81] The patient may have to tolerate periods (minutes to hours) of critical and multifactorial hemodynamic instability the result, among others, of decreased preload, decreased systemic vascular resistance, impaired myocardial performance, or a combination of the three.[80] The many components of hemodynamic instability during LT include severe hypotension, tachycardia/tachyarrhythmias, malignant ventricular tachyarrhythmias, metabolic acidosis, major acute volume shifts (acute hemorrhage, extreme anemia, massive transfusion, and sudden and severe reduction of venous return), prolonged and resistant vasoplegia after reperfusion of the graft (10%–80% of the cases), acute right or left ventricular overload, dynamic left ventricular outflow obstruction, cardiac tamponade, intracardiac thrombosis/pulmonary embolisms (2%–6%), and cardiac arrest (3.7%).[81]

Surgical bleeding or "coagulopathy" in LT patients is much better understood and managed in the last 15 years. Major innovations and advances in surgical techniques have led to a more informed perioperative management of transfusion[83–85] and fluid administration policies.[86,87] The presence of specifically trained ("designated") anesthesiology teams and a proactive perioperative management have led to, reduced blood/blood components use, less fluid overload, and improved postoperative

outcomes.[88] Age per se does not seem to affect surgical time but is among the factors able to significantly affect blood losses and perioperative complications.[89,90] As recently reported by Mousa and colleagues[90] in a large single-center study on the older adults LT recipients, the risk of death was not significantly higher than among recipients younger than 60 years. Among older adults recipients, greater packed red blood cell requirement and longer warm ischemia time were significantly associated with decreased survival.[90] Mousa and colleagues[90] introduced the concept of "restoration of life expectation" provided by the LT procedure on lifespan relative to patients' ages. As already mentioned, a thorough preoperative cardiac assessment is more than justified because of (1) the rate of perioperative adverse CV events (close to 40% of early total post-LT mortality); (2) MACEs more frequent among older adults patients suffering for NASH, DM, hypertension, and COPD.[15] Older age together with DM and COPD were associated with higher rate of cardiac arrest.[81] As appropriately underlined by Cottone and colleagues,[15] a "selection bias" introduced by the "mandatory" strict candidate selection might have affected the intraoperative complication rate, in the real world perhaps even higher than reported.

For the early postoperative period, ICU length of stay shows great variability among LT centers, particularly in case of older and frail recipients. Fast-tracks protocols have long been proposed with outstanding results supported by modern intraoperative management, early extubation,[78–80] and ERAS protocols.[70,71] Good results after LT were reported quite recently with septuagenarian recipients. These older adults patients did not differ from younger patients in surgical complications, need for mechanical ventilation, length of ICU and hospital stays, and readmission after LT.[91] However, a very recent Australian survey reported a higher short- and long-term mortality, longer ICU stay, prolonged artificial ventilation in frail surgical patients admitted to ICU.[92] Therefore, appropriate, candidate selection and tailored comprehensive prehabilitation programs are key to run an LT program in the older adults, whose main aim should be to optimize resources—scarce by definition–—to "expand lifespan expectations."[90]

Beside the comprehensive and up to date "standard" assessment, we have tried to address—frailty assessment included—major anatomical, pathophysiologic, and surgical issues associated with intraoperative and postoperative complications and adverse events (bleeding, transfusion, ischemia times, among others). However, every transplant center, from its own results, should aim, as far as possible, to avoid every preventable adverse events,[90–92] implementing on modifiable variables every measure able to have a positive impact on grafts and patients outcomes.

SUMMARY

The CV metabolic and respiratory stress imposed by the LT surgery to the recipients[79–82] has recently been described by Hogan "akin to running a marathon."[83] To "challenge the marathon," candidates, frail because of ESLD but even more frail because older, should be fully assessed, and when cleared for LT, "intensively" trained. The comprehensive preoperative assessment, including frailty evaluation, should be followed by tailored, dynamic pre-habilitation, and nutritional programs. Infections and infection-related risk factors should be assessed, ruled out or in any case solved. Since the late 1980, older adults candidates have been more and more confidently cleared for LT; older recipients (65 years and older) now account for up to 25% in most of the United States, EU, and Asian series, numbers that are likely to increase in the very near future. Results are constantly improving and according to the most recent data able to restore the lifespan expectation of the older adults: the challenge cannot be refused!

CLINICS CARE POINTS

- Older candidates/recipients are nowadays the rule and not the exception in liver transplant (LT) programs
- Older end-stage liver disease patients are often frail; anesthesiologists should become acquainted with such a peculiar patient, having a solid knowledge of the older adults physiologic profile for a wise management of the perioperative period.
- Preoperative LT evaluation, together with a preoperative "older adults–oriented" pathway, should mandatorily include the frailty assessment using Liver Frailty Index and a functional assessment, this latter extremely useful to explore the cardiovascular and the neurologic profiles and to orient the need for prehabilitation.
- Anesthesiologists involved in LT surgery should become the "true" perioperative transplant physicians, merging the multidisciplinary preoperative work done by surgeons, hepatologists, and cardiologist(s) to ease the perioperative period.
- Having such an active part in the older candidates selection, anesthesiologists will play a relevant role in increasing the already good early- and medium-term LT results, avoiding futile procedures while (hopefully) expanding recipients' [expanding] lifespan expectations.

CONFLICTS OF INTEREST

None.

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