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Preoperative cardiac assessment in liver transplant candidates

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Corresponding Author:	Andrea De Gasperi Azienda Socio Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda ITALY
First Author:	Andrea De Gasperi
Order of Authors:	Andrea De Gasperi
	Gregorio Spagnolin, MD
	Martina Ornaghi, MD
	Laura Petrò, MD
	Gianni Biancofiore, MD
Abstract:	New and extended indications, older age, higher cardiovascular risk, and the long-standing cirrhosis - associated complications mandate specific skills for an appropriate preoperative assessment of the LT candidate. The incidence of cardiac diseases (dysrhythmias, cardiomyopathies, coronary artery disease, valvular heart disease) are increasing among LT recipients: however, no consensus exists among clinical practice guidelines for cardiovascular screening and risk stratification. In spite of different “transplant center-centered protocols”, basic “pillars” are common (electrocardiography, baseline echocardiography, functional assessment). Due to intrinsic limitations, yields and relevance of noninvasive stress tests, under constant scrutiny even if used, are discussed, focusing the definition of the “high risk” candidate and exploring noninvasive imaging and new forms of stress imaging. The aim is to find an appropriate and rational stepwise algorithm. The final commitment is to select the right candidate for a finite resource, the graft, able to save (and change) lives.

Preoperative cardiac assessment in liver transplant candidates

Andrea De Gasperi, MD*, Gregorio Spagnolin, MD*, Martina Ornaghi, MD*, Laura Petrò, MD*, Gianni Biancofiore, MD**

*2° Servizio Anestesia Rianimazione - ASST Grande Ospedale Metropolitano Niguarda – Milan – Italy

** Transplant Anesthesia and Critical Care Unit, University School of Medicine, Azienda Ospedaliera-Universitaria Pisana, Pisa, Italy

Corresponding Author

Andrea DeGasperi, MD

andrea.degasperi@ospedaleniguarda.it

mobile +39 3471597488

Abstract

New and extended indications, older age, higher cardiovascular risk, and the long-standing cirrhosis - associated complications mandate specific skills for an appropriate preoperative assessment of the LT candidate. The incidence of cardiac diseases (dysrhythmias, cardiomyopathies, coronary artery disease, valvular heart disease) are increasing among LT recipients: however, no consensus exists among clinical practice guidelines for cardiovascular screening and risk stratification. In spite of different "transplant center-centered protocols", basic "pillars" are common (electrocardiography, baseline echocardiography, functional assessment). Due to intrinsic limitations, yields and relevance of noninvasive stress tests, under constant scrutiny even if used, are discussed, focusing the definition of the "high risk" candidate and exploring noninvasive imaging and new forms of stress imaging. The aim is to find an appropriate and rational stepwise algorithm. The final commitment is to select the right candidate for a finite resource, the graft, able to save (and change) lives.

Key words: liver transplantation, preoperative cardiac assessment, coronary artery disease, cirrhotic cardiomyopathy, hepatopulmonary syndrome portopulmonary syndrome

1. Introduction

Recently, Hogan et al described the intraoperative cardiovascular stress imposed to the recipients by the liver transplant (LT) procedure as “akin to running a marathon” [1]. The average candidate quite often presents with the peculiar cardiovascular profile associated with End Stage Liver Disease (ESLD), namely high cardiac output, low systemic vascular resistances and splanchnic vasodilatation. The more severe the condition, the more pronounced are the cardiovascular alterations, with consistent differences in case of cholestatic, tumoral or cirrhotic etiology of the ESLD [2-4]. As experienced by every anesthesiologist involved in a LT program, during surgery the patient may have to tolerate periods (minutes to hours) of tachycardia, severe hypotension, acute blood loss, extreme anemia, markedly reduced venous return, prolonged and resistant vasoplegia after reperfusion of the graft, or, on the contrary, massive transfusion and acute right or left ventricular overload in the various phases of the LT [2-4]. To survive such a stressful scenario unscathed, an appropriate (or optimized) cardiovascular performance status is mandatory for the candidate [1-4], as mandatory is the thorough, extensive, tailored preoperative cardiovascular assessment [2-6]. Of particular importance is the form of myocardial dysfunction, potentially masked by the peripheral vasodilatation (cirrhotic cardiomyopathy, CCM). In fact, “severe cardiac diseases” are among the few contraindications to liver transplantation [5], and cardiovascular adverse events are among the most common postoperative complications [7-10]. Indications for LT are changing and expanding [5–6], making hepatic transplantation the second most commonly performed solid organ transplant procedure worldwide [11]. Main driver of the increased demand of LT are the positive outcomes, with 1- and 5-years survival rates above 90% and 80%, respectively, and a life expectancy well beyond the timespan predicted by the natural history of the underlying liver disease [12]. In the absence of major contraindications, no age limits are nowadays suggested [5,6] and elderly candidates (well beyond 65 years old) are nowadays often proposed for the transplant procedure. However long-standing liver cirrhosis (the most common ESLD in LT candidates), portal hypertension, older age, new indications such as non-alcoholic fatty-liver disease (NAFLD) / non-alcoholic steatohepatitis (NASH), (part of the metabolic

syndrome together with diabetes mellitus, DM) and some less common genetic diseases (such as Wilson's disease, Hereditary Haemocromatosis (HH), Primary hyperoxaluria, Familial amyloid polyneuropathy) are associated with a risky cardiovascular profile able. Sicker and more fragile candidates are now accepted for active LT listing and are therefore exposed to an increased incidence of adverse perioperative cardiovascular events [8,10,13].

Among the main tasks of the modern LT anesthesiologist (the true perioperative physician with specific privileges) [4,14] is a proactive role in the preoperative evaluation, a mandatory multidisciplinary process aiming at an appropriate allocation of a limited resource (the graft) to an increasing number of candidates awaiting for LT. More specifically, aims of the pre-transplant cardiovascular assessment are (i) to rule out comorbidities, conditions or drugs [15] able to blunt or dangerously impair the physiological response to the sudden, severe, life-threatening situations possibly occurring during LT; (ii) to predispose the best intraoperative anesthesia strategy to prevent or to appropriately face adverse events, concurring to improve the final clinical outcomes [14]. Candidates too sick or whose pathological condition(s) cannot be reliably corrected to make them eligible for LT ("too sick for transplant") are to be delisted, to avoid a futile transplantation and the waste of a very limited resource [16].

2. Preoperative Cardiovascular evaluation and risk assessment

Smilowitz et al [17] reported a 3% incidence of major cardiovascular and cerebrovascular adverse events (death, acute myocardial infarction, acute ischemic stroke) in a large series of non-cardiac surgical procedures. Interestingly, the adverse events were more commonly represented after thoracic, vascular and transplant surgery. Preoperative cardiovascular diseases and perioperative cardiac adverse events are then a leading cause of negative graft and patients' outcomes. According to the most authoritative statements in the literature [7,9,18], there are two main points to be explored during the pre-transplant cardiovascular risk assessment: (i) if the candidate is able to survive the LT procedure ; (ii) if known or silent cardiovascular

conditions/diseases associated with ESLD might have such a relevant negative impact on the perioperative period to preclude the candidacy if not appropriately corrected. Among them are cardiac dysrhythmias, including atrial fibrillation (AF), reported in 1-6 % of LT candidates and associated with postoperative complications, long QTc (> 440 msecs, reported in close to 50 % of the candidates), complex ventricular arrhythmias or relevant atrioventricular conduction abnormalities (atrioventricular blocks or other rare syndromes, such as Brugada syndrome) [19], cirrhotic cardiomyopathy (CCM), coronary artery disease (CAD), valvular heart disease) Portopulmonary hypertension (POPH), Hepatopulmonary syndrome (HPS) [7-10,13,20]. The rising age and the increased prevalence of metabolic diseases (DM and particularly NAFLD) in LT candidates increase the individual risk of relevant cardiovascular diseases and perioperative cardiovascular complications [5-10]. Prediction of the risk or identification of the disease should ideally lead to an individualized program to optimize cardiac function ("prehabilitation" should be one of the scopes of the program) [9]. Major adverse cardiac events (MACE) after LT (myocardial infarction, heart failure, acute coronary syndrome, pulmonary embolism) occur in close to 10% of the recipients within 90 days after surgery. Large part of the adverse events are non-coronary in origin, but associated with perioperative atrial fibrillation and stroke [8]. However, consensus on a standardized pre LT cardiovascular evaluation and risk stratification, even if long and eagerly awaited, is still lacking [1,5,7,9,10,18,20]. Cardiac assessment is then characterized by a large variation in guidelines, with different clinical pathways often "transplant center oriented" and difficult to be generalized, even if the relevant "pillars" sustaining its rationale are common to the various stepwise paradigms [1,9,10,20-22]. As underlined by Sandal et al [10] while in case of symptomatic disease the pathways are quite well defined, risk assessment in the asymptomatic candidate is variable if not sometimes controversial (age of the candidate to perform cardiac stress test or the indication to coronary artery angiography, CA). EASL guidelines for LT recommend (Grade II – 3) for all the candidates 12-lead electrocardiogram (EKG) and 2D transthoracic echocardiography (TTE) [6]. This is at variance with from the AASLD guidelines, which recommend only basal TTE [5]. In line with the most recent reviews dealing with preoperative cardiac evaluation for non-cardiac surgery [23,24], we and others [1,20,21,25,26] strongly support, together with the above cited basic instrumental tests, a chest radiological imaging, clinical history

and physical examination and a preliminary "subjective" functional assessment of the cardiac reserve using the definition of the metabolic equivalents [METs]. The latter is now better defined by the DASI score questionnaire, more objective, very well correlated in the high risk general surgical population to peak oxygen consumption (VO_2 peak) and complications [27] , even if not yet specifically validated in the LT candidates [28].

2.1 Electrocardiogram (ECG) - Little evidence exists that preoperative ECG findings are indicator(s) of postoperative prognosis. LT is considered a high risk surgery, definition which included mortality rate /MACE > 5% [29]. In the absence of definite indications, relevant features of the basal 12 - lead ECG to be considered are heart rate and rhythm, QTc interval, presence of Q wave, abnormal QRS axis deviation, ST segment depression and a pathologic T wave. According to Josefsson et al [30] the above alterations were significantly more represented, compared to normal controls, in a cohort of LT recipients. In particular Q wave and prolonged QTc interval were associated with post LT adverse cardiac events but not with mortality [8,18]. QTc prolongation might shorten in the post-transplant period [18]. Its role as a predictor of poor outcome, particularly in the setting of CCM , has been questioned by Izzy et al in the very recent report from the 2018 Consensus Conference on CCM [31]. Prolonged QTc is not considered in cirrhotic patients a risk factor for "torsade de pointe" ventricular tachycardia. Instead, Park et al in a retrospective study were able to document an association between the preoperative ECG findings suggesting myocardial ischemia and postoperative 1-year mortality [32]. Further prospective studies are needed to define features (if any) mandatory for an appropriate preoperative risk assessment and the exact role that ECG should have in the preoperative LT assessment. In case of CCM, the recommendations for prolonged QT (> 450 msec in males or > 470 msec in females) recently endorsed by ATS are to treat reversible causes and to avoid medications able to prolong QT (GRADE recommendation 1C) [9]

2.2 Biomarkers - Biomarkers may have an interesting role as non-invasive diagnostic and prognostic tools in the preoperative period [31,33,34]. Some Authors suggest the preoperative use of cardiac Troponin I (cTn I)

level, now used for the general surgical population, as a marker of subclinical myocardial damage [25,35]. Recently Park et al [36] reported on increased early and late mortality in LT recipients with high preoperative cTn I (> 0.07 ng/ml). The same group was able to demonstrate an early increase of all-cause mortality and graft failure in living donor LT recipients with normal preoperative cTn I who experienced pathological increase in the immediate postoperative period. In this case myocardial injury was independently associated with and early adverse outcome [37]. A prospective study dealing with preoperative evaluation of LT candidates was not able to document a role for increased cTn I (> 0.07 ng/ml) as a predictor of cardiac outcomes early after LT [38]. False positive results are possible: a recent case report addressed a donor - recipient transfer as an alternative explanation of an increased cTn I without recipient's cardiac adverse event [39]. Further prospective studies are therefore needed to define the exact role of the perioperative use of cTn I, which reflects severity of both systolic and diastolic abnormalities and portal hypertension, has been associated with mortality in CCM and might be promising in preoperative risk stratification [34,40].

2.3 Rest Transthoracic Echocardiography (TTE) – Rest TTE is recommended by AHA for all the LT candidates and included in all guidelines of cardiovascular risk assessment before LT [5,6,8-10,18,20,26,41]. Pre LT TTE and Doppler should assess left and right atria dimensions, the presence of pericardial effusion, right and left ventricular morphology and dimensions, interventricular septal dimensions, systolic (SD) and diastolic ventricular (dys)function (DD), left ventricular ejection fraction (LVEF) ("normal" if in the range of 53% to 73%, "depressed" if < 53%, hyperdynamic if > 73%), pulmonary artery systolic pressure (sPAP) assessment, morphological and functional valvular aspects (tricuspid valve regurgitation and aortic diameter as an example), patent foramen ovale and intracardiac shunt, the presence of Left Ventricular Outflow Tract Obstruction and its possible dynamic component [18]. Eagerly awaiting for a standardized "ideal " format, relevant TTE parameters for the LT assessment [41, 42,43] seems to be (i) morphology, dimensions, volumes and mass of cardiac left chambers; (ii) measurements of cardiac end systolic function (EF); (iii) measurements of cardiac end diastolic function to rule out the "Doppler evidence of DD": mitral inflow (peak early filling [E wave] and late diastolic filling [A wave] velocities and E/A ratio); tissue Doppler annular early (e') and late (a') diastolic velocities; E/e',an index of LV filling (the cut-off value of > 10 in ESLD

candidates recently raised concerns for being too low) [43]; and (iv) sPAP. These TTE features have recently been associated with adverse cardiac-related outcomes in patients with cirrhosis [42].

According to VanWagner et al, rest TTE is the primary screening modality to rule out SD and DD, heart failure or its potential perioperative development (GRADE recommendation endorsed by ATS 1C) [9]. In a large multicenter study, Batra et [44] were able to document 4-fold increase in early post-LT mortality in patients with cirrhosis and left ventricular hypertrophy (LVH) versus those without, addressing the relevance of this easy to assess preoperative parameter in older and more compromised recipients. There is no well documented LVEF cutoff value to contraindicate the LT: LVEF below 50% is considered a relative contraindication (and worth to be included in stepwise algorithm for deeper preoperative assessment) , while EF below 40% should constitute an absolute contraindication, together with moderate to severe right ventricular failure [9]. A very recent large retrospective study dealt with preoperative LV systolic and diastolic function assessments and all-cause mortality prediction [43]. In this series (839 adult candidates, median age 51, BMI 23.8, MELD 14, EF > 50% in all recipients, DM, Arterial Hypertension (AH) and CAD reported in 21%, 11.6% and 13.3% respectively), 1 and 4 y survival rates were > 90% and none of the patients died for primary cardiovascular reasons. Since the risk of death was higher in patients with LVEF < 60% and with E/A < 0.9, the concomitant use of both parameters should provide better risk stratification and more reliable survival prediction [43]. As to the anesthesiologist, all these preoperative information should provide relevant insights for the entire perioperative period. Major advantages should be (i) better preoperative risk stratification, (ii) definition of specific diagnostic and therapeutic pathways in case of pathological findings, (iii) definition of a tailored intraoperative cardiovascular monitoring, (iv) possible prediction of post-transplant outcomes in term of cardiovascular and renal morbidity and overall mortality [40,43].

2.4.1 Functional Tests in Preoperative Cardiac Assessment

Functional capacity tests, mainly Metabolic Equivalent of Tasks (METs), the cardiopulmonary exercise testing (CPET) and the six-minute walk test (6MWT) have a consolidated role for preoperative risk stratification and

in predicting adverse cardiac and respiratory events after major non cardiac surgery [23,27,28,45,46]. Recently CPET and 6MWT have been considered reliable to test cardiopulmonary endurance and, as a consequence, to define the burden of physical deconditioning during the preoperative LT assessment [1,46-57]. This is why subjective or objective performance markers are often found in stepwise assessment algorithms.

2.4.2 Metabolic Equivalent of Tasks (METs)

METs, frequently used to assess functional status [27] were very recently further refined [28]. One MET is the equivalent of the resting oxygen (O_2) consumption of an average 40 years old, 70 kg male subject. Candidates unable to perform a work equivalent at least to 4 METs (the usual reference being climb two flights of stairs) were considered at increased risk of perioperative cardiac events [45,47]. Recently, to define the ability to predict death or complications after major elective non-cardiac surgery, the subjective assessment (METs) was compared to DASI score (Duke Activity Status Index, based on a well-defined questionnaire), to a serum cardiac biomarker (N-terminal prohormone of brain natriuretic peptide, NT-BNP) and to the measured peak oxygen consumption [27]. The DASI score, but not the sole subjective assessment, was associated with both the prediction of the primary outcome and the measured peak oxygen consumption at CPET [27]. In the most recent nested cohort analysis of that study the Authors were able to define a cut-off of 34 as a threshold to identify surgical patients at increased risk for myocardial injury, myocardial infarction, and moderate-to-severe complications[28]. The role of METs (recommended by the AHA guidelines [23] and included in some stepwise algorithms [1,21,25,26], or nowadays of the DASI score, deserves a specific validation in preoperative LT assessment.

2.4.3 Cardiopulmonary Exercise Test (CPET)

CPET is a symptom-limited exercise test able to measure cardiac, respiratory and metabolic functions [45]. In the high risk surgical patient the main aims of CPET are to provide diagnostic and prognostic information in patients with cardiac or respiratory disease or, as recently proposed, as a preoperative screening test to assess LT candidates [1,47-52]. Standard measures obtained with CPET are maximum aerobic capacity (peak

oxygen uptake, $VO2_{peak}$, used as a surrogate of $VO2_{max}$, the maximum oxygen uptake, sometimes difficult to be achieved in severely compromised candidates) and the anaerobic threshold (AT, the point at which muscle O_2 demand is not met by O_2 supply, causing a switch to anaerobic metabolism), used to measure cardiopulmonary reserve. In the LT setting, reduced aerobic capacity ($VO2_{peak}$ < 60% predicted according to Dharancy et al[47] or below 13 ml/kg/min according to Bernal et al [50][and Ow et al [51]) was able to predict poorer outcomes both on wait list and early after LT. According to Prentis et al, low AT (<9 mL/min/kg) was associated with reduced 90-day survival rates [52]. In a recent preliminary report, CPET was able to uncover silent myocardial ischemia in three LT candidates [53]. According to the systematic review on CPET and LT, the test seems to be able to predict pre- and post- LT mortality, but still lacking is the threshold value [54]. CPET could be used (i) to gauge and objectively document improvements of the functional status after supervised training prehabilitation and appropriate nutritional counseling in sarcopenic or deconditioned ESLD candidates; (ii) whether changes in CPET after the tailored interventions are able to impact pre and post- transplant prognosis [48,54]. The GRADE recommendation for CPET endorsed by ATS is 2C [9]

2.4.5 Six-Minute Walk Test (6MWT)

The 6MWT is a simple, easy and reproducible test since long used to assess the functional capacity of the cardiovascular and respiratory systems, evaluating tolerance to physical efforts [55]. Quite recently it has been introduced in the perioperative evaluation of LT patients [1,9,56,57]. Carey et al [56] studied a cohort of 121 LT candidates with the 6MWT to find a relationship with the survival rate and the quality of life after LT. A 6MWT <250 meters was associated with an increased risk of death on the wait list, while each 100-m increase in the test was significantly associated with increased survival. In a recent USA study performed early after LT, 6MWT was able to uncover frailty and poor functional capacity, suggesting the opportunity for individualized rehabilitative interventions [57]. Shulman et al [46] in a substudy of the METS study [27] assessed the prognostic utility of 6MWT to predict disability-free survival (DFS) after major surgery. Preoperative walked distance during the test correlated weakly with 30 day recovery, with 12 month DFS, and with METS cardiovascular outcomes, while it was comparable or superior to CPET for all the measures outcomes [46]. The final suggestion was to include the DASI questionnaire, NT-proBNP measurement, and

possibly the 6MWT into future perioperative risk assessment algorithms, reinforcing the idea to consider this test as a routine tool in the stepwise preoperative assessment of LT candidates. The GRADE recommendation for the use of 6MWT endorsed by ATS is 2C [9].

According to large part of the "center oriented" stepwise algorithms, normal cardiological and functional profiles (as defined by history, physical examination, ECG, rest TTE and functional assessment) lead to the clearance of the candidate for the LT procedure. Should ECG and rest TTE or any other non-invasive screening for CAD to be repeated regularly if normal? Consensus on the extent and interval to repeat cardiac evaluation while on the wait list is lacking [10]. A clinical trial testing the hypothesis of non-inferiority of no further screening for asymptomatic CAD versus assessment (and which test) at regular interval is now underway [ClinicalTrials.gov, number NCT03674307) [10]. On the contrary, thorough multidisciplinary re-evaluation and further deeper assessment is mandatory in case of clinical decompensation (heart failure of any cause), new symptoms related to CAD, symptoms / evidence of ventricular or supraventricular arrhythmias or AV block [9].

3. Cirrhotic cardiomyopathy and heart failure: definition and assessment

LT candidates (ESLD, alcohol-induced liver disease, hepatitis C virus-correlated cirrhosis [HCV], HH, amyloidosis, NAFLD) are at increased risk of cardiomyopathy, a condition prone to perioperative heart failure (HF), one of the causes of early post LT complications [9]. ESLD patients possess the well-known hyperdynamic cardiovascular profile characterized by peripheral and splanchnic vasodilatation, increased sympathetic activity and dysregulated β adrenergic receptors, among the factors responsible of the increased cardiac output [31]. Even if in presence of high cardiac output, the responses to various stimuli (stress, exercise, blood loss, acute changes in preload and afterload) are abnormal and HF, in spite of an often preserved resting LVEF, may be present. This condition, in the absence of other known cardiac diseases, is defined CCM [31,58]. Among the relevant features of CCM are consistent changes in atrial and ventricular volumes and myocardial structure, blunted chronotropic and inotropic responses to stress (stress-induced

systolic dysfunction, defined as the failure to increase the LVEF by > 5% under stress test). DD related to severity of ESLD, usually precedes SD, may be present at different degrees (mild, moderate, severe, grade 1,2,3 respectively) [9,58], being mainly related to LV increased stiffness, relevant changes including increased left ventricular myocardial mass, subendothelial edema and myocardial fibrosis. Prolonged QT, since recently a cornerstone of the diagnosis of CCM, is no more considered relevant, being reported in close to 50% of the ESLD patients [9,31]. Criteria for the diagnosis of CCM have very recently been updated by the Cirrhotic Cardiomyopathy Consortium [31]. Since CCM is now considered in the spectrum of heart failure, it is mandatory a correct pre LT staging to avoid progression into the more severe stages of decompensation, often masked by the extreme vasodilatory state of advanced ESLD) [31]. With respect to old criteria (Montreal criteria, 2005), new criteria to redefine CCM are discussed in a comprehensive review proposed by the CCM Consortium [31] and by Moller et al [58]: for simplicity a dedicated algorithm modified by Oh et al *[Oh JK, Miranda WR, Birg JG et A proposal for revised echocardiographic algorithm to assess diastolic function and filling pressure. JACC Imaging. Submitted for publication*] has been proposed [31]. Additional markers of CCM are a reduced contractile reserve, potentially not manifest at early stages but identified by the pathologically increased E/e'; LV end diastolic dilatation and increased LV mass index; right sided chambers enlargements and, potentially, right heart failure. The relevance and the problems raised by the need to optimize CCM diagnostic criteria and their main consequences are evident in the discussion following the CCM Consortium statements, in particular dealing with the "blunted" stress response and its definition [59,60]. The importance of the pre-transplant definition of moderate and severe DD resides in the recently demonstrated association with risk of rejection, graft failure and mortality, further stressing the relevance of a precise pretransplant diagnosis [58,60]. As above underlined, CPET may be a useful test to identify candidates with CCM associated cardiovascular limitations [31].

Modern CCM Consortium criteria are the following [31,58]

1) Systolic dysfunction
    a. LVEF < 55% or Global Longitudinal Strain (GLS) < 18% or > 22% in the absence of known heart disease. GLS is reported as a negative value in echocardiography report (normal -18% to -

22%): changes should be reported as absolute value. Since longitudinal contractile function could be impaired before radial function, GLS (composed of circumferential, longitudinal, radial, and transverse strain patterns) might identify contractile dysfunction in subjects with preserved LVEF (EF>50%). New options to diagnose SD are coming from the tissue doppler imaging and speckle tracking echocardiography [58]

2) Diastolic dysfunction

   a. At variance of 2005 Montreal criteria, and according to the more recent guidelines [61-63], assessment of the LV diastolic function using E/A, (a dynamic parameter), is now considered unreliable because affected by preload

   b. Three or > 3 of the below parameters are needed to diagnose advanced DD

      i. • medial e' velocity <7 cm/second

      ii. • E/e' ratio ≥15

      iii. • Left Atrial Volume index (LAVI) >34 mL/m

      iv. • Tricuspid regurgitation velocity (TR) > 2.8 m/second

4. Cardiac Dysrhythmias

Ventricular and supraventricular arrhythmias are not uncommon in the LT candidate: ranging between 1 and 6%, atrial fibrillation (AF) is the most common SV tachyarrhythmia, complex ventricular dysrhythmias being much rarer and possibly related to the underlying cardiac disease [9]. AF has been associated with an increased rate of perioperative cardiovascular complications and deserves, when symptomatic and/or associated with uncontrolled ventricular response, a thorough cardiological investigation and an appropriate perioperative management, included the intraoperative cardiovascular monitoring [9,64]. The need of parenteral (Low Molecular Weight Heparin, LMWH) or oral anticoagulation (vitamin K antagonists, VKA, or direct oral anticoagulants, DOACs) while on the wait list is usually planned with the cardiologist and the hepatologist. For the reversal immediately before surgery a proactive approach mandates a consultation with

a cardiologist and /or with an expert in hemostasis, according to the most recent available guidelines [9,65,66-70]. In case of DOACs, the need for reversal depends upon timing of the last dose before surgery, renal function and, if available, blood level of the drug to test the anticoagulant activity. Specific antagonists for dabigatran is now available (idarucizumab) [68]. In case of VKA or DOACs for which antagonists are not yet available [69], Prothrombin Complex Concentrates may be a feasible solution [70]. If and when present, and particularly in the case of peculiar conditions (long QT syndrome or Brugada syndrome), dysrhythmias mandate a thorough preoperative investigation and an appropriate and proactive perioperative strategy planned with the cardiologist: the individualized strategy should include (i) avoidance of drugs/ anesthetics able to induce or worsen the arrhythmia [71,72]; (ii) availability of appropriate antiarrhythmic drugs : (III) availability of temporary or implanted electrical devices for cardioversion and defibrillation [19,9]

5. Coronary Artery Disease (CAD)

In the last twenty years the population of LT candidates has changed: much wider indications (alcohol-related cirrhosis, NAFLD / NASH) and candidates sometimes in their seventies have consistently increased the risk of CAD and its potential complications in recipients [1,5,6,9,16,18,25]. Consensus recommendation [9] states that non-revascularized severe multivessel CAD constitutes an absolute contraindication to LT, while ”moderate” obstruction not involving left main or proximal left anterior descending (LAD) coronary arteries, even if non revascularized, is considered a relative contraindication[9]. Risk factors for CAD in LT candidates include age (unfortunately not univocal the figures, but usually between 50 and 60 years, gender making the difference), prior cardiovascular disease, AH, dyslipidemia, DM, smoking, LVH, chronic renal failure [1,7,9,16,18,20,22,23,25,73-76]. CAD is associated with a decreased survival after LT. Angiografically detected CAD is strongly correlated with the number of CAD risk factors, two or more risk factors heavily impacting on survival [16,25]. Prevalence of CAD among LT candidates, < 5% in Italy (2–4%) [73], is higher (7–25%) in the rest of Europe and USA [1,7,8-10,16,18,22,73,74]. CAD is usually defined as the presence of any stenosis of the coronary arteries, the disease being present in case of stenosis ≥50%, with detailed

definition for single and multivessel disease [16]. Coronary artery stenosis is significant if ≥50%, severe (or obstructive) when ≥70% , or ≥ 50 %. in left main coronary artery. Silent CAD, the really feared condition associated with perioperative life-threatening consequences if not recognized and appropriately managed, (see below) should be ruled out during the preoperative assessment [77]. According to Snipelsky et al, severe CAD was associated with increased mortality despite interventions [75]. Yong et al were able to document increased mortality also in case of non-severe multivessel CAD [76]. However, the most recent studies document the relevance of an adequate pretransplant treatment on the post-operative outcome, notwithstanding CAD severity or extent [9,77]. The outcome of LT recipients with severe coronary artery stenoses are, after adequate treatment, comparable to non-CAD patients [1,9,10,16,18,20,77]. Management options to treat CAD include surgical and/or medical treatment, percutaneous coronary interventions (PCIs), coronary artery stenting with appropriately lasting double antiplatelet therapy (1 to 3 months vs. 6 to 9 months) [9,10,18,20,78-81]. Dual antiplatelet therapy (DAPT), the combination of aspirin and an oral inhibitor of the platelet $P2Y_{12}$ receptor, is the effective treatment to prevent coronary artery stent thrombosis in the period at major thrombotic risk after implantation [81]. Irrespective of the type of the implanted stent (bare metal stents [BMS], now obsolete and no more used, polymer-free drug coated stents, and the newer generation drug-eluting stents [DES] [81]), a minimum of 1 month of DAPT according to the stent type should be considered when transplant surgery cannot be postponed for longer [9,81]. Aspirin should be maintained for the perioperative period an continued thereafter. After stenting, CAD candidates, otherwise rejected, can be confidently considered for LT with extremely positive results [9,16,77-81]. If, for technical or clinical reasons, PCI is not indicated, staged or concomitant coronary artery bypass graft (CABG) is the possible option [82-86]. Pre-LT CABG is feasible in Child-Pugh A patients with good outcome (one-year survival rate of 80%) [82,83]. By contrast, the single CABG procedure in Child-Pugh B and C candidates has a survival rate of 45% and 16%, respectively [83]. The concomitant procedure of CABG and LT has been scarcely reported in the literature and should be reserved for Child-Pugh B or C patients [83-85]: in a case series of ESLD patients with severe triple-vessel disease, at 25 months of follow-up, graft and patient survival was 80% (one death

due to hepatitis C recurrence) [84]. Off- pump CABG without systemic heparinization was recently considered as a feasible option [86].

6. CAD Screening and risk assessment: the challenge, the present and the future

No consensus exists on the best approach to stratify cardiovascular risk and, in particular, to screen silent CAD in LT recipients, main targets being diagnostic accuracy and reliable prognostic cardiovascular outcome after LT [9,10]. Two major questions are eagerly awaiting an answer (i) which candidate (the "high risk candidate") needs further tests after the basic assessment ; (ii) which test has to be used for an appropriate screening [1,5,7,9,10,16,18,20,22,29,80,87-106]. It is therefore mandatory to try and find a final consensus on these two points since available guidelines are different among Professional Societies .

1. ESC/ESA (2014) recommends for CAD screening before high risk surgery (as LT is) stress imaging in subjects with > 2 risk factors (as assessed by Revised Cardiac Risk Score, RCRI, and poor functional capacity (METs<4) (class1, level of evidence C) [29].
2. AASL (2013) recommends dobutamine stress echocardiography (DSE) as the initial screening (Class 1B), with subsequent coronary artery angiography (CA) if clinically indicated [5].
3. AHA (2012) stated that "non invasive stress testing may be considered in LT candidates with no active cardiac conditions on the basis of CAD risk factor, regardless the functional status"[7]. The choice of noninvasive stress imaging (DSE vs nuclear myocardial perfusion scanning , NMPS) is left to the local expertise. The number of CAD risk factors considered "reasonable" to justify stress testing in asymptomatic candidates is "3 or more", with no differentiation in case of DM [7].

A very recent retrospective study [22] was able to document that the sum of AHA risk factors could be of significant diagnostic and prognostic utility. According to Alexander et al [22], non-invasive stress testing should be considered in asymptomatic candidates with ≥3 risk factors (any factor): this threshold was associated with a good discriminatory capacity for severe CAD and an increased risk of postoperative major cardiac adverse event.

6.1 Non-invasive stress imaging tests

Dobutamine stress echocardiography (DSE), Nuclear Myocardial Perfusion Scanning(NMPS), cardiac computed tomography (CTCA) with calcium scoring (CACS), stress cardiac magnetic resonance (CMR) ("one-shop stop" in the "cardio-hepatic assessment") have been considered as preoperative screening tests for cardiovascular disease for the LT candidate. Hot debate still exists on which stress test (exercise or pharmacological) has to be used, or if a non-invasive imaging (CTCA with CACS or stress CMR) should be considered in alternative to screen candidates at risk. CA remains the reference standard for the diagnosis and quantification of the coronary stenoses in case of positive stress tests [1,9,10,20,80, 87-97].

Exercise stress testing could have poor predictive value due to the (not infrequent) limited ability of the LT candidates to reach the target heart rate [1,9,10,25]. The use of vasodilating or inotropic agents should obviate the need for exercise in frail or physically limited candidates and increase the chance to detect CAD [20]. Stress testing maybe non diagnostic when submaximal (interruption for side effects etc.) and suboptimal to assess its prognostic power. Moreover, many patients are evaluated on drugs able to offset the diagnostic and prognostic power of non-invasive stress testing [93]. In asymptomatic individuals DSE lacks the sensitivity to reliably screen LT candidates for asymptomatic CAD and the test should be abandoned for preoperative cardiac risk stratification in low risk patients [10, 87-90]. In the most recent retrospective study dealing with DSE and LT, Doytchinova et al [90] were able to document low sensitivity, (24%) but very high NPV (90%): false negative results, even if rare, might be present, with devastating consequences [99]. In the editorial commenting on Doytchinova's study, Pierard underlined the need for limiting DSE to high risk patients [91]. In case of a positive stress test, CA is mandatory since the incidence of "false positive "(FP) tests might range between 5% and 15%. In case of "FP" test, a major problem in the interpretation of the test could come from the consequences that microcirculatory disorders (detected by DSE but in the absence of critical stenosis at CA) might have in the intra and early postoperative period in diabetic or NAFLD / NASH candidates. It is conceivable that stress echocardiography, performed only on the basis of wall motion abnormalities, might not be enough, due to a suboptimal diagnostic accuracy. Much more useful could be to

assess more parameters of positivity, as Coronary flow Velocity Reserve (CFVR) on LAD and contractile reserve [94]. Single-photon emission CT (SPECT) or Nuclear Myocardial Perfusion Scanning (NMPS), when used, are able to identify patients at very low risk of major adverse cardiac events after LT [1,87,88,95]. Due to the high NPV, noninvasive stress testing or stress imaging, when negative, should be relevant to rule out CAD and adverse cardiac events () [1,95]: instead, the low rate of positive yield documented at CA (the presence of critical stenosis) might demonstrate quite a high rate of false positive results [93,95]. Same concerns (if not negative conclusions) were raised by Soldera et al. in the ultimate, most recent systematic review and meta-analyses on DSE, NMPS and CA in LT candidates [88]. Pooled sensitivity was 28% and 61% for DSE and MPS and specificity was 82% and 74%, for diagnosis of CAD using CA as gold-standard, respectively.

The most authoritative position (2018) so far available is provided by the working group endorsed by the American Society of Transplantation (AST), Liver and Intestinal (LICOP) and Thoracic and Critical Care (TCC COP) Communities of Practice [9].

1) LT candidates with DM **or** ≥2 traditional CAD risk factors, (high pretest probability of CAD) should be considered for invasive or noninvasive angiography in case of (i) known CAD; (ii) abnormal noninvasive test. The GRADE recommendation is 2C [9]. A major question is how to place "new" LT indications (alcoholic cirrhosis, NASH, NAFLD etc) in this algorithm and whether they should be considered as DM (single factor able to justify the test) or included in the "reasonable number" of 2 or 3 risk factor. A definite position is eagerly awaited
2) Noninvasive stress testing (DSE / NMPI) should be considered on an individual basis, according to pretest probability for having CAD (GRADE 1 C). Major limitations are (i) very low PPV, 0-22%) ; (ii) pharmacologic stress testing not able to determine maximal chronotropic response; (iii) unreliable assessment of coronary flow reserve due to resting vasodilation.

A possible solution, to be tested in a large multicenter study, would be the use of a score (possible choice would be CAR –OLT, RCRI, AHA) [9,87,100] and, according to the score, the definition of a reliable threshold

to indicate the stress test or a noninvasive imaging for further investigations. Renal function, assessed by glomerular filtration rate(> or < 50 ml / min 1.73 m^2) could constitute an indication for contrast use [9]

6.2 Cardiac Computed Tomography and Calcium score

Among the newer and more sophisticated noninvasive cardiac imaging modalities is cardiac computed tomography [9,10,96-98,101-105]. Computer tomographic coronary angiography (CTCA) is since long an accepted alternative to CA, when negative, to rule out CAD. It is also a potential alternative, due to newer technologies enabling the acquisition of excellent anatomic details of the coronary arteries in beating hearts, to diagnose and grade the severity of CAD. CTCA with contrast allows for imaging of the heart chambers, coronary arteries, and pulmonary vessels in three dimensions and could be considered an alternative, noninvasive tool to identify atherosclerotic disease in silent CAD. Sensitivity (98-99%) and specificity (89-91%) in detecting coronary artery plaques are reported to be very high. Due to the high NPV, a normal result is able to exclude significant CAD, avoiding further investigations. Coronary artery calcium score (CACS), proposed in the early nineties by Agatston et al [101] is a consolidated tool to identify and quantify calcification of the coronary plaques. The severity of luminal stenosis is correlated with CACS (defined in Hounsfield Units) and is generally classified as absent (0), minimal (1–10), mild (11–100), moderate (101–400), or extensive (>400). A CACS <10 documents the absence of any (significant) coronary obstructive lesion: the quantification of coronary artery calcium on CT is correlated with the severity of luminal narrowing, stenosis severity, and total plaque burden in the arteries secondary to the atherosclerotic disease [97,98]. A CACS >400 (extensive) is significantly associated with the presence of significant (≥50%) or critical (≥70%) coronary artery stenosis on CA in asymptomatic LT candidates [102-104], while preoperative CACS was predictive of early postoperative cardiovascular complication in OLT recipients [105]. According to VanWagner et al. [9], due to a sensitivity close to 90% and a negative predictive value above 95% for excluding significant CAD (as very recently confirmed by Moon et al) [97], noninvasive CTCA may be considered an acceptable alternative to invasive CA in “low risk” patients with regular, non-tachycardic rhythm, able to lie still and to perform breath-holding maneuvers. Therefore severe ascites, orthopnea and hepatic

encephalopathy should be considered contraindications [9]. In candidates with coronary artery stenosis ≥50% on CTCA or in cases of CACS >400, CA is mandatory, to quantify the stenosis and to define the need for interventional procedures [9] since in this case, the incidence of critical CAD requiring revascularization is high. False positive result are possible in case of elevated diffuse calcification, as PPV is low (25%) [1]. Major limitations to CTCA in ESLD patients are nephrotoxicity and the need for relative bradycardia. The prognostic role of CTCA, according to Moon et al needs further research [97]. Studies comparing CTCA with CA are needed to clarify the role of CTCA in detecting CAD among LT population [80].

6.3 Cardiovascular Magnetic Resonance Imaging (CMRI)

CMRI was proposed as an integrated modality ("one-stop shop", one examination on a standard MRI scanner) to evaluate cardiac function, stress response, structure, coronary disease and viability while studying thoracoabdominal vasculature and liver anatomy [98,106]. After initial promising results in 2013 [98], Reddy et al recently reported the results obtained in 252 OLT candidates over 8 years showing that negative CMR stress examination had 100% CAD event-free survival at 12 months [106.] Patients with low baseline heart rate (secondary to autonomic dysfunction or beta-blockade) could benefit more from cardiac CT or NMPI rather than DSE, while in candidates with concomitant renal dysfunction NMPS or DSE may be preferred over cardiac CT (or CMRI).

6.4 Coronary Angiography

CA is the gold standard to assess CAD in LT candidates when other tests (noninvasive imaging such as CCTA/CACS or stress tests) are positive and "true positivity" (presence or absence of critical stenosis requiring treatment) has to be confirmed [9]. CA allows simultaneous diagnosis and treatment of the lesions with minimal risk (< 1%), particularly with the trans-radial approach [9,80] in spite of altered hemostasis, altered renal function and potentials for pseudoaneurysms (GRADE recommendation 1C) [9]. For candidates with advanced renal dysfunction a nephrologist consultation is recommended (GRADE recommendation 1C) [9]. According to Kutkut et al, CA may be indicated in very selected cases also in the presence of negative stress test results [80]. Assessment of candidates who had CABG should be based on their pre-transplant LVEF and

ischemic testing. CA should be considered in case of reduced LVEF or evidence of ischemia to assess graft patency (GRADE recommendation 1C) [9]. However a very recent authoritative viewpoint admitted that "it remains unclear when to proceed with invasive coronary angiography"[10]. Not surprisingly, a standardized protocol for assessing (and managing) CAD in LT recipients is, as yet, lacking, even if long and eagerly awaited. The results of the most recent study dealing with CAD screening are in favor of aggressive protocols, to give to candidates with significant CAD the chance of an appropriate treatment and reasonable long term outcomes [9,80].

7. Valvular Heart Disease

Precise assessment of valvular heart disease, its severity and the impact on cardiorespiratory function are relevant part of the preoperative evaluation. The role of TTE is prominent (GRADE recommendation 1C) [9], while transesophageal echocardiography (TEE) might ease the intraoperative management [33]. Mild to moderate valvular heart diseases are usually well tolerated during the surgical procedure and do not constitute a contraindication to LT [9,25]. Mild or moderate tricuspid (TR) and mitral regurgitation (MR) are associated with cirrhotic cardiomyopathy together with ventricular remodeling. Moderate to severe TR is associated with poor postoperative graft and patient outcome. Deeper investigation to differentiate fluid overload or decompensated Portopulmonary hypertension (PoPH) is warranted [9,25]. In case of MR, attention should be paid to avoid bradycardia and hypovolemia. Mild to moderate asymptomatic Aortic Stenosis (AS) does not seem to be a contraindication. Preload, afterload and systolic function, together with low to normal heart rate, are the main hemodynamic targets to avoid coronary artery hypoperfusion and intraoperative catastrophe [25] . Severe or symptomatic AS, if nor corrected, precludes the LT, due to severe hemodynamic instability, critically reduced myocardial perfusion and poor outcome [9,25]. Valvular surgery before LT can be proposed only in Child-Pugh A patients, due to the severe prognosis in Child-Pugh B or C patients admitted to valve replacement surgery [107-108]. Few cases of simultaneous valve replacement with Child- Pugh B and LT have been reported, but the procedure, extremely challenging, should be reserved

for very selected cases: results are poor [109,110]. Small series of combined LT and aortic valve replacement are reported when cardiac surgery prior to LT was not possible: the results are so far encouraging [108]. In case of moderate-severe and severe forms of AS, percutaneous balloon valvuloplasty or transcatheter aortic valve implantation (TAVI), after an extensive multidisciplinary approach, is a feasible option [111-113], requiring a short (one month) DAPT period.

8. Portopulmonary Hypertension

Portopulmonary hypertension (PoPH) is a serious complication of portal hypertension, is reported in 2–5% of the candidates: it is not correlated with the severity of the ESLD [9,25,114, 115]. It is characterized by specific anatomic features of the pulmonary vascular bed (pulmonary artery medial hypertrophy with smooth muscle proliferation and a transition to myofibroblasts, a form of vasoproliferation) and an exposition to vasoconstrictive agents (increased endothelin-1 *vs* reduced prostacyclin synthesis) [114]. Physical signs and symptoms may be absent or mild and nonspecific (dyspnea, chest pain, mild hypoxia). POPH screening relies upon TTE using the right ventricle systolic pressure (RVSP) estimation. Other common TTE features are tricuspid regurgitation, right ventricular dilatation, right ventricular dysfunction, or a combination [9,25,114-116]. Right heart catheterization (RHC) is mandatory in case of TTE-estimated PAPs > 45–50 mmHg (GRADE recommendation 1C) [9, 114-116], althought a more conservative approach suggests 38 mmHg for RHC [116]. The combination of main pulmonary artery diameter at CT and TTE might improve the diagnostic accuracy [117]. TTE should be repeated while on waiting list , the optimal interval being still unclear)[114,115]. Diagnostic criteria include mean pulmonary artery pressure (mPAP) >25 mmHg and pulmonary vascular resistance (PVR) >240 dyne/s/cm^{-5} (> 3 Wood Units) documented during RHC: central venous pressure (CVP) and pulmonary wedge pressure (PAWP) should be in the normal range (PAWP <15 mmHg) [114,115]. Pulmonary hypertension secondary to volume overload (CVP and PAWP above normal range) or to the hyperdynamic status (very high cardiac output) has to be ruled out by RHC. True precapillary POPH is associated with an increased transpulmonary gradient (TPG) (the difference

between MPAP and PAWP, normal value being 12 mm Hg), elevated PAWP alone being not a criterion to exclude a priori POPH diagnosis[114,115]. PoPH is classified according to mPAP at RHC as mild (25–35 mmHg), moderate (35–45 mmHg), and severe (>45 mmHg). According to very recent guidelines [9,114,115], while mild PoPH does not constitute a contraindication to LT, patients with moderate POPH (mPAPs >35 < 50 mmHg) should be temporarily delisted, referred to a PoPH specialist and treated (pharmacologic therapy relays upon pulmonary vasodilators, prostacyclin analogs, phosphodiesterase inhibitors, endothelin receptor antagonists), reassessed (RHC and TTE) to evaluate the hemodynamic improvement (mPAP <35 mmHg, PVR <400 dyne/s/cm–5, good right ventricular function), and relisted if a "sustained" improvement is achieved [9,25,114, 115]. While moderate PoPH with preserved right ventricular function not responsive to medical treatment constitutes a relative contraindication to LT [9], persistent severe PoPH associated with right heart failure and not responsive to medical therapies is an absolute contraindication, being very high the risk of right ventricular failure and post LT mortality [9,25,114,115]. When appropriately indicated, survival after LT is good]114,115].

9. Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS), reported in 5 –32% of ESLD LT candidates, is characterized by (i) abnormal arterial oxygenation (alveolar –arterial gradient > 15 mm Hg breathing room air in the sitting position) ,(ii) portal hypertension and (iii) intrapulmonary vascular dilatation (IPDV). Low PVR and high cardiac output are part of the hemodynamic profile. According to current guidelines [114] the severity of HPS is determined by the degree of hypoxemia (mild $PaO_2 \geq 80$ mm Hg; moderate (PaO_2 = 60-79 mm Hg; severe (PaO_2 = 50-59 mm Hg), and very severe ($PaO_2 < 50$mm Hg) [113, 114]. HPS, always to be considered in case of hypoxia in ESLD patients, mandates a thorough evaluation to exclude obstructive and restrictive conditions (pleural effusions, hydrothorax, atelectasis caused by ascites or diaphragmatic dysfunction, aspiration secondary to encephalopathy, forms of COPD). Clinical signs and symptoms in patients with HPS include digital clubbing, cyanosis, platypnea (dyspnea that worsens moving from supine to upright position)

and orthodeoxia (improved SaO_2 moving from upright to supine position). Unlike in other pulmonary diseases, hypoxia, due to V/Q mismatching and anatomic shunting secondary to IPVD, improves dramatically with a high inspired O_2 concentration (anatomic shunt). The screening approach to find significant hypoxemia using SpO_2 < 96%, recommended by the current guidelines[115], has recently been questioned by a multicenter study due to the low sensitivity (28%)[118], making arterial blood gases mandatory to establish the presence and the severity of hypoxia. Diagnosis of HPS should be confirmed by contrast enhanced TTE (CE-TTE) ("bubbling") (1B), able to detect intrapulmonary shunting associated with IPDV. In patients with an intracardiac shunt (persistent foramen ovale or atrial septal defect) bubbles, after the peripheral injection of agitated saline, typically appear in the left cardiac chambers within 1 to 2 cycles of their appearance in the right atrium. In case of IPVD shunt , bubbles will appear in the left atrium 3 to 6 cardiac cycles after their first appearance in right ventricle [115,116]. Lung perfusion using labeled ^{99m}Tc macroaggregated albumin with brain uptake imaging is another method for detecting and quantifying IPVD: high brain shunt (>6%) could constitute a further confirmation of HPS in presence of confounding intraparenchimal pulmonary pathologies [114,115]. High inspiratory O_2 concentration is the first line measure during transplant surgery in case of hypoxemia. Therefore the response to high O2 concentration should be evaluated before surgery. Methylene blue might be considered an option in refractory hypoxia, before considering ECMO support [13,25,115]. Patients diagnosed with HPS might have an increased risk of postoperative respiratory complications compared with cirrhotic patients without, but medium-term outcome is now considered similar [25]. There is currently no medical treatment for HPS: LT is the option , granted of MELD exception points for higher waiting list priority: hypoxia resolution might take months to resolve [115,116].

10. Summary

A multidisciplinary consensus to define the optimal paradigm to guide the cardiovascular assessment of LT candidates is lacking and eagerly awaited. Extensive worldwide clinical experience and favorable clinical results suggest as a good, feasible and practical the combination of risk stratification and functional assessment to build a rational stepwise algorithm which should include both surgical complexity and candidates' comorbidities to define the "high risk". Even though different forms of testings are used in

different centers or countries, the “pillars” sustaining the rationale of the protocols are similar among the various stepwise paradigms broadly and successfully applied to the LT candidates. The first commitment of this effort is to optimize pathways and processes, eliminating useless, time-wasting tests, concentrating resources and attention on the “true” high risk patients. At the very end of the process, the main aim is the proper selection of the LT candidates (whose number is on the raise) to be matched with a precious and finite resource, the graft, able to save (and change) lives.

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Practice points

- Older candidates and wider LT indications have increased the cardiovascular risk of the LT recipients
- Screening for cardiac diseases and risk stratification for perioperative cardiac complication are pivotal in the preLT assessment

- In an individualized pre transplant evaluation protocol, ischemic and non ischemic cardiac diseases are to be included
- Noninvasive stress tests are suboptimal to detects angiographically defined CAD, particularly in asymptomatic candidates
- Significant variability in current guidelines and clinical practice is reflected in the various "center –centered" stepwise algorithms

Research agenda

- The role of biomarkers (cTn I) or new imaging techniques (CTCA / CAS and cMRI) in cardiac risk stratification
- Consensus on a risk stratification model to define high risk candidates
- Consensus on stress tests indication (which test / which candidate/ how often)
- Consensus on a common stepwise flowchart to be adapted to single centers

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Abbreviations in the text

AH	Arterial Hypertension
AF	Atrial fibrillation
AS	Aortic Stenosis
BMS	bare metal stents

CA	Coronary artery angiography
CABG	Coronary Artery Bypass Graft
CACS	Coronary Artery Calcium Score
CAD	Coronary artery disease
CCM	Cirrhotic cardiomyopathy
CE-TTE	contrast enhanced Trans thoracic echocardiography
CFVR	Coronary Flow Velocity Reserve
CMRI	Cardiovascular Magnetic Resonance Imaging
CPET	CardioPulmonary Exercise Testing
CTCA	Computer Tomographic Coronary Angiography
cTn I	Cardiac Troponin I
DAPT	Dual antiplatelet therapy
DASI	Duke Activity Status Index
DD	Diastolic Dysfunction
DES	Drug eluting stent
DM	Diabetes Mellitus
DOACs	direct oral anticoagulants
DSE	Dobutamine stress echocardiography
ECG	Electrocardiogram
ESLD	End stage liver disease
EF	Ejection Fraction
HH	Hereditary Haemocromatosis
IPVD	Intrapulmonary Vascular Dilatation
LAD	Left Anterior Descending Coronary Artery
LMWH	Low Molecular Weight Heparin
LVEF	Left Ventricular Ejection fraction
LVH	Left Ventricular Hypertrophy
LT	liver transplantation
MACE	major cardiovascular adverse events
MELD	Model of End Stage Liver Disease
METs	metabolic equivalent of tasks
MR	Mitral Regurgitation
NAFLD	Non alcoholic fatty-liver disease

NASH	Non-alcoholic steatohepatitis
NMPS	Nuclear Myocardial Perfusion Scanning
NPV	Negative Predictive Value
NT BPN	N-terminal prohormone of brain natriuretic peptide [
PCI	Percutaneous Coronary Intervention
PoPH	Portopulmonary hypertension
PPV	Positive Predictive Value
RHC	Right heart catheterization
SD	Systolic Dysfunction
sPAP	Pulmonary Artery Systolic Pressure
SPECT	Single-photon emission Tomography
TAVI	Transcatheter aortic valve implantation
TTE	Transthoracic echocardiography
VKA	Vitamin K antagonists
6MWT	6 minutes walking tests